The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

The chemistry of
sulphenic acids and their derivatives

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—SOH

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SAUL PATAI

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Dedicated to

Professor Eliezer Rachmilewitz and his team

with deep gratitude

S.P.

Foreword

This is an additional volume in the subseries on sulphur-containing functional groups in 'The chemistry of functional groups' series. The previous volumes were *The chemistry of the thiol group* (1974), with several relevant chapters in *Supplement E: The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues* (1980); *The chemistry of the sulphonium group* (1981); *The chemistry of sulphones and sulphoxides* (1988) and *The chemistry of sulphinic acids, esters and their derivatives* (1990). After the present volume, the final volume of the sub-set should be published by early 1991 on *Sulphonic acids and their derivatives*.

Three chapters did not materialize for this volume. These are on 'General and theoretical aspects', on 'Mass spectra' and on 'PES'. The material of all these three chapters will be incorporated in the relevant chapters in the 'Sulphonic acids' volume.

The authors' literature search extended in most cases until the end of 1988 and sporadically even to the first half of 1989.

I will be most grateful to readers who would take the trouble to bring to my attention mistakes or omissions in this volume or in other volumes of 'The chemistry of functional groups' series.

Jerusalem
January 1990

SAUL PATAI

The Chemistry of Functional Groups

Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same same time preserving the readability of the text. The Editor set himself the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES—as well as activating and directive effects exerted by the group, and its basicity, acidity or complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the

synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E and F). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff members of the publisher also rendered me invaluable aid. My sincere thanks are due to all of them, especially to Professor Zvi Rappoport who, for many years, shares the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, Israel

SAUL PATAI

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
All	allyl
An	anisyl
Ar	aryl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt
Fc	ferrocene
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_5)
Hex	hexyl(C_6H_{11})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
i-	iso

Ip	ionization potential
IR	infrared
ICR	ion cyclotron reasonance
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Pip	piperidyl($C_5H_{10}N$)
Ph	phenyl
ppm	parts per million
Pr	propyl (also *i*-Pr or Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_4N)
R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TMEDA	tetramethylethylene diamine
Tol	tolyl(MeC_6H_4)
Tos	tosyl (*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, pp. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

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CHAPTER 1

Structural chemistry

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The Chemistry of Sulphenic Acids and their Derivatives
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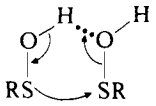
I. INTRODUCTION

There is special interest in the structural features of a functional group, such as the sulphenic acid group, that confers the status of 'transient species' on some of its compounds, while other compounds containing this functional group are stable. The explanation of such behaviour is revealing about the functional group concerned, also about the chemistry of the nearby structural features, and this chapter will explore these structural details of sulphenic acids and their derivatives.

A. The Structural Environment of the Sulphenic Acid Functional Group in Compounds Containing it

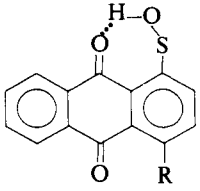
The description 'transient species' applies to the simplest alkanesulphenic acids, since they reveal in their reactions the extraordinarily high nucleophilicity of the sulphur atom combined with electrophilic properties for the group. The opportunity for self-condensation is endowed on the sulphenic acid grouping by its combined highly nucleophilic/electrophilic properties (equation 1)[1].



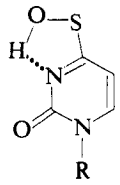
$$\longrightarrow \quad RS(O)SR + H_2O \qquad (1)$$

Stable sulphenic acids are characterized by the presence of either (a) polar groupings, or (b) bulky groupings, or both, adjacent to the sulphenic acid moiety. Also, polar solvents confer stability on sulphenic acids in solution[2–5].

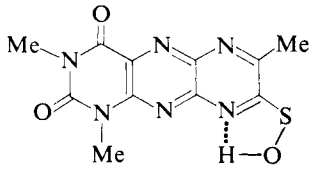
Nearby polar groupings moderate what has been called[1,6] the high 'α-effect' nucleophilic reactivity of sulphenic acids. This 'α-effect' behaviour is seen for structures that carry two nucleophilic groups or atoms joined by a single bond (familiar 'α-effect' species that comprise two adjacent nucleophilic centres are hydrazines and hydroxylamines). Polar groupings may also provide a stabilizing effect through electron withdrawal from the carbon atom carrying the sulphenic acid grouping, but their main stabilizing function is achieved through providing intramolecular hydrogen bond acceptance from the sulphenic acid grouping. Compounds **1–7** are representative stable sulphenic acids; others (**10–12**) are displayed later in this chapter.



(1) R = H, SOH



(2) R = Me, β-D-ribosyl



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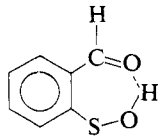

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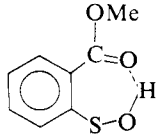
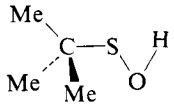


(5)

Steric 'protection' may also be offered to the sulphenic acid functional group by the polar environment, but 2-methylpropanesulphenic acid (**6**)[3] and triptycene-9-sulphenic acid (**7**)[7] are stabilized only on the basis of the steric environment of their reactive sulphenic acid moiety.



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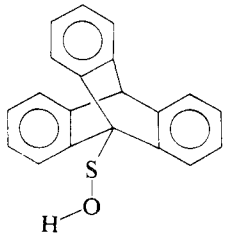


(7)

These principles have been deduced by Davis and coworkers[2] to be a simple set of criteria suitable for explaining the readiness for self-condensation (equation 1) shown by some sulphenic acids, but not by others.

An intermolecular hydrogen bond, from the hydrogen atom of one sulphenic acid group to the oxygen atom of another, is postulated to be the primary requirement for launching a sulphenic acid on the highly favoured self-condensation pathway (equation 1). From this there follows an explanation for the stability of the few known stable sulphenic acids (**1–7**, and others, **10–12**, described later in this chapter). These are believed to be unwilling, or unable, to participate in intermolecular hydrogen bonding at the expense of the energy loss associated with the breaking of their intramolecular hydrogen bond, which in these structures is part of six- or seven-membered ring chelate. (The greater stability of the seven-membered ring chelate over the six-membered analogue is, incidentally, another conclusion emerging from this study.)[2]

Highly favoured hydrogen-bonded 'facial contact', which allows the two reactant molecules to adopt a relative orientation that is close in geometry to the transition state of

the self-condensation reaction (equation 1), is considered to be the prime cause of transient existence for most sulphenic acids[2].

II. STRUCTURAL STUDIES OF SULPHENIC ACIDS

The fact that short-lived alkanesulphenic acids, generated by flash vacuum pyrolysis of alkyl sulphoxides, happen to be the simplest structural types, allows physical methods to be applied that, it so happens, are inherently incapable of yielding interpretable results with more complex structures. They have been studied, for example, by microwave spectrometry; and photoelectron spectroscopy has also yielded useful information.

A. Methanesulphenic Acid

The two possible tautomeric forms **8** and **9** are easily distinguished, in favour of the all-single-bond structure **8** in the gas phase, on the basis of microwave spectrometric data (equation 2)[8].

(2)

(**8**) (**9**)

The bond lengths and molecular geometry of methanesulphenic acid reported by Block and coworkers[8] are summarized in Figure 1. The C–S bond length measured for methanesulphenic acid (1.806 Å) is close to that for alkyl sulphoxides (1.808 Å) and alkyl sulphides (1.802 Å) but longer than that for alkyl sulphones (1.765 Å); further detail is provided in Tables 1 and 2, later in this chapter.

Dihedral angle CSOH = 93.9°

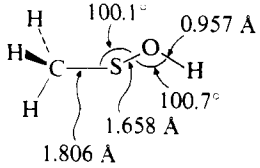
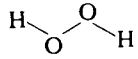


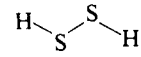
FIGURE 1

Internal rotation of the methyl and hydroxyl groups is indicated in the microwave spectra by splitting of certain rotational transitions into quartets. Analysis of these splittings reveals a 2.4 kcal mol^{-1} threefold potential barrier to internal rotation about the C–S bond, and 5.4 kcal mol^{-1} and 4.1 kcal mol^{-1} potential barriers, respectively, for the *cis* and *trans* orientations concerning rotation about the S–O bond. Compared with internal rotation in H_2O_2[9] and H_2S_2[10], the hindering potential for rotation about the S–O bond in methanesulphenic acid is more like that seen about the S–S bond than about the O–O bond (Figure 2).

Microwave spectral assignments have also been made, and reported in this study, for ^{13}C, ^{34}S, ^{18}O, –O–^2H, C^2H_3 and $C^2H_3{}^{34}SOH$ isotopomers[8], prepared by standard methods.



$\phi = 118°$; V_{cis} 7.0, V_{trans} 1.1 kcal mol^{-1}



$\phi = 90.6°$; V_{cis} 7.2, V_{trans} 6.8 kcal mol^{-1}

FIGURE 2

Further structural details for isotopically-normal methanesulphenic acid are to be found in this paper[8], including its dipole moment, 1.87 *D*. The mass spectrum reveals the survival of the molecular ion, *m/z* 64, following electron impact ionization.

B. Infrared Spectra of Sulphenic Acids

The clear evidence for the existence of only one tautomer of methanesulphenic acid derived from microwave spectroscopy is in contrast with earlier infrared spectrometric information for 2-methylpropanesulphenic acid (**6**)[11], which suggests the presence of both tautomers of this compound in the neat liquid phase. The observed absorption frequencies 3400 (O–H stretch) and 2600 cm^{-1} (S–H stretch) were interpreted in an unequivocal and straightforward fashion and this conclusion has been confirmed by more extensive recent studies[12].

FIGURE 3

In this work, both tautomers of benzenesulphenic acid (Figure 3) and of 2-methylpropanesulphenic acid, sufficiently stable for study on a cold finger between −196 and −50 °C, were identified in neat samples. For the former [broad OH stretch (3300), weaker SH (2600) and S=O (1000 cm^{-1})] and for the latter [broad OH stretch (3250), weaker SH (2630) and S=O (1060 cm^{-1})] additional evidence is provided by the infrared spectra in support of the intramolecular hydrogen bond (cf. the broad OH absorption features seen in the spectra; Figure 4).

In support of this interpretation, the deuteriated isotopomer $C_6H_5SO^2H$ shows corresponding absorption at 2435 and 1905 cm^{-1}, and calculated values on the basis of reduced masses for ^{1}H and ^{2}H are 2408 and 1864 cm^{-1}. These results unambiguously relate the observed infrared absorption features with the two tautomers, and confirm the notion that the sulphenic acid proton alternates within the functional group between S and O atoms.

Anthraquinone-1-sulphenic acids (**1**; R = H or SOH)[13], triptycene-9-sulphenic acid (**7**)[7] and the stable crystalline 2-oxoazetidine-4-sulphenic acids (**10–12**)[14,15] are concluded to adopt exclusively the single-bond tautomer (as in **8**) on the basis of infrared data (intense absorptions at 1179, 1154, 770 cm^{-1} attributed to S–O; broad O–H peak at 3160 cm^{-1}).

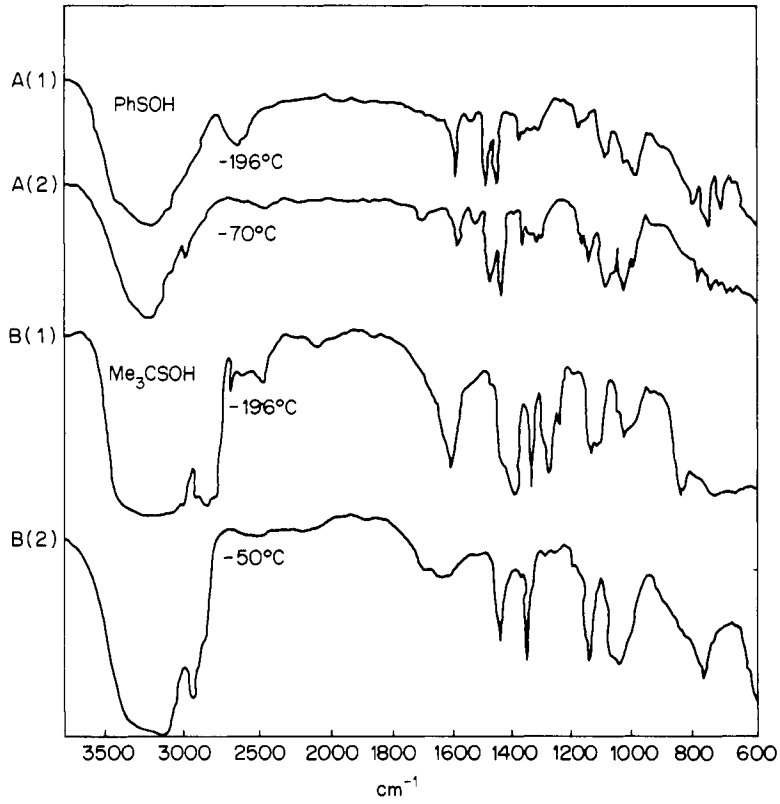
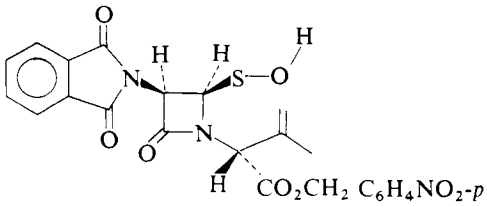
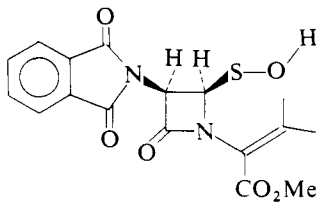


FIGURE 4. Infrared spectra of: (A) benzenesulphenic acid at (1) −196°C, (2) −70°C; (B) 2-methylpropanesulphenic acid at (1) −196°C, (2) −50°C. Reprinted with permission from Davis and Billmers, *J. Org. Chem.*, **50**, 2593. Copyright (1985) American Chemical Society

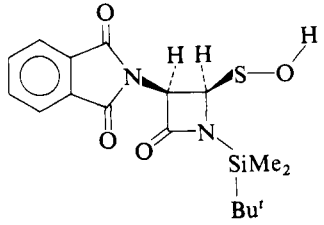
The double bond isomer (as in **9**) is characterized by a broad absorption (3570 cm^{-1}) for the O–H stretch. Structure **12** shows a broad O–H infrared peak (KBr medium) at 3250 cm^{-1} [115]. 1,3,6-Trimethyl-lumazine-7-sulphenic acid (**3**)[16] appears to adopt the double-bond-containing form in the solid state (S–H, 2500; S=O, 1050 cm^{-1}), but exists as a mixture of tautomers in solution.



(10)



(11)



(12)

C. Mass Spectrometry of Sulphenic Acids

Such measurements as have been made show little that is unexpected; the electron impact mass spectrum of the exceptionally stable *N-tert*-butyldimethylsilyl azetidinonesulphenic acid (**12**) includes a prominent $[M-SOH]^+$ peak, indicating relatively facile C–S cleavage[15].

D. NMR Studies of Sulphenic Acids

Attempted NMR study of 2-methylpropanesulphenic acid (**6**) (from methyl *t*-butyl sulphoxide at 80 °C in various solvents) became an exercise in following its decomposition.[11] No resonance was detected for the proton of the sulphenic acid moiety. An additional *t*-butyl resonance about 2 c.p.s. upfield from the *t*-butyl resonance of the sulphoxide starting material was seen for non-aromatic solvents, and 7–20 c.p.s. downfield in aromatic solvents, and assigned to the aliphatic grouping of 2-methylpropanesulphenic acid. This diamagnetic shift caused by the aromatic solvents was suggested as being due to π-complexation between the –SOH grouping and solvent, causing the *t*-butyl group to be deshielded.

The NMR spectrum of the 2-oxoazetidinesulphenic acid *p*-nitrobenzyl ester (**10**) showed an exchangeable proton resonance at 7.25 ppm in C^2HCl_3:$(C^2H_3)_2SO = 1:1$[14]. The corresponding spectra of methyl ester (**10**, Me in place of $CH_2C_6H_4NO_2$), and the double bond isomer of the latter (**11**), showed an exchangeable proton resonance at 7.34 ppm and at 7.56 ppm, respectively[14].

E. Molecular Orbital Calculations

The stability of the HSOH tautomer is calculated to be greater than that of the double bond form[17],

$$H\text{–}S\text{–}O\text{–}H \rightleftharpoons H_2S{=}O \qquad (3)$$

but both structures are predicted to be stable, as shown experimentally for the oxidation product from H_2S[18, 19].

MO calculations[20] for methanesulphenic acid give generally good agreement with the experimental data acquired by Block and coworkers[8].

F. Studies of Sulphenic Acids, their Anions, Sulphinyl Radicals and *S*-Peroxyl Radicals formed by Ambient and Low-temperature Oxidation of Thiols

Oxidation by ozone and photochemically generated O atoms, of H_2S and methanethiol in dilute argon matrices, has been shown to provide tautomeric forms of HSOH

and CH_3SH, respectively, judging by infrared data [3600–3595 (OH) and 1096 cm^{-1} (S=O)][18, 19].

Specific thiol groups in some enzymes have been thought to undergo oxidation to stable sulphenic acids[21, 22] even though the thiol function, as part of the cysteine residue, is carried on a simple aliphatic chain. (On this basis, methanesulphenic acid, which was not known at the time these statements were being written[21, 22], should have been thought to be a stable compound.) This thesis has been advanced most forcefully for the enzyme glyceraldehyde-3-phosphate dehydrogenase[21].

If cysteinesulphenic acid residues are proved to exist in proteins, the sulphenic acid functional group could be a very useful probe for the nearby polar environment that must be responsible for stabilizing the functional group in this situation.

Hogg and Rashid[23] have studied further the generation of blue colour in alkaline solutions of (red) *o*-nitrobenzenethiol exposed to air. The assignment of sulphenate ion structure (λ_{max} 588 nm) as source of the blue colour is supported by the finding that the blue colour was intensified by adding hydrogen peroxide or *tert*-butyl hydroperoxide:

$$ArS^- + H_2O_2 \longrightarrow ArSO^- + H_2O \qquad (4)$$

Di-*tert*-butyl peroxide, dibenzoyl peroxide, iodine or $FeCl_3$ had no such blue-colour-intensifying effect. Dibenzoyl peroxide or iodine rapidly form disulphides with thiols, the former via the mixed anhydride ArS–O–COPh.

The presence of a radical trap, *N*-*tert*-butyl nitrone, did not modify the blue-colour-intensifying effect of the peroxides, showing that radical intermediates were not responsible for the spectroscopic data.

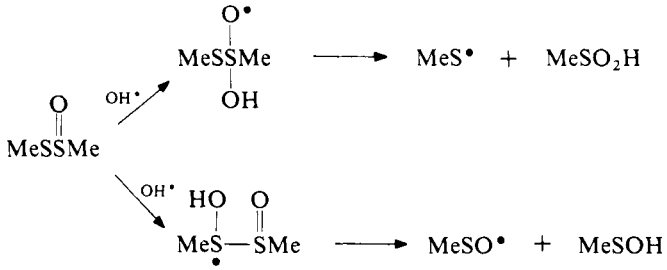
However, sulphinyl radicals RSO• are more stable than thiyl or sulphonyl radicals (RS and $RSO_2^•$, respectively)[24] and should have been easily detected if they were intermediates in this autoxidation process.

The cysteinesulphinyl radical CysSO• is soon formed by disproportionation of the corresponding thioperoxyl radical CysSOO•, itself formed at low temperatures in frozen aqueous glasses from the reaction of the cysteinethiyl radical with oxygen[25]:

$$CysS^• + O_2 \longrightarrow CysS{-}O{-}O^• \qquad (5)$$

This thioperoxyl radical showed typical peroxyl radical ESR characteristics, and λ_{max} 540 nm, and was totally unlike carbon peroxyl radical ESR[25]. In a 8M $HClO_4$ glass, at higher temperatures at which radical migration becomes possible, the thioperoxyl radical reacts with cysteine to give CysSO• and CysSOH ('cysteinesulphenic acid')

Analogous simple sulphinyl radicals are formed through the reaction of hydroxyl radicals with thiolsulphinates (Scheme 1)[26].



SCHEME 1

Numerous other reports of the formation of simple sulphur radicals can be found, some including ESR data (equation 6)[27, 28].

$$PhCH_2O\text{–}S\text{–}Me \longrightarrow [PhCH_2^{\bullet} + Me\text{–}S\text{–}O^{\bullet}] \longrightarrow \text{products} \qquad (6)$$

The thermal decomposition pathway open to simple alkyl sulphoxides includes all obvious possibilities for radical intermediates, but no structural study has been carried out to investigate these proposals (Scheme 2)[8].

$$\begin{aligned}
CH_3SOCH_3 &\longrightarrow CH_3SO^{\bullet} + CH_3^{\bullet} \\
CH_3SOCH_3 + CH_3SO^{\bullet} &\longrightarrow CH_3SOH + CH_3SOCH_2^{\bullet} \\
CH_3SOCH_3 + CH_3^{\bullet} &\longrightarrow CH_4 + CH_3SOCH_2^{\bullet} \\
CH_3SOCH_2^{\bullet} &\longrightarrow CH_2{=}S{=}O + CH_3^{\bullet} \\
CH_3SOCH_2^{\bullet} + CH_3^{\bullet} &\longrightarrow CH_3SOCH_2CH_3 \\
CH_3SOCH_2CH_3 &\longrightarrow CH_3SOH + CH_2{=}CH_2
\end{aligned}$$

SCHEME 2

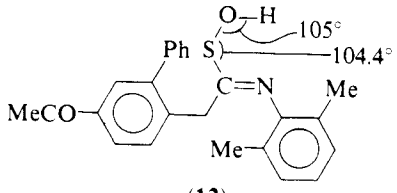
Oxidation of 4-trifluoromethyl-2-nitrobenzenethiol with 0.5 equivalent of hydrogen peroxide is sufficient to convert one-half of the thiol into sulphenate ion if this interpretation (Scheme 2) is correct. The ^{18}F NMR characteristics of the reaction mixture amounted simply to two equal singlets at 1289 Hz(ArS^-) and 1263 Hz($ArSO^-$), with a small signal at 1199 Hz($ArSO_2^-$) amounting to about 4% of the total NMR signal, thus confirming the proposed stoichiometry.

Within these data is information on the relative electronic relay from the trifluoromethyl group at the behest of the thiolate, sulphenate and sulphinate ions. There is very little difference between thiolate and sulphenate anions in this respect, but considerably greater electron withdrawal by sulphinate.

Davis and coworkers[6] used 2-(benzenesulphonyl)-3-phenyloxaziridine as mild oxidant for thiols, leading to relatively stable substituted benzenesulphenic acids (such as **4** and **5**) and providing the first direct evidence for the intermediacy of sulphenic acids in mild oxidation of thiols.

G. Species formed by Oxidation of Thioamides

These can be considered alongside alkenesulphenic acids, since they represent a special type of α,β-unsaturated sulphenic acid. However, they are otherwise untypical in their reactions. X-ray data have been reported for compound **13**[29].



(**13**)

H. Acidity and Basicity of Sulphenic Acids

Stable sulphenic acids can be conveniently prepared by aqueous alkaline hydrolysis of disulphides, followed by protonation of the resulting stable sulphenate anions with mineral acids. An example is the pyrimidine sulphenic acid (**2**)[30], isolated as its silver salt after preparation in this way. Treatment of the silver salt in aqueous solution with hydrochloric acid yielded a precipitate of silver chloride and an aqueous solution of the sulphenic acid (**2**).

1. Ultraviolet spectra of sulphenic acids

No systematic study has been reported, but isolated examples of UV spectra have appeared. Thus, the spectra of pyrimidinesulphenic acids (**2**) in aqueous solution show pH dependence (Figure 5)[30].

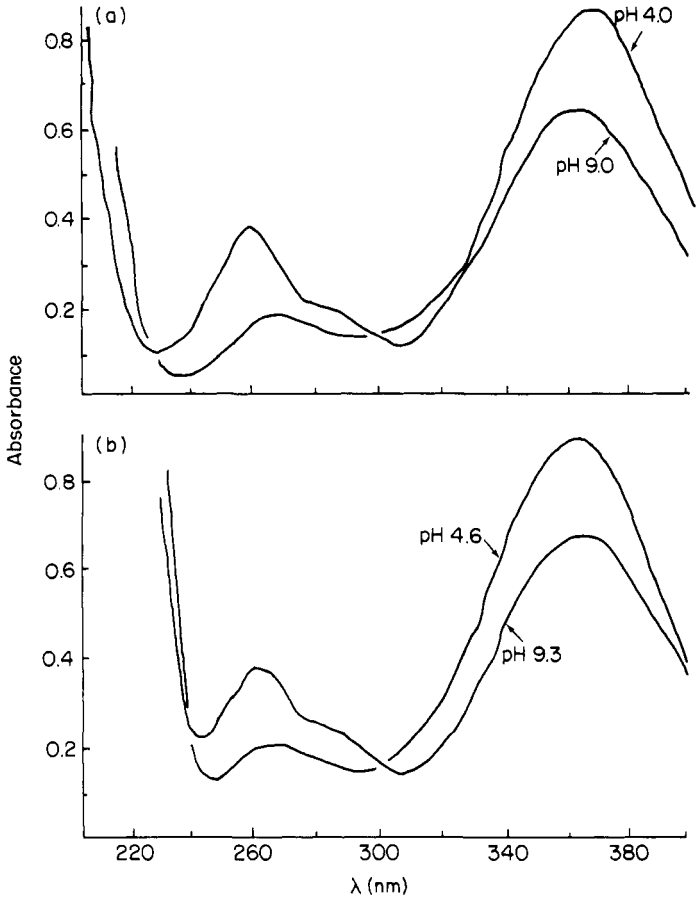
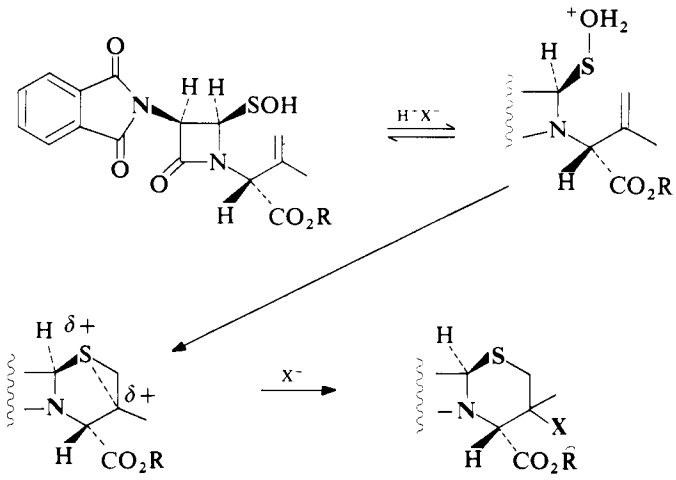


FIGURE 5. Ultraviolet spectra (H_2O) of (a) **2**; R = Me; (b) **2**; R = β-D-ribosyl at different pH values. Reprinted with permission from Pal *et al.*, *J. Am. Chem. Soc.*, **91**, 3636. Copyright (1969) American Chemical Society

2. Acidity and basicity

While no pK data have been determined, circumstantial evidence suggests that arenesulphenic acids ArSOH are at least as acidic as phenols. Since they are liberated from their salts by dilute hydrochloric acid (pH = 1), they cannot be very much more acidic than phenol itself. This conclusion is derived from the behaviour of sulphenate anions discussed in the preceding sections[31].

Similarly, basicity measurements have not been carried out, but protonation of the sulphenic acid OH grouping is implicated in nucleophilic displacement processes in strong acids (e.g. Scheme 3)[14]. The ion-exchange behaviour of the pyrimidinesulphenic acids (**2**)—they are retained as cations from solutions of low pH as a result of protonation—also confirms their modest basicity[30].



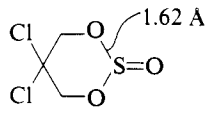
SCHEME 3

III. BOND LENGTHS AND BOND GEOMETRY OF SULPHENIC ACIDS COMPARED WITH THOSE OF OTHER SULPHUR–OXYGEN FUNCTIONAL GROUPS

A. Experimentally Determined Values

The S–O bond in methanesulphenic acid (Figure 1) is slightly longer (1.66 Å) than the corresponding bond in a representative sulphite (1.62 Å, compound **14**)[32], but there are many structural variations to consider that can vary the S–O bond distance considerably.

Some examples of S–O bond lengths for sulphenic acid derivatives are given in relation to those of other sulphur species, in Table 1. The S–O bond is shorter if one or more electronegative F atoms are attached to sulphur.

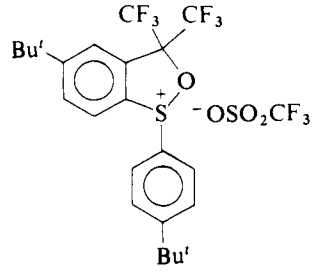


(**14**)

TABLE 1. S–O covalent bond lengths[33]

Type	Substituents (R,R′) in R–S–O–R′		Bond length (Å) (sulphur–oxygen)
Sulphur–Oxygen Double Bond: Hexavalent Sulphur			
Sulphones $R–SO_2–R'$	F, F, O		1.40
	O O O		1.42
	N N O		1.43
	C C O		1.44
Sulphurane oxide R_4SO	F F F F		1.40[34]
	C C O O		1.44[34]
Sulphur–Oxygen Double Bond: Tetravalent Sulphur			
Sulphoxides RSOR′	F F		1.42[35]
	O O		1.45[35]
	N N		1.48[35]
	C C		1.49[35]
Sulphur–Oxygen Single Bond			
Sulphonates $R–SO_2–O–R'$	F O O	S(VI)–O–	1.56[35]
Sulphates $R–O–SO_2–O–R'$	O O O	S(VI)–O–	1.58[36]
Sulphites R–O–SO–O–R′	O O	S(IV)–O–	1.63[35]
Divalent Sulphur			
Sulphenates R–S–O–R	C C	S(II)–O–	1.66[35]
Sulphenic Acids	C H	S(II)–O–	1.66[8]

To complete the comparison of relationships of bond lengths with structure, representative sulphuranes and alkoxysulphonium salts need to be included in the discussion. In alkoxysulphonium salts where the anion is non-nucleophilic (e.g. alkoxysulphonium triflates, **15**), the structure is wholly ionic[37]. The alkoxysulphonium triflates (**15**) are categorized as possessing a hypervalent sulphur–oxygen bond. A linear –O–S–O– arrangement in 'orbitally deficient' sulphuranes of trigonal bipyramidal geometry leads to electron-deficient 3-centre 2-electron bonding directed along the S–O axis, with the remainder of the electron density delocalized from the central atom towards the electronegative oxygen substituents: $^{\ddagger-}O{-}{-}{-}S^{+}{-}{-}{-}O^{\ddagger-}$, and the S–O bonds are much longer (1.78–1.79 Å) than other sulphur–oxygen functional groups (**16–19**). Some shortening (to 1.75–1.78 Å) of the sulphurane S–O bonds occurs with increasing numbers



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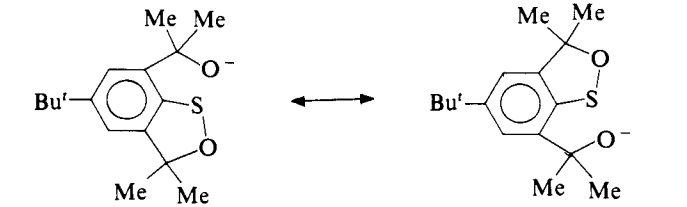
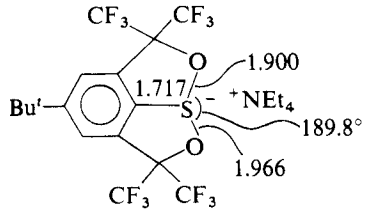
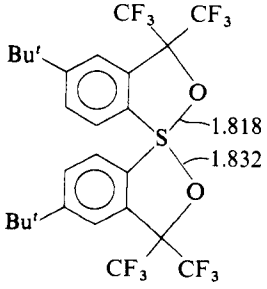


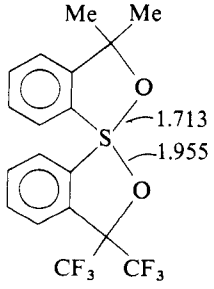
(16)



(17)



(18)



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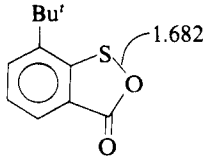

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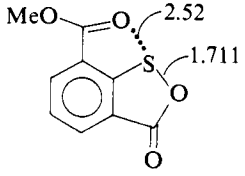


(21)

of electronegative oxygen substituents[38]. Compounds **20** and **21** reveal the substantial S---O interactions seen in certain divalent sulphur–oxygen compounds.

Since S–O hypervalent bonds are easily polarized, their bond lengths and geometry are much more sensitive to changes in local environment than covalent bonds (see Tables 1 and 2)[39].

B. Comparisons of Experimentally Determined Bond Lengths with Calculated Values

In Table 2, calculated and experimentally determined C–S bond lengths, in compounds CH_3–X and CF_3–X, are compared with those for corresponding compounds with P and Cl in place of sulphur.

The C–S bond-lengthening effect of adjacent CF_3, seen in CF_3SO_2H compared with CH_3SO_2H in Table 2, is a common feature of sulphinyl and sulphonyl compounds[45] and is shown in S–O bond lengths also; S=O in $(CF_3)_2SO$ at 1.469 Å is longer than S=O in F_2SO (1.416 Å), or in Cl_2SO (1.443 Å). Its effect is also seen in the C–S bond lengths for CF_3SOH compared with CH_3SOH in Table 2, so sulphenic acids appear to behave like other sulphur oxyacids in this respect. There is no such effect in CF_3SH, which shows a *shorter* C–S bond length than CH_3SH[46].

TABLE 2. Experimentally determined and calculated‡ values for C–X bond lengths in CH_3X and CF_3X (Å)

	CH_3–X			CF_3–X		
X	Measured	3-21G	3-21G*	Measured	3-21G	3-21G*
SH	1.819[a]	1.894	1.828	1.801[b]	1.852	1.779
SOH	1.806[c]	1.869	1.801	~1.88[d]		1.801
SO_2H	~1.77[e]	1.827	1.755	~1.86[f]	1.858	1.782
PH_2	1.858[g]	1.910	1.861	1.904[h]	1.898	1.841
POH_2	~1.80[i]	1.846	1.802	~1.90[j]	1.870	1.817
Cl	1.778[k]	1.892	1.812	1.752[l]	1.835	1.742

‡ 3-21G (no d orbitals on sulphur); 3-21G* (d orbitals on sulphur), to determine effects of d orbitals. Better agreement of calculations with experimental data is seen for the 3-21G* calculations.

[a] T. Kojima, *J. Phys. Soc. Jpn.*, **15**, 1284 (1960).

[b] C. J. Marsden, *J. Mol. Struct.*, **21**, 168 (1974).

[c] Reference 8; V. Typke, *Z. Naturforsch., A*, **33A**, 842 (1978) gives ~1.81 Å.

[d] See Reference 45.

[e] M. Hargittai and L. Hargittai, *J. Chem. Phys.*, **59**, 2513 (1973); B. P. van Eijck, A. J. Korthoff and F. C. Mijlhoff, *J. Mol. Struct.*, **24**, 222 (1975).

[f] J. Brunvoll, I. Hargittai and M. Kolonits, *Z. Naturforsch., A*, **33A**, 1236 (1978).

[g] L. S. Bartell, *J. Chem. Phys.*, **32**, 832 (1960).

[h] I. Yang, C. Britt, A. Cowley and J. Boggs, *J. Chem. Phys.*, **48**, 812 (1968).

[i] C. J. Wilkins, K. Hagen, L. Hedberg, Q. Shen and K. Hedberg, *J. Am. Chem. Soc.*, **97**, 6352 (1975).

[j] See Reference 46.

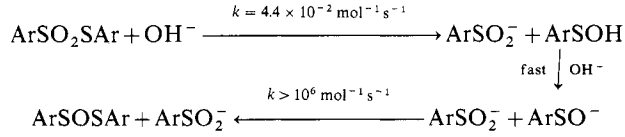
[k] J. L. Duncan, *J. Mol. Struct.*, **6**, 447 (1970).

[l] L. S. Bartell and L. O. Brockway, *J. Chem. Phys.*, **23**, 1860 (1955); V. Typke, M. Dakkouri and H. Oberhammer, *J. Mol. Struct.*, **44**, 85 (1978).

IV. SULPHENATE ANIONS

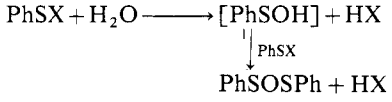
A. Nucleophilicity

An aryl arenethiolsulphinate ArS(O)SAr builds up to high concentrations during the alkaline hydrolysis of the corresponding aryl arenethiolsulphonate $ArSO_2SAr$ as described by Kice and Rogers[47]. This startling result (which appears to mean that aqueous alkali is acting as a reducing/deoxygenating agent) in fact indicates that the nucleophilicity of $ArSO^-$ is greater than that of OH^-. As soon as the arenesulphenate ion is formed as a result of the hydrolysis, it is consumed (Scheme 4).



SCHEME 4

This state of affairs is similar to that seen in the reaction of an arenesulphenic acid with an arenesulphenyl halide in the presence of water (Scheme 5)[47].



SCHEME 5

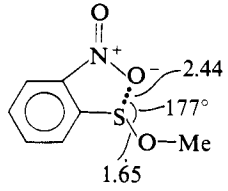
Kice and Cleveland suggest[1] on the basis of this study that benzenesulphenic acid PhSOH is 10^4–10^5 more nucleophilic than water, as expressed in its reactivity towards sulphenyl halides in the presence of water.

V. SULPHENATE ESTERS, SULPHENYL HALIDES AND SULPHURANES

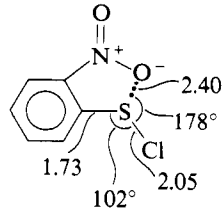
A. X-Ray Crystallography

X-ray data have been reported for methyl *o*-nitrobenzenesulphenate (**22**)[48].

The relevant distances and bond angles are shown on structure **22**, and strong interaction between the NO_2 and sulphenate groupings is indicated. Similarly, strong interactions are seen in the solid-state conformations of related species (e.g. the sulphenyl halide **23**).



(**22**)



(**23**)

The C–S bond length (1.63–1.70 Å) in sulphenyl cyanides (thiocyanates) is very much shorter than that in arenesulphenate esters (1.77 Å)[32], and the C–S–C bond angle for CH_3–S–CN (99.6° by X-ray crystallography)[49] is closely similar to that in the gas phase (99° 2′, as determined by microwave spectroscopy[50]). Little can be learned by comparing this with the slightly larger C–S–O angle in methyl arenesulphenates (100°), since values for bond angles in such situations will reflect the cumulative influence of adjacent groupings.

Electron diffraction data for *o*-nitrobenzenesulphenyl chloride (**23**)[51] give direct evidence for a quasi-apical arrangement of O and Cl atoms close to the sulphur atom, demonstrating that sulphur–oxygen interaction must be strong, close contact being established so as to control the conformation of this and perhaps other sulphur compounds in the vapour phase. It is tempting to make comparisons between sulphenic acid derivatives in which such interactions occur with a nearby oxygen function, with the sulphurane species whose bonding has been discussed in the preceding section of this chapter. Further structural consequences, to be reflected in chemical behaviour, must be awaiting study in yet-undiscovered or unstudied compounds, as a consequence of the establishment of strong sulphur–oxygen interactions discussed in this chapter. The structural similarities with sulphur–sulphur interactions seen in the 6*a*-thiathiophthene series[52] are mirrored in these sulphur–oxygen interactions, which seem to be present in a wide variety of compounds.

B. NMR Spectra

The ^{1}H NMR spectrum of *tert*-butyl methanesulphenate CH_3SOBu^t shows the methyl singlet at τ2.63 ppm[53]. The *tert*-butyl singlet was close to the usual shift value.

C. Mass Spectrometry

Trimethylsilyl sulphenate esters $RSOSiMe_3$ derived from the azetidinonesulphenic acids (**10** and **11**) show a prominent $[M-SOSiMe_3]$ peak in their electron impact mass spectra, indicating facile C–S cleavage, as for their parent sulphenic acids[54].

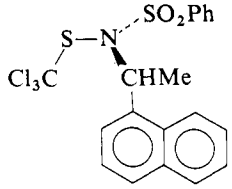
VI. SULPHENAMIDES[55]

A. Mass Spectrometry

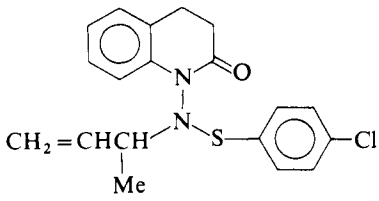
In $R^1S{-}NR^2R^3$, C–S and S–N cleavage are the dominant features[56], with S–N cleavage predominant. S–N homolysis of arenesulphenamides is illustrated in their disproportionation into aryl disulphides and azobenzene[57].

B. X-Ray Crystallography

The particular sulphenamide **24** is nearly planar about N (sum of the bond angles at N is 365.5°) with the C–S–N plane perpendicular to the plane of the two bonds connecting nitrogen to its substituents[58]. However, as discussed in a later section, two dia-



(**24**)



(**25**)

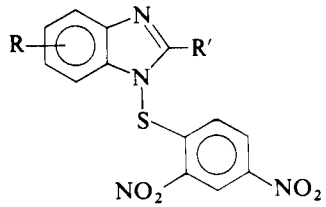
stereoisomers of such compounds can coexist due to a substantial barrier to rotation about the S–N bond. The diastereoisomers, however, are interconvertible through inversion at pyramidal nitrogen[58]. The SO_2–N bond is considerably shorter than the sulphenamide S–N bond, consistent with p_π–d_π orbital overlap, i.e. a form of bonding not normally considered significant for divalent sulphur compounds, but facilitated in **24** by electron withdrawal by the CCl_3 group[58].

X-ray analysis[59] gives a contrasting result for **25**, showing a pyramidal arrangement about the sulphenamide N.

C. Torsion Barriers about the S–N Bond in Sulphenamides

Sulphenamides show substantial barriers to rotation (*ca* 19 kcal mol^{-1}) for examples in which the sulphenamide nitrogen is a part of a heterocyclic ring (e.g. *N*-2,4-dinitrobenzenesulphenylbenzimidazoles **26**)[60].

^{1}H-NMR spectra of *N*,*N*-dibenzylsulphenamides show chemical shift non-equivalence of diastereotopic protons in their prochiral methylene groups, reflecting torsion about the S–N bond, slow on the NMR time scale[61].



(26)

R = H, Cl; R′ = Et, CH_2Ph, CH_2Cl, CHMePh

The compounds **26** (R = H, $R^1 = C_6H_5CH_2$, $ClCH_2$) exhibited AB quartets for the methylene protons while those in **26** ($R^1 = CH_3CH_2$) appeared as the AB portion of an ABX_3 spin system. Compound **26** (R = Cl, $R^1 = CH_3CH_2$, $C_6H_5CH_2$, $ClCH_2$) exhibited similar spectra but with two AB multiplets of unequal intensities arising from the presence of both 5- and 6-chloro-isomers[60].

The chiral probe in **26** [$R^1 = CH(CH_3)C_6H_5$], the 2-phenylethyl group, leads to two methyl doublets of unequal intensity, reflecting the presence in differing amounts of two diastereoisomers which differ in configuration about the sulphenamide chiral axis[60].

Complete line-shape analysis at a number of temperatures in the neighbourhood of the coalescence point led to free energy of activation near 19 kcal mol^{-1} for the topomerization for all these compounds (**26**)[60].

The earlier history[55, 62] of NMR studies of sulphenamides revealed the problems of interpretation that could arise. Temperature-dependent NMR of $Cl_3CSN(CH_2Ph)_2$ (AB quartet at low temperatures for the benzyl protons, $J = 15$ Hz) and coalescence temperature $T_c = 28 \pm 3$ °C were explained in terms of two enantiomeric benzyl groups, within each of which the protons were diastereotopic as a result of hindered inversion at the nitrogen atom.

D. Origin of the Rotation Barrier in Sulphenamides

Bonding involvement of sulphur d-orbitals is a long-standing topic of speculation[62], and p_π–d_π orbital overlap continues to provide a favoured explanation[63]. Augmentation of the height of the barrier by steric interactions of nearby groupings is, of course, possible.

Adequate coverage of the topic is easily available in References 55, 62 and 63.

E. Stereomutation of Sulphenamides

Stereomutation of sulphenamides can occur in two distinct ways, each separately or both simultaneously; inversion at nitrogen (inversion of configuration), and rotation about the S–N bond (conformational change) (Figure 6).

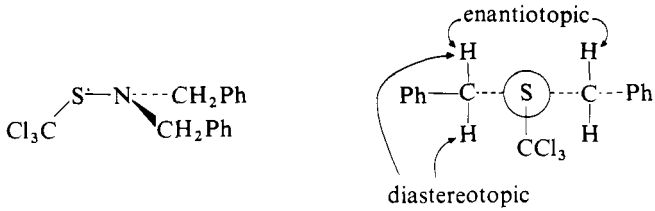
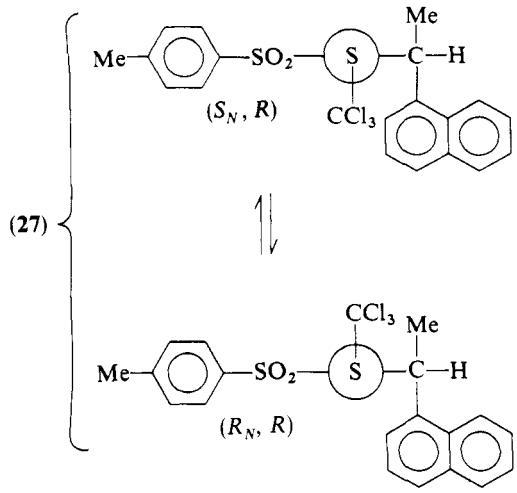


FIGURE 6

A classic diastereoisomeric transformation operating on these principles has been reported[64] for an analogue of the trichloromethanesulphenamide shown in Figure 6; if, instead of two identical benzyl groups, different N-substituents are chosen, one of which carries a chiral centre, then diastereoisomers are possible if the nitrogen atom is held in a pyramidal configuration. Crystallization of *N*-toluene-*p*-sulphonyl-*N*-(*R*)-(1-naphthylethyl) trichloromethanesulphenamide (**27**), which exists as a mixture of diastereoisomers in solution [the major one being the (*R*,*R*)-diastereoisomer], deposits the pure (*R*,*R*) isomer.



The C–S–N plane in a sulphenamide carrying two identical N-substituents, such as benzyl (Figure 6), effects interchange of the two groups as a whole, rendering the benzyl protons enantiotopic, but this plane does not offer interchangeability of the two protons on each individual benzyl group, and such protons are therefore diastereotopic. The ^{1}H NMR spectrum of this particular compound, then, comprises a single AB quartet in

the aliphatic region, due to the chemical shift non-equivalence of the benzyl methylene protons.

Exchange of the methylene environments at higher temperatures was thought to arise from inversion at N accompanied by rapid rotation about the S–N bond. Restricted rotation about S–N was ruled out as the rate-limiting process because this should give rise to two diastereotopic benzyl groups at low temperatures, giving two singlet resonances for the methylene protons. However, Raban also acknowledged that restricted rotation in a non-planar structure would also give rise to an AB quartet[65].

Later work[66] indicated that slow rotation about the S–N bond could be rate-limiting, and Raban and coworkers came to the same conclusion through finding that *N*-trichlorosulphenyl 2,2-dimethylsuccinimide, in which the nitrogen must be planar, or very nearly so, also showed temperature-dependent NMR, for which restricted rotation about the S–N bond is the only possible explanation[61].

F. ^{13}C and ^{15}N NMR Spectra of Sulphenamides

The resonance for *N*,*N*-diethyl benzenesulphenamide in $CHCl_3$ at -334.4 ppm [with respect to CH_3NO_2 doped with $Cr(acac)_3$] is upfield of that for the corresponding sulphinamide (-305.1 ppm, neat) and sulphonamide N (-298.9 ppm in $CHCl_3$), indicating a greater shielding for the sulphenamide nitrogen atom by the benzene ring. The benzene carbon atom attached to S in this sulphenamide has a ^{13}C NMR chemical shift value 141.5 ppm in $CHCl_3$, consistent with the inductive deshielding effect of the sulphur atom. The other ring carbon atom resonances are about normal, but with those for C-2 and C-4 shifted slightly upfield, consistent with the known electron-donating capacity of sulphenamide S through the π-system[67].

Rotational barriers about the N–S bond (in sulphenamides compared with sulphinamides and sulphonamides) are revealed by ^{15}N NMR[68]. They have been discussed as originating in combinations of contributions from N-hybridization, p_π–d_π donation and substituent electronegativity.

G. Optical Activity of Sulphenamides

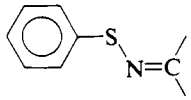
Asymmetric induction by the adjacent chiral centre on the chiral sulphenamide axis in *N*-arenesulphonyl 2,4-dinitrobenzenesulphenamides prepared from optically-active amines creates an excess of one sulphenamide diastereoisomer over the other (see discussion in Section E above).

Chirality within a substantial portion of a molecule which absorbs near the visible wavelength region usually leads to a large optical rotation and Cotton effects of large amplitude[69, 70]. The sign of optical rotation of a sulphenamide diastereoisomer or of a diastereoisomer mixture containing a predominant amount of one diastereoisomer is diagnostic for absolute configuration. The principle has a long history, being essentially the Freudenberg Rule of Shift[70]. The simple rule that emerges from Raban and coworkers' studies[69] is that a chiral aliphatic amine has the (*R*)-configuration if its sulphonylsulphenamide derivative (e.g. **27**) is laevorotatory (λ 589 nm).

VII. SULPHENYLIMINES (*N*-ALKYL/ARYL THIO-OXIMES)[62, 71]

A. Spectrometric Studies Bearing on Structure

These compounds (e.g. **28**) show the same general characteristics as their saturated analogues, the sulphenamides.



(28)

Thus, rotation barriers for the S–N bond in *S*-aryl sulphenylimines (**28**) are about 20 kcal mol^{-1} [72]. Ultraviolet spectrometric studies suggest the occurrence of delocalization of the nitrogen lone pair into the aromatic π-system of **28**[72] and this is consistent with a planar nitrogen inversion mechanism for stereomutation, as for analogous sulphenamides. NMR studies reveal electron transmission through the S–N bond diagnostic of a d_π–p_π contribution to S–N bonding[72]. However, there is little effect of the aryl substituent on the inversion barrier, in substituted *S*-arylsulphenylimines R^2S–N $=CR^1_2$ [73], but compounds with $R^1 = CF_3$ show a lower rotation barrier[73].

B. Sulphenamide Radical Cations

Although formed by anodic or one-electron ($AlCl_3$ or $TiCl_4$ in CH_3NO_2) oxidation of sulphenamides[74, 75], these stable species are considered in this section, since they are structural relatives of sulphenylimines (equation 7).

$$RS\text{–}NR^1R^2 \longrightarrow RS{=}N^+{\bullet}R^1R^2 \qquad (7)$$

Magnetic resonance non-equivalence and coalescence at elevated temperatures, seen for examples in which $R^1 = R^2$, reveals the adoption of a chiral conformation and restricted rotation, as for the sulphenamides[75].

VIII. ACKNOWLEDGEMENT

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **2**

Stereochemistry and chiroptical properties

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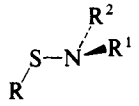
The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

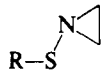
Stereochemistry in general may be divided into two categories: the stereochemical course of reactions, including regio- and stereoselectivities on the one hand, and the structural stereochemistry which deals with stereogenic units[1] and their properties on the other. Chiroptical properties of molecules derive from the chirality generated by chiral units, i.e. they can be classified under the second stereochemical category. This chapter deals with the second category, the structural stereochemistry of the sulfenyl group and the stereogenic units which include sulfenyl sulfur. Other aspects of stereochemistry of this class of compounds, which are associated with neighboring chiral centers, or with regio- or stereoselectivities of reactions involving sulfenic acid derivatives, but do not depend upon sulfenyl sulfur as part of a configurational unit, will not be discussed. These various aspects are dealt with in the appropriate chapters discussing individual reactions, such as the sulfenate–sulfoxide rearrangements[2-5] and the addition of sulfenyl halides to double bonds[6, 7].

The only sulfenic acid derivatives which are known to form observable configurational units are the sulfenamides (**1**, $RSNR^1R^2$), in which the S–N moiety constitutes a stereolabile configurational unit. Even in those, in which the stability of the configurational unit is sufficient to enable observation of the resulting enantiomers or diastereomers by NMR methods, no stable stereoisomers have as yet been resolved and isolated†. The present chapter is thus a review on the stereochemistry and chiroptical properties of sulfenamides. Various aspects of sulfenamide chemistry have been reviewed in the literature[9-15].

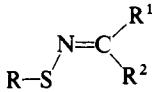
Sulfenamides (**1**) owe their stereochemical behavior to the stereolabile S–N configurational unit. At its ground state conformation, in the maximally labeled case (i.e. $R^1 \neq R^2$),



(**1**)



(**2**)



(**3**)

† Recently, the first sulfenamides have been reported that appear to be sufficiently stereostable on the isolation time scale to permit their eventual resolution into enantiomers. However, resolution has so far not been achieved[8].

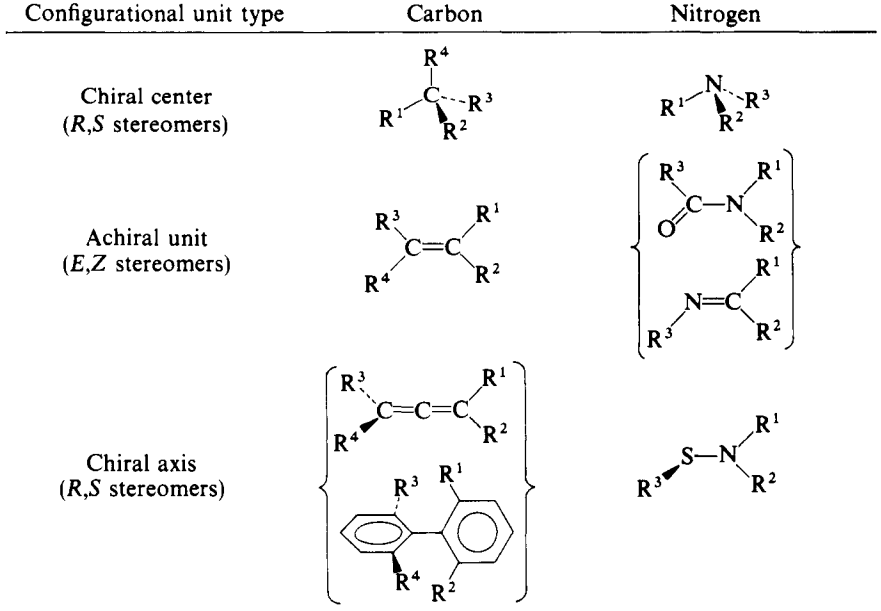
an acyclic compound **1** is chiral due to the S–N chiral axis. In other sulfenamides, such as N-sulfenylaziridines (**2**), the nitrogen of the SN group can be a center of chirality, or it may constitute an achiral stereogenic unit in N-sulfenylimines (**3**) and analogous compounds. In all of these cases the stereoisomers generated by the stereogenic SN unit interconvert rapidly on the isolation time scale and hence cannot be isolated. Stereoisomers resulting from the stereolabile SN unit have been observed using NMR spectroscopy, taking advantage of the relatively fast 'NMR time scale'. Stereoisomers which undergo rapid stereomutation on the isolation time scale can have sufficiently long lifetimes to permit their individual observation in the NMR spectrum. In order to appreciate the moelcular features derived from the SN stereogenic unit, we first draw a comparison between stereostable and stereolabile stereogenic units.

II. STEREOMUTATION MECHANISMS AND NMR DETECTION OF STEREOLABILE CONFIGURATIONAL UNITS

A. Stereolabile Configurational Units

The concept of stereoisomerism dates back to the postulation of the tetrahedral carbon atom[16–18], and even today the central theme of stereochemistry deals with the asymmetric carbon atom and the optical activity which it generates in compounds which include this stereogenic unit. This is due to the simultaneous development of methods for the resolution of enantiomers and observation of chirality by means of measurement of optical activity. The need for expansion of these concepts to configurational units which are stereochemically *unstable* arose also with the development of the experimental means for their observation: NMR spectroscopy.

Stereolabile configurational units are associated with nitrogen compounds, in analogy to stereostable carbon configurational units (Scheme 1). Thus a stable carbon chiral



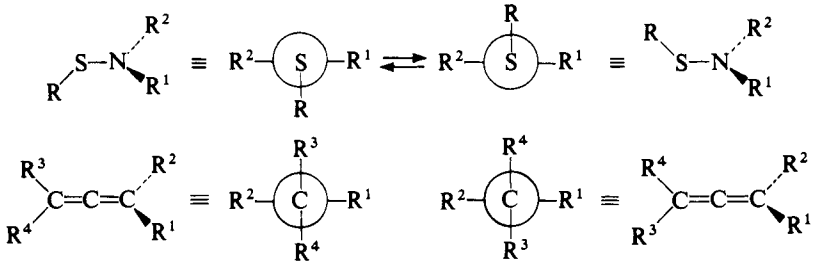
SCHEME 1. Analogy between carbon-stereostable and nitrogen-stereolabile configurational units

center has its stereolabile nitrogen analogue in the form of a trisubstituted nitrogen center. Like the carbon center, the N chiral center can be assigned the *R* or *S* configuration using the Cahn, Ingold, Prelog (CIP) rules[19]. Inversion of the nitrogen pyramid interconverts stereoisomers, just as interchange of two ligands on an asymmetric carbon interconverts stereoisomers. The only stereochemical difference between these two stereogenic units lies in the *mechanism* by which each unit is converted into its epimer: for the nitrogen pyramid the most accessible mechanism is inversion, whereas bond cleavage is usually necessary in order to bring about an inversion of configuration at a chiral carbon.

Alternatively, this difference may be viewed as a difference in the *magnitude* of the interconversion barrier: an 'inversion' mechanism at carbon, i.e. the reorganization of bonds to produce the inverted configuration (in analogy to the Berry pseudorotation at pentacoordinate atoms), has a substantial activation energy and is highly improbable. Normally, therefore, indirect methods are employed in order to interconvert the configuration at a carbon chiral center. We thus refer to chiral centers for which the interconversion barriers are relatively low, such that they are unresolvable at room temperature, as stereolabile configurational units. The amine chiral center generally falls within this category. The term 'configuration' denotes the structure of any stereoisomer which upon ligand interchange becomes a different stereoisomer, regardless of its steric stability or barrier for interconversion. The term conformation is used to quantitatively describe a particular geometry (such as a certain value of a continuous dihedral angle).

Likewise, the achiral olefin configurational unit has its parallel in nitrogen chemistry in the amide and imine functional groups. Both structural types define *E,Z* isomers, and it is again only the magnitude of the barrier for interconversion which places each functionality in either the stereolabile or stereostable configurational unit category. Clearly the criterion of stability of the configurational unit alone does not unambiguously distinguish carbon from nitrogen stereochemistry. Indeed, some suitably substituted ('push–pull') ethylenes have rotational barriers which are lower than those observed for amides, and hence in these compounds the olefin stereogenic unit is a stereolabile configurational unit[20].

Of greatest significance for sulfenamide chemistry is the third configurational unit type, the chiral axis. In carbon chemistry, stable chiral axes are found in allenes. Another group of carbon compounds possessing axial dissymmetry is the family of *ortho* substituted biphenyls (Scheme 1)[21]. Interestingly, depending upon the steric bulk of the *ortho* substituents, biphenyls can either be stable or labile configurational units. Thus the concept of stereolabile unit is again not exclusively associated with nitrogen chemistry, and can be found in carbon chemistry as well. The stereolabile nitrogen analogue is quite abundant in several structures containing N-heteroatom single bonds: sulfenamides (N–S), hydrazines (N–N), hydroxylamines (N–O) as well as other heteroatom-heteroatom-bond containing molecules: disulfides (S–S), peroxides (O–O) and others.



SCHEME 2. Analogy between sulfenamide and allene chiral axes

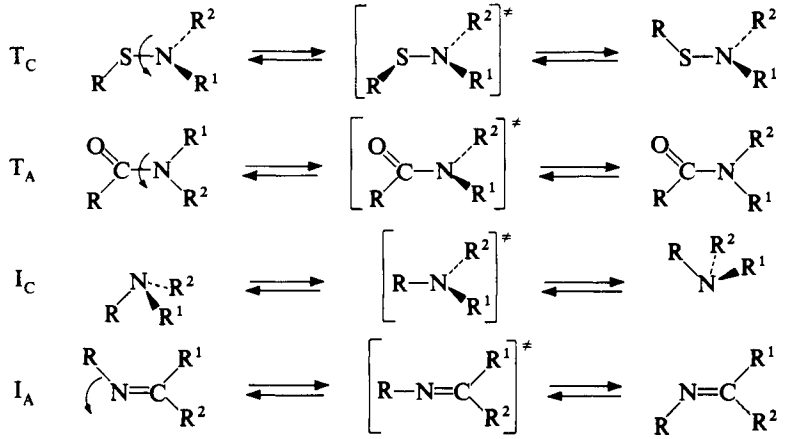
The enantiomeric sulfenamide ground state structures are shown in Scheme 2, along with the analogous allene enantiomers. In order to assign *R,S* configurations to sulfenamides, 'ligancy complementation' must be performed according to the CIP rules: a phantom atom of lowest priority is introduced as a second ligand at sulfur, analogous to R^4 in the allene. The configuration can then be assigned readily using the sequence rules for chiral axes[19].

It is evident that both the labile achiral unit in amides and the chiral axis in sulfenamides are generated by substantial rotational barriers. The difference between the two derives from different ground state structures. Sulfenamides have a nonplanar ground state, which in the general case ($R^1 \neq R^2$) is chiral. By contrast, the ground state of amides is planar and achiral (C_s symmetry as long as the ligands are achiral groups). The different types of stereolabile units are associated with different mechanisms for stereomutation, and are characterized also by different (and hence distinguishable) NMR consequences. These are discussed in the following section.

B. Classification of Stereomutation Types

1. Simple inversions and rotations

Since carbon stereochemistry is mostly static in nature, in the sense that interconversion of stereoisomers is not readily accessible and usually requires breaking and making of σ bonds, it is best characterized by structures and configurations of molecules. By contrast, when dealing with stereolabile compounds one rarely encounters pure stereoisomers since their stereochemistry is usually studied under conditions of dynamic equilibrium. The stereochemistry of stereolabile compounds is thus conveniently characterized by the *type of process* which effects stereomutation.



SCHEME 3. Stereomutation mechanisms at stereolabile configurational units

According to the ground state configuration and the type of geometrical changes associated, stereomutations can be divided into four different categories: T_C (*t*orsion, *c*hiral), T_A (*t*orsion, *a*chiral), I_C (*i*nversion, *c*hiral) and I_A (*i*nversion, *a*chiral)[22, 23]. These are exemplified in Scheme 3. Thus a labile nitrogen chiral center undergoes pyramidal

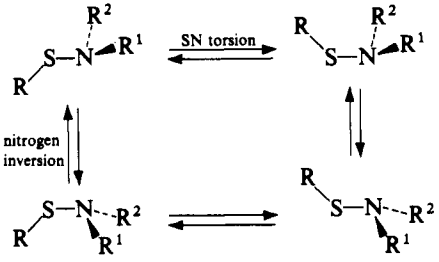
inversion, which brings about interconversion of enantiomers: the process is a chiral inversion (I_C). Likewise, the sulfenamide chiral axis is characterized by a chiral ground state and hence belongs to one of the chiral stereomutation types. Acyclic sulfenamides **1** undergo a torsional process about the NS bond which interconverts their enantiomeric configurations, and is termed T_C. Achiral labile units (amide, imine) are planar in the ground state (C_s symmetry), and their stereomutation involves exchange between diastereomers. This exchange can either be a torsional process, like in amides, and is termed T_A, or a planar inversion in imines (in-plane change of the CNR angle from *ca* 120° through 180° to −120°), and is termed I_A.

Inversion processes (I_C and I_A) involve primarily bond angle changes, whereas the torsional stereomutations are described by dihedral angle changes. It should be noted that this stereochemical classification only covers the elementary conformational changes, which indeed constitute the majority of stereomutations. The more complex processes, such as ring reversal, the Berry pseudorotation of pentacoordinate species and the various correlated rotation mechanisms characteristic of propeller shaped and other complex molecules[24], are not covered by this classification, although each of these processes can be recognized to involve primarily either torsion or inversion (i.e. either dihedral- or bond-angle changes: torsion, inversion and torsion, respectively), and might be included in the T or I category of a more extended classification.

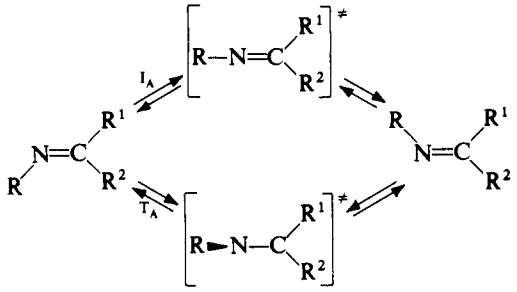
It should also be noted that the term 'chiral' in this categorization scheme does *not* necessarily imply that the molecule is chiral. In **1**, for instance, only when $R^1 \neq R^2$ is the sulfenamide molecule actually chiral. However, the stereomutation mechanism, as well as its NMR consequences (as discussed in Section II.C), are identical whether or not $R^1 = R^2$.

2. Combined mechanisms: The 'AND' and 'OR' cases

There is, in fact, a fundamental mechanistic difference between the chiral and achiral stereomutation types. In order to bring about a complete interchange of enantiomers in sulfenamides **1**, *both* rotation about the SN bond *and* nitrogen inversion must take place (Scheme 4). In an achiral unit, such as imines, however, *either* rotation *or* planar inversion operates during the stereomutation and interconverts the *syn*, *anti* isomers. These two mechanistic combinations have been termed 'AND' and 'OR', respectively[15]. In the AND combination, which applies in the stereomutation of sulfenamides, the process type and the configurational unit are defined according to the *slower* one of the consecutive conformational changes: if the rate-determining change is torsion about the SN bond, the unit is T_C. If the process is dominated by nitrogen inversion, i.e. inversion is slow relative to torsion, it is termed I_C. Thus in N-sulfenylaziridines **2** nitrogen inversion is slower than SN torsion, and the process is an I_C stereomutation[25–28]. The free-energy barrier measured for the process is that of the rate-determining step, and all of the structural



SCHEME 4. The combined rotation AND inversion mechanism in sulfenamides



SCHEME 5. Planar inversion OR rotation (I_A OR T_A) mechanism in imines

features (substituents, solvent) affecting the barrier relate *only* to that step. No information concerning the faster process can be obtained by the DNMR measurements, other than an upper limit for the energy barrier, set by the barrier for the slower, dominant process.

The OR case, found in imines **3**, is a single step stereomutation: there is only one step, which must be rate determining. The mechanism is simply the fastest of all possible transformations, passing through the lowest transition state (Scheme 5). Thus, in contrast to the AND mechanism, only the *faster* possible mechanism can be observed: planar inversion, rotation or a blend of the two whereby the change in dihedral angle (torsion) is accompanied by some flattening of the CSN bond angle[29].

Although the stereomutation of sulfenamides, as well as that of the related hydroxylamines, requires both inversion of the nitrogen pyramid as well as torsion about the N–S (or N–O bond in the case of hydroxylamines), these two steps could occur either sequentially or simultaneously. It is possible for the stereomutation to involve two steps separated by an intermediate or alternatively to occur in a single step which involves both torsion and inversion.

Simple arguments lead to the conclusion that sequential torsion and inversion should be preferred in most systems to a mechanism in which simultaneous torsion and inversion take place in a single step. We can examine this problem most easily by considering the probable effects of geometry on the energies of activation for torsion and inversion. We wish to ask if the inversion barrier will be substantially different at the torsional ground state and at the transition state for torsion. Similarly, we must ask if the torsional barrier will be changed at the inversional transition state. The simplest possibility is that there are no, or only minor, changes in the barriers, i.e. that the barriers are essentially independent of each other. In that case the energy of activation for the simultaneous process would be of the order of the sum of the energies of activation for the individual processes. In this case it is clear that the favored mechanism will involve sequential torsion and inversion. Similarly, if the barrier to torsion is raised at the inversion transition state and the barrier to inversion is raised at the torsion transition state, we can conclude that the barrier to the simultaneous process must be greater than either of the barriers for the separate processes. Only if we can argue that it is possible for the barrier to inversion to be lowered at the torsional transition state or for the barrier to torsion to be lowered at the inversional transition state, might we conclude that the simultaneous barrier is a viable possibility.

A major contributor to both torsion and inversion barriers in sulfenamides (as well as the related hydroxylamine and hydrazine systems) is the destabilizing four-electron interaction between filled nonbonded orbitals on nitrogen and the attached heteroatom (conjugative destabilization, see Section III.C.1). This interaction is minimized at the torsional ground state, since the dihedral angle between the lone pair on nitrogen and the

p lone pair on sulfur is close to 90°. At the torsional transition state the dihedral angle is close to 0°, and overlap of the two orbitals is at a maximum. In going from the inversional ground state to the inversional transition state, the energy increases as the lone pair on nitrogen changes from a hybrid orbital with substantial s character to a pure p orbital. We can conclude that the torsional barrier will be substantially increased for a planar nitrogen (i.e. at the inversional transition state) since now the overlap at the transition state is between two pure p orbitals, rather than a sulfur p orbital and a nitrogen hybrid orbital. We can likewise conclude that the nitrogen inversion barrier will be increased at the torsional TS, since now the nitrogen lone pair hybrid orbital will not only increase in energy due to the conversion into pure p, but it will form a repulsive interaction with the sulfur p lone pair.

The qualitative arguments in favor of sequential inversion and torsion, presented above, have been borne out in theoretical studies involving SCF-MO calculations on several related and isoelectronic systems, including the hydrazyl anion[22, 23], dimethylhydroxylamine[30, 31] and the hydroxymethyl and mercaptomethyl carbanions ($HOCH_2^-$, $HSCH_2^-$)[32]. A theoretical energy surface calculated for the stereomutation of the latter (Figure 1) illustrates this point: clearly the lowest pathway leading from one corner to the other involves consecutive passages along the edges, i.e. consecutive rotation and inversion. The combined, simultaneous rotation–inversion, leading directly from one structure to its enantiomer along the diagonal, climbs through the highest (central) point on the entire surface and hence is not a realistic process.

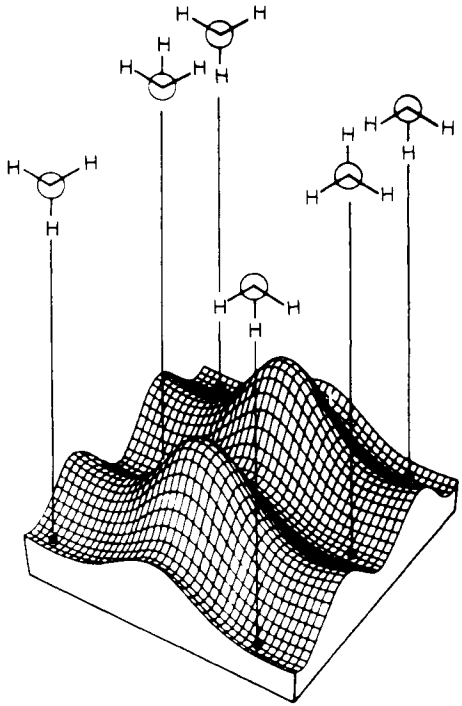
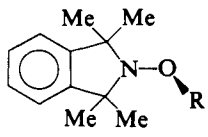


FIGURE 1. Calculated rotation–inversion potential energy surface for $^-CH_2SH$[32]. Reprinted with permission from Bernardi *et al.*, *J. Am. Chem. Soc.*, **97**, 2209. Copyright (1975) American Chemical Society

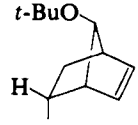
As discussed above, since the increased four-electron repulsion at the simultaneous transition state had the same effect on nitrogen inversion and on SN torsion, the simultaneous process should be disfavored with respect to the sequential processes. If the four-electron interaction had led to opposite effects on the two pure barriers, we might have come to a different conclusion. Indeed, the effect of increased steric bulk on the stereomutation in hindered trialkylamines has led to the conclusion that a simultaneous or combined rotation–inversion process is appropriate in those systems[33]. Here increased steric bulk leads to much reduced inversion barriers but to increased torsional barriers. Here too, we can conclude that steric repulsion at the torsional transition state would be reduced at the inversional transition state, with bond angles of 120°, as compared with the inversional ground state with much smaller bond angles. As a consequence, when very bulky groups are present at nitrogen it is possible for the torsional barrier to be increased and the inversion barrier to be greatly reduced. When the groups are bulky enough, it is possible for the decrease in steric interactions at the torsional transition state, which occurs upon the flattening of the nitrogen pyramid, to lead to an energy lowering that is greater than the energy required for nitrogen inversion. In this case the simultaneous rotation–inversion process is favored. This situation has been found to occur in the trialkylamine series[33].

A similar situation could, of course, occur in the sulfenamides or trisubstituted hydroxylamines. However, this would require that the steric interactions be great enough to overcome not only the problem of barrier addition but also the increased four-electron interactions at the transition state for the simultaneous process. This has been suggested to occur in the case of trialkylhydroxylamines **4** in which the two substituents attached to nitrogen are tertiary[34]. In this series of compounds the barriers to stereomutation increased as the R group at oxygen was changed from primary to secondary to tertiary. This points to a T_C mechanism, since increase in steric bulk should result in a decreased barrier to inversion. However, the barriers were decreased as solvent polarity was increased but exhibited an increase under conditions where protonation at nitrogen could occur. This points to an inversion mechanism. These results together led the authors to conclude that the most probable mechanism is one in which the transition state involved both torsion about the N–O bond and flattening of the nitrogen pyramid. In conclusion we should stress that while such a simultaneous mechanism is a viable possibility in extremely hindered systems, it is unlikely that such simultaneous mechanisms occur in most sulfenamides or hydroxylamines.



(4)

R = $-CH_3$, $-C(CH_3)_3$, $-CH_2C_6H_5$, $-C(CH_3)_2CO_2CH_3$, $-CH_2C(CO_2CH_3)=CH_2$,



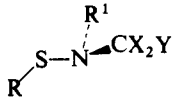
C. NMR Investigation of Stereomutation in Sulfenamides

As mentioned earlier, NMR spectroscopy has been the major tool for the investigation of the stereochemistry of stereolabile compounds in general, and of sulfenamides in particular, due to the relatively fast NMR time scale. NMR spectroscopy probes the stereochemical relationships between pairs of groups within a molecule, which may be homotopic, enantiotopic or diastereotopic[35, 36]. In the case of exchange between diastereomers, pairs of stereochemically related groups are likewise probed for their steric relationships, which now occur between *different* molecules. Pairs of groups are now

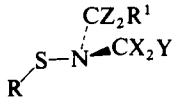
related *by external comparison*, and can be homotopic or diastereotopic[35, 36]. By means of this process the chiral (T_C and I_C) and achiral (T_A and I_A) configurational units can be observed and unequivocally discriminated between one another. Observation of the chiral stereolabile units requires the presence of either a prochiral ($-CX_2Y$)[37, 39] or a chiral probe group in the molecule, which serve as 'chirality sensors'. (Any type of chiral group attached to the stereolabile configurational unit can, in principle, be used for this purpose; in practice, however, the most convenient one, and indeed the only one used so far in sulfenamide chemistry, is the carbon chiral center–CXYZ.)

1. *Prochiral probe groups*

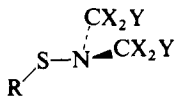
Incorporation of one or two prochiral groups in sulfenamide **1** enables observation of the interconversion of stereoisomers. Prochiral ligands which are convenient for this purpose are: benzyl ($-CH_2C_6H_5$), isopropyl ($-CH(CH_3)_2$), ethyl (CH_2CH_3) and $-C(CH_3)_2CH_2OCH_3$. There are in principle four different types of sulfenamide molecules substituted with prochiral groups (**5**–**8**), which are slightly different in their NMR behavior. However, they all enable observation of stereomutation and measurement of the associated free-energy barriers.



(5)



(6)



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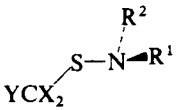


(8)

The benzyl methylene protons in $RCH_2C_6H_5$, for example, are enantiotopic (and hence also isochronous, i.e. chemical shift equivalent) as long as R is an achiral group†. They are exchanged through reflection on a (σ) symmetry plane bisecting the molecule. When R is a chiral group, however, this plane is no longer a plane of symmetry, and the methylene protons become diastereotopic, i.e. they will, in principle, give rise to two different NMR signals, which together constitute an AB system‡. The same analysis applies also to all other $-CX_2Y$ groups (except that uncoupled X groups do not give rise to coupled AB systems, of course), and it follows that all prochiral groups serve as chirality sensors.

Three of these, structures **5**, **6** and **8** (but not **7**), contain T_C configurational units, and their prochiral substituents will sense the chiral geometry and exhibit chemical shift nonequivalence for the X groups of CX_2Y at sufficiently low temperatures, when the exchange rate is low relative to the NMR time scale. Upon warming of the sample, the rate of torsion about the S–N bond increases until it becomes rapid on the NMR time scale. Torsion about the S–N bond interconverts the two enantiomers which differ in configuration at the S–N chiral axis. While this reaction formally corresponds to a racemization reaction, the sample is already racemic. As a consequence the process has

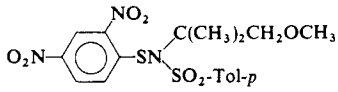
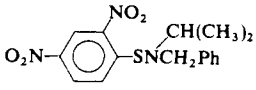
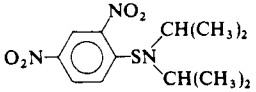
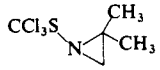
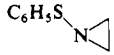
† Strictly speaking, the protons are enantiotopic as long as they are exposed to an achiral environment. Chiral solvents or solutes may render the protons diastereotopic in much the same way as a chiral R group. However, here and elsewhere in this chapter it is assumed that achiral solvents are used under achiral conditions.

‡ Symmetry arguments provide only 'yes' and 'no' answers, and no indication of the *extent* to which the chemical shifts of diastereotopic groups are different. It follows that only when the groups actually give rise to different signals is there positive evidence of chirality in the molecule. The reverse situation, in which the methylene protons are isochronous, may result from insufficient spectral resolution and does *not* constitute evidence of an achiral environment. The possibility of accidental equivalence of diastereotopic groups may, however, be significantly reduced by running the spectra in several solvents.

been referred to as a degenerate racemization. When torsion becomes rapid on the NMR time scale the diastereotopic X groups become enantiotopic on time average, in a process which is referred to as topomerization. The topomerization is evidenced by a change in the NMR spectrum from nonequivalence in the chemical shifts of the X groups, when they are diastereotopic, to equivalence, when they are enantiotopic on time average. In the intermediate temperature range the well known dynamic NMR (DNMR)[40-52] phenomena associated with signals of exchanging groups are observed, i.e. the broadening and coalescence of the signals from the exchanging groups. In compound **7**, however, the S–N group is not stereogenic, because of the identity of the two groups attached to the sulfenamide nitrogen atom, and the molecule is achiral. Although torsion about the S–N bond is not a degenerate racemization in this case, it does correspond to topomerization, and the consequence in the NMR spectrum (i.e. broadening and coalesence) are exactly the same as for the other compounds.

In terms of observation of T_C stereomutation by means of prochiral probe groups, compounds **5**–**7** are essentially equivalent. Structure **5** is a chiral molecule, the chirality of which can be monitored as a function of temperature with the aid of the prochiral group as described above. In **6** two such prochiral groups are incorporated in the molecule, and both of them can serve to observe the temperature-dependent spectra. This could be helpful in extending the useful temperature range, and reduces the risk of accidental equivalence. However **6**, like **5** is a chiral molecule, and the presence of a second prochiral group does not significantly change the situation. Both of these types of sulfenamides have been studied extensively, and a few examples are collected in Table 1. A somewhat different situation exists in **7**, in which two *equal* prochiral groups have been incorporated. While each of the prochiral groups in **7** functions in exactly the same manner as in **5** and **6**,

TABLE 1. Sulfenamides constituting chiral configurational units probed by various prochiral groups

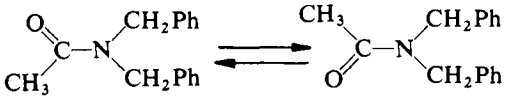
Entry	Compound	Stereomutation type	Analogous model compound	References
1	$CCl_3SN(CH_3)CH_2C_6H_5$	T_C	**5**	28, 53
2	RC_6H_4–SN(CH(CH$_3$)$_2$)–SO_2Ph	T_C	**5**	54, 55
3		T_C	**5**	56
4		T_C	**6**	53
5		T_C	**7**	56
6	$Cl\text{-}SN(CH_2CH_3)_2$	T_C	**7**	57
7		I_C	**6**	27, 28
8		I_C	**7**	58
9	$CCl_3SN(CH_2C_6H_5)$	T_C	**7**	28, 53
10	$(CH_3)_2CHO\text{-}SN(CH_3)CH_2Ph$	T_C	**8, 5**	59

namely the X groups become diastereotopic when SN torsion or nitrogen inversion are slow on the NMR time scale, **7** is *not* a chiral molecule. It has C_s symmetry in the ground state conformation, with a σ plane passing through C–S–N and interchanging the two prochiral groups as a whole, but *not* the X groups within each CX_2Y group. Thus, the molecule as a whole is achiral, while each prochiral group senses chirality of the remaining molecular fragment. The X groups within each CX_2Y group are diastereotopic, while the two CX_2Y groups are enantiotopic. This case demonstrates our earlier statement that chirality of the molecule is not required in order to observe a chiral configurational unit, and that the term 'chiral' refers here to a specific ground state conformation and mode of stereomutation rather than to a dissymmetric or an asymmetric molecule. Specific sulfenamide cases exemplified by **7** are shown in Table 1.

Molecules of type **8**, with the prochiral group attached to the sulfur side, are the least useful for monitoring the stereochemistry of sulfenamides: while the prochiral group will function as before when the ground state is truly chiral (i.e. when $R^1 \neq R^2$), it will fail to observe T_C or I_C stereomutations of an achiral sulfenamide when $R^1 = R^2$. This is because in the latter case the σ plane present in the molecule bisects the XCX angle, and hence renders the two X groups enantiotopic in the ground state. Consequently, no chemical shift changes or exchange phenomena can be seen for the prochiral group as the chiral stereomutation (T_C or I_C) takes place.

It must be emphasized that since the T_C and I_C transformations are connected through the AND combination, they have exactly the same NMR consequences, and hence are indistinguishable. The assignment of a chiral stereomutation to either process is done indirectly, using structural arguments such as the effect of steric bulk on the magnitude of the barrier, as well as the effect of conjugation. These arguments are discussed later in greater detail in Section III.C.4.

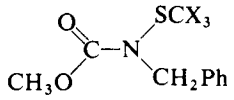
On the other hand, chiral stereomutations are readily distinguished from achiral ones on the basis of NMR signals of the prochiral probe groups. This can be illustrated by an analysis of the T_A stereomutation of the amide molecule **9**, *N*,*N*-dibenzylacetamide[60, 61]. The σ plane associated with the C_s symmetry of the molecule bisects both prochiral benzyl groups, and thus renders the protons in each group enantiotopic. However, the two benzyl groups are diastereotopic with respect to each other, since one is *syn* and the other one *anti* to the carbonyl oxygen, or, generally speaking, since they are not related by any symmetry operation of the molecule. As a result the benzyl groups appear as singlets in the NMR spectrum (as opposed to an AB quartet in case of a similar molecule, but with a *chiral* configurational unit, such as $CCl_3SN(CH_2Ph)_2$[28, 53], see Table 1). The coalescence of these singlets at higher temperatures will monitor the stereomutation of the achiral amide configurational unit. In the example of the chiral unit it is the coalescence of the AB quartet, generated by the benzyl methylene protons, which serves to monitor the stereomutation.



(9) **(9)**

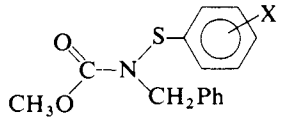
In amide **9** the rotational process interchanged between two homomers, identical structures, and the pair of benzyl groups were compared *internally*, undergoing topomerization from diastereotopic to homotopic on time average along the process. This is a special case of an amide with two identical nitrogen ligands. In the general case the exchange is between diastereomers, and a single probe group (which need not be prochiral) exchanges between the *externally* compared diastereotopic environments.

Symmetry requires that the thermodynamic equilibrium constant between the diastereomers be different from one, resulting in *unequally intense* singlets for the probe group in both isomers. Thus, in the general T_A and I_A cases exchange is observed of unequally intense signals arising from each of the diastereomers.



(10a) X = Cl

(10b) X = F



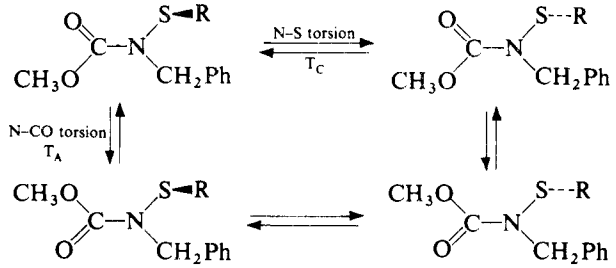
(11a) X = *p*-OCH_3 **(11e)** X = *m*-NO_2

(11b) X = *p*-CH_3 **(11f)** X = *p*-NO_2

(11c) X = H **(11g)** X = 2,4-$(NO_2)_2$

(11d) X = *p*-Cl

Compounds **10** and **11** provide a particularly illustrative example of the different NMR consequences of chiral and achiral labile configurational units, since both types (T_C and T_A) are present in the same molecule (Scheme 6)[62-64]. By means of the NMR signals of the prochiral benzyl group alone both rotational barriers, about the S–N and about the N–CO bonds, are observed and assigned. Let us analyze this process in some detail.



SCHEME 6. T_A and T_C processes in *N*-benzyl-*N*-sulfenylcarbamates **10** and **11**

At relatively low temperature, when both processes are slow on the NMR time scale, the benzyl methylene protons are diastereotopic because they reflect the chirality generated by the T_C configurational unit. Hence they should give rise to an AB quartet. In addition, the slow amide (T_A) rotation partitions the bulk of material between *syn* and *anti* molecules. The environments of the benzyl group as a whole are different (diastereomeric) in these two diastereomers, i.e. the benzyl groups in the two diastereomers are diastereotopic by external comparison. As a result, the methylene proton signals are further split into two AB quartets of unequal intensities, each representing one of the amide diastereomers. This spectral pattern is indeed observed for **10a**[62] and **11e**[63, 64], at temperatures at which both processes are frozen relative to the NMR time scale, and is displayed in Figure 2 (210 K), as well as in Figure 3 (−79°C), at somewhat reduced resolution.

Upon raising the sample temperature both rotations become faster. Two different situations may be expected: in the first one, warming up results initially in rapid rotation about the amide bond, while sulfenamide torsion is still slow relative to the NMR time scale. Conversely, initial warming may result in rapid rotation and coalescence of signals due to the S–N bond, followed at higher temperature by coalescence phenomena due to rapid rotation about the amide bond. In compound **10a** the former situation is observed:

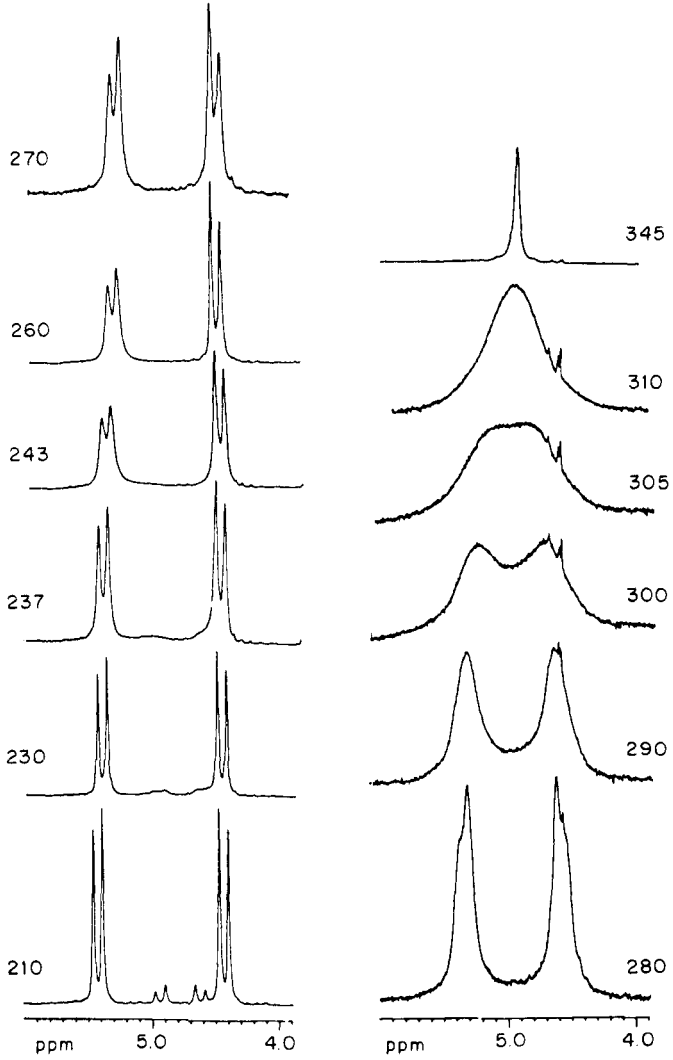


FIGURE 2. 200 MHz ^{1}H-DNMR spectra of **10a** in toluene-d_8 solution[62]. Temperatures are given in degrees K. Reprinted with permission from Kost and Egozy, *J. Org. Chem.*, **54**, 4909. Copyright (1989) American Chemical Society

gradual warming results in initial broadening of the minor AB quartet with eventual coalescence and formation of a single AB quartet (270 K, Figure 2). This coalescence process represents amide rotation, which changes over this temperature range from slow to fast relative to the NMR time scale, resulting in topomerization of the *syn, anti* benzyl groups. Further warming eventually causes SN torsion also to become fast, such that the remaining quartet broadens and coalesces (305 K), and finally turns into a sharp singlet (345 K) when both processes are rapid on the NMR time scale.

The reverse situation, in which the T_C stereomutation occurs first upon warming, followed by the T_A process at higher temperature, is found in **11e** (Figure 3)[63, 64]. The low-

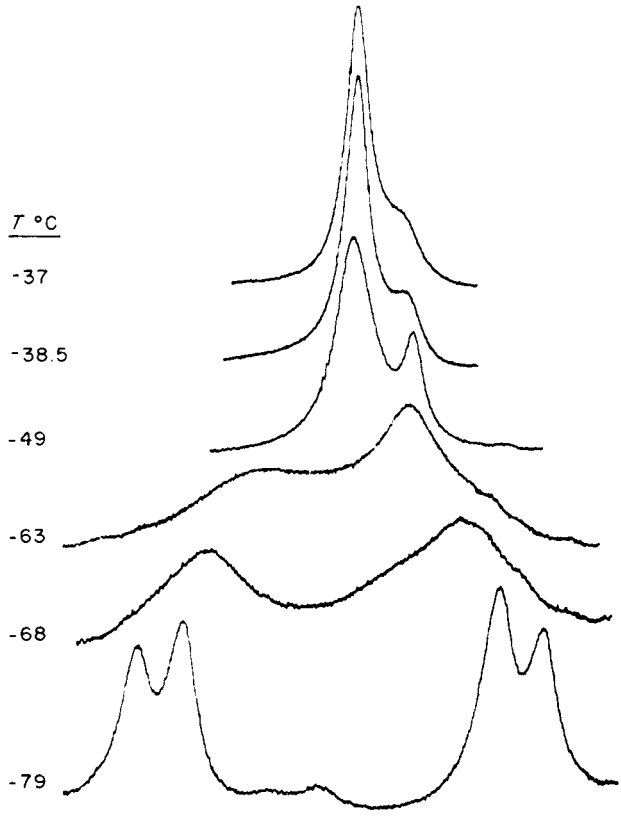


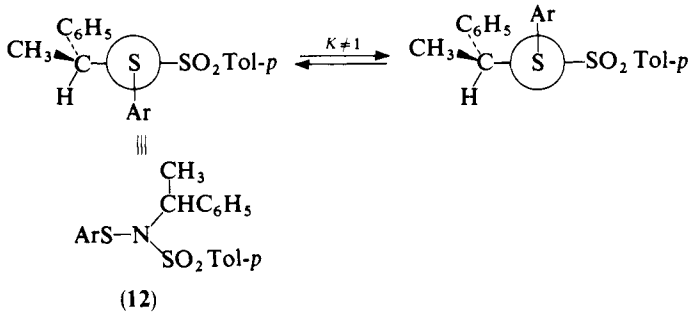
FIGURE 3. 100 MHz ^{1}H-DNMR spectra of **11e** in toluene-d_8 solution[64]. Temperatures are given in °C. Reproduced by permission of the Royal Society of Chemisty

temperature spectrum, although not nearly as well resolved as in Figure 2, represents the minor and major AB quartets in analogy to the spectrum of **10a**. Initial rise in temperature first brings about coalescence of each quartet into a singlet, as SN torsion becomes relatively rapid. Further warming accelerates also the amide rotation, until eventually coalescence of the unequal singlets into one singlet occurs. Both processes can readily be followed by computer simulation, and barriers for SN torsion as well as for amide rotation have been determined for all N-sulfenylcarbamates of series **10** and **11**.

2. Chiral probe groups

If a chiral probe group, such as $-CH(CH_3)C_6H_5$, is incorporated in a sulfenamide molecule, it can serve to observe and assign the stereomutation in a manner quite similar to that of a prochiral group. Both types of probe groups sense the chirality of a stereolabile chiral unit while stereomutation is slow on the NMR time scale. There are, however, several differences which are outlined below.

Consider, for example, sulfenamide **12** which bears two chiral units: a stereogenic carbon atom and the stereolabile S–N axis (Scheme 7)[65]. Since there are two chiral units, stereomutation of the SN unit no longer constitutes a degenerate racemization, but rather



(12)

SCHEME 7. Diastereomerization in sulfenamides containing a stable chiral center

an interconversion of diastereomers. As a result, the chemical shifts of *all* of the nuclei in the molecule, and not just those of the probe group, change when torsion about the SN bond takes place. Pairs of stereochemically related nuclei are not compared internally, like the X groups in the prochiral probes, but externally, between the two diastereomeric molecules. In terms of monitoring the torsional process as a function of temperature this probe is as useful as a prochiral one: The diastereotopic (by external comparison) methyl groups are rendered homotopic upon rapid rotation about the SN bond, relative to the NMR time scale, resulting in coalescence of the methyl signals into a time-averaged signal. There may sometimes be an advantage to using such a probe group, because it may offer additional pairs of exchanging nuclei or sets of nuclei, and thus enable a more accurate measurement. This also reduces the risk of accidental chemical shift equivalence of the exchanging groups, as there are several of those in the molecule.

On the other hand, however, an additional factor is introduced which must be considered, and may sometimes complicate the measurement: Since the exchange process is now a diastereomerization, the two sets of signals representing each diastereomer differ in their intensities, reflecting the equilibrium constant. If the two conformations of the molecule differ by only a few kcal mol^{-1} in their free energies, the signals representing the minor isomer will be too small to be observable. In this case, of course, the introduction of the chiral center interferes with the observation of stereomutation. Even in cases where at the slow exchange limit temperature both diastereomers can be seen in the NMR spectrum, an unfavorable equilibrium constant causes difficulty in following the coalescence process, for the signals due to the minor isomer tend to fade and disappear as soon as line broadening commences.

The special utility of chiral probe groups in sulfenamide stereochemistry manifests itself in the observation of chiroptical properties and asymmetric induction. Because sulfenamides constitute stereolabile configurational units, they can rarely be found in solution in nonracemic mixtures. As a result the chiroptical properties of individual enantiomers cannot be studied. The incorporation of an optically active chiral probe group changes this situation: now sulfenamide stereomutation interconverts diastereomers, which differ in configuration at the SN chiral axis, (*R*,*R*)-**12**⇄(*R*,*S*)-**12**. The concentration ratio of the diastereomers reflects the asymmetric induction from the chiral center to the stereolabile chiral axis. Since there is now an excess of molecules with one particular configuration at the SN axis over the other, chiroptical properties can be studied, as well as thermodynamic asymmetric induction by various chiral centers.

III. SULFENAMIDES AS CHIRAL AXES

This part is divided into three main sections. The first (Section III.A) deals with studies on sulfenamides centered around thermodynamic equilibria of diastereomeric sulfenamides.

Section III.B describes ground state structures based on X-ray crystallographic studies, whereas Section III.C focuses on studies of barriers to stereomutation in sulfenamides, i.e. on their kinetic behavior, whether it is probed by a chiral or a prochiral probe group.

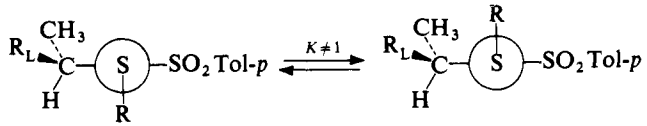
A. Thermodynamic Asymmetric Induction

As mentioned above, observation of chiroptical properties characteristic of the SN chiral axis is only possible in the presence of a stereostable chiral unit in the molecule, as in **12**. The chiral unit, of known chirality, interacts with the stereolabile SN chiral unit to form two diastereomers which differ in configuration at the SN axis, (*R,R*)-**12**⇄(*R,S*)-**12**. The concentration ratio of the diastereomers at the thermodynamic equilibrium, which is different from unity, reflects the extent to which the permanent chiral center discriminates between the two SN configurations. The greater this ratio, the stronger the asymmetric induction from the chiral center into the SN axis.

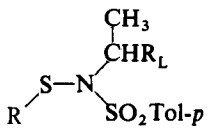
In the first two subsections (III.A.1 and III.A.2) we describe the experiments dealing with two major aspects of asymmetric induction: studies of the chiroptical properties of sulfenamides in the presence of a carbon chiral center, and a NMR study on the extent of thermodynamic asymmetric induction by different asymmetric centers. The third and fourth subsections (III.A.3 and III.A.4) describe phenomena which can only be observed in diastereomeric sulfenamides and relate to their thermodynamic equilibrium, and therefore belong in this main section, but which are not directly related to asymmetric induction.

1. Chiroptical properties

Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD) spectra have been measured for several optically active sulfenamides, **13**–**16**[65, 66]. All of the compounds were prepared from optically pure primary amines of *R*-configuration (**17**), in which R_L represents the largest ligand. The diastereomeric excess present at equilibrium enables observation of chiroptical properties due to the SN axis, since these are only partly canceled out by molecules of opposite chirality at the SN unit. If an isolated transition in the UV spectrum corresponding to a single Cotton effect in the ORD or CD spectra can be identified, that is due only, or primarily, to the SN chromophore, then reversal of the equilibrium concentrations of the SN epimers would ideally lead to reversal of this Cotton effect, without significantly affecting other Cotton effects in the molecule. However, at



(13)–(16)



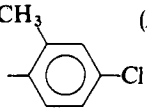
(13)–(16)

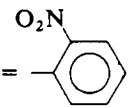
(**a**) R_L = Ph

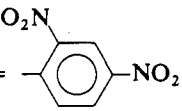
(**b**) R_L = α-naphthyl

(**c**) R_L = CH_2Ph

(**13**) R = CCl_3

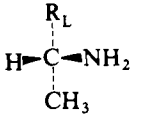
(**14**) R = 

(**15**) R = 

(**16**) R = 

equilibrium, SN epimerization alone is not possible without concomitant epimerization at the permanent chiral center, resulting in a complete reversal of the entire CD/ORD spectrum, without evidence that any single Cotton effect represents the SN chiral moiety.

If such an isolated transition were to exist, replacement of the stable chiral center by other centers of similar configuration, in terms of steric ordering of ligands (**17**), would result in a largely *unchanged* Cotton effect due to the SN axis. This is because chiral centers of like handedness would effect similar asymmetric induction, i.e. the dominant diastereomers would have the same configuration at the SN unit, and hence similar Cotton effects†. While the *sign* of the Cotton effects would remain constant, the *magnitude* would change, depending on the extent of asymmetric induction by each of the asymmetric centers.



(**17a**) R_L = Ph
(**17b**) R_L = α-naphthyl
(**17c**) $R_L = CH_2Ph$

In practice, the shape of the observed Cotton effects for sulfenamides **13–16**, in both the ORD and the CD spectra, proved to be much more complex[65, 66]. In all compounds strong Cotton effects were found in the wavelength range 200–300 nm, without any apparent relationship between induced SN configuration and the sign or magnitude of the effects. Overlap of Cotton effects, as well as coupled effects from extended chromophores, contributed to the complexity of spectra, and prevented the identification of a Cotton effect which might be assigned to the SN chiral axis. Thus, the ORD spectra of **14a–14c** (Figure 4) all feature intense extrema near 200 nm; however, these are maxima for **14a** and **14b**, but a trough for **14c**, although all three have corresponding configurations at the asymmetric carbon center.

The large magnitude of some of these short-wavelength Cotton effects suggested that they were generated, at least in part, by the SN moiety, which functions as an 'inherently dissymmetric chromophore', i.e. as a source of chirality and a chromophore at the same time, in analogy to the disulfide group[68].

Longer-wavelength Cotton effects, above 300 nm, were observed in the ORD/CD spectra of compounds **15** and **16**, and are related to the nitro-substituted arenesulfenyl ring. In the spectra of **16a–16c** (Figures 5–7) these Cotton effects are negative, they are centered near 350 nm and are reasonably well defined. Thus they seem to qualify as isolated transitions associated with the SN bond: probably the chromophore is extended over the SN bond and the arenesulfenyl ring. The crossover wavelengths are 357 nm, 347 nm and 353 nm, respectively, indicating that a change in the asymmetric center does not significantly alter this transition, and hence that it is not due to the chiral center but instead belongs to the sulfenamide chromophore.

Since the Cotton effects associated with the dinitrobenzenesulfenyl ring are the longest-wavelength transitions in **16a–16c**, they also dominate the sign of rotation at the sodium D line: the negative tails reach out uniformly to the 600 nm region in all three compounds, resulting in negative rotations. This forms the basis for a proposed method for the determination of the absolute configuration of primary amines[65, 67]. A *N*-(4-toluenesulfonyl)-2,4-dinitrobenzenesulfenamide derivative is prepared from the amine of

† This discussion refers to replacement of the chiral amine from which the sulfenamide is prepared (**17**), and it assumes that asymmetric induction is primarily due to the difference in *steric* interaction of R_L and CH_3, respectively, with the SN axis (**13–16**). Obviously, if other than steric interactions are important (e.g. hydrogen bonding), the sense of induced asymmetry, as well as the resultant Cotton effects, may change.

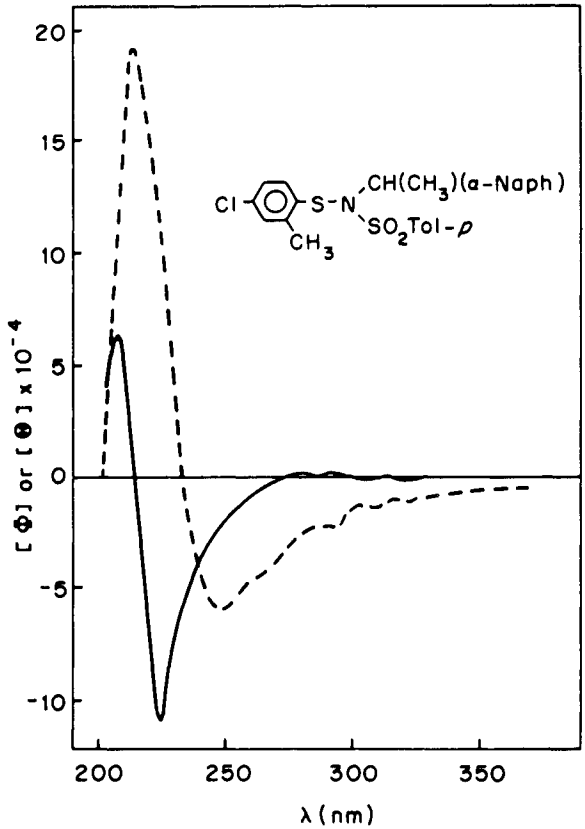


FIGURE 4. ORD and CD spectra of **14b** in absolute ethanol[65]. CD, —; ORD, – – –. Reprinted with permission from Raban and Lauderback, *J. Org. Chem.*, **45**, 2636. Copyright (1980) American Chemical Society

unknown configuration, and the optical rotation at the sodium D line is measured. If it is negative, the configuration of the amine corresponds to **17** (where the methyl group may be replaced by another medium-sized ligand). A positive rotation signifies that the predominant SN configuration is opposite to that in **16a–16c**, resulting from the opposite asymmetric induction by the amine chiral center, i.e. that the amine has the opposite configuration.

This method was later tested and extended to a larger series of *N*-(4-toluenesulfonyl)-2,4-dinitrobenzenesulfenamides **16**[67]. Eight different optically active amines were incorporated into sulfenamides **16**, and the optical rotation of the latter at the sodium D-line measured. The results are shown in Table 2. Clearly the sign of rotation at the sodium D-line corresponds without exception to the absolute configuration of the amine, as predicted by the method, despite the absence of any correlation between the rotation of the amine itself and its absolute configuration.

In principle, this method of observation of chiroptical properties due to the stereolabile SN chiral axis, utilizing equilibrium asymmetric induction, is not restricted to sulfenamides. Since the measurements are not done by NMR spectroscopy, the method does not depend on stereostability (i.e. slow interconversion) relative to the NMR time scale.

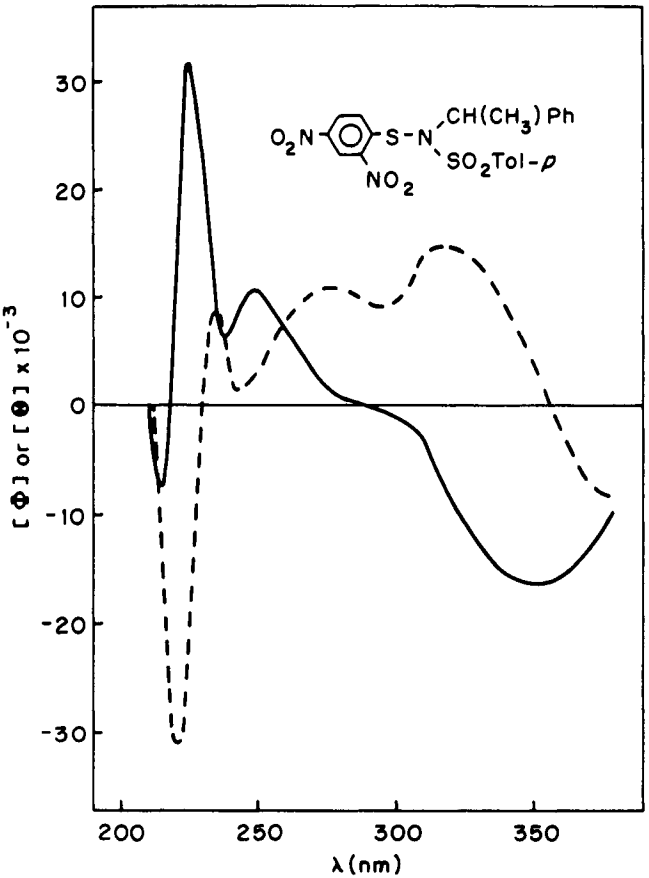


FIGURE 5. ORD and CD spectra of **16a** in absolute ethanol[65]. CD, —; ORD, – – –. Reprinted with permission from Raban and Lauderback, *J. Org. Chem.*, **45**, 2636. Copyright (1980) American Chemical Society

TABLE 2. Optical rotations of sulfenyl sulfonamides **16** at the sodium D-line[67].

Compound	R_L	$[\alpha]_D$ (EtOH) amine	$[\alpha]_D$ ($CHCl_3$) sulfenamide	Configuration known	predicted
16a	C_6H_5	+31.8	−141.6	*R*	*R*
16b	α-Naphthyl	+51.9	−572.9	*R*	*R*
16b′	α-Naphthyl	−47.9	+575.4	*S*	*S*
16c	$CH_2C_6H_5$	−32.8	−29.6	*R*	*R*
16d	CH_2CH_3	+3.2	+15.3	*S*	*S*
16e	$(CH_2)_4CH_3$	−7.3	−6.6	*R*	*R*
16f	$C(CH_3)_3$	+1.5	+16.7	*S*	*S*
16g	*p*-C_6H_4Br	+25.9	−109.7	*R*	*R*

Rather than a *kinetic* method, depending on a relatively long lifetime, this is a *thermodynamic* method, reflecting different equilibrium concentrations of stereoisomers, regardless of the rate at which they interconvert. Thus, various other potentially chiral functional groups may similarly be attached to an asymmetric carbon center, producing

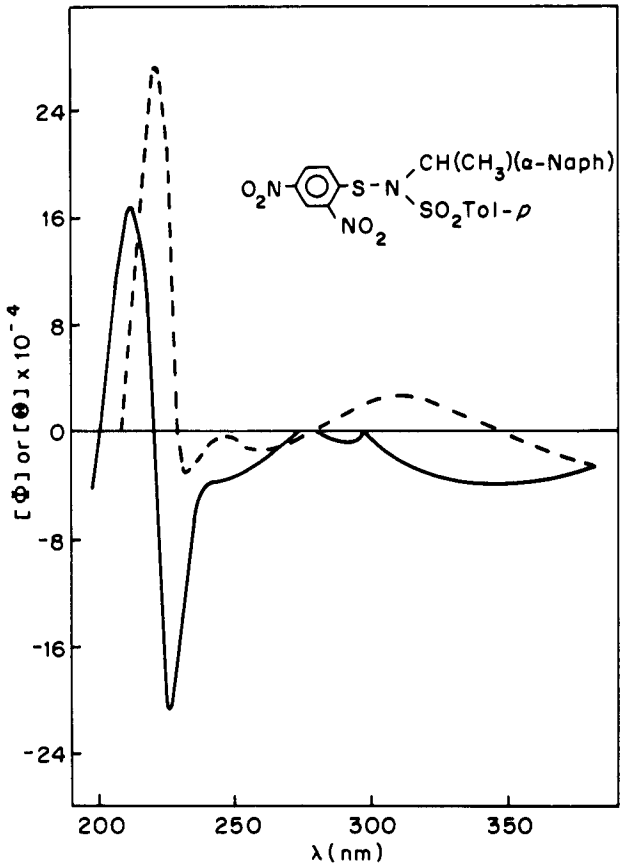


FIGURE 6. ORD and CD spectra of **16b** in absolute ethanol[65]. CD, —; ORD, ···. Reprinted with permission from Raban and Lauderback, *J. Org. Chem.*, **45**, 2636. Copyright (1980) American Chemical Society

diastereomers which differ in configuration at the stereolabile chiral stereogenic unit. The equilibrium concentrations of the diastereomers, which must be unequal, may likewise generate characteristic Cotton effects in the ORD and CD spectra, and provide otherwise inaccessible information on the chirality of chiral units of low stereostability.

We speculate on these potential observations of chirality in stereolabile configurational units because, although as yet unobserved, they may prove to be pertinent to other sulfenic acid derivatives and preliminary experiments (L. Craine, unpublished results) seem to indicate that the method may indeed be extended to other stereolabile systems. Thus sulfenate esters (RS–OR[1]) may show characteristic chiroptical spectra in molecules like **18** (Scheme 8). In **18** the expected isolated long-wavelength transition due to the dinitrobenzenesulfenyl group may serve as a probe for the chirality of the sulfenate functional group, in analogy to the chiroptical spectra of dinitrobenzenesulfenamides discussed in this section. This is in spite of the fact that the stereostability of the sulfenate configurational unit is too low to permit even NMR investigation of the stereomutation processes.

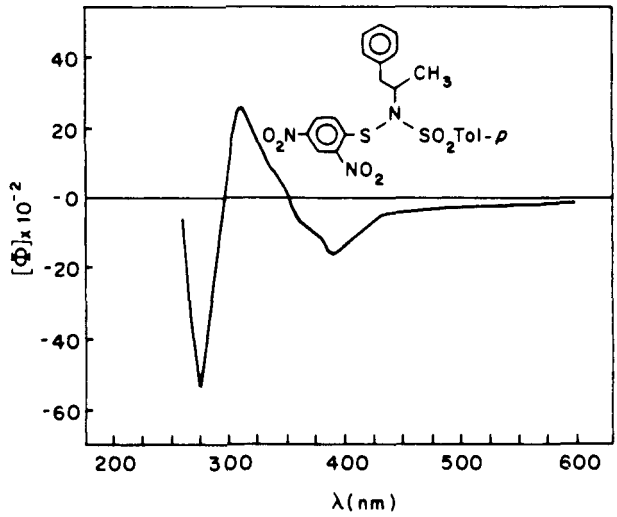
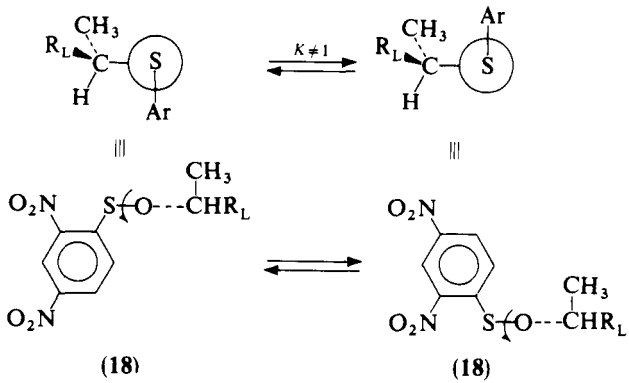


FIGURE 7. ORD spectrum of **16c** in absolute ethanol[65]. Reprinted with permission from Raban and Lauderback, *J. Org. Chem.*, **45**, 2636. Copyright (1980) American Chemical Society



SCHEME 8. Diastereomerization in a sulfenate ester

In fact, this method may be extended further for the study of various other stereolabile configurational units. Thus, axial chirality may be studied in molecules having single bonds between atoms bearing nonbonding electron pairs: disulfides ($RS\text{–}SR^1$), hydroxylamines ($RR^1N\text{–}OR^2$), hydrazines ($RR^1N\text{–}NR^2R^3$), peroxides ($RO\text{–}OR^1$) and others, whether or not their stereomutations can be followed by NMR spectroscopy.

2. *NMR investigation of equilibrium asymmetric induction*

The experiments described in the previous section utilized the asymmetric induction due to the stereostable chiral center to facilitate the observation and measurement of chiral properties generated by the SN chiral axis. Thus the asymmetric carbon was used as

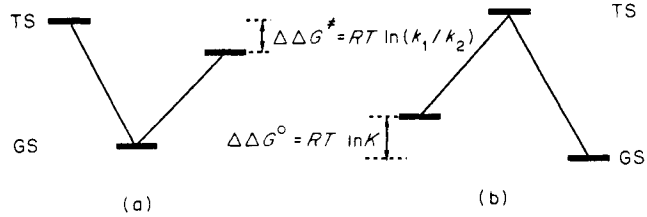


FIGURE 8. Schematic energy diagrams for asymmetric induction. (a) Kinetic asymmetric induction (asymmetric synthesis, kinetic resolution). (b) Thermodynamic asymmetric induction

a chiral probe for sulfenamide chirality. In this section a different aspect of asymmetric induction is discussed: through measurement of the equilibrium constant between diastereomers differing in configuration at the SN axis, information is gained about the inducing power of various differently substituted asymmetric carbon centers, and about the susceptibility of the stereolabile unit towards asymmetric induction[69]. Thus the SN chiral axis serves in this experiment as a probe for the thermodynamic asymmetric induction by various chiral centers.

Asymmetric induction is a subject of great interest due to its importance in synthesis and in biological chemistry. Normally the term is used for *kinetic* induction, i.e. the formation of a new chiral unit under the influence of an existing unit. The configuration of the new chiral unit is biased by the presence of the inducing chiral unit, due to the formation of diastereomeric transition states leading to the two diastereomeric products (or enantiomeric products if the inducing unit is not present in the product) which differ in configuration at the newly formed unit. The extent of induction depends on properties of the diastereomeric transition states, specifically, on the difference in their free energies. However, there is little that can be studied directly about the structure of transition states. By contrast, equilibrium asymmetric induction depends on the difference in free energies of ground state species, which are more amenable to study. This is illustrated in Figure 8 by means of schematic energy diagrams of the type used by Mislow[70]. In asymmetric synthesis, a single ground state (or a pair of enantiomeric, isoenergetic ground states in the case of kinetic resolution) leads to diastereomeric transition states which differ in free energies. The product ratio equals the ratio of rate constants which, in turn, is related to the difference in activation free energies as follows:

$$[R,R]/[R,S] = k_1/k_2 \tag{1}$$

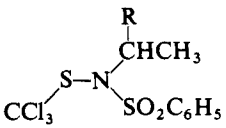
$$\Delta\Delta G^{\neq} = RT \ln(k_1/k_2) \tag{2}$$

In thermodynamic asymmetric induction the energy diagram is inverted: a single transition state separates two interconverting diastereomers at equilibrium. The ratio of diastereomers is the equilibrium constant, and relates to the difference in free energies of formation:

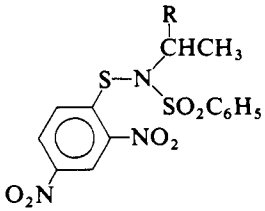
$$\Delta\Delta G^{\circ} = RT \ln K \tag{3}$$

Properties of the diastereomers have been observed by NMR spectroscopy, however several other spectroscopic and structural methods can be applied for the study of ground state diastereomers.

The equilibrium constants for pairs of diastereomers in the sulfenamide series **19** and **20** were measured from integrated signal intensities of corresponding diastereotopic groups



(19)



(20)

(a) R = phenyl
(b) R = 2-naphthyl
(c) R = *o*-tolyl
(d) R = *t*-butyl
(e) R = 1-naphthyl

in the ^{1}H-NMR spectra[69, 71]. The results were quantitatively evaluated in terms of the stereochemical analogy model of Ruch and Ugi[72]. This model can be used to quantify kinetic asymmetric induction by means of a linear free-energy relationship (LFER), equation 4. The ratio of stereoisomers K (or the ratio of rate constants in kinetic asymmetric induction) is related to two constants: ρ, a reaction constant representing the sensitivity of a given reaction towards asymmetric induction; and χ, the chirality function, which expresses the ability of the stereostable unit to induce chirality. For a chiral center $CR^1R^2R^3$, χ is given by equation 5, where λ_i are ligand constants for the three ligands.

$$\ln K = \rho\chi \tag{4}$$

Thus:

$$\chi = (\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1) \tag{5}$$

$$\ln K = \rho(\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1) \tag{6}$$

The ligand constant λ scale is defined by setting $\lambda_H = 0$ and $\lambda_{Me} = 1$. Thus for **19** and **20** the Ruch–Ugi equation reduces to equation 7:

$$\ln K = \rho(\lambda_R^2 - \lambda_R) \tag{7}$$

The reaction constants for **19** and **20** were determined from the equilibrium constants measured for **19a** and **20a**, using a previously determined λ value for the phenyl group, 1.24. The resulting reaction constants were 0.61 and 3.1, respectively. From these ρ values and the corresponding equilibrium constants the ligand constants for other ligands were

TABLE 3. Equilibrium constants and ligand constants[69]

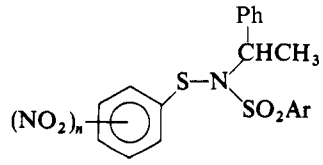
Compound	Ligand	K	λ	λ(Ruch–Ugi)[a]
19a	Phenyl	1.2	(1.24)[b]	1.24
19b	2-Naphthyl	1.3	1.32	
19c	*o*-Tolyl	1.4	1.39	
19d	*t*-Butyl	5.7	2.24	1.45
19e	1-Naphthyl	2.0	1.66	1.28
20a	Phenyl	2.5	(1.24)[b]	1.24
20b	2-Naphthyl	2.4	1.23	
20c	*o*-Tolyl	2.4	1.23	
20d	*t*-Butyl	4.5	1.36	1.45
20e	1-Naphthyl	8.5	1.47	1.28

[a] Taken from Reference 72.
[b] This value was assumed and used to calculate ρ.

calculated for both series. These are listed in Table 3, along with corresponding ligand constants reported by Ruch and Ugi[72].

Examination of Table 3 clearly indicates substantial equilibrium asymmetric induction, as is evident from the different equilibrium constants for the different ligands. While the results seem to indicate a pattern, whereby bulkier ligands have greater λ values, the correspondence between ligand constants obtained from **19** and **20** and those reported earlier is not satisfactory. This is not surprising in view of earlier experiments by Horeau and coworkers[73] and by Anders, Ruch and Ugi[74], which failed to fit the original ligand constants to new experimental systems. The discrepancy of equation 6 in providing a reliable quantitative treatment of asymmetric induction is likely due to its simplicity: a single ligand constant can only account for one type of interaction by the ligand, which is assumed to be its steric bulk. A ligand can operate in more than one way (dipole–dipole interactions, hydrogen bonding), as long as the relative effectiveness of each of the factors is constant for that ligand in all of its reactions. In this case the single-parameter equation should still be sufficient for handling the various asymmetric induction reactions. If, however, ligands operate in different ways in various induction reactions, deviations from the Ruch–Ugi relationship are expected.

A rather striking example of the interplay between steric and electronic effects on equilibrium asymmetric induction is provided by a related sulfenamide system, **21**, in which the electronic demand by the arenesulfenyl ring is changed by altering the number of attached nitro groups[56, 69]. As the number of nitro groups is increased from zero to two, the equilibrium constant as well as the reaction constant ρ increase substantially (Table 4). This is despite the fact that little is changed in terms of steric crowding near the stereolabile chiral unit. The change in ρ must then reflect the change in electronic withdrawal from the SN bond by the nitro groups.



(21)

TABLE 4. Equilibrium constants in nitrobenzenesulfenamides **21**[69, 56]

Compound	*n*(position)	Aryl	*K*	ρ	$\Delta G^{\neq}$ (kcal mol^{-1})
21a	0	phenyl	1.0	0	13.0
21b	1(4)	phenyl	1.8	2.0	14.7
21c	1(2)	*p*-tolyl	1.9	2.2	18.4
21d	2(2, 4)	*p*-tolyl	2.4	3.1	19.7
21e	3(2, 4, 6)	*p*-tolyl	1.1	0.3	13.8

This gradual increase in asymmetric induction has been attributed to an increase in the rigidity of the arenesulfenyl fragment: conjugation of the sulfur p-lone pair with the aromatic ring is more intense in the presence of electron withdrawing substituents. This conjugation requires coplanarity of the aryl ring with the CSN plane, and thus an

electronic demand is translated into increased effective steric bulk. This phenomenon has been termed the electrosteric effect[75], and will be discussed in greater detail in the section dealing with substituent effects on sulfenamide rotational barriers.

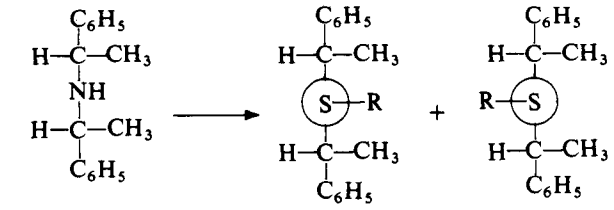
When a third nitro group is incorporated in the molecule (**21e**), the trend in ρ and in the equilibrium constant breaks down completely: the trinitrobenzenesulfenamide is equally susceptible to asymmetric induction as the unsubstituted sulfenamide **21a**. The reason is that with a second substituent in the *ortho* position, steric bulk near the SN bond prevents coplanarity of the aryl and CSN planes at the ground state, and thus conjugation, as well as the extra rigidity due to the nitro groups, apparent in the increased ρ values of **21b–21d**, is no longer possible.

Despite the apparent inconsistency in ρ values, and the rather poor generality of the chirality function, its usefulness is demonstrated by the data in Table 4: clearly the sudden mechanistic change in series **21** is reflected in ρ, in a parallel fashion to the trend in SN torsional barriers (which is discussed in section III.C.5.d). The drop in ρ in **21e** indicates a loss of effective steric bulk, i.e. loss of rigidity near the SN bond. Thus the method is sensitive also to stereoelectronic effects and may yield useful mechanistic information.

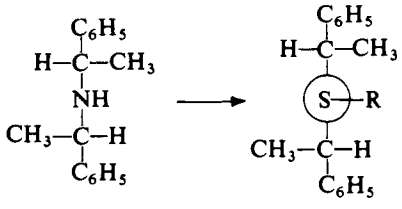
3. *The pseudoasymmetric axis in sulfenamides*

In Section II.C.1 we discussed the NMR consequences of incorporating one or two prochiral probe groups into a sulfenamide molecule, and in Section II.C.2 the effect of a chiral probe group on the NMR spectra of sulfenamides was treated. We now discuss the stereochemistry and NMR spectra of sulfenamides containing two constitutionally equal stereotopic chiral units, in addition to the stereolabile SN chiral unit. The SN configurational unit can become an axis of pseudoasymmetry in molecules of this kind.

The example used to illustrate this phenomenon is the sulfenamide molecule **23**, synthesized from 2,4-dinitrobenzenesulfenyl chloride and *bis*-phenethylamine (**22**)[76, 77]. The latter amine has two constitutionally equivalent chiral centers, and hence can exist as *d,l* or *meso* diastereomers. The commercial product contained a mixture of both, and could be separated into its components by fractional crystallization of the benzoic acid salts from isopropanol. Each of the amines was reacted with the sulfenyl chloride to form the diastereomeric sulfenamides **23**.



(22a) (*meso*) **(23a)** (*s*) **(23b)** (*r*)



(22b) (*d, l*) **(23c)**

At room temperature SN torsion in **23** is slow on the NMR time scale, and its rigidity introduces an additional element of stereochemistry to the molecule. In **23c**, prepared from the *d,l* amine, the amine residue has a local C_2 symmetry axis coinciding with the SN bond, and hence the molecule is invariant with respect to a 180° rotation of the residue relative to the R–S bond. It follows that in **23c** the SN functionality is *not* a configurational unit, since the two SN rotamers are identical (they are topomers rather than isomers). Thus the rotational process in this case is not a stereomutation (exchange of stereoisomers), but rather a topomerization: since **23c** is asymmetric, the methyl groups (as well as all other pairs of stereochemically related groups) cannot be interchanged by any symmetry operation and must be diastereotopic. Rotation about the SN bond interchanges their chemical environments within the molecule, i.e. constitutes a topomerization. In terms of the NMR spectrum, the diastereotopic methyl groups give rise to two doublets of equal intensity, since they are part of the same molecule, **23c** (Figure 9).

The situation is quite different when **22a**, the *meso* amine, is reacted with the sulfenyl chloride. The resulting sulfenamide has a plane of symmetry and is achiral. However, the two SN rotamers, **23a** and **23b**, are diastereomers. Clearly, the SN moiety is a configurational unit, since its rotation interchanges two diastereomers. In this case the SN axis is a *pseudoasymmetric* axis. The rotamers are designated, according to the CIP rules[19], *s* and *r*, respectively. These designators are different from the *S* and *R* designators for chiral configurations, in that they are invariant with respect to mirror reflection, while the latter are inverted by mirror reflection[19, 78].

Within each one of the rotamers **23a** and **23b** the asymmetric carbons are enantiotopic, as are each of the other pairs of related subgroups, such as the methyl groups. As a result each of the achiral diastereomers gives rise to one doublet for both methyl groups. However, the methyl groups of the two diastereomers are diastereotopic by external comparison, and the doublets from the two isomers differs in chemical shift. These are

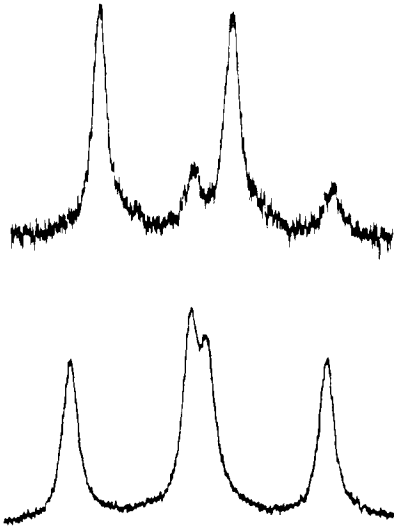


FIGURE 9. The methyl region of the ^{1}H-NMR spectra of *N,N-bis*-1-phenethyl-2,4-dinitrobenzenesulfenamides **23**[77]. Upper spectrum: equilibrium mixture ($K = 4.5$) of the *r,s meso*-sulfenamides. Lower spectrum: *d,l*-sulfenamide **23c**. Reprinted with permission from Raban *et al.*, *J. Am. Chem. Soc.*, **97**, 5178. Copyright (1975) American Chemical Society

unequal in their intensities, and the intensity ratio (4.5/1)[77] corresponds to the equilibrium constant between the two *meso* diastereomers (Figure 9).

It is evident from this discussion and from Figure 9 that the *d,l* and *meso* isomers of secondary amines bearing two constitutionally equivalent chiral ligands (which need not be chiral centers) can readily be distinguished by this method. A suitable sulfenamide is prepared from the amine, and its NMR spectrum is examined. If the spectrum features unequally intense signals due to stereotopically related groups on the chiral ligands, it may be concluded that the amine was the *meso* diastereomer. Equal signals suggest, though they do not constitute definitive proof, that the configuration of the amine was *d,l*.

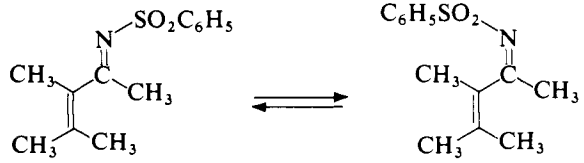
When the temperature is raised SN torsion becomes rapid in both **23a**⇄**23b** and **23c**, and exchange phenomena and coalescence of the methyl signals are seen in the NMR spectra. While in both cases the process is torsion of the sulfur nitrogen bond, the two events differ in their stereochemical description: the former (**23a**⇄**23b**) is a stereomutation, in which diastereomers are interconverted by epimerization at the SN pseudochiral axis, while the latter is a topomerization, in which the molecule as a whole is not altered, but internally-diastereotopic groups exchange chemical environments. The free energies of activation which were calculated for these processes reflect their basic similarity: the barrier for topomerization in **23c** (19.6 kcal mol^{-1}) is intermediate between the barriers for the forward and reverse interconversions of the diastereomers (forward: 19.5 kcal mol^{-1}, reverse: 20.5 kcal mol^{-1})[76, 77].

4. Diastereomeric transformation

The phenomenon of asymmetric transformation has been known and documented for many years[79]. It consists of the segregation of diastereomers upon passage between the solid and liquid phases, by way of epimerization of one of the configurational units present in the molecule. In order for the transformation to take place, epimerization must be facile under the crystallization or dissolution conditions, i.e. one of the configurational units must be stereolabile. The most widely studied reaction of this kind is the crystallization and mutarotation of glucose, in which the configuration at the anomeric center is epimerized by ring-chain tautomerism (opening of the cyclic hemiacetal to the intermediate open-chain aldehyde, and ring closure to form the diastereomer with opposite configuration at the anomeric site). Only one of the epimers crystallizes out, shifting the equilibrium in solution towards that epimer.

Recently the phenomenon has been interpreted as an extension to the Gibbs Phase Rule[80], and it is clear that selective crystallization of a single diastereomer from a rapidly equilibrating mixture in solution (or melt) should be regarded as the rule and not as an exception.

Since asymmetric transformation is observed in rapidly equilibrating systems even when there is no asymmetry in the molecule, such as in the N-benzenesulfonylimine **24**[29], the term diastereomeric transformation has been proposed and seems more appropriate[81]. In **24** the equilibrating stereolabile configurational unit is an *achiral* unit, the C=N double bond, illustrating that asymmetry is not essential for the transformation.



E-(**24**) *Z*-(**24**)

Diastereomeric transformation in sulfenamides has been observed in several compounds[82, 83], and will be exemplified by **19e**[66]. The room temperature equilibrium mixture of **19e** in methylene chloride solution has a 1.85:1.0 ratio of diastereomers, as determined by the relative intensities of the C-methyl doublets in the NMR spectrum (Figure 10). Crystallization of **19e** affords crystals of a single isomer. Since epimerization is rapid on the isolation time scale, the equilibrium mixture maintains the constant diastereomer ratio in solution. Thus, the conditions for crystallization of a single isomer are present throughout the crystallization process. As a result the entire mixture is converted by this phase transition into a single sharp-melting isomer, which was shown by an X-ray diffraction analysis to have the absolute (*R*, *R*) configuration[84].

When solid (*R*, *R*)-**19e** is dissolved at room temperature, instantaneous equilibration takes place and the resulting solution features the NMR spectrum of the equilibrium mixture. However, equilibration can be slowed down by dissolving the solid at low temperature. When crystals of **19e** were dissolved in methylene chloride at *ca* −70 °C, and the NMR spectrum was taken at −50 °C without prior warming of the solution, a single methyl doublet was observed, corresponding to the high field doublet of the equilibrium mixture. This direct correlation between the crystalline material and the major isomer in

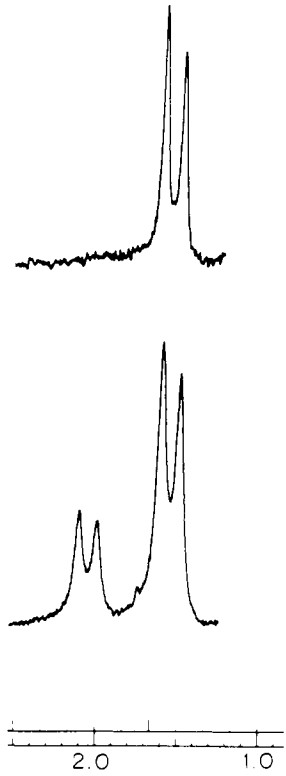
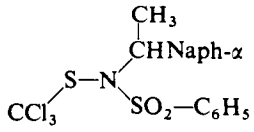


FIGURE 10. The methyl region of the ^{1}H-NMR spectra of **19e** in methylene chloride. The upper spectrum was measured at −50 °C after dissolution at *ca* −70 °C. The lower spectrum was measured at −50 °C after dissolution at room temperature[66]. Reprinted with permission from Raban and Lauderback, *J. Am. Chem. Soc.*, **93**, 2781. Copyright (1971) American Chemical Society



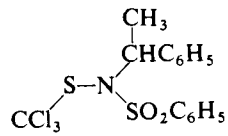
(**19e**)

solution permitted unequivocal assignment of NMR signals: the high-field doublet (δ1.72 ppm, $J=7$ Hz) corresponds to (*R*, *R*)-**19e**, while the minor isomer, represented by the low-field methyl doublet (δ2.06 ppm, $J=7$ Hz), has the (*R*, *S*) configuration[66].

The correspondence between the single epimer in the solid state and the major isomer of **19e** in solution does not mean that, in general, the more abundant diastereomer in solution is necessarily also the one which crystallizes out. The latter is determined by the relative solubilities of the isomers in the particular solvent (i.e. the ratio of dissolution and crystallization rate constants, k_d/k_c, for each of the epimers), as well as by the relative rates of crystallization (k_c^1/k_c^2), which need not be related to their relative thermodynamic stabilities. In fact, in the example of the imine **24** cited above[29], the *minor* isomer in solution is the one that crystallizes out and constitutes the single diastereomer in the crystalline state.

After dissolving the crystals of **19e** at low temperature, the sample can be warmed up to a convenient temperature, at which the rate of growth of the signals due to the minor isomer can be followed. This enables conventional kinetic measurements of the rate of epimerization at the SN axis, in a manner quite analogous to the mutarotation of glucose. At this temperature the kinetics relative to the *isolation* time scale are monitored, whereas in DNMR spectroscopy rates within the NMR time scale are measured. Thus, by utilizing kinetic measurements of the system undergoing diastereomeric transformation, the temperature range for the overall rate measurements can be increased dramatically.

In conventional DNMR measurements the range of useful temperatures at which exchange line broadening can be observed is usually quite limited. As a result the only reliable activation parameters which can normally be extracted from the data are the activation free energy $\Delta G^{\neq}$ and the first-order rate constant at or near the coalescence temperature. Quantities $\Delta H^{\neq}$ and $\Delta S^{\neq}$ depend critically on the spread of data over a large temperature range, and hence are inherently of low accuracy in DNMR measurements. The extension from the NMR time scale to the isolation time scale is associated with an increase in temperature range of *ca* 100° C, and thus offers substantial improvement in the derived activation enthalpies and entropies. This is illustrated for the kinetic measurements of a closely related sulfenamide, **19a**[83].



(**19a**)

In **19a** DNMR spectroscopy was used in conjunction with line-shape analysis to measure rate constants in the temperature range of exchange line broadening, 28–92 °C, and diastereomeric transformation at low temperature was used to measure equilibration rate constants in the range −48 to −65 °C. While each of the data sets alone leads to linear Eyring correlations of limited quality, due to experimental scatter of the data, the

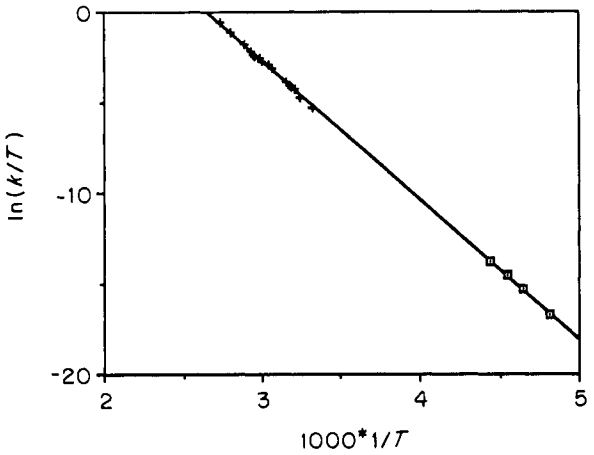


FIGURE 11. Eyring plot for **19a** in the temperature range −65 to 92 °C[83]. Conventional kinetics at low temperature: □; DNMR rate constants: ×. Reprinted with permission from Raban *et al.*, *J. Am. Chem. Soc.*, **94**, 2738. Copyright (1972) American Chemical Society

combined linear correlation, as shown in Figure 11, is substantially more accurate. The activation parameters derived from these data were $\Delta H^{\neq} = 15.2 \pm 0.1$ kcal mol^{-1} and $\Delta S^{\neq} = -6.7 \pm 0.4$ eu, and it was concluded that a small but reliable negative entropy of activation exists, in contrast to large activation entropies often obtained in DNMR measurements as a result of systematic errors and insufficient spread of the data over temperature[83].

B. Ground State Geometry by X-Ray Structure Analysis

The crystal structure of one representative sulfenamide species, **19e**, has been studied by single-crystal X-ray diffraction analysis[84]. The major structural features are characteristic of sulfenamides in general, and support our understanding of the dynamic processes that these systems undergo. The structure of **19e** in the solid state, as obtained from this analysis, is depicted in Figure 12.

Since sulfenamides undergo stereomutation by the T_C AND I_C mechanism (see Section II.B.2.), it is important to determine which of these two processes is rate limiting and dominates the reaction. Diverse evidence suggests a T_C dominated mechanism in acyclic sulfenamides. The crystallographic structure presented here provides additional evidence to this effect, and sheds more light on the ground state structure of sulfenamides: examination of the geometry near the nitrogen atom reveals that it is the center of a nearly flat pyramid. The sum of bond angles at nitrogen is 356.5°, just 3.5° less than is required for a fully planar arrangement. This is also seen in the Newman projection, viewed along the sulfenamide NS bond (Figure 13).

Since at the ground state of this sulfenamide molecule the nitrogen is essentially planar, clearly pyramidal inversion cannot be associated with a high activation barrier. Thus it was concluded that SN torsion is the rate-determining step in the T_C AND I_C stereomutation of the compound.

The second feature which emerges from the projection in Figure 13 is a confirmation of the postulated chiral conformation of the SN axis, corresponding to the structures depicted in Scheme 2 (Section II). This is the first direct observation of the chiral structure of sulfenamides (as opposed to indirect NMR evidence), and an unequivocal de-

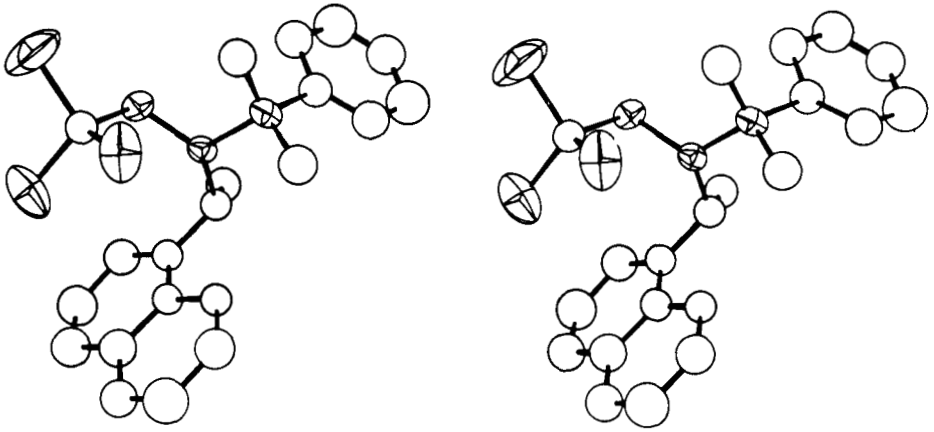


FIGURE 12. A stereoview of the crystal structure of **19e**[84]. Reprinted with permission from Kay *et al.*, *J. Am. Chem. Soc.*, **93**, 5224. Copyright (1971) American Chemical Society

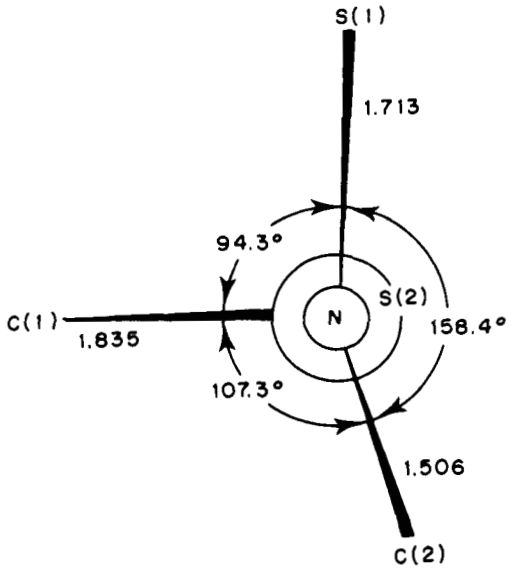
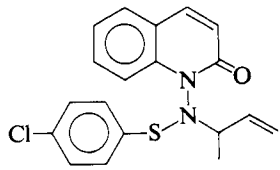


FIGURE 13. *Newman projection* of the crystal structure of **19e** viewed along the N–S (sulfenamide) bond[84]. Reprinted with permission from Kay *et al.*, *J. Am. Chem. Soc.*, **93**, 5224. Copyright (1971) American Chemical Society

monstration that chirality is due to the SN chiral axis rather than to a chiral center. In fact, the presence of an adjacent chiral center of known absolute configuration (the *R* configuration) enabled the assignment of configuration (*R*) to the SN axis in the diastereomer forming the single crystal and in the predominant diastereomer at equilibrium in solution at room temperature.

The only other known crystal structures of sulfenamides are those of two stereoisomers of **25**[85]. In this molecule there are two different stereolabile stereogenic units, the SN and

NN chiral axes, as well as a carbon chiral center. Substantial evidence shows that an exceptionally high T_C barrier around the NN bond (26.1 kcal mol^{-1}) permits isolation of the stable diastereomers[86, 87]. This system thus represents the first resolvable, stereostable hydrazine chiral axis†. In the crystal both axes are chiral, as is also the nitrogen. The two crystalline stereoisomers differ in the configurations of *both* the SN and the NN axes, having the same configuration at the asymmetric carbon atom. Both crystal structures confirm again the basic chiral structure of sulfenamides, with the arenesulfenyl ring eclipsing the nitrogen lone pair, i.e. the C–S–N plane is approximately perpendicular to the N–N–C (exocyclic) plane.



(25)

C. Rotational Barriers

By far the most extensively studied subject related to sulfenamide stereochemistry is the measurement of rotational barriers and the investigation of their dependence on structural factors. The great interest in this problem is probably due, to a large extent, to the early discovery of some unusual substituent effects on SN torsional barriers. Before we discuss this phenomenon, however, let us first comment on the origin of the substantial T_c barriers found in sulfenamides.

1. On the origin of torsional barriers

The substantial barriers for rotation about formal single bonds found in sulfenamides are not unique to these compounds, but are representative of a larger general class of compounds possessing high torsional barriers. This class of compounds includes substituted disulfides, hydrazines, hydroxylamines, peroxides and similar compounds, all of which have single bonds between heteroatoms. The common feature of this general class of compounds is, of course, the presence of lone pairs of electrons on adjacent atoms. It is thus reasonable to assume that the substantial torsional barriers result, at least in part, from repulsive interactions between adjacent lone pairs at the rotational transition state, commonly referred to as 'lone-pair repulsion' or 'conjugative destabilization'.

A recent theoretical study confirmed this assumption, and directly demonstrated the connection between electron occupancy in the π system and the barrier type and ground state conformation[22, 23]. The study used as a model compound the hydrazyl system NH_2NH (**26**), in which changes in electron occupancy alone (from the cation through the radical to the anion) bring about changes in the barriers and the stereochemical classification. Thus, the hydrazyl cation has two electrons in the N–N π orbital, and the overall π interaction, present in the planar conformation **26a**, is bonding (Figure 14). As a result this planar geometry constitutes the torsional ground state for the cation, which must therefore belong to an achiral structural type: T_A or I_A. This situation is like that in imines and amides, in which the ground state is planar.

† In addition to isolation of stable diastereomers, Atkinson and coworkers also carried out enantiomeric resolution of an acid derivative of a similar substituted hydrazine molecule[88].

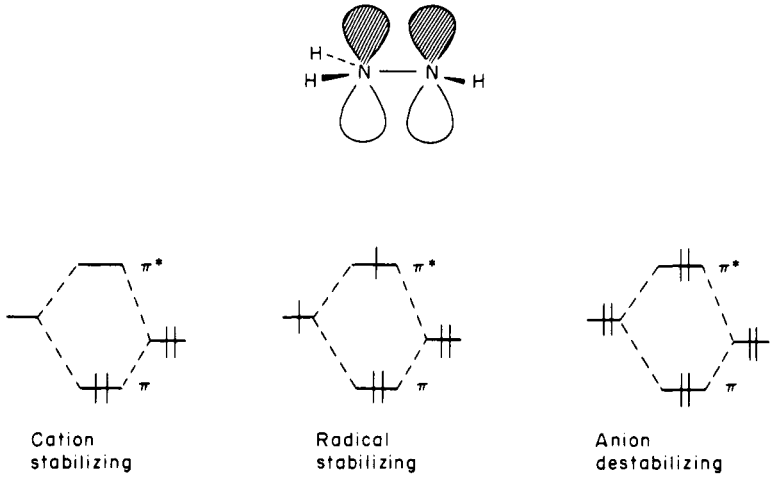
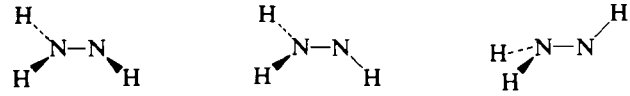


FIGURE 14. π Interactions and electron occupancies in the hydrazyl cation, radical and anion in conformation **26a**[23]. Reprinted with permission from Kost *et al.*, *J. Org. Chem.*, **54**, 4903. Copyright (1989) American Chemical Society

When the NH_2 group is constrained to be planar and two additional electrons are added into the hydrazyl π system to form the anion, both π and π^* orbitals in conformation **26a** are each doubly occupied, and the net π interaction is destabilizing. This forces the molecule out of planarity to adopt a nonplanar ground state conformation (**26b**) in order to avoid the repulsive interaction, and hence places it in one of the chiral categories: T_C or I_C. Conformation **26a** is thus the torsional transition state for the anion. Since the change in mechanism of stereomutation was effected only by the change in the number of electrons in the π system, without any other structural modification, it is evident that the substantial torsional barriers in analogous T_C systems, such as sulfenamides, hydrazobenzenes and hydroxylamines, must be primarily due to the π interaction of adjacent lone pairs.



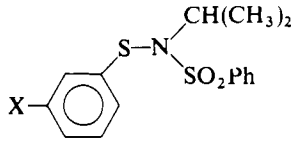
(26a) **(26b)** **(26c)**

When the planarity constraint imposed upon the NH_2 group is removed, the preferred ground state for the hydrazyl anion is **26c**, in accord with the T_C AND I_C stereomutation mechanism for the isoelectronic sulfenamides and hydroxylamines. The SCF-MO calculations indicated nearly equal T_C and I_C barriers for the parent (unsubstituted) hydrazyl anion (8.1 and 7.5 kcal mol^{-1}, respectively)[23]. In substituted acyclic sulfenamides, however, experimental evidence shows that stereomutation is generally dominated by torsion. The simultaneous rotation–inversion process, through the planar transition state **26a**, had an activation free energy of the order of the sum of the individual activation barriers[23]: 17.2 kcal mol^{-1}.

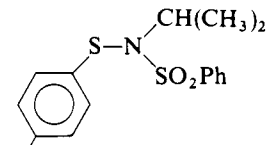
On top of this basic T_C barrier, resulting from four-electron repulsion, is added an increment due to various structural modifications, including steric bulk and polar substituents.

2. Polar substituent effects

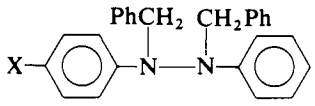
a. Substitution on the arenesulfenyl ring. As mentioned in the Introduction, much of the research on sulfenamide stereochemistry was motivated by the discovery of an *a priori* unexpected polar substituent effect. In light of the discussion in the previous section (III.C.1), which concluded that the primary origin of the torsional barrier is a repulsive π interaction at the transition state, it might have been expected that electron withdrawl away from the SN bond should lower the electron density in the SN π system and decrease the repulsion. As a result it would have been reasonable to anticipate a decrease in torsional barriers. It was found, however, that torsional barriers *increased* markedly in various arenesulfenamides when *meta* or *para* electron-withdrawing substituents were present in the phenyl ring attached to the sulfenyl sulfur atom.



(27)



(28)



(29)

(a) X = OCH_3
(b) X = CH_3
(c) X = H
(d) X = Cl
(e) X = CN

The T_C barriers for *N*-isopropyl-*N*-benzenesulfonyl-arenesulfenamides **27** and **28** were measured by following the coalescence of signals due to the isopropyl-methyl groups, and are shown in Table 5[55]. These results are best analyzed by applying the free-energy form of the Hammett equation (equation 8), i.e. by plotting the free energies of activation ($\Delta G^{\neq}$)

TABLE 5. Free energies of activation for T_C stereomutation in *meta* (**27**) and *para* (**28**) substituted arenesulfenamides[a,b].

Compound	X	T_c (°C)[c]	$\Delta G^{\neq}$ (kcal mol^{-1})
27a	CH_3	−8.5	13.5
27b	H	−7	13.6
27c	Cl	4	14.2
27d	NO_2	10	14.5
28a	OCH_3	−14	13.2
28b	CH_3	−18	13.0
28c	H	−7	13.6
28d	Cl	5	14.2
28e	NO_2	35	15.8

[a] Taken from Reference 55.
[b] Spectra taken at 60 MHz in *ca* 10% toluene-d_8.
[c] Coalescence temperature.

as a function of Hammett substituent constants (Figures 15 and 16). It is immediately evident from these figures that the T_C barrier increases with the increasing electron demand by the substituents. The SN torsional barriers in series **11** also showed a similar trend (Figure 17)[63, 64]. In fact, similar dependence of T_C barriers on polar substituents was also observed in analogous substituted *N,N'*-dibenzylhydrazobenzenes (**29**)[89], indicating

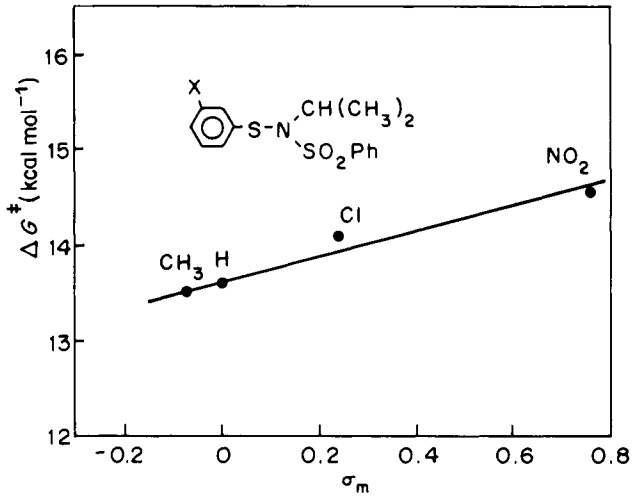


FIGURE 15. Hammett plot for series **27**[55]. Reprinted with permission from Raban and Jones, *J. Am. Chem. Soc.*, **93**, 2692. Copyright (1971) American Chemical Society

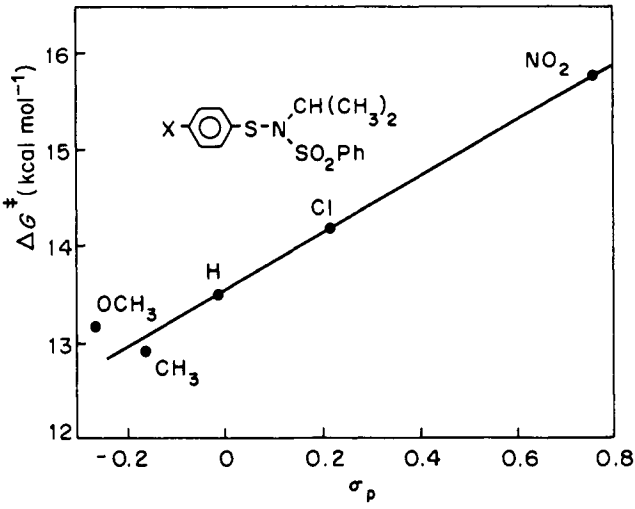


FIGURE 16. Hammett plot for series **28**[55]. Reprinted with permission from Raban and Jones, *J. Am. Chem. Soc.*, **93**, 2692. Copyright (1971) American Chemical Society

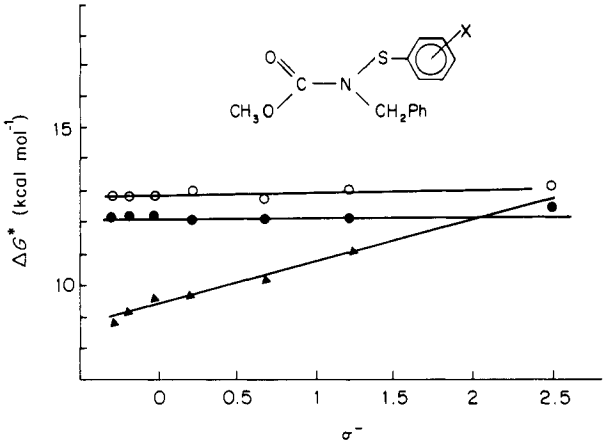


FIGURE 17. Hammett plot for series **11**[64]. Free energies of activation for S–N torsion: ▲; for *syn*→*anti* amide rotation: ●; for *anti*→*syn* amide rotation: o. Reprinted by permission of the Royal Society Chemistry

that this is not a property of sulfenamides alone, but a general effect for systems with heteroatom–heteroatom bonds. The observation of the effect in the hydrazo system also rules out the possibility of an effect which depends on the presence of d-orbital conjugation as was originally supposed.

$$\Delta G^{\neq} = -2.3\, RT\rho\sigma + \Delta G_0^{\neq} \tag{8}$$

For the sake of comparison with different reaction series, a modified Hammett analysis, eliminating the temperature dependence of ρ, was developed[55]. Given that stereomutation of sulfenamides is an intramolecular reaction with no bond breaking or formation and without any charge development, the activation entropies $\Delta S^{\neq}$ are not substantially different from zero. Therefore $\Delta G^{\neq}$ is essentially independent of temperature. Under these conditions a temperature-independent reaction constant ρ' can be defined as follows:

$$\rho' = T\rho \tag{9}$$

and the Hammett relationship (equation 8) becomes

$$\Delta G^{\neq} = -2.3\, R\rho'\sigma + \Delta G_0^{\neq} \tag{10}$$

ρ' is extracted from the slope of a plot of $\Delta G^{\neq}$ as a function of σ-substituent constants, and is converted to a hypothetical reaction constant at 300 K, ρ_{300}, for the sake of comparison with regular reaction constants obtained at this temperature.

$$\rho_{300} = \rho'/300 \tag{11}$$

For all three series of compounds substantial negative ρ_{300} reaction constants were calculated: **27**, $\rho' = -282 \pm 20$ and $\rho_{300} = -0.9 \pm 0.1$; **28**, $\rho' = -582 \pm 55$ and $\rho_{300} = -1.9 \pm 0.2$; **11**, $\rho' = -275 \pm 29$ and $\rho_{300} = -0.9 \pm 0.1$. For reactions of this type, in which no formal charges develop or are delocalized, these reaction constants appear rather large. The fact that *meta* and *para* substituted arenesulfenamides of series **27** and **28** do not fit on the same Hammett correlation, as well as the fact that a better fit is obtained for **11** with

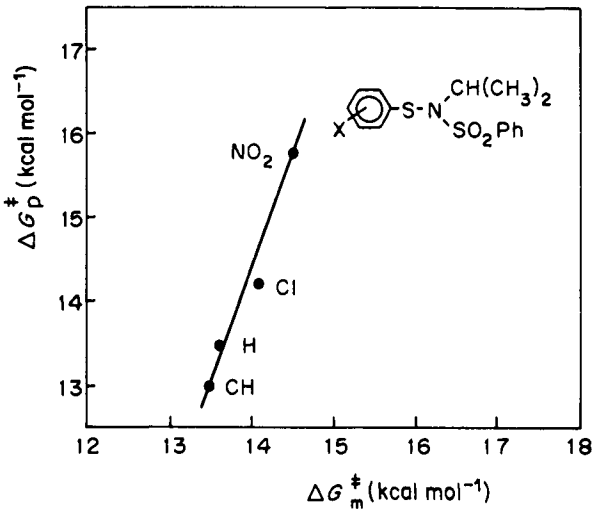
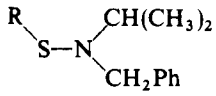


FIGURE 18. Exner plot of free-energy barriers for series **28** against the corresponding barriers for **27**[55]. Reprinted with permission from Raban and Jones, *J. Am. Chem. Soc.*, **93**, 2692. Copyright (1971) American Chemical Society

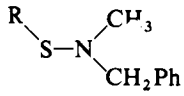
σ^-- than σ-substituent constants, is evidence that a substantial resonance effect is involved in this reaction, more than in usual reaction series which correlate with σ. This is represented quantitatively for **27** and **28** by means of an Exner plot[90] (Figure 18), correlating the T_C barriers for *para*- with those for the corresponding *meta*-substituted sulfenamides. A slope near unity (< 1.2)[90] in these plots is expected for reactions in which the substituents influence the rate primarily through an inductive effect. Conversely, a large slope indicates a substantial resonance involvement of the substituents during the course of the reaction. In this case the slope was as large as 4.5, and represented a substantial electronic influence of the substituents on the reaction center through resonance. The mechanistic implication of these findings will be discussed in Section III.C.5.d.

b. Direct substitution at sulfenyl sulfur. The direct (inductive) substituent effect on sulfenamide T_C barriers was studied by attaching substituent groups with heteroatoms bonded to sulfenyl sulfur[57, 59, 91]. Sulfenamides with chlorine, oxygen, nitrogen and sulfur substituents attached to the sulfenyl sulfur (**30**–**32**) have been studied, and the resulting



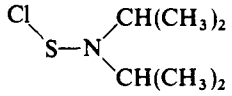
(30)

(a) R = Cl
(b) R = OCH(CH$_3$)$_2$
(c) R = N(CH$_3$)$_2$
(d) R = N(CH$_2$C$_6$H$_5$)CH(CH$_3$)$_2$
(e) R = SCH(CH$_3$)$_2$



(31)

(a) R = Cl
(b) R = OCH(CH$_3$)$_2$
(c) R = N(CH$_3$)CH$_2$Ph
(d) R = SSN(CH$_3$)CH$_2$Ph



(32)

TABLE 6. Torsional barriers in sulfenamides with heteroatoms at sulfur[a]

Compound	Heteroatom	Electro-negativity[b]	Coalescence temp.(°C)	$\Delta G^{\neq}$ (kcal mol^{-1})	Reference
30a	Cl	3.16	31	15.1	91
31a	Cl	3.16	39	15.5	59
32	Cl	3.16	5	14.5	57
30b	O	3.44	48	16.0	91
31b	O	3.44	15	14.3	59
30c	N	3.04	−51	10.9	91
30d	N	3.04	−55	10.7	91
31c	N	3.04	−55	10.7	59
30e[a]	S	2.58	−62	10.1	91
31d	S	2.58	−46	10.1	59

[a] All spectra except that of **30e** were taken in toluene-d_8. **30e** was measured in acetone-d_6.
[b] Reference 92.

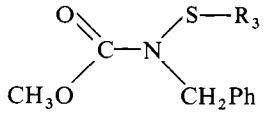
free energies of activation, along with the corresponding coalescence temperatures and electronegativities of the heteroatoms, are listed in Table 6. It is evident from the Table that torsional barriers increase monotonically with increasing Pauling–Allred electronegativity of the substituent atom. Thus the sulfenamides with sulfur or nitrogen attached to sulfenyl sulfur have dramatically lower barriers than compounds substituted by oxygen or chlorine. This is true also for inductive withdrawal by electronegative atoms not directly attached to the sulfur: trichloromethyl- and trifluoromethyl-sulfenamides have been used frequently for various studies[53, 66, 83], because the T_C barriers obtained for these molecules are substantially higher and easier to measure than those for analogous alkanesulfenamides.

The data for the chlorosulfenamides **30a**, **31a** and **32** should be considered less accurate, since topomerization in these compounds can occur by a competing mechanism, in addition to the T_C mechanism[57, 59]. Heterolysis of the S–Cl bond, as well as bimolecular exchange, can effectively increase the rate of topomerization, and the evidence suggests that this depends on the nature of the solvent[59]: more exchange can be expected in chloroform solution, and essentially no exchange in toluene solution.

3. *Steric effects*

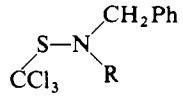
Steric bulk of the substituents on both sides of the SN bond has a profound effect on the magnitude of the T_C energy barrier. In fact, the dependence of barrier heights on steric bulk has been used as an important criterion for the assignment of the type of stereomutation: T_C or I_C. The torsional process is slowed down by bulky substituents, due to increased congestion at the eclipsed transition state (see Scheme 3 in Section II.B.1). By contrast, an I_C process is accelerated by increasing steric bulk of the substituents at nitrogen, since flattening of the nitrogen pyramid releases ground state congestion.

These steric effects are illustrated in Table 7 for three series of compounds. In the first series (**33**) the steric bulk of the substituent on the nitrogen side is varied gradually, from methyl to adamantyl[53]. The barrier clearly increases along this line, following the steric bulk of the alkyl substituent and leaving little doubt that the dominant process in the topomerization is indeed torsion. In the second series the steric bulk of the substituent attached to sulfur is changed on going from CCl_3 (**10a**) to CF_3 (**10b**), without greatly affecting the electron withdrawal[62]. Again a strong effect on the barrier is found, whereby the smaller of the two groups (CF_3) is associated with a T_C barrier which is 1.8 kcal mol^{-1}



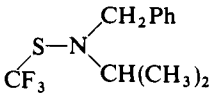
(10)

(a) R = CCl_3
(b) R = CF_3



(33)

(a) R = CH_3
(b) R = CH_2CH_3
(c) R = $CH(CH_3)_2$
(d) R = 1-adamantyl



(34)

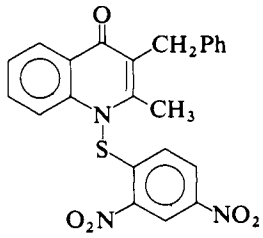
TABLE 7. Steric effects on sulfenamide T_C barriers

Compound	R	$\Delta G^{\neq}$ (kcal mol^{-1})	Solvent	Reference
33a	CH_3	14.4	$CDCl_3$	53
33b	CH_2CH_3	15.6	$CDCl_3$	53
33c	$CH(CH_3)_2$	16.0	$CDCl_3$	53
33d	1-Adamantyl	16.9	C_6H_5Br	53
10a	CCl_3	14.3	$C_6D_5CD_3$	62
10b	CF_3	12.5	$C_6D_5CD_3$	62
34	CF_3	13.3	$CDCl_3$	53

lower than that measured for the larger group. An even greater difference in T_C barriers due to the trihalomethyl groups attached to sulfur is found in the third series, **33c** and **34**: 2.7 kcal mol^{-1}! Thus increasing steric bulk on either nitrogen or sulfur has the effect of raising the torsional barrier. Here again, the trend in barrier heights permits assignment of the dominant process. As we shall see in the discussion on I_C barriers, these two substituents have the opposite effect on inversion barriers, i.e. ground state destabilization is greater for the more bulky trichloromethyl than for the trifluoromethyl group.

By utilizing a combination of steric and electronic effects, sulfenamide molecules with substantially high T_C barriers have been designed and synthesized. The aim of these syntheses is the preparation of a compound possessing a stereostable sulfenamide stereogenic unit, that may potentially be resolved into stereoisomers which differ in configuration at the SN axis. These may be either stereostable diastereomers, or optically active enantiomeric sulfenamides which owe their optical activity to the SN chiral axis. A recent study reports the successful preparation of sulfenamides which are stereostable with respect to the isolation time scale, and hence may be amenable to stereomeric resolution[8].

The 4-quinolone derivative **35** has a T_C barrier too high to be measured by DNMR spectroscopy (> 22 kcal mol^{-1}), but it has not yet been resolved into stereoisomers[8]. By contrast, the 2-quinolone derivative **36** has a much lower torsional barrier (16.9 kcal-mol^{-1}). This remarkable difference in barriers was interpreted as evidence for an *exo* passage of the arenesulfenyl ring at the torsional transition state for both compounds: had the transition state involved passage of the dinitrophenyl ring near the *peri* hydrogen of the aromatic ring, there would not have been a significant steric effect due to the substituent at the 2-position, and **35** and **36** would have had similar barriers. This leads to the conclusion that the steric interaction involved in passage of the dinitrophenyl ring near the *peri* hydrogen is very intense, and would lead to barriers in excess of 22 kcal mol^{-1}.



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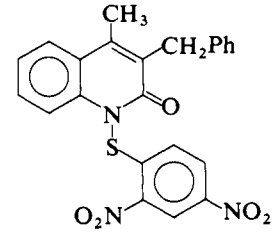

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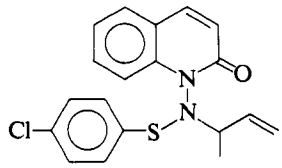

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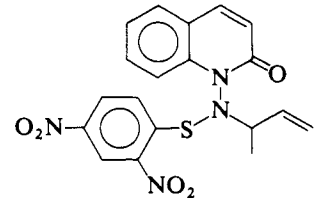
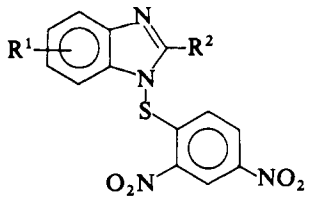


(37)

That this is indeed the case can be seen from a study on a series of hydrazine derivatives of 2-quinolone, studied by Atkinson and coworkers[85-87]. The barrier for rotation about the NN bond in **25** is 26.2 kcal mol^{-1}, substantially higher than that for **35**. This is because in the hydrazine molecules one of the ligands on the exocyclic nitrogen *must* pass near the *peri* hydrogen and experience the severe steric interactions, which apparently are avoided in sulfenamides **35** and **36**, by the *exo*-type stereomutation.

A particularly interesting compound of the series studied by Atkinson is the 2,4-dinitro substituted sulfenamide **37**. The electron-withdrawing groups attached to the sulfenyl phenyl ring raise the SN torsional barrier, and enable observation, at $-40\,^{\circ}C$, of four diastereomers due to permutations of the configurations of both of the labile chiral axes, the SN and NN bonds, and the presence of the stereostable chiral center[87].

Previous attempts to prepare sulfenamides with high T_C barriers included a series of *N*-2,4-dinitrobenzenesulfenyl-benzimidazoles (**38**, **39**) with various alkyl substituents at the 2 position, which have the same *peri* interactions as **35** and **36**[93]. The barriers measured for **38** and **39** (Table 8) were nevertheless lower than those found in **35** and **36**, indicating again that stereomutation takes place by an *exo*-type passage, which in the five-membered ring compounds is less hindered.



(**38**) $R^1 = H$ (**39**) $R^1 = Cl$

(**a**) $R^2 = CH_2CH_3$
(**b**) $R^2 = CH_2Ph$
(**c**) $R^2 = CH_2Cl$
(**d**) $R^2 = CH(CH_3)Ph$

TABLE 8. Torsional barriers[a] in *N*-2,4-Dinitrobenzenesulfenylbenzimidazoles[93]

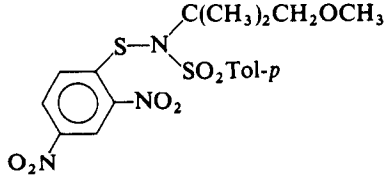
Compound	R^1	R^2	Regioisomer ratio[b]	Coalescence temp.(°C)	$\Delta G^{\neq}$ (kcal mol^{-1})
38a	H	CH_2CH_3		101	18.9
38b	H	CH_2Ph		120.5	19.1
38c	H	CH_2Cl		74	19.6
38d[c]	H	$CH(CH_3)Ph$		89	19.6
39a	Cl	CH_2CH_3	1.85	97	18.6
39b	Cl	CH_2Ph	1.4	118.5	19.1
39c(major)	Cl	CH_2Cl	1.5	80	19.0
39c(minor)	Cl	CH_2Cl		75	19.3

[a] Measured at 300 MHz in toluene-d_8 solutions.

[b] Ratio of regioisomers which differ in position of the Cl atom.

[c] The equilibrium constant for the diastereomers which differ in configuration at the SN chiral axis is 6.3.

Even higher T_C barriers were realized in other sulfenamides accommodating both strongly electron-withdrawing groups on sulfur and very bulky substituents. Thus **40**[75] had a free energy of activation of 21.4 kcal mol^{-1}, whereas the barrier for **41** could not be measured by NMR spectroscopy, since no coalescence was observed up to 160 °C ($\Delta G^{\neq} > 23$ kcal mol^{-1})[28].



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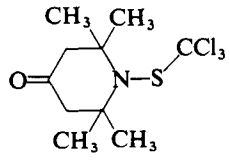


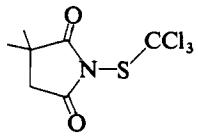
(41)

4. Criteria for distinguishing T_C from I_C barriers

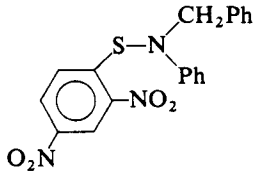
The assignment of either T_C or I_C stereomutation to the observed changes and coalescence of diastereotopic groups in the NMR spectra of sulfenamides is usually straightforward and unambiguous. This is in sharp contrast to the situation in the analogous substituted hydroxylamines, in which the barriers are comparable in magnitude and often quite difficult to assign[15]. Some of the criteria for distinguishing T_C-dominant from I_C-dominant stereomutations were mentioned briefly in earlier sections. This section summarizes the various criteria.

a. Conjugation. When the nitrogen of the SN bond is attached to an aromatic ring or to a carbonyl group, conjugation with that group strongly stabilizes the planar conformation at nitrogen. The extent of stabilization is such that in many cases the planar geometry becomes the ground state conformation, as in amides, while in others a very low energy barrier separates the shallow pyramidal ground state from the planar transition state. In all of these cases the torsional barrier is so much higher than the inversion barrier that an I_C stereomutation can be ruled out. Examples of compounds in which the stereomutation is bound to be torsion-dominant, as a result of the conjugation criterion, are **42** and **43**. The substantial T_C barriers in these compounds (**42**, $\Delta G^{\neq} = 11.8$ kcal mol^{-1} in $CDCl_3$ solution[53], and **43**, $\Delta G^{\neq} = 17.8$ kcal mol^{-1} in toluene-d_8 solution[53]) suggest that in nonconjugated similar *N,N*-dialkylsulfenamides comparable T_C barriers might be expected. Thus, for example, when the N-phenyl ring in **43** is replaced by an isopropyl group

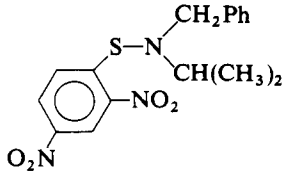
(**44**), the observed barrier drops from 17.8 to 16.5 kcal mol^{-1}, and must hence also be a T_C barrier.



(**42**)

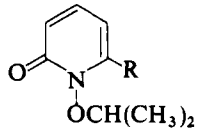


(**43**)

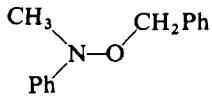


(**44**)

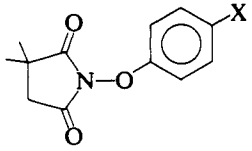
The conjugation effect has also been applied successfully in other AND type stereomutations in hydroxylamines (**45**[94], **46**[94] and **47**[95]) and in hydrazobenzenes (**29**)[89], to ascertain that indeed T_C barriers are measured.



(**45**) R = H, Cl



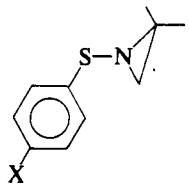
(**46**)



(**47**)

b. Steric effects. This criterion relates to the opposite effect of steric bulk on torsion and on inversion: in a T_C-type torsion, in which at the ground state the nitrogen ligands are approximately in a plane (R^1–N–R^2) perpendicular to the R–S–N plane, rotation approaching the transition state brings the ligands closer together, until they completely eclipse at the T_C transition state. As a result, bulky substituents cause greater destabilization at the transition state than at the ground state, and the overall energy barrier for the process increases. By contrast, in an I_C process the major steric crowding occurs at the pyramidal ground state, and is partly relieved at the transition state. Thus, bulky substituents cause ground state destabilization and hence accelerate nitrogen inversion. Examples of this effect were discussed in Section III.C.3 and are discussed again in Section IV (Table 14).

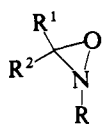
c. Substituent effects. T_C stereomutations in arenesulfenamides are characterized by the dependence of barrier heights on polar substituent effects, represented quantitatively by significant negative Hammett reaction constants, ρ_{300}. Examples of this phenomenon were discussed in Section III.C.2.a. However, no such dependence of I_C barriers on substituents was found. Thus, in a series of substituted *N*-arenesulfenylaziridines **48**, the nitrogen inversion barriers were essentially equal and independent of the substituent[25, 27]. The presence or absence of a polar substituent effect on the barrier to stereomutation in N-arenesulfenamides can thus serve as a criterion for the type of process observed, T_C or I_C.



(**48**)

d. Constraint into a small ring. Another way of ascertaining that only one of the two possible stereomutation mechanisms is observed is the constraint of part of the molecule into a small ring. Thus, the incorporation of the nitrogen into a three-membered ring in **48** resulted in increased nitrogen inversion barriers, and in the dominance of the I_C process[25, 27]. While rotation cannot be excluded in this case and both processes are still possible, the strain associated with the small ring strongly reduces the rate of nitrogen inversion.

If both atoms of the sulfenamide moiety are constrained into a ring, torsion can be ruled out, and the only process which can be observed by NMR spectroscopy is I_C. In this method it is not necessary to form a three-membered ring in order to increase the I_C barrier, as long as the size of the ring does not permit ring reversal via torsional processes with significant barriers. While this method has not yet been realized for sulfenamides, it enabled observation and measurement of I_C barriers in cyclic hydroxylamine derivatives with three- four- and five-membered rings (e.g. **49**[96-99], **50**[100], **51**[101-103] and **52**[104]) without the interference of a torsional process.



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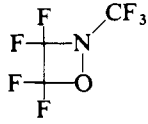

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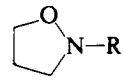

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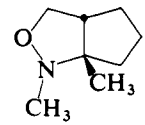


(52)

5. The origin of polar substituent effects

Several rationales have been proposed over the years to account for the intuitively disturbing polar substituent effects on sulfenamide T_C barriers (Section III.C.2.), and eventually discarded with the accumulation of new evidence. The fact that electron-withdrawing substituents attached to the arenesulfenyl ring increase the SN T_C barriers is difficult to accommodate within the view that repulsive interactions between lone pairs on S and N generate the high barriers (Section III.C.1). In this section the various rationales are discussed, with the evidence for and against each one.

a. p–d π Conjugation. The earliest explanation for the polar substituent effect invoked π conjugation between the nitrogen lone pair and a vacant sulfur d orbital at the torsional ground state[53, 55]. Thus the ground state is stabilized by (p–d)π conjugation, forming a partial double bond between sulfur and nitrogen and leading to substantial barriers to torsion about the SN bond. Substituent dependence of the barrier is due to the effect of substituents on the energy of the vacant d orbital on sulfur: electron-withdrawing substituents lower its energy, and hence decrease the HOMO–LUMO (n→d) energy gap and intensify the ground state stabilization. As a result the torsional barrier is increased, and a negative Hammett reaction constant is obtained (Section III.C.2).

On the basis of a number of later studies, however, this explanation could be abandoned. A study on nitrogen inversion barriers in substituted *N*-arenesulfenylaziridines **48** showed no similar substituent dependence of barriers[25, 27]. In fact, within experimental error the nitrogen inversion barriers were constant and did not vary with the variation of substituents (the data are presented in Section IV, Table 14). Changes in *para* substitution are expected to affect the nitrogen inversion barriers, as conjugation between the nitrogen lone pair and the ligand on nitrogen is changed. This was demonstrated in a series of *para*-substituted *N*-phenylaziridines[105]. Since involvement of the nitrogen lone pair in **48** in partial double bonding to sulfur is also expected to stabilize the planar

transition state for nitrogen inversion, and hence to lower nitrogen inversion barriers, and since no decrease of the barriers was observed in the presence of electron-withdrawing groups, it was concluded that (p–d)π bonding was unimportant in this system[27].

Similar results were obtained in **11**, a series of arenesulfenamides in which the nitrogen is also part of a carbamate system[63, 64]. In this system there are two torsional processes requiring high activation energies, rotation about the SN and the N–CO bonds. The stereochemical and NMR properties of compounds of series **11** were described in detail in Section II.C.1. The SN torsional barriers in series **11** (Table 9, Figure 17) show the usual trend, i.e. a negative Hammett reaction constant $\rho_{300} = -0.9 \pm 0.1$. If (p–d)$\pi$ bonding were the dominant factor affecting the SN barrier as substituents are changed, one would expect to find the opposite trend in amide rotational barriers: an increase in electron-withdrawing power of the substituent should lead to a decrease in the N–CO barrier. This is because increased double-bond character at the SN bond means that the nitrogen lone pair is partly shifted towards sulfur, and is hence less available for conjugation with the carbonyl π system. Since this conjugation is responsible for the planarity and high T_A barrier of the amide functional group, the increase in SN barriers should be accompanied by a parallel decrease in N–CO barriers. The failure to observe any significant changes in the T_A barrier height is evidence that no shift of electron density from the amide to the sulfenamide bond occurs upon changing substituents, and hence, again, that (p–d)π conjugation is insignificant.

Additional convincing evidence for the lack of *d*-orbital involvement in sulfenamides comes from a similar study on substituent effects on torsional barriers in *N,N'*-dibenzylhydrazobenzenes, **29** (Table 10)[89]. In this series the SN chiral axis is replaced by

TABLE 9. Sulfenamide (T_C) and amide (T_A) barriers in arenesulfenylcarbamates[a]

Compound	X	K[b]	$\Delta G^{\neq}_{CN}$[c] (kcal mol^{-1})	$\Delta G^{\neq}_{SN}$ (kcal mol^{-1})
11a	4-OCH_3	4.7	12.1	8.7
11b	4-CH_3	4.6	12.1	9.1
11c	H	5.0	12.1	9.4
11d	4-Cl	6.5	12.0	9.5
11e	3-NO_2	4.5	12.0	9.9
11f	4-NO_2	8.0	12.0	10.9
11g	2,4-$(NO_2)_2$	4.0	12.3	16.2

[a] From Reference 64. Spectra were measured at 100 MHz in toluene-d_8 solutions.

[b] Carbamate *syn–anti* equilibrium constant.

[c] Barrier for T_A rotation from the minor to the major amide diastereomer.

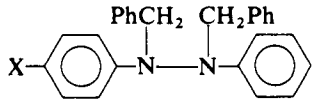
TABLE 10. T_C rotational barriers in hydrazobenzenes[a]

Compound	X	Temp.(K)[b]	$\Delta G^{\neq}$ (kcal mol^{-1})
29a	OCH_3	265	13.1
29b	CH_3	281	13.9
29c	H	290	14.2
29d	Cl	290	14.4
29e	CN	318	15.8

[a] Reference 89. 270 MHz ^{1}H-NMR spectra were measured in toluene-d_8 solution.

[b] Temperature corresponds approximately to coalescence temperature.

the NN chiral axis, and yet the same trend in T_C barriers is observed as for sulfenamides, represented by a negative reaction constant $\rho_{300} = -1.09$. Since obviously no d orbitals can be involved in affecting the T_C barriers in **29**, it must be concluded that the similar trend in barriers in *both* types of compounds (hydrazines and sulfenamides) is not due to d-orbital interactions, and must be due to another factor.



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b. Four-electron repulsion mechanism. The results obtained for the *para*-substituted sulfenylcarbamates **11**, whereby increase of SN-torsional barriers with increasing electron demand by the substituents was *not* accompanied by a parallel decrease in amide rotational barriers, were initially explained by invoking a substituent effect on the four-electron repulsive interaction[64, 106]. According to the model the repulsive π interaction at the T_C transition state (Figure 19), which is responsible for the barrier, intensifies in the presence of an electron-withdrawing substituent and thus raises the transition state energy and the activation barrier. This is because electron withdrawal lowers the energy of the sulfur p-lone pair orbital, and as a result decreases the energy gap between the interacting orbitals. This is associated with greater π overlap and more intense interaction, and hence with a greater repulsion and a higher torsional barrier.

This model is a transition state effect, and hence it has no effect on the adjacent torsional process, amide rotation, and on its barrier height: we have established earlier (Section II.C.1) that it is highly unlikely that both torsional processes would take place simultaneously. Consequently both the amide ground and transition states, as well as the difference between them (i.e. the barrier), are independent of factors affecting the SN torsional transition state. In this way the model could also account for the lack of substituent effect on amide torsional barriers in series **11**.

According to the model, the maximum repulsive interaction is expected in the case of overlap between degenerate lone-pair orbitals, when the energy gap is zero. Thus in the

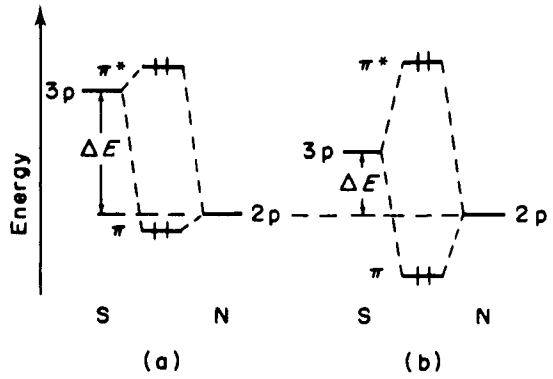


FIGURE 19. Schematic diagram of the four-electron interaction between lone pairs on sulfur and nitrogen at the SN torsional transition state: (a) without a substituent; (b) with an electronegative substituent: smaller ΔE and greater interaction[64]. Reproduced by permission of the Royal Society of Chemistry

series of hydrazobenzenes **29** the highest T_C barrier should be observed for the symmetrically substituted member **29c**, and all other members of the series should have lower barriers with a consequent convex broken Hammett correlation. However, the results in Table 10 clearly indicate that this expectation is not borne out by experiment, and hence that the effect of substituents on the intensity of the four-electron repulsion cannot be the dominant mechanism by which SN barriers are affected by substituents.

c. Negative hyperconjugation. An alternative interaction to (p–d)π conjugation which might account for additional SN double bonding at the torsional ground state could be negative, or (n–σ^*), hyperconjugation. This interaction and the way by which it may be affected by changes in substituents is depicted schematically in Figure 20. A more electronegative substituent R causes greater stabilization of the T_C ground state, and consequently a higher barrier, by a combination of changes: (a) the R–S σ and σ^* orbitals are lowered; as a result the n–σ^* energy gap decreases and the stabilizing interaction between these orbitals intensifies. (b) Lowering of the σ orbital increases the gap between the n and σ orbitals, thus decreasing the overlap and the repulsive four-electron interaction which destabilizes the partial SN double bond. (c) An electronegative R also polarizes the σ and σ^* orbitals, as shown in Figure 20, resulting in better n–σ^* overlap, and hence in stronger two-electron stabilization[62].

Experimental evidence has shown that when strongly electronegative groups are attached directly to sulfur, the effects of hyperconjugation are indeed important. Thus, the polar substituent effects described in Section III.C.2.b (Table 6) are best understood in terms of this interaction[57, 59, 91]. The high barriers for rotation about the SN bond in

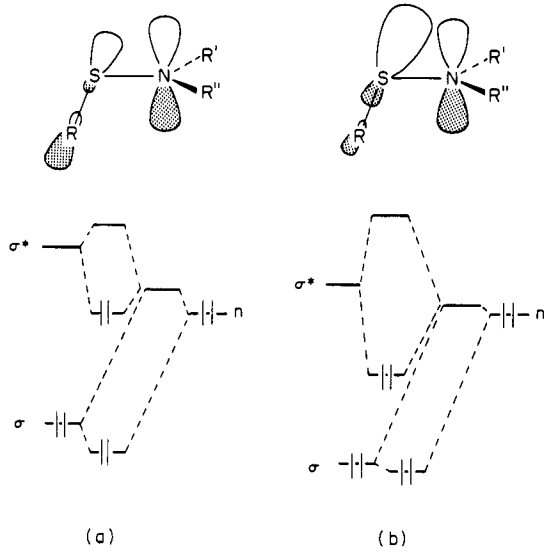
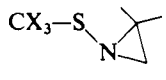


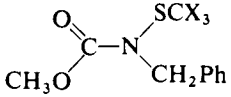
FIGURE 20. Schematic illustration of the n→σ^* hyperconjugation. (a) With a nonelectronegative substituent R, the n,σ^* energy gap is relatively large, the interaction weak. The n,σ gap is such that the four-electron (repulsive) interaction is significant and partly offsets the n,σ^* stabilization. (b) With an electronegative R group, both σ and σ^* orbitals are lowered, resulting in: I, weaker n,σ repulsive interaction; II, stronger stabilizing n,σ^* interaction, due to smaller gap, and due to III, a more polarized σ^* orbital with a greater coefficient on S and hence better overlap[62]. Reprinted with permission from Kost and Egozy, *J. Org. Chem.*, **54**, 4909. Copyright (1989) American Chemical Society

trichloro- and trifluoro-methanesulfenamides, in many of the studies reviewed in this chapter, are also attributed to (n–σ^*) hyperconjugation.

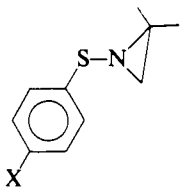
Two interesting studies of the effect of hyperconjugation on sulfenamides are those of trichloro- and trifluoromethanesulfenyl-aziridines, **53**, and the corresponding carbamates, **10**. Since hyperconjugation causes an increase in the double-bond character of the SN bond, it not only should increase the T_C barrier, but also decrease the nitrogen inversion barrier in **53** by stabilizing the planar I_C transition state. Indeed hyperconjugation was demonstrated in **53**, where the I_C barriers (**53a**, $\Delta G^{\neq} = 9.2$ kcal mol^{-1}, **53b**, $\Delta G^{\neq} = 10.4$ kcal mol^{-1})[26, 27] were lower than those measured for the arenesulfenyl analogues (**48**, $\Delta G^{\neq} = 12.5$ kcal mol^{-1})[27], more than could be accounted for by the differences in steric bulk[27]. However, in this study only nitrogen inversion barriers could be measured, and the simultaneous effect of hyperconjugation on the T_C barriers could not be evaluated.



(**53**) (**a**) X = Cl
(**b**) X = F



(**10**) (**a**) X = Cl
(**b**) X = F



(**48**)

By contrast, in compounds **10** the effect of hyperconjugation could be demonstrated twice, on sulfenamide as well as on amide rotational barriers[62]. Table 11 lists the torsional barriers for both processes in carbamates **10**. When these barriers are compared with those for the analogous arenesulfenylcarbamates (**11**, Table 9)[63, 64] the simultaneous operation of hyperconjugation on both barriers is evident: the electronegative substituents in **10** lower the energy of the S–C σ^* orbital and increase the bonding interaction between sulfur and nitrogen. This results in enhanced SN torsional barriers. The increased bonding in the SN bond is effected by a partial shift of the nitrogen lone pair from the vicinity of the N–CO bond towards the SN bond. As a result the π-bonding intensity between nitrogen and the carbonyl group decreases, and the energy of the planar ground state for amide rotation increases, and causes a lower activation barrier for this process.

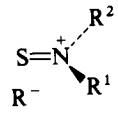
The fact that amide T_A barriers in **10** are lower than the corresponding barriers in **11**, and hence that hyperconjugation is significant in this system, together with the fact that the T_A barriers in **11** are independent of the substituent on the aromatic ring, proves that hyperconjugation is insignificant in **11**. Likewise, the lack of substituent dependence of I_C barriers in the arenesulfenylaziridine series **48**, despite the drop in barrier in **53**, is evidence that hyperconjugation is unimportant in **48**, and, by analogy, that it cannot account for the aromatic substituent effect on T_C barriers observed in various arenesulfenamides and manifest in negative Hammett reaction constants.

TABLE 11. T_A and T_C barriers in trihalomethanesulfenylcarbamates[a]

Compound	X	K^b	$\Delta G^{\neq}_{CN}$[c] (kcal mol^{-1})	$\Delta G^{\neq}_{SN}$ (kcal mol^{-1})
10a	Cl	7.0	11.6	14.3
10b	F	6.9	11.6	12.5

[a] Reference 62. Spectra measured in toluene-d_8 solution, at 200 MHz.
[b] *Syn–anti* equilibrium constant at 210 K.
[c] Barrier for T_A rotation from the minor to the major amide diastereomer.

The conclusion that in aromatic sulfenamides hyperconjugation is insignificant while in trihalomethanesulfenamides it is quite effective is readily understood, when the valence bond (VB) representation of hyperconjugation is considered. In terms of VB theory, hyperconjugation consists of an admixture of resonance structure **54** into the normal Lewis structure of sulfenamides. Only those substituents which are able to stabilize **54** can support hyperconjugation. The trihalomethyl groups, as well as directly attached heteroatoms like chlorine, methoxy and similar groups, form much more stable anions than a substituted phenyl ring. Consequently the ionic canonical structure corresponding to **54** in the presence of these groups is considerably more stable than with an aromatic ring (**55**), and hence its contribution to the overall structure is only significant in their presence and not in the presence of an aromatic ring. Inversion barrier lowering was also observed in α-fluoro-aziridines and in hydroxy- and methoxymethylaziridines, and was likewise attributed to hyperconjugation[107, 108].



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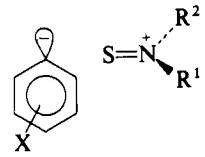

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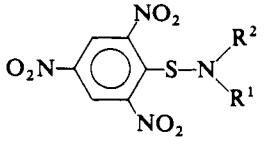
The large slope in the Exner plot (Section III.C.2.a, Figure 18) of the T_C barriers for *para*- vs *meta*-substituted arenesulfenylsulfonamides is also inconsistent with the involvement of hyperconjugation in arenesulfenamides. If the ionic structure **55** were to contribute substantially to the ground state of arenesulfenamides, one would expect the substituents at most to affect its stability by an inductive influence, and not by resonance, since the negative charge is in a σ orbital perpendicular to the π plane. However, the Exner plot is evidence for a large resonance effect and rules out the possibility that in arenesulfenamides the substituent effect on T_C barriers results from hyperconjugation.

Theoretical evidence in support of these ideas was provided by a computational study on nitrogen inversion barriers in aziridines[109]. The first two of the three criteria for hyperconjugation (energy stabilization, geometrical deformation and charge delocalization) were observed in fluoromethylaziridine relative to methylaziridine: lower I_C barrier and higher T_C barrier, and a decrease of the N–CH_2F bond length and increase of the C–F bond length in the planar I_C transition state relative to the ground state. Charge transfer from nitrogen towards the fluorine, as required by the canonical structure represented by **54**, was only observed in the HOMO orbital, but was evidently offset by opposite transfer in other MOs, for the net calculated charge transfer was negligible[110].

d. The electrosteric effect. The discovery that introduction of strongly electron-withdrawing groups into the phenyl ring of benzenesulfenamides leads to dramatically increased SN torsional barriers, led to the expectation that the barrier could be made high enough to make the SN stereogenic unit stable relative to the *isolation* time scale. This would be accomplished by introducing a third nitro group to compounds like **40**, and would lead to the eventual isolation of stereostable isomers differing in configuration at the SN chiral axis, either diastereomers or optically active enantiomers. An elaborate synthesis of 2,4,6-trinitrobenzenesulfenyl chloride was developed[111], and a number of trinitrobenzenesulfenamides (**56**) were synthesized and their T_C barriers determined by NMR spectroscopy[56, 75]. Table 12 lists some of these compounds and their T_C barriers, along with the corresponding 2,4-dinitro analogues (**57**) for comparison. It is immediately



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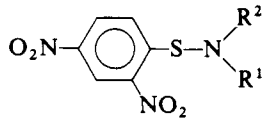


(57)

TABLE 12. Torsional barriers in 2,4,6-trinitrobenzenesulfenamides and 2,4-dinitrobenzenesulfenamides[a]

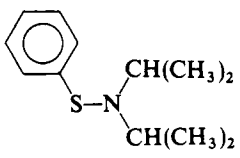
Compound	R^1	R^2	Solvent	$\Delta G^{\neq}$ (kcal mol^{-1})
56a	CH_2Ph	$CH(CH_3)_2$	$CDCl_3$	15.6
56b	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_6D_5CD_3$	17.6
56c	CH_2Ph	2,4,6-$Me_3C_6H_2$	$CDCl_3$	12.0
56d	CH_2Ph	4-$TolSO_2$	$CDCl_3$	14.6
56e	$CH(CH_3)_2$	4-$TolSO_2$	$CDCl_3$	14.2
56f	$CH(CH_3)Ph$	4-$TolSO_2$	$CDCl_3$	13.8
56g	$C(Me)_2CH_2OMe$	4-$TolSO_2$	$CDCl_3$	15.6
56h	$CH(CH_3)Ph$	$C(CH_3)_3$	$CDCl_3$	18.2
57a	CH_2Ph	$CH(CH_3)_2$	$C_6D_5CD_3$	16.5
57b	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_6D_5CD_3$	20.6[b]
57c	CH_2Ph	2,4,6-$Me_3C_6H_2$	$CDCl_3$	13.4
57d	CH_2Ph	4-$TolSO_2$	$C_6D_5CD_3$-DMSO-d_6	17.0
57e	$CH(CH_3)_2$	4-$TolSO_2$	$C_6D_5CD_3$	20.1
57f	$CH(CH_3)Ph$	4-$TolSO_2$	$C_6D_5CD_3$	19.7
57g	$C(Me)_2CH_2OMe$	4-$TolSO_2$	$C_6D_5CD_3$	21.4

[a] Reference 75.

[b] Same barrier reported in $C_6D_5NO_2$, Reference 112.

evident from the Table that introduction of the third nitro group does *not* result in the expected increase in barrier, and that, in fact, a rather dramatic *drop* in barrier is observed.

Evidence that the drop in barrier is not a result of some special interaction of the *ortho*-nitro group, but a general result of replacing *both* of the *ortho* protons by bulkier substituents, is found in Table 13. These data relate to substitution of the *ortho* positions by chlorine atoms: substitution of chlorine in the *para* position raises the T_C barrier (**58** vs **59**), and thus perchlorination of the phenyl ring might be expected to further raise the barrier. However, the perchloro sulfenamide **60** has the lowest barrier in this series, again indicating a special effect of the *ortho* groups.



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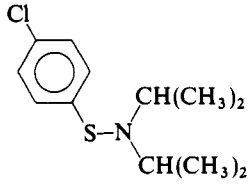

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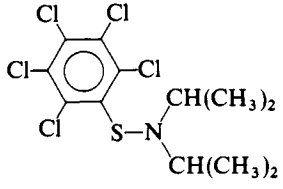


(60)

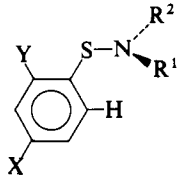
TABLE 13. T_C barriers in chlorinated benzenesulfenamides[a]

Compound	Solvent	T_c(°C)	$\Delta G^{\neq}$ (kcal mol^{-1})
58	CH_2Cl_2	−12	14.3
59	CH_2Cl_3	−6	14.6
60	$CDCl_3$	−35	12.1

[a] Reference 75. Data at 60 MHz.

Various pieces of evidence suggested that the increase in barriers with increasing substituent electronegativity at the phenyl ring, as well as the interruption of the effect upon replacement of the second *ortho* proton, both resulted from a combination of steric and electronic effects. Clearly the *ortho* effect described here is a steric one, while the polar substituent effect is electronic in nature. The correlation between the sensitivity of sulfenamides **21** to asymmetric induction, reflected by the Ruch–Ugi reaction constants and corresponding equilibrium constants (Section III.A.2, Table 4), and the T_C barriers also connects steric with electronic effects. Also the fact that the *amount* by which the free energy of activation drops with the introduction of a second *ortho* substituent strongly depends on the steric bulk of the ligands at nitrogen points in this direction.

All of these facts were interpreted in terms of electronic effects of the aromatic substituent which are manifest in an effective change in steric bulk, and were termed the electrosteric effect[75]. The ground state of substituted benzenesulfenamides in which there is at least one *ortho* proton adopts the conformation represented by **61**. In this conformation the aromatic ring is conjugated with the sulfur p-lone pair. When torsion about the SN bond takes place the *ortho* proton of the aromatic ring gradually experiences increasing steric interaction with one of the other ligands on nitrogen, the smaller of R^1 or R^2. At the torsional transition state, when the ring and one nitrogen ligand are eclipsed, the steric congestion forces the aromatic ring to twist out of coplanarity with the CSN plane, and hence out of conjugation with the sulfur lone pair. The loss of conjugation energy adds up to the activation free energy, and *is different for the various substituents*. Electron-withdrawing substituents stabilize the conjugated geometry more than others, and consequently the loss of conjugation during SN torsion is associated with greater activation energies. Thus, the electronegativity of the substituent causes additional rigidity to the molecule, which is manifest in a less facile torsional process, as well as in greater sensitivity towards thermodynamic asymmetric induction.



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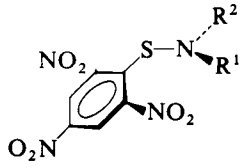


(62)

The conjugation between the aromatic ring and the sulfur lone pair is a direct resonance interaction, and is affected by the substituents primarily in a resonance fashion. This is in accord with the observation of the large slope (4.5) in the Exner plot for *N*-arenesulfenylsulfonamides **27** and **28**, and for the better fit of SN barriers to σ^- substituent constants.

When both *ortho* positions are occupied by relatively bulky groups, the steric congestion between one of them and the nitrogen and its ligands is too severe even in the

conformation represented by **61**, and consequently the aromatic ring is twisted out of conjugation *already in the torsional ground state* **62**. This means that the ground state is destabilized by the loss of conjugation energy, and that no additional loss of conjugation occurs during torsion. As a result *ortho*-disubstituted benzenesulfenamides have lower T_C activation barriers. This is a thermodynamic effect, operating at the ground state, and hence also influences thermodynamic asymmetric induction. The effective steric bulk of the aromatic ring in *ortho*-disubstituted compounds (**21e**, Table 4) is *smaller* than in sulfenamides with one free *ortho* position, because in the ground state **62** the *ortho* group is further removed from the chiral center, and therefore the equilibrium constant of the two diastereomers is small, indicating little asymmetric induction.

The angle of twist of the aromatic ring at the torsional transition state depends on the size of the nitrogen ligands. This explains the observation that when the latter are relatively small, the drop in barrier upon substitution of the second *ortho* position is smaller than when they are very bulky[75]: when the ligand on nitrogen is a primary alkyl group, like benzyl, the loss of conjugation at the transition state is only partial, resulting in a smaller addition of activation energy to the barrier. Therefore when the *ortho* positions are both substituted, the drop in barrier is also only partial. An example of this effect can be found in Table 12: the difference in free energies of activation for the N-benzyl compounds **56a** and **57a** is $\Delta\Delta G^{\neq} = 1.0$ kcal mol^{-1}; by sharp contrast, the corresponding difference for the highly hindered **56g** and **57g** is $\Delta\Delta G^{\neq} = 5.8$ kcal mol^{-1}!

To summarize, it appears that the only mechanistic model which at present accounts for all the experimental observations on sulfenamide T_C barriers is the electrosteric effect.

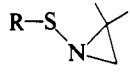
IV. SULFENAMIDES AS CHIRAL CENTERS

In general sulfenamides undergo T_C AND I_C stereomutation dominated by rotation. Only in special cases is nitrogen inversion sufficiently retarded so that it becomes the rate-determining step of the overall process. When this is the case, the sulfenamide stereomutation is said to be dominated by inversion, i.e. in the vicinity of the transition state the reaction coordinate is composed primarily of bond angle changes and may be termed I_C. The sulfenamide stereogenic unit is referred to as a stereolabile chiral center in this situation, rather than a chiral axis, where the nitrogen is the center of chirality.

Nitrogen inversion can be slowed down by incorporation of the nitrogen atom in a small ring. Thus *N*-sulfenylaziridines undergo I_C stereomutation, and the sulfenamide functionality constitutes a chiral center. Numerous sulfenylaziridines have been prepared and studied, and their I_C barriers are listed in Table 14.

Ample evidence supports the assignment of I_C to the rate-determining step of the stereomutation. Applying first the steric criterion (Section III.C.4.b) we find that **63b**, with the bulky *t*-butyl substituent, has a 1 kcal mol^{-1} *lower* barrier than **63a** which is substituted by a methyl group[28]. This is consistent with steric destabilization of the pyramidal ground state for inversion by the bulky substituent, and not with the extra steric crowding associated with bulky substituents at the torsional transition state.

The absence of a polar substituent effect in series **48**[25, 27] is in sharp contrast with the usual trend found in acyclic sulfenamides, whereby the rate of stereomutation is strongly



(63) **(a)** R = CH_3
(b) R = *t*-Bu

TABLE 14. Nitrogen inversion (I_C) barriers in *N*-sulfenylaziridines[a]

Compound	T_c(°C)	Solvent	$\Delta G^{\neq}$ (kcal mol^{-1})	Reference
63a	−3	$CDCl_3$	13.4	28
63b	−25	$CDCl_3$	12.2	28
48a	−20	CH_2Cl_2	12.6	27
48b	−21	CH_2Cl_2	12.5	27
48c	−23	CH_2Cl_2	12.4	27
48d	−21	CH_2Cl_2	12.5	27
48e	−23.5	CH_2Cl_2	12.4	27
48f	−17	CH_2Cl_2	12.8	27
48g	−10	CH_2Cl_2	13.3	27
53a	−86	CH_2Cl_2 + $CHFCl_2$	9.2	27
53b	−61	CH_2Cl_2	10.4	27

[a] Data at 60 MHz.

affected by the nature of the substituent, with a negative Hammett reaction constant (cf. Section III.C.2.a). Thus the aromatic substituent effect also supports an I_C mechanism for aziridine stereomutation. Likewise, examination of the hyperconjugation effect in aziridines **53**[27], in comparison with acyclic sulfenamides **10**[62], reveals opposite trends: in **53** the powerful σ-acceptor trihalomethyl groups *lower* the barriers dramatically relative to the arenesulfenylaziridines (**48**), whereas in **10** the T_C barriers are *raised* relative to series **11**. These results are all consistent with an inversion mechanism in the aziridine series vs a torsion mechanism in acyclic sulfenamides.

The effect of hyperconjugation on aziridine barriers was also confirmed in a theoretical study[109].

Interestingly, some information on the torsional process is also gained from measurement of the I_C barriers. Since inversion is the rate-determining process in sulfenylaziridines, no direct structural effects on torsional barriers can be obtained. However, the I_C barrier sets an upper limit for the T_C process. And yet we find that the I_C barriers in Table 14 are consistently *lower* than T_C barriers in similarly substituted acyclic sulfenamides. For instance, the open chain sulfenamides **33a** and **33b** (Section III.C.3, Table 7), having two primary N-alkyl substituents which may be compared in steric bulk to the 2,2-dimethylaziridine, have substantially higher barriers (14.9 and 14.4 kcal mol^{-1}, respectively) than **53a** (9.2 kcal mol^{-1}). Thus we must conclude that also the inaccessible T_C barrier is lower than 9.2 kcal mol^{-1}, or generally that the aziridine moiety has a profound barrier-lowering effect on the torsional process.

The origin of this effect is the four-electron interaction at the torsional transition state. In acyclic sulfenamides the nitrogen lone pair is either a p or a hybrid orbital with substantial p character, which overlaps efficiently at the T_C transition state with the p lone pair on sulfur. In the aziridines, however, the nitrogen is more pyramidal than in acyclic compounds, and consequently the lone pair has more s character. As a result the overlap between the lone pairs on nitrogen and sulfur is less effective, resulting in greatly reduced four-electron repulsion and lower T_C barriers.

V. SULFENAMIDES AS ACHIRAL STEREOGENIC UNITS

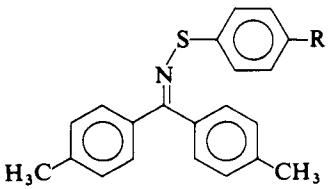
When interchange of stereotopic groups in a molecule causes interconversion of *E,Z* diastereomers, the molecule contains an achiral stereogenic unit. In the case of *N*-sulfenylimines **3**, the sulfenamide is part of the imine stereolabile achiral unit. These

compounds have been studied in some detail, and have served to elucidate the mechanism of stereomutation in imines in general. This section deals with stereomutation in the achiral sulfenylimine stereolabile unit.

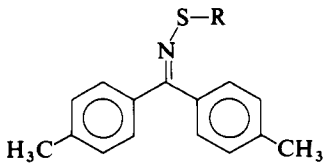
A. Barriers to Stereomutation in N-Sulfenylimines

The study of *E,Z* isomerism in imines using the methods of dynamic NMR spectroscopy has been very extensive[113]. Since the barrier in the *N*-sulfenylimines (iminosulfuranes) is the major topic of this section, we shall only briefly discuss barriers in other imines. We shall discuss the mechanism of the stereomutation (torsion–inversion ambiguity) since investigations of barriers in *N*-sulfenylimines have been important in resolving this question to the point that workers in the field now agree that imines (including sulfenylimines) undergo stereomutation by inversional mechanisms. The evidence on this point is discussed at the end of this section.

The earliest studies of stereomutation in *N*-sulfenylimines were by Hudson and coworkers[114–116] and by Davis and coworkers[117, 118] who reported initially on the arenesulfenyl derivatives **64** and **66**, respectively. Barriers for some representative compounds are given in Table 15. In their later studies, the range of compounds was considerably broadened by both groups. Hudson and coworkers examined an extensive series of compounds **64** and **65** with various alkyl and aryl substituents attached to the sulfenyl sulfur. They found that there was only a slight increase in the barrier when the *para* substituent in **64** was made electronegative; all of the barriers studied ($R = OCH_3$, CH_3, H, Cl, NO_2) fell within a fairly narrow range of 18.5–18.8 kcal mol^{-1}.



(64)



(65)

Davis and coworkers also measured barriers in the arenesulfenyl derivatives **64** ($R = H$, NO_2). The barriers in the iminosulfuranes were compared with those in the related sulfinamides and sulfonamides and the corresponding selenium analogues. They noted a number of trends in the barriers. The barriers in the selenium compounds were significantly higher than those in their sulfur analogues. This trend is similar to that which had been noted for the dependence of nitrogen inversion barriers in aziridines with the electronegativity of the atom attached to nitrogen[119]. However, the barriers in the sulfur series show a decrease in the order $S < SO < SO_2$, which indicates that the barrier is lowered as the electron-withdrawing ability of the ligand is increased. This trend was not explained in terms of a ligand electronegativity effect, since the trend is in the opposite direction from the postulated for ligand electronegativity effects on inversion barriers. It might seem to indicate a conjugation effect, and indeed the replacement of a *para* hydrogen by a *para* nitro group in both the sulfinamide and sulfonamide series did result in a lowering of the barrier by about 1 kcal mol^{-1}.

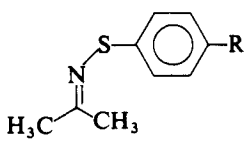
In the sulfenamide series, on the other hand, there was no significant difference in barriers between the compounds **64a** and **64b** bearing benzenesulfenyl and 4-nitrobenzenesulfenyl groups at nitrogen. This insensitivity of barriers in *N*-arenesulfenyl-

TABLE 15. Barriers for stereomutation in sulfenylimines

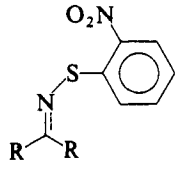
Compound	R	Solvent	T_c (°C)	$\Delta G^{\neq}$ (kcal mol^{-1})	Reference
64a	H	$CDCl_3$	62	18.2	118
		$CDCl_3$	72	18.6	116
64b	NO_2	$CDCl_3$	66	18.4	118
		$CDCl_3$	75	18.8	116
66a	H		104.5	20.3	117
66b	Cl		110	20.6	117
66c	NO_2		108	20.5	117
65a	CH_3	$CDCl_3$	69	18.5	116
65b	CCl_3	$CDCl_3$	−3	14.6	116
65c	$C(CH_3)_3$	$CDCl_3$	57.5	18.0	116
65d	$C(Ph)_3$	$CDCl_3$	33	16.3	116
67a	H	$CDCl_3$	1	13.6	116
67b	4-Tolyl	$CDCl_3$	62	18.2	116
67c	$PhCH_2$	$CDCl_3$	107	20.1	116
67d	CH_2Cl	$CDCl_3$	53	18.4	116
67e	CF_3	$CDCl_3$	32	14.7	116
68a	4-Tolyl	$CDCl_3$	72	18.6	116
68b	CF_3	$CDCl_3$	6	14.3	116

imines to the presence of electron-withdrawing substituents in the arene ring attached to sulfur is in accord with the work of Hudson and coworkers, discussed above, and was also noted by Meese and Walter[120]. Although there are differences in the barriers obtained by different groups, all are agreed that the effect of substituents R in **64** is very small. This trend (or rather lack of a significant trend) parallels that observed for barriers to nitrogen inversion in arenesulfenylaziridines, which are similarly insensitive to the presence of electron-withdrawing substituents in the aromatic ring[27].

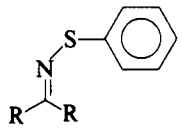
Although compounds **64** are insensitive to the electron-withdrawing ability of the group R, a fairly significant dependence is found in compounds **65** when the R group is changed from CH_3 to CCl_3. The presence of the more electronegative group results in a very significant drop in the barrier, from 18.5 to 14.8 kcal mol^{-1}. This cannot be due entirely (or even mainly) to steric effects, since the replacement of a methyl group at sulfur by *t*-butyl or even triphenylmethyl only lowers the barrier to 18.0 or 16.3 kcal mol^{-1}, respectively. The effect of substituents at the imino carbon in compounds **67** and **68** on the barrier is also observable. Of particular importance in the discussions of the mechanistic ambiguity is the observation of a significant lowering of the barrier when the groups at



(66)



(67)



(68)

imino carbon are strong σ withdrawing groups such as CF_3, **67e** and **68b**. One even notes an effect when CH_2Cl groups are present at the imino carbon, **67d**.

B. Mechanistic Ambiguity in Sulfenylimines

The torsion–inversion ambiguity in imines has been the subject of numerous studies and considerable discussion in the literature[121]. In the case of the imines the mechanistic ambiguity is of a different sort from that discussed above for the sulfenamides. Here we deal with an *achiral* configurational unit which gives rise to *E,Z* isomerism. However, we have here, too, the possibility for two sorts of stereochemical changes, inversion and torsion. Again inversion is recognized as a process in which the major structural change involves the change of a bond angle while torsion is characterized by a change in dihedral angle. These two processes can be abbreviated as I_A and T_A, in which the subscript refers to the achiral nature of the *E,Z* stereogenic unit. The relationship between these two elementary processes differs very greatly from the AND relationship between the I_C and T_C processes in the stereomutations of sulfenamides. In the case of the imines this relation between the two processes, torsion (T_A) and inversion (I_A), has been described as an OR relation since either of the two elementary processes, by itself, can effect the stereomutation (Scheme 5; for a discussion on the AND and OR mechanisms, see Section II.B.2). While evidence pertinent to the elucidation of the mechanism of stereomutation in imines has involved studies in many different systems, experiments carried out on sulfenylimines have made a useful contribution to elucidating the situation not only in the N-sulfenylimine system but for imines in general.

In the *N*-sulfenylimine system stereomutation at the C–N double bond can occur by either torsion about the C–N double bond OR by inversion at nitrogen (in-plane shift). The transition states for these two possibilities differ only in the CNS bond angle, which will have a value of 180° for inversion but will have a smaller value for a torsional transition state. If we had torsion about the S–N without any other deformation of bond angles, we would find a CNS bond angle close to 120°, appropriate for sp^2 hybridization. Of course, this would not be likely and some deformation would undoubtedly occur. Nevertheless, we suggest that if the bond angle were in the neighborhood of 180°, we should refer to the process as inversion, while if it is much smaller, in the neighborhood of 120°, we would speak of a torsional process. It has been pointed out that there is a continuum of possible transition states with intermediate values between these two extremes and that it is possible that in some compounds the transition state would be intermediate between these two extremes[29]. The question of whether the mechanism for stereomutation in imines should be described as a torsional or inversional mechanism has been studied using both molecular orbital calculations and experimental evaluation of barriers to stereomutation.

While there have been numerous papers which have advocated both mechanistic possibilities, most workers are now in agreement that most, if not all, imines undergo stereomutation by an I_A mechanism. The behavior of the *N*-sulfenylimines is in accord with this conclusion. The effects of substituents attached to the sulfenyl sulfur atom on the barrier to stereomutation have been used to support the inversion mechanism. Thus, as mentioned above, the presence of electronegative substituents in the aryl ring attached to sulfur in **64** or **66** has very little effect on the barrier, paralleling the behavior of the barriers to inversion in *N*-arenesulfenylaziridines. By contrast, the replacement of an alkyl or aryl group at sulfur by a trichloromethyl group results in a lowering of the barrier, which cannot be due to steric factors alone but must be due to the electron-withdrawing character of the haloalkyl group. This finding that σ (inductively) withdrawing groups attached to sulfur result in lowered barriers, while p withdrawing groups (e.g. 4-nitrophenyl) do not, parallels the findings for I_C nitrogen inversion in *N*-sulfenyl-

aziridines[27]. This similarity in substituent effects between aziridines, which are known to undergo stereomutation by nitrogen inversion, with substituent effects on stereomutation in imines, has been used to argue for an inversion mechanism for imines as well. The interpretation of the effect of σ withdrawing groups in the two systems is similar. One can postulate an overlap of the nitrogen lone pair with the σ^* orbital associated with the polarized S–CCl_3 bond. This interaction (negative hyperconjugation or n–σ^* conjugation) results in greater stabilization at the inversional transition state when the nitrogen lone pair is a pure p orbital than when it resides in a hybrid orbital as is characteristic of the ground state. On the other hand, the absence of an effect due to electronegative substituents in the S-aryl ring of **64** or **65** is consistent with the absence of a conjugative interaction between the nitrogen lone pair and the S-aryl ring. Although these similarities do argue for an inversion mechanism, it can also be argued that a rotation mechanism should also exhibit the n–σ^* hyperconjugation effect since the S–N bond will be very strongly polarized at the transition state with a positive imino carbon atom and a negative charge on nitrogen. It does seem, though, that if there were a large change in the charge on nitrogen on going from the ground state to the transition state, one would observe an effect for the substituents in the S-aryl ring of **64** and **65**.

The effect of the presence of haloalkyl groups in **67** and **68** represents even more convincing evidence in favor of the inversion mechanism. If the mechanism were a torsional one, with a positive charge on the imino carbon atom, one would expect much higher barriers for compounds **67e** and **68b**. However, instead of increased barriers these compounds exhibit significantly lowered barriers. This can be explained within the framework of an I_A barrier by postulating an (n–σ^*) hyperconjugation effect between the nitrogen lone pair and the σ^* orbital associated with the polarized C–CF_3 bond. This interaction results in significant stabilization only when the nitrogen lone pair has a large amount of p character, i.e. at the inversional transition state.

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER 3

Analytical aspects of sulfenic acids and their functional derivatives

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I. INTRODUCTION

A. Scope of the Chapter

The sulfenic acids and their functional derivatives constitute a rather small group of organic compounds; however, they are not devoid of scientific and technological significance. Consequently, it is surprising to find only very few publications in the literature dealing with actual analytical research on these organic compounds, and most reported analytical methods are buried in experimental sections dealing mainly with other research subjects.

The present chapter discusses identification and determination problems concerning the basic structure depicted in formula **1**, where the various X groups attached to the

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sulfur atom define the actual functional group. Keeping in mind the organization of the entire book, spectroscopic and spectrographic methods of analysis that endeavor to unveil structural features associated with formula **1** will not be included in this chapter, as they should be amply covered elsewhere. A brief description of the various classes of organic compounds involved is in place.

RSX R = alkyl, aryl (**1**)	Sulfenic acids (**1a**)	X = OH
	Sulfenyl halides (**1b**)	X = F, Cl, Br, I
	Sulfenamides (**1c**)	X = NR′R″; R′,R″ = alkyl, aryl
	Sulfenic esters (**1d**)	X = OR′; R′ = alkyl, aryl

Sulfenic acids (**1a**) have been reviewed[1]. Organic compounds containing this functional group have proved to be rather elusive, and only a few examples of this type of compound are known to be stable under ordinary laboratory conditions[1-4]. Establishment of internal hydrogen bonding seems to be a necessary but not a sufficient condition for the stability of these compounds[5], and therefore they all contain additional stabilizing functional groups in the R moiety of **1a**. Working under conditions of flash pyrolysis, it has been possible to capture the ephemeral simple sulfenic acids at low temperatures, determine some of their spectral properties and cause them to react with appropriate scavengers for further characterization[6-10]. The instability of sulfenic acids notwithstanding, they have been proposed as intermediate states of many reactions involving organosulfur compounds[1, 11, 12], including biochemical processes[13, 14].

Sulfenyl halides (**1b**) are readily prepared and have shown versatility in their application as reagents in the synthesis of many organic compounds which do not necessarily contain sulfur[12]; for example, compounds **4–6** have been proposed for the protection of the N-end in peptide synthesis, and compounds **3, 4** and **6** as dehydrating agents for allyl alcohol derivatives (see Table 1). Additional examples of derivatization of **1b** will be given in latter sections of this chapter.

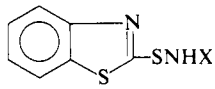
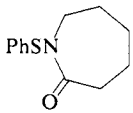
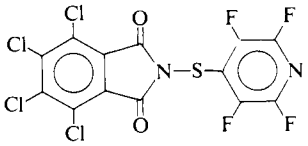
TABLE 1. Some commercially available sulfenyl halides for use as derivatizing reagents[a]

No.	Compound	CA registry	NMR[b]	FTIR[c]	CSD[d]	References
2	ClCOSCl	[2757-23-5]		1-139A	758B	18
3	CCl_3SCl[e]	[594-42-3]		160H[f]	892[g]	*h*
4	2-$O_2NC_6H_4SCl$	[7669-54-7]	1-1134A	1-1330A	2555B	22-24[h]
5	4-$O_2NC_6H_4SCl$	[937-32-6]			2555C	
6	2,4-$(O_2N)_2$-C_6H_3SCl	[528-76-7]	1-1174B	1-1370B	1431C	22, 25[h]
7	Ph_3CSCl	[24165-03-5]			3518B	23, 24, 26, 27
8	2-(PhN=N)-C_6H_4SBr	[2849-62-9]				28

[a] These compounds are very toxic and irritant and should be handled carefully.
[b] Volume-spectrum numbers in Reference 15 are indicated.
[c] Volume-spectrum numbers in Reference 16 are indicated.
[d] CSD = Chemical Safety Data. Entry number in Reference 17 is indicated.
[e] The sale of this reagent has been apparently discontinued by various suppliers of laboratory chemicals.
[f] Entry number in Reference 19.
[g] Entry number in Reference 20.
[h] Reagent listed in Reference 21.

Sulfenamides (**1c**) may be readily prepared from the corresponding sulfenyl halide, providing the R group, and an amine, providing the NR′R″ end. These compounds have generated interest in applied research, as some of them have proved to be excellent

TABLE 2. Some commercially available sulfenamides for use as derivatizing reagents[a]

No.	Compound	CA registry	CSD[b]	Reference
9	Ph_3CSNH_2	[38499-08-0]	3518A	26
10				
a	X = *t*-Bu	[95-31-8]		
b	X = *cyclo*-Hex	[95-33-0]		
11		[36452-23-0]		
12				

[a] These compounds are very toxic and irritant and should be handled carefully.
[b] CSD = Chemical Safety Data. Entry number in Reference 17 is indicated.

promoters of rubber vulcanization[29]. Some examples of commercially available sulfenamides are listed in Table 2.

Sulfenyl esters (**1d**) show much higher stability than the corresponding free acids. This may allow derivatization schemes that would be impossible to carry out with **1a**. Again, sulfenyl esters have been proposed as intermediate stages in organic reactions[12]. Table 3 shows some commercially available sulfenyl esters. Compound **14** is especially noteworthy, because it has been proposed as an effective dehydrating reagent for numerous organic processes.

TABLE 3. Some commercially available sulfenic esters for use as derivatizing reagents[a]

No	Compound	CA registry	CSD[b]	Reference
13	$2,4\text{-}(O_2N)_2\text{-}C_6H_3SOX$			
a	$X = CHMeCH_2C_6H_4Cl$			
b	X = CHMeCHMePh			
14	$Ph_2S[OC(CF_3)_2Ph]_2$	[32133-82-7]	2198B	30

[a] These compounds are very toxic and irritant and should be handled carefully.
[b] Chemical Safety Data. Entry number in Reference 17 is indicated.

B. Routine Analyses

Some general remarks about analytical methods are in place before finishing the present introduction. The modern research worker in universities and research institutes

usually has at his disposal a large battery of sophisticated analytical instruments and supporting equipment. This hardware empowers the research worker, at least potentially, to perform exquisite operations to unveil hidden details of molecular structure, evaluate precisely the properties of a compound, or follow changes taking place in dynamic systems, often at very high rates. All this potential, however, does not come without an expensive price, including working space, actual investment in equipment, running costs of operation and maintenance, and frequently also the fixed cost of dedicated highly trained personnel. Many results reported in the present chapter and elsewhere in the book could hardly have been attained without the help of such systems.

There are however situations where such a price becomes prohibitive, such as when frequently repeated analyses are required, as in some research programs, environmental control and chemical product quality control. It is the task of analytical research to find methods for specific analytical problems that can yield the answers at a reasonable price, lest the problem remains unanswered and possibly other tasks be affected. Perusal of a book on standards—say ASTM—will show a large proportion of analyses that may be reliably performed with simple laboratory equipment and instrumentation. Although simplicity in itself is not the objective to be pursued in analytical research, simple methods in routine situations are often rewardingly effective. The scarcity of analytical literature on the sulfenic functional group makes it difficult to determine such compounds in environmental and occupational protection routines, in industrial and laboratory applications, as they have been suspected of mutagenic action[31] and other untoward effects[17, 20]. It is for this reason that later in this chapter emphasis is placed on the necessity of developing effective derivatization schemes or reliable quantitative reactions that will allow one to determine the functional group or specific compounds by methods such as titration, chromatography, spectrophotometry or even colorimetry.

II. ANALYSIS OF SULFUR AND OTHER HETERO ATOMS

It is traditional in organic chemistry to report the elemental analysis of new compounds as compared with the values calculated for the expected molecular formula. Examination of formula **1** will show that sulfur is always present in the compounds that concern us, together with an additional hetero element, namely oxygen, nitrogen or a halogen, as the case may be. Many analytical problems, including routine analyses, may be solved by determining the main pair of hetero elements involved, or at least one of them. Furthermore, it is possible to distinguish compounds containing certain hetero atoms from others that do not contain them, by the use of specific response detectors in gas chromatography. This application may be useful not only for the simplification of complex chromatograms, but also for the direct determination of specific components of the sample mixture. Analytical methods for nitrogen and the halogens were reviewed elsewhere in *The Chemistry of Functional Groups* series[32, 33]. The direct determination of these elements and the application of specific response detectors for gas chromatography will be considered briefly in this section.

A. Automatic Elemental Analyzers

Today there exist in the market analytical instruments that perform elemental analyses in a few minutes, sometimes for two or three elements simultaneously. The ease and speed of such analyses enable the use of this method for routine quantitative analysis of specific compounds and materials, without requiring high-level training of the operators. Although the details of operation vary from model to model and between one manufacturer and another, all these instruments can be considered as modern versions of the classical Pregl determination of C and H by conversion to CO_2 and H_2O, Dumas'

method of N determination by conversion to N_2, the calorimetric bomb method for S determination by conversion to SO_2 and SO_3, and Schültze's method for O by conversion to CO, combined with the capabilities of electronic control, effective catalysts and instrumental measuring methods, such as infrared detectors and gas chromatographic analyzers.

The determination of nitrogen can be carried out alone or simultaneously with other elements. Thus N, CHN, CNS and recently also CHNS analyzers are available. Figure 1 shows the operation principle of a simultaneous CHN analyzer[34]: the sample in a tin container is dropped into the combustion tube (3), which is maintained at 950–1150 °C. An oxygen/helium mixture is passed through the tube in order to cause ignition of the sample, which is enhanced by the simultaneous combustion of the sample container, bringing the local temperature up to 1600–1800 °C. The flue is passed over cerium oxide and copper oxide in the combustion tube (2), over silver wool to remove some impurities, and finally over copper wire (4), which is maintained at about 550 °C, causing the reduction of the N oxides to N_2, and the removal of all the oxygen excess. The cooled combustion products are passed through a short silica gel column (5) to remove the water, and then through a longer silica gel column (6) to remove the carbon dioxide. The nitrogen remaining in the helium carrier gas is measured with a thermal conductivity detector TCD (7). The other two adsorbed compounds are successively removed from their columns by heating and measured afterwards with the same detector.

Part	Function	Packing
1	Sample feeder	
2	Combustion tube	CuO wire, Ag wool
3	Sample receiving tube	CeO_2
4	Reduction tube	Cu wire, $PbCrO_4$
5	H_2O adsorption	Silica gel
6	CO_2 adsorption	Silica gel
7	TCD	
8	Integrator	

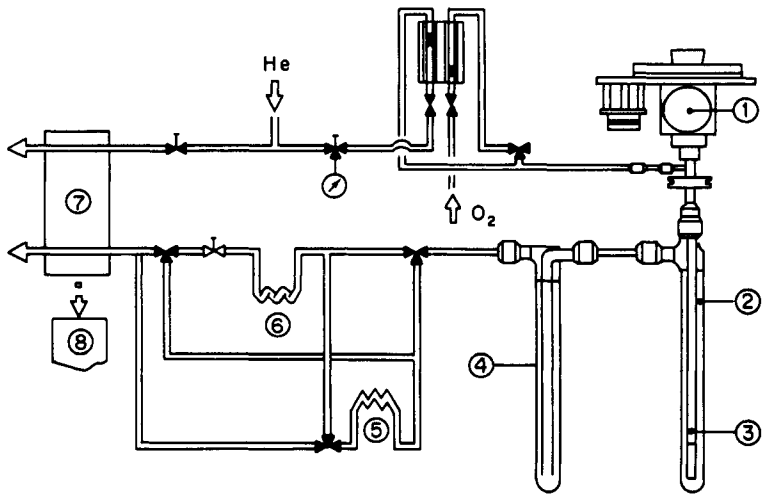


FIGURE 1. Schematic flow diagram of Heraeus' CHN–O–Rapid elemental analyzer fitted for CHN analysis. Diagram reproduced by permission of the manufacturer

The simultaneous CHNS analyzer[35], depicted schematically in Figure 2, operates in a similar way; however, in the present case also the total combustion of S to a mixture of SO_2 and SO_3, and the reduction of the latter to SO_2 must be assured, by passing over the appropriate catalysts and reagents. At the high local temperatures reached in the combustion section of both analyzers, it is certain that all the pertinent elements are gasified and further converted in the catalyst section. The most significant difference between both instruments resides in the analysis procedure of the reduced combustion products. In the example depicted in Figure 2 the product mixture is separated in a chromatographic column, from which N_2, CO_2, H_2O and SO_2 emerge in that order and are measured with a thermal conductivity detector (TCD).

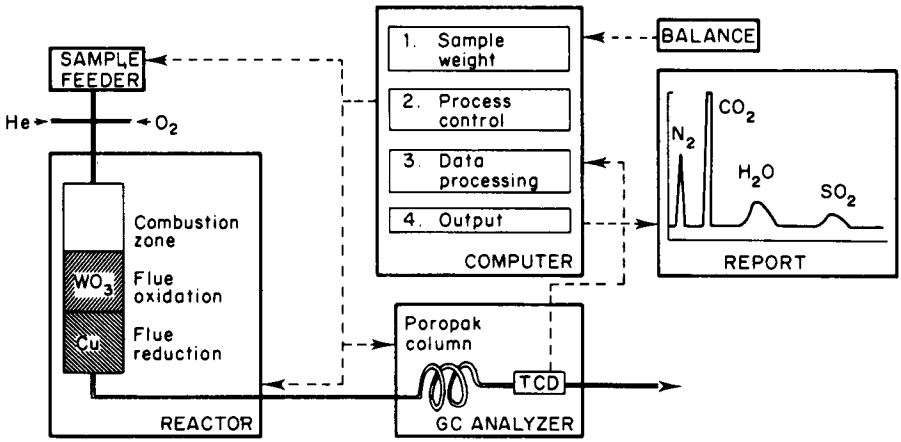


FIGURE 2. Schematic flow diagram of Carlo–Erba's CHNS–O 1108 elemental analyzer fitted for CHNS analysis, according to Reference 33

Oxygen elemental analyzers are usually sold as adaptation kits for the CHN analyzers. Thus, for example, Figure 3 illustrates the modifications made to the CHN apparatus shown in Figure 1, in order to enable the performance of the new task[34]: the sample is dropped into a tube (3) heated to about 1120 °C, through which a hydrogen/nitrogen mixture is passed. The hydropyrolysis products are passed through a carbon bed (2), in which all the oxygen is converted to CO. After removing possible impurities in a silver wool packing (2) and a soda lime bed (4), carbon monoxide is measured with a nondispersive infrared (ND-IR) photometer.

Sulfur elemental analyzers are available in three forms: as dedicated units[36], as modification kits for CHN analyzers[37], and as the simultaneous CHNS analyzer[35] which was mentioned above. Figure 4 shows the modified outlay which enables the instrument of Figure 1 to operate with the new task. Both the S-dedicated and the modified instruments operate essentially in a similar way: first, the sample is burned at high temperature in an oxygen-containing stream and, after contaminants such as soot and moisture have been removed, the sulfur dioxide produced is measured by means of a nondispersive infrared photometer.

Although the operation principles of these analytical instruments are straightforward and their actual performance is usually reliable, there are situations[38] where special

Part	Function	Packing
1	Sample feeder	
2	Sample receiving tube	
3	Cracking tube 1120 ± 20 °C	Carbon black, Ag wool
4	Purification tube	Soda lime
5	ND-IR photometer for CO	
6	Integrator	

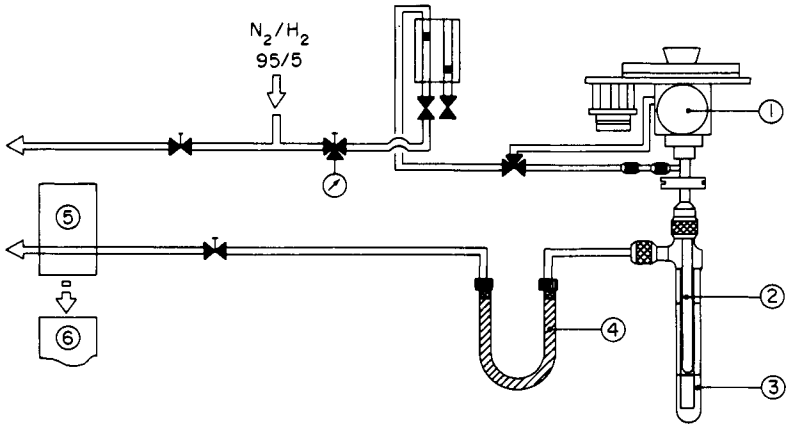


FIGURE 3. Schematic flow diagram of Heraeus' CHN–O–Rapid elemental analyzer fitted for O analysis. Diagram reproduced by permission of the manufacturer

Part	Function	Packing
1	Sample feeder	
2	Combustion tube 1150 °C	Quartz wool
3	Sample receiving tube	
4	Absorption / drying tube	Sicapent
5	ND-IR photometer for SO_2	
6	Integrator	
7	Porapak column	Porapak N

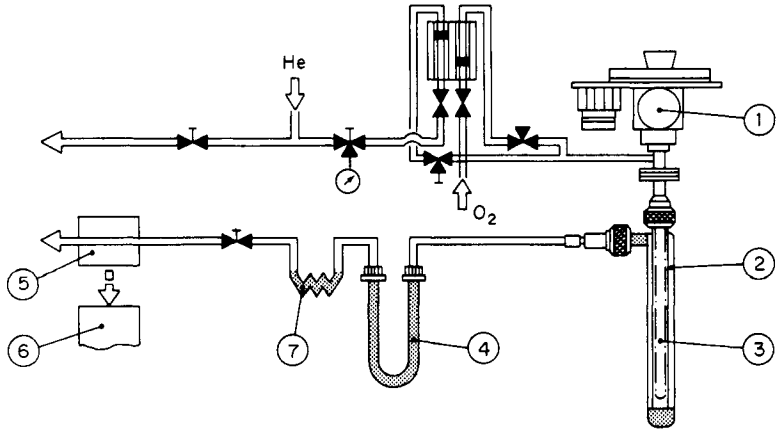


FIGURE 4. Schematic flow diagram of Heraeus' CHN–O–Rapid elemental analyzer fitted for S analysis. Diagram reproduced by permission of the manufacturer

consideration must be given to the nature of the analyzed material. Some of the problems that may arise are the following:

a. Liquid samples need to be introduced into the combustion chamber in special capsules, in order to assure quantitative results. This, however, may be insufficient for the more volatile liquids.

b. Samples containing alkaline earth elements, in a form that is prone to sulfate formation, may give erroneous sulfur results if the temperature in the combustion chamber is not sufficiently high in order to assure total sulfate decomposition within the relatively short combustion cycle. The usual remedies for this, such as treating the sample with phosphoric acid, may cause other analytical errors, e.g. by partial volatilization of the compounds of interest to us before they enter the combustion chamber.

c. It is dubious whether oxygen analyzers can give correct results in all cases, even when determining the content of 'truly organic' samples, such as organic phosphates, sulfates or siloxanes, unless appropriate modifications are introduced in the routine methods of operation.

d. Determination of samples with high halogen content may cause severe damage to some of the instruments described in the present section.

B. Specific Response Detectors for GC

Gas chromatography is ideally suited for identification and determination of individual compounds. Nevertheless, samples are frequently very complex, with overlapping and coincident peaks that may confuse the analysis. Although combinations such as GC-MS or GC-FTIR are now commonplace, these instruments are unwieldy for most routine analyses. In such cases element-specific detectors may be of help, as they greatly simplify complex chromatograms. This subject has been recently reviewed, including a critical appreciation of the performance of the various detector types with many elements and under varied operating conditions[39]. Because of the thoroughness of this review, only a few literature references are given in Table 4 for the various hetero elements associated with formula **1**. The detector based on microwave-induced plasma spectroscopy is included in Table 4 mainly owing to its potential capacity of yielding the elemental analysis of the compounds eluted in a GC run.

TABLE 4. Some literature sources on element-specific detectors[a]

Detector type	Sulfur Reference	Halogen Reference	Nitrogen Reference
Alkali flame ionization (AFID)	40–42	43–45	42,43,46
Flameless alkali sensitized (FASD)			47–51
Flame photometric (FPD)	52–56	57–59	
Chemiluminescence (CLD)		60,61	61–64
Fluorine induced luminescence	61,65		
Electrolytic conductivity (ELCD)	66–69	66–68	68,70
Coulometric (CD)	71–73	73,74	
Electron capture (ECD)	53,75–77	53,75–77	53,75–77
Microwave-induced plasma spectrometry	78–85	82–88	78,79,83

[a]For a comprehensive review see Reference 39.

III. QUANTITATIVE ANALYSIS OF SULFENIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES

A few direct determination methods have been proposed for sulfenic acids and their functional derivatives.

Unstable sulfenic acids (**1a**) show IR spectral evidence[9] at $-196\,^{\circ}C$ for a tautomeric behavior, as depicted in equation 1, and at about $-50\,^{\circ}C$ there is evidence for a dimeric association. Apparently there is no reported titration with a basic solution according to equation 2 for the few stable ones known[1-4].

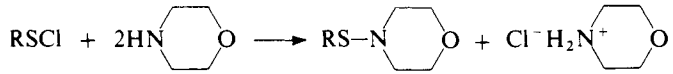
$$RSOH \rightleftharpoons RS(O)H \tag{1}$$

$$RSOH + OH^- \rightleftharpoons RSO^- + H_2O \tag{2}$$

The quantitative reduction of sulfenyl halides according to equation 3[89] seems to have general application. The liberated iodine may be subsequently titrated. The only interference with this reaction may stem from other oxidizing agents present in the solution.

$$2RSCl + 2KI \longrightarrow RSSR + 2KCl + I_2 \tag{3}$$

An alternative approach for the determination of sulfenyl halides is shown in equation 4, where the sample is treated with excess morpholine and the resulting sulfenamide is determined by GC[90]. Potassium phthalimide can also be used for determination of sulfenyl halides, by derivatizing according to equation 5, followed by GC[91].



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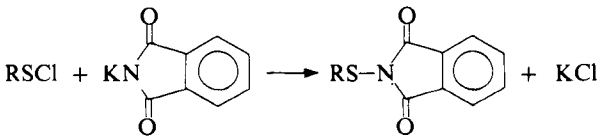
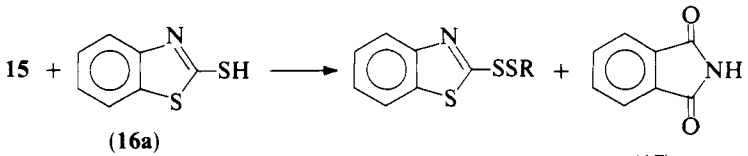


(5)

(**15**)

Sulfenyl halides, and especially the aliphatic ones, slowly decompose in solution[90]. Special attention should therefore be paid to the selection of solvent and column operational parameters before attempting chromatographic separation of these compounds.

Sulfenimides (**15**) can be treated with excess of 2-mercaptobenzothiazole (**16a**) as shown in equation 6, and the excess of this reagent titrated potentiometrically with a base[90]. A blank titration should be run in order to account for interfering acidic components of the sample.



(6)

(**16a**) (**17**)

Sulfenimides (**15**) may be reduced by iodide ions as shown in equation 7, in a process resembling equation 3, and the liberated iodine titrated[92]. An analogous process was carried out with sulfenamides derived from penicillin[93]. The acidity of the solution is important, since sulfenamides will probably lead to nonquantitative reactions in neutral solutions[94].

$$2\,\mathbf{15} + 2\,KI + 2H^+ \longrightarrow RSSR + 2\,K^+ + I_2 + 2\,\mathbf{17} \qquad (7)$$

Electrochemical methods can possibly be developed into quantitative determination methods. The polarography of sulfenamides and sulfenimides has been reported[95]. A cyclic voltametry study of trialkylsulfenamides showed a one-electron oxidation of the functional group, yielding relatively stable radical cations, where the S–N bond showed a π-bond overlap with three-electron occupancy[96].

IV. DERIVATIZING THE SULFENIC FUNCTION

A. General Considerations

The attributes of derivatizing reactions and of derivatives listed below should be considered when developing analytical methods. It is however frequently the case that not all of these ideal goals can be achieved, and a sensible compromise should be worked out, depending on the nature of the analytical problem in hand.

a. Selectivity. From the viewpoint of the present chapter, this means functional selectivity, namely, only the particular sulfenic function of interest (S–X in formula **1**) reacts, while all other functional groups remain untouched. This implies also a relatively high yield of the desired derivative type, as compared to the by-products. Compound selectivity is usually more difficult to attain. When selectivity for a particular compound is required, functional selectivity may be easily supplemented with the application of an appropriate analytical chromatographic technique.

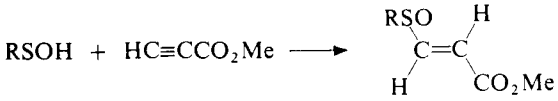
b. Stability. Derivatives should be stable under ordinary laboratory conditions and also under those involved in the analytical process, such as separation, concentration, dilution, sample preparation and the actual measurements.

c. Analytical compatibility. The derivatizing moieties should enhance the properties to be measured. When the measured properties belong to the original compound, the derivatizing agent should not obscure them.

d. *Ease of handling.* This is a very important practical consideration which depends on the nature of the analytical problem. The derivatizing process should be easy to perform with in a reasonable time. When derivatives need to be isolated, it is helpful that they be solid, crystallizable from some inert solvent, nonvolatile, nontoxic, etc. Unfortunately, the latter properties are frequently absent from the derivatizing agents themselves.

B. Some Derivatives

Unstable sulfenic acids (**1a**) undergo addition to carbon–carbon double and triple bonds and other unsaturated moieties. Addition to olefinic and acetylenic groups is regio- and stereospecific, yielding a sulfoxide. This property has been used to scavenge the unstable sulfenic acids produced by flash pyrolysis of sulfoxides. A typical unsaturated compound used as substrate for this addition reaction is methyl acetylenecarboxylate, shown in reaction 8[8]. The intermediate alkenesulfenic acids underwent the cyclization shown in reaction 9[6]. This addition reaction is in fact the reversal of the pyrolysis leading to sulfenic acid, and the sulfoxide moiety of the products possibly stems from the corresponding tautomer on the right-hand side of reaction 1.



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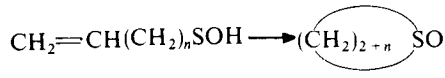
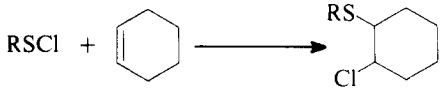


(9)

$n = 2, \ldots, 5$

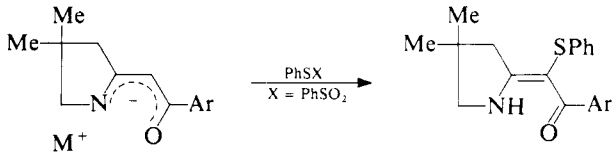
Sulfenyl halides (**1b**) also add to carbon–carbon unsaturations. For example, reaction 10 was used to determine the yield of sulfenyl halides in a synthesis starting from thiolacetates[97].



(10)

R = aryl, alkyl

Regiospecific addition reactions of sulfenyl halides to carbon–carbon double bonds may be designed in analogy to reaction 11[98, 99], by using adequate enaminone and organometallic base reagents to produce the analogue of intermediate **18**.



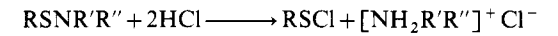
(11)

(**18**)

Probably the most convenient derivatizing reaction for sulfenyl halides is their conversion to sulfenamides. Reactions 4 and 5 afford good derivatizing schemes. Phthalimide (**17**) may be used in the presence of a mild base such as triethylamine, to attain similar results[25, 90, 100, 101]. *N*-Sulfenylsuccinimides and maleimides may also be prepared in the same manner[90, 101]. Other reactions of sulfenyl halides that may be developed into analytical tools may be conversion to disulfides by reaction with thiols[102,103]. A list of commercially available thiols, which may be used to prepare convenient disulfide derivatives, is shown in Table 5.

Sulfenamides (**1c**) react at both the nitrogen and sulfur sites to yield derivatives of potential analytical interest.

Various electrophilic reagents have been used for the attack at the N center. Hydrogen chloride in aprotic media may reverse the amidation process, as shown in equation 12[91]. When this reaction goes to completion, the sulfenyl chloride may be titrated iodometrically as was shown in reaction 3. Methyl iodide may also reverse the amidation process; however, in this case the sulfenyl iodide will disproportionate as shown in reaction 13 to yield iodine, which may be titrated[91].



(12)

TABLE 5. Some commercially available thiols for use as derivatizing reagents[a]

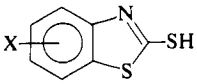
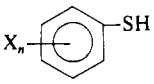
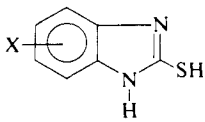
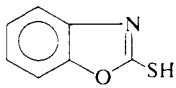
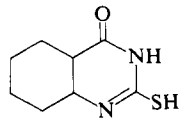
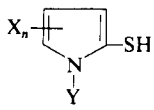
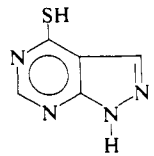
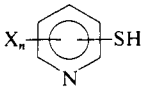
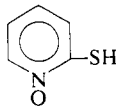
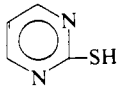
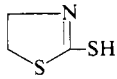
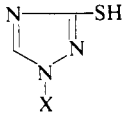
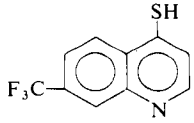
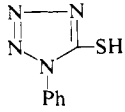
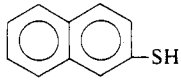
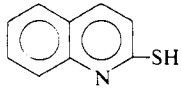
No.	Compound	CA registry	NMR[b]	FTIR[c]	CSD[d]
16					
a	X = H	[149-30-4]	2-575D	2-701D	2208A
b	X = 5-Cl	[5331-91-9]	2-576A	2-702A	
c	X = 6-EtO	[120-53-6]	2-576B	2-702B	1558A
d	X = 5-Me	[27231-36-3]			
19					
a	$X_n = 2,5\text{-}Cl_2$	[5858-18-4]	1-980C	1-1179D	1117B
b	$X_n = 2,6\text{-}Cl_2$	[24966-39-0]	1-979D	1-1186D	1117C
c	$X_n = 3,4\text{-}Cl_2$	[5858-17-3]	1-980B	1-1180A	1117D
d	$X_n = 4\text{-}NO_2$	[1849-36-1]	1-1143D	1-1341A	2606A
e	$X_n = 2,3,5,6\text{-}F_4$	[769-40-4]	1-982A	1-1181A	3268B
f	$X_n = 2,3,4,5,6\text{-}F_5$	[10351-06-1]			
20	$Ph_3C\text{-}SH$	[3695-77-0]	1-985C	1-1173D	
21					
a	X = H	[583-39-1]	2-562C	2-691B	2207C
b	X = 5-NO_2	[6325-91-3]			2211B
22		[2382-96-9]	2-571B	2-698C	2208B
23		[13906-09-7]	2-758C	2-882D	
24					
a	$X_n = Y = H$	[872-35-5]			2210B
b	$X_n = 4,5\text{-}Ph_2$, Y = H	[2349-58-8]	2-489A	2-617B	
c	X_n = H, Y = Me	[60-56-0]			
25		[5334-23-6]	2-587B		

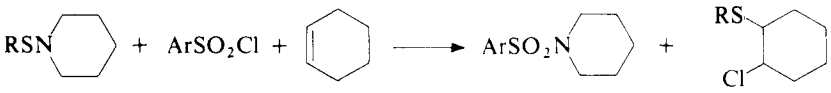
TABLE 5. (*continued*)

No.	Compound	CA registry	NMR[b]	FTIR[c]	CSD[d]
26					
a	2-SH, $X_n = H$	[2637-34-5]	2-640A	2-760A	2212D
b	4-SH, $X_n = H$	[4556-23-4]	2-640D	2-760D	2213A
c	4-SH, $X_n = 2,3,5,6\text{-}Cl_4$	[10351-06-1]			
27[e]		[1121-31-9]	2-776C	2-914C	2213B
28		[1450-85-7]	2-699A	2-819A	
29[e]		[96-53-7]	1-687C	1-830C	2214A
30					
a	X = H	[3179-31-5]	2-497A	2-626D	
b	X = Me	[24854-43-1]		2-628A	2452C
31		[64415-07-2]		2-863A	
32		[86-93-1]	2-500A	2-631D	
33		[91-60-1]			2491C
34		[2637-37-8]	2-739C	2-862C	3025D

[a] These compounds are very toxic and irritant and should be handled carefully.
[b] Volume-spectrum numbers in Reference 15 are indicated.
[c] Volume-spectrum numbers in Reference 16 are indicated.
[d] Chemical Safety Data. Entry number in Reference 17 is indicated.
[e] Reagent listed in Reference 21.

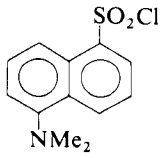
$$\begin{array}{l} RSNR'R'' + MeI \longrightarrow \{[RSNMeR'R'']^+ I^-\} \\ \qquad\qquad\qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\qquad\quad \{RSI\} + MeNR'R'' \\ \qquad\qquad\qquad\qquad\quad \downarrow\{RSI\} \qquad\quad \downarrow MeI \\ \qquad\qquad\qquad\qquad\quad RSSR + I_2 \quad [Me_2NR'R'']^+ I^- \end{array} \tag{13}$$

Reaction of a sulfenamide with tosyl chloride in the presence of cyclohexene is shown in equation 14[91]. Again, the electrophilic *p*-toluenesulfonyl group yields the sulfonamide and probably an intermediate sulfenyl chloride, which reacts with the olefinic double bond as in reaction 10.



(14)

A fluorescent dansyl derivative of the amido end[108, 109] could probably be obtained by using dansyl chloride (**35**) as the reagent in reaction 14. Acylations of the amido end of **1c**, on the other hand, were claimed to be 'unsure', as they lead to other derivatives, or gave poor yields[103]. Acetic, maleic and phthalic anhydrides, and acetyl and benzoyl chlorides were tested for this purpose. Other research workers, however, claimed good results in similar cases[104].



(**35**)

Useful derivatives of the sulfenic end of sulfenamides may be obtained by treatment with thiols. For example, the removal of the N-end protecting sulfenyl group in a peptide synthesis may be accomplished as shown in reaction 15, where *t*-BuSH, *i*-PrSH, PhSH and thioglycolic acid were used for this purpose[25]. The disulfides so obtained may be identified by their R_f values in TLC[105] or their retention times in HPLC. Table 5 presents some commercially available thiols that may provide useful chromophores in the R′ moiety, for spectrophotometric determination and fluorescence quenching or enhancement. The thiol selected for this derivatizing reaction may be one leading to solid dithio compounds, possessing the convenient characteristics mentioned in Section IV.A. For example, 2-mercaptobenzothiazole (**16a**), as shown in equation 6[100, 101].

$$RSNHR + HSR' \longrightarrow RSSR' + NH_2R \tag{15}$$

The acid-catalyzed hydrolysis of alkyl arenesulfenates proceeds with different stoichiometries, depending on the water concentration, as shown in reactions 16 and 17[106].

$$3\,ArSOMe + H_2O \xrightarrow{H^+} ArSSAr + ArS(O)OMe + 2\,MeOH \tag{16}$$

$$4\,ArSOMe + 2\,H_2O \xrightarrow{H^+} ArSSAr + ArS(O)OMe + 4\,MeOH \quad (17)$$

A complex mechanism has been proposed for these processes, as follows:

$$ArSOMe + H_2O \xrightarrow[slow]{H^+} ArSOH + MeOH \quad (18)$$

$$2ArSOH \longrightarrow ArSS(O)Ar + H_2O \quad (19)$$

$$ArSS(O)Ar + ArSOMe + H^+ \longrightarrow \underset{\textbf{(36)}}{ArS\overset{Ar}{\overset{|}{S}}{}^+S(O)Ar} + MeOH \quad (20)$$

$$\textbf{36} + MeOH \longrightarrow ArSSAr + ArSO_2Me + H^+ \quad (21)$$

Reactions 18 through 21 are summarized in reaction 16, for the process at low water concentrations (lower than 1%). In the presence of higher water concentrations, the sequel of reactions 22 and 23 takes place instead of reaction 21, and the overall process then becomes summarized by reaction 17.

$$\textbf{36} + H_2O \longrightarrow ArSSAr + ArSO_2H + H^+ \quad (22)$$

$$ArSO_2H + ArSOMe \longrightarrow ArSSO_2Ar + MeOH \quad (23)$$

Asymmetric disulfides were obtained in various yields by heating sulfenic esters with thioboranes, according to reaction 24[107].

$$3\,PhSOMe + B(SR)_3 \longrightarrow 3\,PhSSR + B(OMe)_3 \quad (24)$$

V. ACKNOWLEDGMENTS

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The Chemistry of Sulphenic Acids and their Derivatives
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CHAPTER **4**

NMR and ESR of sulphenic acids and their derivatives

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The Chemistry of Sulphenic Acids and their Derivatives
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I. INTRODUCTION

A problem with the discussion of sulphenic acids and their derivatives is to decide what constitutes a derivative of the acid RSOH. Ester, $RSOR^1$; amides, $RSNR^1_2$; and chlorides, RSCl clearly fall within the acid family. We have taken the view that disulphides are within the scope of this review, but have limited the discussion to what seemed interesting, and where the ESR or NMR phenomena under discussion derive directly from the presence of sulphenyl-like sulphur. The conformations of peptides and proteins containing disulphide bridges have been much studied by NMR spectroscopy, but we have not reported these in any detail. However, much ESR spectroscopy has been reported for small peptides with S–S bridges, and in those cases where the electron is located on sulphur the radical species follow similar trends to the related non-biological molecules. Such studies are included in this chapter.

The ESR data on sulphenic acids are extensive and important. We have started this chapter with the ESR review in recognition that it is an area of more general interest than the rather limited non-biological NMR studies on sulphenic acids and their derivatives.

The system used for labelling carbon atoms and protons in sulphenic acids and related compounds is

$$\overset{\delta}{C}H-\overset{\gamma}{C}H-\overset{\beta}{C}H-\overset{\alpha}{C}H-S-X-\overset{\alpha'}{C}H-\overset{\beta'}{C}H$$

where X = NR, O, S. Where ambiguities may occur, as in unsymmetrical disulphides, other unambiguous labels are used.

II. ELECTRON SPIN RESONANCE STUDIES

A. Introduction

Of all the various acids and acid derivatives of sulphur, those of sulphur in a formal oxidation state +2, the sulphenic acids, are the most extensively studied and fruitful as far as ESR investigation is concerned. The reasons for this are not hard to find. The neutral radicals of structure **1** (X = O, NR) are known and have their counterparts in the sulphinic acid series, but for sulphenic acid derivatives the radical **1** (X = S) has also been observed. Moreover, the accessibility of the HOMO and LUMO of sulphenic acid derivatives enables the ready formation of both the radical cations **2** (X = NR, S) and radical anions **3**

(X=S) from oxidative and reductive processes, respectively. Because of their biological importance, disulphides, which can be thought of as thioesters of sulphenic acids, have been studied in most detail in this context.

$$[R\text{–}S\text{–}X]^{\bullet} \quad [R\text{–}S\text{–}XR]^{+\bullet} \quad [R\text{–}S\text{–}XR]^{-\bullet}$$

(1) **(2)** **(3)**

Radicals of structure **1** may be described by the resonance structures **1a** and **1b**, and the corresponding radical cations **2** by structures **2a**, **2b** and **2c**. ESR studies are particularly helpful in attempting to assign the correct structure to the radical, and solid state experiments have enabled the spin density at sulphur to be calculated in many cases.

$$R\text{–}S\text{–}X^{\bullet} \qquad R\text{–}\dot{S}{=}X$$

(1a) **(1b)**

$$R\text{–}\overset{+\bullet}{S}\text{–}XR \qquad R\text{–}S\text{–}\overset{+\bullet}{X}R' \qquad R\text{–}\dot{S}{=}\overset{+}{X}R$$

(2a) **(2b)** **(2c)**

We shall describe each type of sulphenic acid derivative in turn, dealing first with the methods used to generate the various types of radical, followed by a discussion of the ESR studies that have been undertaken.

B. The Sulphinyl Radical, RSO•†

1. Formation of RSO•

Freeman and Keindl[1] have extensively reviewed the many methods of generating sulphinyl radicals. Therefore, we shall only report here those that have been used for ESR studies.

The most obvious method of forming the RSO• radical is hydrogen atom abstraction from the parent sulphenic acid (equation 1). Unfortunately, this method is only applicable to stable sulphenic acids, but has been used successfully for the *tert*-butylsulphinyl radical, Bu^{t}SO•[2]. A more general, though less direct, method involving the intermediacy of the sulphenic acid is the oxidation of alkane and arene thiols using either a Ti(III)/H_2O_2 couple (equation 2)[3,4] or Ce(IV)[5,6]. The related oxidation of disulphides using Ti(III)/H_2O_2 (equation 3) has also proved successful for generating arenesulphinyl radicals[4].

$$RSOH + Bu^tO^{\bullet} \longrightarrow Bu^tOH + RSO^{\bullet} \qquad (1)$$

$$RSH \xrightarrow{OH^{\bullet}} RS^{\bullet} \xrightarrow{H_2O_2} RSOH \xrightarrow{HO^{\bullet}} RSO^{\bullet} \qquad (2)$$

$$ArSSAr \xrightarrow{{}^{\bullet}OH} Ar\dot{S}(OH)SAr \longrightarrow ArSO^{\bullet} + ArSH \qquad (3)$$

†Though the RSO• radical is formally related to sulphenic acids, it is widely referred to as a sulphinyl radical.

A general and useful method of generating both alkane and arenesulphinyl radicals is the photolysis of the corresponding sulphinyl chlorides in an organic solvent (equation 4)[4]. ESR spectra generated by this method are reported to be much better resolved than those generated by $Ti(III)/H_2O_2$. Photolysis of the analogous sulphoxides is less applicable, though the method has been used for the formation of an arenesulphinyl radical (equation 5)[7].

$$RSOCl \xrightarrow{h\nu} RSO^{\bullet} + Cl^{\bullet} \quad (4)$$

$$ArS(=O)CHPh_2 \xrightarrow{h\nu} ArSO^{\bullet} + {}^{\bullet}CHPh_2 \quad (5)$$

Photolysis of alkyl alkanesulphenates has been claimed to generate, via a cascade of reactions, alkanesulphinyl radicals (equations 6–8)[8]. However, it now appears that these radicals were incorrectly assigned (see later)[4].

$$RSOCMe_3 \xrightarrow{h\nu} RS^{\bullet} + Me_3CO^{\bullet} \quad (6)$$

$$Me_3CO^{\bullet} + RSOCMe_3 \longrightarrow Me_3COH + RSOCMe_2CH_2^{\bullet} \quad (7)$$

$$RSOCMe_2{}^{\bullet}CH_2 \longrightarrow Me_2C{=}CH_2 + RSO^{\bullet} \quad (8)$$

γ-Irradiation of cysteine yields a thiyl radical, $RS^{\bullet}$, that is efficiently trapped by dioxygen to form the corresponding sulphinyl radical, presumably by way of the thio peroxy radical, $RSOO^{\bullet}$[9]. γ-Irradiation of dimethyl sulphoxide produces the methanesulphinyl radical directly[10].

2. g-Values and hyperfine coupling constants

Sulphinyl radicals are characterized by relatively large linewidths, generally in the range 1.0–3.5 G[4]. For arylsulphinyl radicals generated by photolytic methods, linewidths are reduced to *ca* 0.5 G[4]. However, $MeSO^{\bullet}$ has a linewidth of 11 G at 160 K. Linewidths increase both as the temperature is raised or lowered, the latter due to an increase in solvent viscosity[4]. Because of these linewidth effects the $MeSO^{\bullet}$ radical is unlikely to be observable at room temperature[4].

Despite broad linewidths, ESR spectra have been recorded for a variety of $RSO^{\bullet}$ radicals, including R = alkyl, aryl and alkoxy. *g*-Values and hyperfine coupling data obtained from these spectra are contained in Table 1. Some representative spectra of alkyl and aryl sulphinyl radicals are shown in Figure 1, and these clearly identify coupling between the unpaired electron with the α-CH protons of the alkyl group and with the ring protons of the aryl group.

Inspection of Table 1 allows some general conclusions to be drawn about *g*-values and hyperfine coupling constants *a*(H) and these are listed below. No attempt is made at this point to draw any conclusions from these observations, and we shall leave such discussions to Section II.B.4 where the structure of $RSO^{\bullet}$ radicals is discussed.

TABLE 1. g-Values and hyperfine coupling constants of sulphinyl radicals, RSO•

RSO•	Solvent	Temp. (K)	g-Value	Hyperfine coupling (G) a(H) (G)	Ref.
MeSO•	Et_2O	160	2.0100	11.5 (3H)	4
	Me_2SO crystal	173	2.0123[a]	11.6 (3H)	10
	Cyclopropane	178	2.0097[b]	6.57 (3H)[b]	8
EtSO•	Et_2O	157	2.0110	9.1 (2H)	4
	Cyclopropane	171		3.25 (2H)[b]	8
PrSO•	Et_2O	168	2.0111	8.9 (2H)	4
	Cyclopropane	177		3.51 (2H)[b]	8
Pr^{i}SO•	Et_2O	163	2.0110	10.0 (1H)	4
	Cyclopropane	168		0.86 (1H)[b]	8
BuSO•	Et_2O	181	2.0111	9.1 (2H)	4
Pr^{i}CH$_2$SO•	Et_2O	175	2.0105	7.9 (2H)	4
	Cyclopropane	183		4.24 (2H)[b]	8
EtMeCHSO•	Et_2O	212	2.0110	8.6 (1H)	4
	Cyclopropane	163		*ca* 0.9 (1H)[b]	8
Bu^{t}SO•	Toluene or isopentane		2.0106		2
HOCH$_2$CH$_2$SO•	Et_2O	208	2.0110	8.6 (2H)	4
	H_2O, pH 1.5		2.0109	9.5 (2H)	3
	EtOH/H_2O, pH 1–2	263	2.106	10.5 (2H)	6
EtOCH$_2$CH$_2$SO•	H_2O, pH 1–2		2.0109	9.1 (2H)	3
MeCOOCH$_2$CH$_2$SO•	EtOH/H_2O, pH 1–2	263	2.0106	9.5 (2H)	6
HOCH$_2$CHOHCH$_2$SO•	EtOH/H_2O, pH 1–2	263	2.0113	11.0 (1H), 7.0 (1H)	6
HSCH$_2$CHOHCHOHCH$_2$SO•	EtOH/H_2O, pH 1–2	263	2.0106	11.9 (1H), 6.6 (1H)	6
HS(CH$_2$)$_4$SO•	EtOH/H_2O, pH 1–2	263	2.0106		6

(*continued*)

TABLE 1. (*continued*)

RSO•	Solvent	Temp. (K)	*g*-Value	Hyperfine coupling (G) *a*(H) (G)	Ref.
$HO_2CCH_2SO^•$	H_2O, pH 1.5		2.0108	10.7 (2H)	3
	pH 7		2.0110	9.5 (2H)	3
$MeO_2CCH_2SO^•$	H_2O, pH 1–2		2.0099		3
$H_3\overset{+}{N}CH_2CH_2SO^•$	H_2O, pH 1–2		2.0106	9.6 (2H)	3
$H_3\overset{+}{N}(HO_2C)CHCH_2SO^•$	H_2O, pH 1–2		2.0103	9.3 (2H)	3
	H_2O	110	2.0103	14	9
		298	2.0106	9.5 (2H)	5
$HO_2CCH_2CH_2SO^•$	H_2O, pH 1–2		2.0107	10.7 (2H)	3
$HO_2SCH_2CH_2SO^•$	H_2O, pH 1–2		2.0105	9.5 (1H)	3
$MeCH(CO_2H)SO^•$	H_2O, pH 1–2		2.0103	7.8 (1H)	3
$HO_2CCH_2CH(CO_2H)SO^•$	H_2O, pH 1–2		2.0100	8.6 (1H)	3
HO_2CCH_2NHCO $\diagdown$ $CHCH_2SO^•$ $\diagup$ $HO_2C(NH_3^+)CHCH_2CONH$		298	2.0110	10.72 (1H, 7.23 (1H)	5
$C_6H_5SO^•$	Et_2O	198	2.0090	2.40 (3H, *ortho*- and *para*-H) 0.70 (2H, *meta*-H)	4
	H_2O	298	2.0084	2.60 (3H, *ortho*- and *para*-H)	4
$4\text{-}MeC_6H_4SO^•$	Et_2O	193	2.0089	2.30 (2H, *ortho*-H), 0.75 (2H, *meta*-H) 2.85 (CH_3)	4
	Mesitylene	353	2.0090		7
$3\text{-}MeC_6H_4SO^•$	Et_2O	183	2.0090	2.40 (3H, *ortho*- and *para*-H) 0.75 (*meta*-H and CH_3)	4
$2\text{-}MeC_6H_4SO^•$	Et_2O	176	2.0092	2.50 (2H, *ortho*- and *para*-H)[c] 0.75 (2H, *meta*-3 and 5-H)[c] 1.25 (CH_3)[c]	4

$4\text{-}ClC_6H_4SO^{\bullet}$	Et_2O	204	2.0092	2.50 (2H, *ortho*-H), 0.45 (4-Cl)	4
$4\text{-}H_3\overset{+}{N}C_6H_4SO^{\bullet}$	H_2O	298	2.0085	3.25 (2H, *ortho*-H)	4
$2\text{-}HO_2CC_6H_4SO^{\bullet}$	H_2O	298	2.0088	2.6 (2H, *ortho*- and *para*-H) 0.70 (2H, *meta*-H)	4
$SO_2^{\bar{}}$	H_2O	298	2.0055	14.67 ($a(^{33}S)$)	11
	$K_2S_2O_5$ crystal	298	2.0065	16.7 ($a(^{33}S)$)	11
$HOSO^{\bullet}$	Et_2O Cyclopropane		2.0053	7.6–9.5 (1H)	12, 13
$DOSO^{\bullet}$	Cyclopropane	150	2.0053	7.8 (1D, *t*)	13
$MeOSO^{\bullet}$	Cyclopropane	160	2.0047	0.80 (3H)	13
$EtOSO^{\bullet}$	Cyclopropane	160	2.0049	0.40 (2H)	13
$PrOSO^{\bullet}$	Cyclopropane	160	2.0049	0.50 (2H)	13
$Pr^iOSO^{\bullet}$	Cyclopropane	160	2.0051		13
$BuOSO^{\bullet}$	Cyclopropane	160	2.0049	0.55 (2H)	13
$PhCH_2OSO^{\bullet}$	Cyclopropane	160	2.0049		13
$Bu^tCH_2OSO^{\bullet}$	Cyclopropane	160	2.0047	0.80 (2H)	13
$CH_2{=}CHCH_2OSO^{\bullet}$	Cyclopropane	160	2.0049		13
$ClSO^{\bullet}$	solid	77	2.008	0.9 (^{35}Cl)	14
$BrSO^{\bullet}$	solid	77	2.020	7 (^{81}Br)	14

[a] Calculated as the average of the anisotropic *g*-values.
[b] These values have been reassigned to a radical of different structure; see text.
[c] Assignments are tentative.

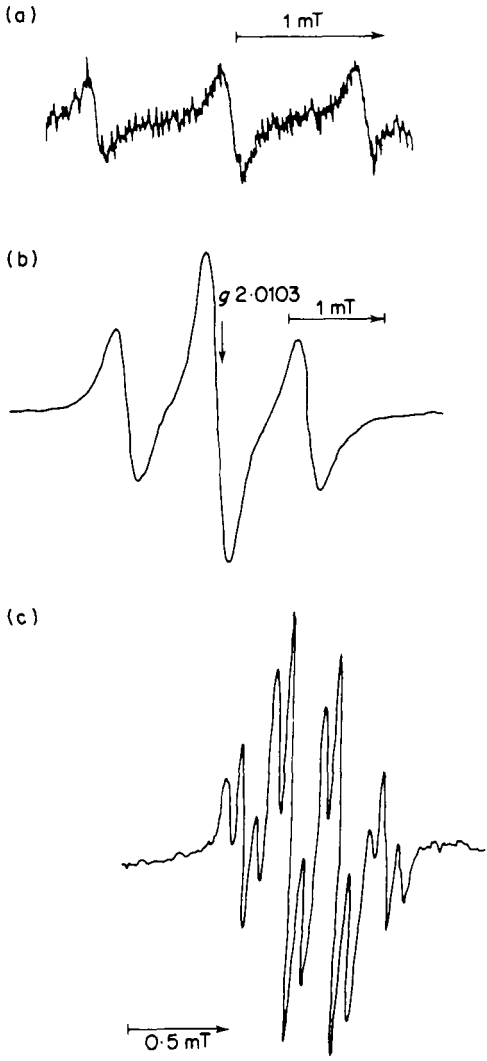


FIGURE 1. ESR spectra of some sulphinyl radicals: (a) PrSO• at 194 K, (b) $H_3\overset{+}{N}CH(CO_2H)CH_2SO^{\bullet}$ at 298 K, (c) PhSO• at 198 K. Reproduced by permission of The Royal Society of Chemistry from References 3 and 4

(i) g-Values describe in the order R = alkyl > aryl > alkoxy, which presumably reflects the ability of these groups to remove electron density and therefore spin density from the sulphur atom (Section II.B.3)

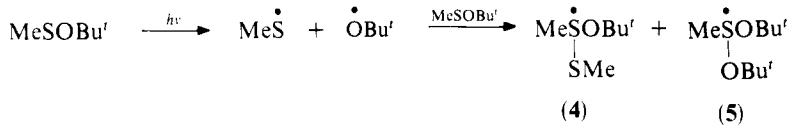
(ii) For the same type of R group (R = alkyl, aryl, alkoxy), g (RSO•) > $g(RSO_2^{\bullet})$[15].

(iii) The value of a(H) for the α-CH protons is somewhat larger for RSO• radicals as compared with the corresponding $RSO_2^{\bullet}$[15].

(iv) For arylsulphinyl radicals coupling is observed with the ring protons, and the magnitude of such coupling is *ortho*-H ≈ *para*-H > *meta*-H. Again, this is the reverse of that found for $ArSO_2^{\bullet}$[15].

Not evident from Table 1 is the temperature dependence of a(H) for the α-CH protons of alkylsulphinyl radicals. This will be discussed further in Section II.B.4.

Before concluding this section, comment must be made on the conflicting values of a(H) reported for several RSO• in Table 1. These appear to stem from the incorrect assignment of the radicals observed in the study of Kawamura, Krusic and Kochi[8]. Gilbert and colleagues have tentatively reassigned these radicals either structure **4** or **5**[4].



(4) (5)

3. *RSO• radicals in solid matrices*

Compared with the number of studies of RSO• radicals in solution, studies involving RSO• in solid matrices are few. Indeed only MeSO• and $SO_2^{\bullet}$ appear to have been studied in any depth[10, 11]. However, these solid state observations are crucial to our understanding of the structure of the RSO• radical species because, uniquely, they allow the spin density within the sulphinyl system to be defined.

The spectrum of MeSO• trapped in a single crystal of dimethylsulphoxide is shown in Figure 2[10]. The central part of the spectrum consists of two overlapping quartets from magnetically different sites, for which the proton hyperfine coupling, a(H), is 11.6 G (Table 1). The signals are accompanied by two further quarters some 500 times less intense. These

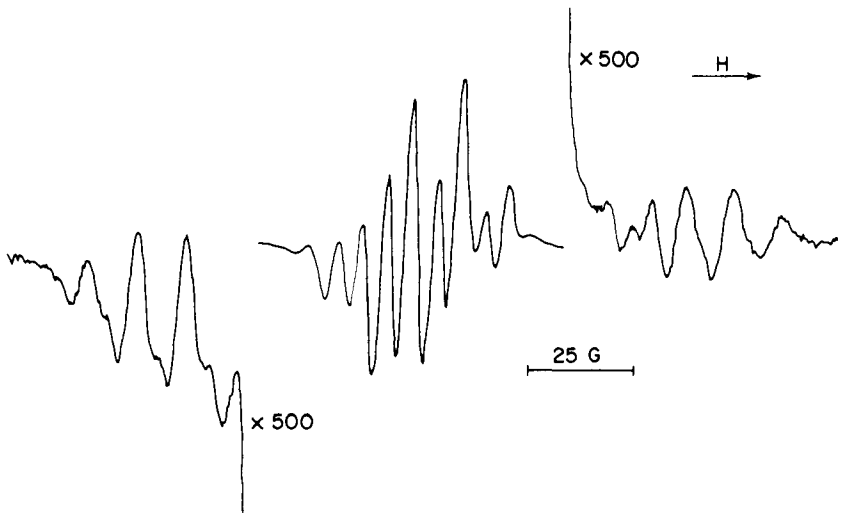


FIGURE 2. The ESR spectrum of MeSO• in a single crystal of DMSO recorded at 183 K. Reprinted with permission from K. Nishikida and F. Williams, *J. Am. Chem. Soc.*, **96**, 4781 (1974), Copyright (1974) American Chemical Society

correspond to the $m_I = \pm 3/2$ components of the ^{33}S spectrum present in natural abundance (natural abundance of ^{33}S is 0.74%). The $m_I \pm 1/2$ lines are hidden in the central spectrum. Both the g-values and the $a(^{33}S)$ hyperfine coupling constants are anisotropic (Table 2), with the direction corresponding to the smallest g-value almost coinciding with that of the largest hyperfine splitting. This direction is presumably that of a sulphur 3p orbital containing the unpaired electron (see below). A similar situation pertains for $SO_2^{\bullet-}$ (Table 2)[11], though this radical exhibits cylindrical symmetry. For $SO_2^{\bullet-}$, ^{17}O hyperfine coupling data are also available. These, too, are anisotropic (Table 2).

TABLE 2. Principal values of the g-tensors and $a(^{33}S)$ and $a(^{17}O)$ hyperfine splitting tensors of sulphinyl radicals

Radical	Principal values of g	Principal values in gauss of $a(^{33}S)$	$a(^{17}O)$	Ref.
MeSO$^{\bullet}$	2.023	−14		10
	2.011	−21		
	2.003	59		
$SO_2^{\bullet-}$	2.0057	−4	−3	11
	2.012	−4	−3	
	2.0019	58	30	

The data in Table 2 enable the isotropic and anisotropic components of the $a(^{33}S)$ and $a(^{17}O)$ hyperfine coupling to be determined (Table 3). The isotropic component is a result of the unpaired spin density in the appropriate s orbital, the anisotropic component from the unpaired spin density in the corresponding p orbital. The isotropic value for the $a(^{33}S)$ hyperfine coupling for MeSO$^{\bullet}$ of 8 G (Table 3) is remarkably similar to the calculated value, 6.9 G, for HSO$^{\bullet}$ using a UHF s,p,d basis set[16]. Comparison of a_{iso} and a_{aniso} with the theoretical values for sulphur of 970 G and 28 G[17], respectively, results for MeSO$^{\bullet}$ in a spin density of 91% in the sulphur 3p orbital and only 0.8% in the 3s orbital. Thus, the unpaired electron resides in essentially a p orbital on sulphur, with only some 8% on the oxygen atom. Similar comparison for $SO_2^{\bullet-}$ indicates that 75% of spin density resides in a sulphur 3p orbital, with 43% in the 2p orbitals of the two equivalent oxygen atoms. Thus, sulphinyl radicals are clearly π-radicals. The lower spin density at sulphur in $SO_2^{\bullet-}$ as compared with MeSO$^{\bullet}$ is probably a result of the higher electronegativity of oxygen than of carbon. This observation quantitatively corroborates the qualitative observation made earlier for solution studies (Section II.B.2) that g-values decrease as the group attached to the sulphur atom is more able to withdraw electron density. Thus, the data point to **1b** (X = O) as the major contributor to the overall structure of sulphinyl radicals. Indeed, for MeSO$^{\bullet}$ it may be considered as the only contributor.

TABLE 3. Isotropic and anisotropic components of the $a(^{33}S)$ and $a(^{17}O)$ hyperfine couplings and orbital spin densities in sulphinyl radicals

Radical	a_{iso} (G)		a_{aniso} (G)		%s		%p		%(s+p)		p/(s+p)	
	^{33}S	^{17}O	^{33}S	O^{17}	S	O	S	O	S	O	S	O
MeSO$^{\bullet}$	8.		25.5		0.8		91.1		91.9		0.99	
$SO_2^{\bullet-}$	16.7	8.0	20.7	11.0	1.7	0.41	73.9	21.2	75.6	43.2	0.98	0.98

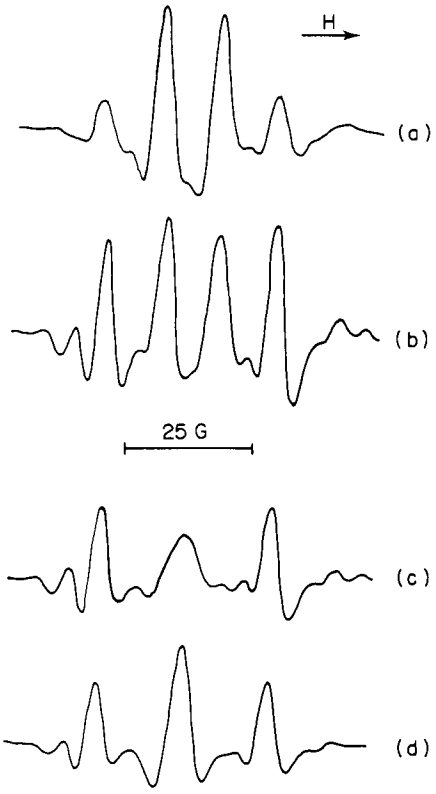
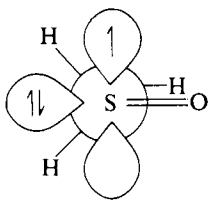
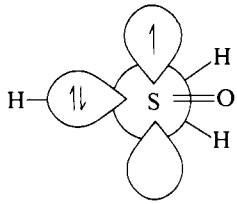


FIGURE 3. Temperature dependence of the solid state spectrum of MeSO•: (a) 215 K, (b) 134 K, (c) 115 K, (d) 88 K. Reprinted with permission from K. Nishikida and F. Williams, *J. Am. Chem. Soc.*, **96**, 4781 (1974), Copyright (1974) American Chemical Society

The ESR spectrum of MeSO• is temperature dependent (Figure 3). At 215 K the spectrum exhibits a 1:3:3:1 quartet [a(H) = 11.6 G] as expected for a freely rotating methyl group. However, at 88 K the spectrum collapses to a 1:2:1 triplet [a(H) = 17.3 G], consistent with a frozen conformation in which two protons have identical hyperfine coupling and the coupling of the third proton is zero. Either of structures **6** and **7** is compatible with this interpretation, the proton lying in the plane perpendicular to the unpaired electron having zero coupling.



(**6**)



(**7**)

The angular dependence of the hyperfine coupling to the methyl protons is described by equation 9, where ρ_s is the sulphur 3p spin density (equal to 0.91) and $B = 25.3$ G. Simulation of the temperature-dependent spectra yields an energy barrier to rotation of 11 kJ mol^{-1}[1,10].

$$a(\mathrm{H}) = \rho_s B \cos^2 \theta \tag{9}$$

4. *Structure of RSO• radicals in solution*

The proton hyperfine coupling for MeSO•, 11.5 G, observed in solution (Table 1) is precisely that calculated from equation 9 for a freely rotating methyl group, i.e. where $\langle \cos^2 \theta \rangle = 1/2$. The exceptionally broad linewidths for this radical unfortunately preclude a study of the temperature dependence of a(H). However, it should be mentioned that the hyperfine coupling observed for MeSO• is much larger than that for $MeSO_2^•$ (*ca* 1–2 G), consistent with a higher spin density at sulphur in MeSO• ($\rho_s = 0.92$) compared with $MeSO_2^•$ ($\rho_s = 0.40$)[15].

For larger primary alkylsulphinyl radicals, e.g. EtSO•, PrSO• and Bu^{i}SO•, the central line of the 1:2:1 triplet broadens markedly on lowering the temperature (Figure 4). This is explicable in terms of an interconversion between conformers that have non-equivalent α-H hyperfine couplings. Conformations **8** (and its equivalent **9**) or **10** (and its equivalent **11**) give rise to a(H) values (using equation 9) of 17.3 G for H-1 and 0 G for H-2, and thus an average of 8.7 G. The range observed is 7.9–10.7 G (Table 1), and such variation can be accommodated by small deviations ($\pm 5°$) from the conformations **8**–**11**. Spectral simulation for PrSO• enables an energy barrier for C–S bond rotation of 18 ± 2 kJ mol^{-1} to be calculated, somewhat greater than that for MeSO• in a solid matrix.

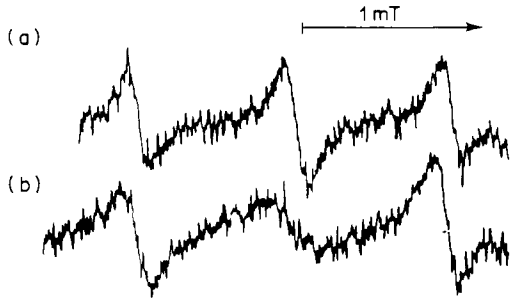
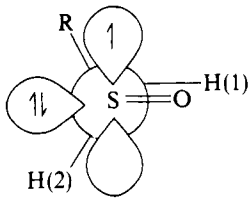


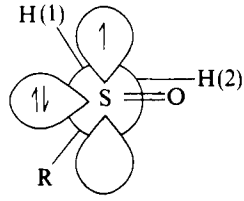
FIGURE 4. ESR spectrum of PrSO• at (a) 194 K and (b) 158 K. Reproduced by permission of the Royal Society of Chemistry

The isopropyl sulphinyl radical, Pr^{i}SO•, exhibits only a small temperature dependence for a(α-H), and it appears that the preferred conformation **12** [calculated from the observed value of a(H) and equation 9] is significantly preferred. Similar conformations are inferred from a(H) values for the sulphinyl radicals formed from glutathione, thioglycerol, dithiothreitol and dithioerythritol[6].

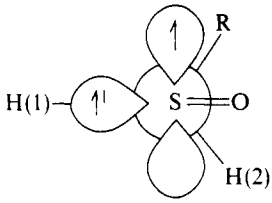
Aromatic sulphinyl radicals display significant coupling to the aryl ring protons. Taken together with the lower g-values of aryl- as opposed to alkylsulphinyl radicals, this indicates that significant transfer of spin density from sulphur to the aryl ring occurs. The



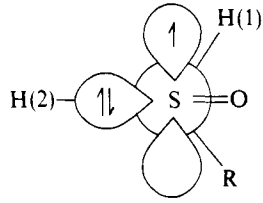
(8)



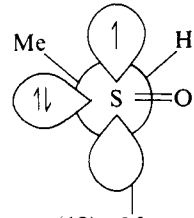
(9)



(10)



(11)



(12) Me

relative magnitude of the hyperfine couplings, i.e. *ortho, para* > *meta*, is that observed from π-type species, whereas for the alternative σ-radical, e.g. $RSO_2^{\bullet}$, the order is reversed[15].

Alkoxysulphinyl radicals, ROSO•, are also considered to have a π-type structure, largely on the basis of the similarity of their g-values with that of $SO_2^{\bullet-}$[13].

C. The Thioaminyl radical, $[R^1SNR^2]^{\bullet}$, and Dialkylaminothiyl Radical, $R^1R^2NS^{\bullet}$

1. Formation

Thioaminyl radicals (e.g. **13**) are most easily, and most commonly, generated by one of two methods, both of which involve hydrogen atom abstraction from the parent sulphenamide. Thus, oxidation of sulphenamides with PbO_2 rapidly yields the desired radicals (equation 10)[18–26]. Alternatively, photolysis or thermolysis in the presence of a system capable of generating $Bu^tO^{\bullet}$ (e.g. Bu^tOOBu^t or $Bu^tO_2COCOO_2Bu^t$) produces the same radical[20–29] (equation 11). Sometimes direct photolysis of the sulphenamide is itself sufficient to produce thioaminyls[30, 31].

$$R^1SNHR^2 \xrightarrow{PbO_2} \underset{(13)}{R^1\dot{S}NR^2} \qquad (10)$$

$$R^1SNHR^2 + Bu^tO^{\bullet} \xrightarrow{-Bu^tOH} R^1\dot{S}NR^2 \qquad (11)$$

Other, less general, methods that have been employed are the photolysis of sulphenimides[29, 31] (equations 12 and 13), the reaction of a sulphenyl chloride with azidotrimethylsilane[32] (equation 14), the direct addition of a radical to di-*t*-butyl-sulphur

diimide[33] (equation 15) or the reaction of alkenes and alkynes with tetrasulphur dinitride S_4N_2 or tetrasulphur tetranitride S_4N_4 to form cyclic sulphenimidyl radicals[34–37] (equations 16 and 17).

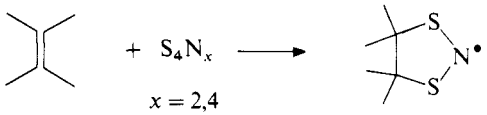
$$ArN(SBu^t)_2 \xrightarrow{h\nu} Ar\dot{N}SBu^t + Bu^tS^\bullet \quad (12)$$

$$Ar^1SO_2N(SAr^2)_2 \xrightarrow{h\nu} Ar^1SO_2\dot{N}SAr^2 + Ar^2S^\bullet \quad (13)$$

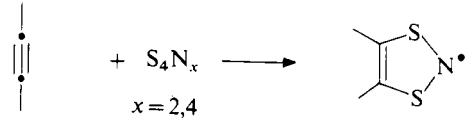
$$RSCl + Me_3SiN_3 \longrightarrow (RS)_2N^\bullet \quad (14)$$

$$Bu^tN{=}S{=}N\,Bu^t + R^\bullet \longrightarrow R(Bu^t)NS{-}\dot{N}Bu^t \quad (15)$$

$R = CF_3$, Me_3Si, Bu_3Si, CF_3S



(16)



(17)

Many thioaminyls are very stable, some for as long as a week. Unlike most nitrogen-centred radicals, they do not readily react with dioxygen to form the corresponding nitroxide (**14**) (equation 18). (Only *S,N*-dialkyl radicals react with dioxygen[27]). Proof for this has come via the independent synthesis of such nitroxide radicals from the appropriate thiyl radical and nitroso compound (equation 19). The ESR parameters for radicals such as **14** are quite different from those of the corresponding **13**. For example, the *g*-value and hyperfine coupling constants for **15** are 2.0065 and *a*(N) 9.92 G, *a*(*ortho*-H) 3.79 G, *a*(*meta*-H) 1.27 G, *a*(*para*-H) 4.10 G, whereas those for **16** are 2.0061 and *a*(N) 12.64 G, (*ortho*-H) 1.87 G, *a*(*meta*-H) 0.85 G, *a*(*para*-H) 2.01 G[29]. Similarly, for **17** *g* is 2.0075 and *a*(N) 12.35 G, while the corresponding values for **18** are 2.0069 and 17.14 G, respectively[27].

$$R^1\dot{S}NR^2 + \tfrac{1}{2}O_2 \longrightarrow R^1SNR^2 \quad (18)$$

(**14**)

$$R^1S^\bullet + R^2NO \longrightarrow R^1SNR^2 \quad (19)$$

$Bu^t\dot{S}NPh$	Bu^tSNPh	$Pr^i\dot{S}NBu^t$	Pr^iSNBu^t
(**15**)	(**16**)	(**17**)	(**18**)

Aminothiyl radicals (e.g. **19**) can be generated from the appropriate disulphide[38, 39] (equation 20) either by photolysis or thermolysis.

$$R_2NS\text{–}SNR_2 \xrightarrow[\Delta]{h\nu \text{ or}} R_2NS^{\bullet} \qquad (20)$$

(19)

2. *g*-Values and hyperfine coupling constants

Some spectra typical of thiioaminyl radicals are shown in Figure 5. The most simple is that for $Bu^tSNPr^{i\bullet}$, which shows quite clearly that coupling to both the ^{14}N nucleus and the α-C*H* attached to nitrogen occurs. ^{14}N coupling is a general phenomenon (see Table 4). Coupling of the unpaired electron to the hydrogen atoms of *S*-alkyl, *S*-aryl and *N*-aryl groups is also observable (Figure 5) and, in favourable cases, so is coupling to the ^{33}S nucleus present in natural abundance. A detailed analysis of the spectra of thioaminyl radicals is contained in Table 4. In general, the intensity of the ESR spectra is temperature-dependent, growing weaker at lower temperature and stronger at higher temperatures. The phenomenon is reversible and may be attributed to radical dimerisation (equation 21)[40]. Careful inspection of Table 4 allows the following observations regarding *g*-values and hyperfine coupling constants to be made.

$$R^1SNR^{2\bullet} \rightleftharpoons R^1SN(R^2)\text{–}N(R^2)SR^1 \qquad (21)$$

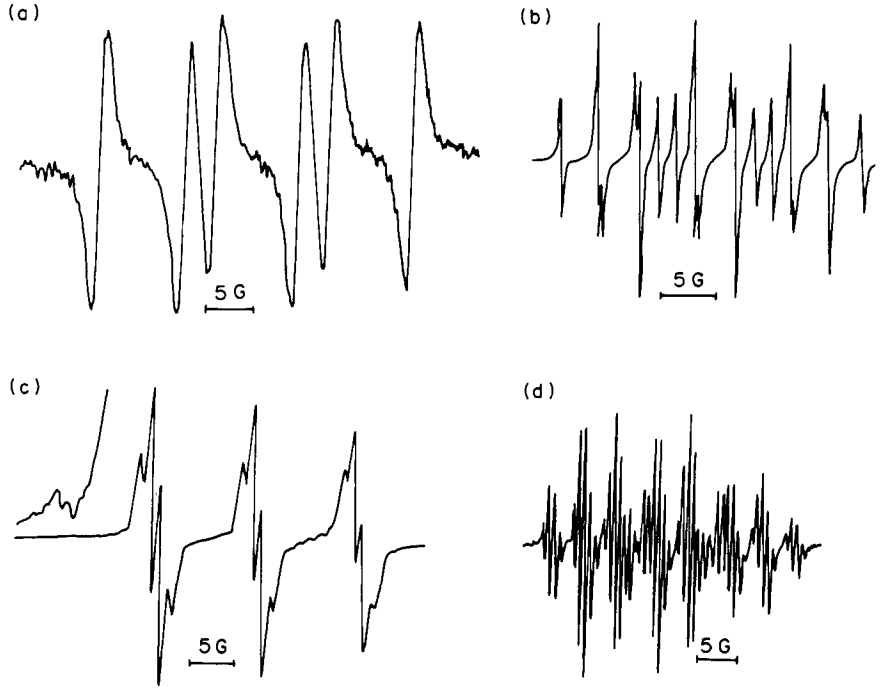


FIGURE 5. ESR spectra of some thioaminyl radicals: (a) $Bu^tSNPr^{i\bullet}$, (b) $Bu^tSN(3,5\text{-}Bu^t_2C_6H_3)^{\bullet}$, (c) $PhSNCPh_3^{\bullet}$, (d) $3,5\text{-}Cl_2C_6H_3SN(3,5\text{-}Bu^t_2C_6H_3)^{\bullet}$. (a) and (d): Reprinted with permission from References 20 and 27. Copyright (1980 and 1983) American Chemical Society. (b) and (c): Reproduced by permission of the Chemical Society of Japan

TABLE 4. *g*-Values and hyperfine coupling constants *a*(X) for thioaminyl radicals[a]

Radical	Temp. (K)	*g*-Value	Hyperfine coupling (G)							Ref.
			a(N)	*a*(*o*-H)[b]	*a*(*m*-H)[b]	*a*(*p*-H)[b]	*a*(H)	*a*(^{33}S)	*a*(other)	
Pr^iSNBu^t•	288	2.0075	12.35				3.53 (1H)			27
$Pr^iSN(3,5\text{-}Bu^t_2C_6H_3)$•	290	2.0065	9.86	(3.79)		(4.21)	2.64 (1H)			29
Bu^nSNBu^t•	288	2.0075	12.13				3.09 (2H)			27
$Bu^nSN(3,5\text{-}Bu^t_2C_6H_3)$•	290	2.0065	9.75	(3.73)		(4.21)	2.59 (2H)			20
Bu^tSNMe•	213		12.5				16.4 (3H)			27
Bu^tSNEt•	313	2.0073	12.4				15.2 (2H)			27
Bu^tSNPr^i•	288	2.0073	12.41				9.08 (1H)			27
Bu^tSNBu^n•	288	2.0073	12.38				15.37 (2H)			27
Bu^tSNBu^t•	288	2.0073	12.44							27
	203	2.0074	12.28					5.93	6.2 (^{13}C)	27
$Bu^tSNcyclo C_6H^{\bullet}_{11}$	288	2.0073	12.34				9.08 (1H)			27
Bu^tSN(1-adamantyl)•	297	2.0074	12.40							27
$Bu^tSNCPh^{\bullet}_3$	293	2.0076	12.28							28
Bu^tSNPh•	290	2.0065	9.92	(3.79)	(1.27)	(4.10)				29
$Bu^tSNC_6D^{\bullet}_5$	290	2.0065	9.92							29
$Bu^tSN(4\text{-}MeC_6H_4)$•	290	2.0062	9.83	(3.83)	(1.27)		4.71 (3H)			29
$Bu^tSN(3\text{-}ClC_6H_4)$•	290	2.0065	9.76	(3.64) (3.79)	(1.29)	(4.09)				29
$Bu^tSN(4\text{-}ClC_6H_4)$•	290	2.0068	9.67	(3.75)	(1.32)					29
$Bu^tSN(4\text{-}BrC_6H_4)$•	290	2.0065	9.58	(3.79)	(1.29)					29
$Bu^tSN(3\text{-}NO_2C_6H_4)$•	290	2.0068	9.64	(3.56)	(1.31)	(3.75)				29
$Bu^tSN(4\text{-}NO_2C_6H_4)$•	290	2.0071	8.68 (1.00)[c]	(3.25)	(1.21)					29
$Bu^tSN(3\text{-}MeOC_6H_4)$•	290	2.0065	9.88	(3.54) (4.08)	(1.29)	(4.29)				29
$Bu^tSN(4\text{-}MeOC_6H_4)$•	290	2.0061	9.45	(3.75)	(1.09)		0.54 (3H)			29
$Bu^tSN(3\text{-}AcC_6H_4)$•	290	2.0066	9.78	(3.70)	(1.22)	(3.97)				29
$Bu^tSN(4\text{-}AcC_6H_4)$•	290	2.0069	9.32	(3.52)	(1.23)					29
$Bu^tSN(3,5\text{-}Bu^t_2C_6H_3)$•	290	2.0065	9.93	(3.68)		(4.20)				29
Cl_3CSNBu^t•	288	2.0061	12.91							27
Ph_3CSNMe•	290	2.0074	12.6				16.6 (3H)			26
Ph_3CSNEt•	290	2.0073	12.5				14.2 (2H)			26

$Ph_3CSNCH_2Ph^{\bullet}$	290	2.0073	12.3				14.8 (2H)			26
$Ph_3CSNPh^{\bullet}$	290	2.0062	9.95	(3.81)	(1.28)	(4.26)				26
$Ph_3CSN(3,5\text{-}Bu^t_2C_6H_3)^{\bullet}$	290	2.0062	9.88	(3.85)		(4.43)		4.3	5.5 (^{13}C) 10.3 (^{13}C)	26
cyclo$C_6H_{11}SNBu^t{}^{\bullet}$	288	2.0075	12.25				3.05 (1H)			27
$PhSNBu^t{}^{\bullet}$	289	2.0069	11.78	1.0		1.0				24,40
$C_6D_5SNBu^t{}^{\bullet}$	289	2.0070	11.77					6.1		40
$PhSNCPh_3^{\bullet}$	293	2.0071	11.71	1.19		1.19		6.83		28
PhSN(1-adamantyl)$^{\bullet}$	289	2.0070	11.77							40
$PhSNCOBu^t{}^{\bullet}$	297	2.0082	7.49	1.69		1.69				30
$PhSNCOPh^{\bullet}$	297	2.0081	7.09	1.68		1.68				30
$C_6D_5SNCOPh^{\bullet}$	297	2.0082	7.08							30
$PhSNSO_2(4\text{-}MeC_6H_4)^{\bullet}$	288	2.0074	8.47	1.82		1.82				31
$C_6D_5SNSO_2(4\text{-}MeC_6H_4)^{\bullet}$	288	2.0074	8.45					11.9		31
$PhSNPh^{\bullet}$	293	2.0059	9.59	0.78 (3.70)	0.27 (1.26)	0.84 (4.18)				25,41
$PhSNC_6D_5^{\bullet}$	293	2.0059	9.56							25
$C_6D_5SNPh^{\bullet}$	293	2.0059	9.59	(3.78)	(1.23)	(3.78)				25
$PhSN(4\text{-}MeC_6H_4)^{\bullet}$	293	2.0059	9.55	0.79 (3.79)	0.27 (1.17)	0.82	4.83 (3H)			25, 41
$PhSN(4\text{-}MeOC_6H_4)^{\bullet}$	293	2.0059	9.56	0.78 (3.87)	0.20) (1.10)	0.83	0.58 (3H)			25,41
$PhSN(4\text{-}ClCl_6H_4)^{\bullet}$	293	2.0061	9.48	0.78 (3.79)	0.30 (1.28)	0.80 (0.33) (Cl)				25,41
$PhSN(4\text{-}BrC_6H_4)^{\bullet}$	293		9.43	(3.73)						25
$PhSN(3\text{-}NO_2C_6H_4)^{\bullet}$	293		9.25 (0.26)[c]	0.89 (3.45)	0.26 (1.25)	0.92 (3.74)				25
$PhSN(4\text{-}NO_2C_6H_4)^{\bullet}$	293	2.0065	8.77 (0.89)[c]	0.95 (3.35)	(1.23)	0.95				25
$C_6D_5SN(4\text{-}NO_2C_6H_4)^{\bullet}$	293	2.0065	8.75 (0.88)[c]	(3.37)	(1.22)					25
$PhSN(3\text{-}AcC_6H_4)^{\bullet}$	293		9.45	0.83 (3.59)	0.25 (1.22)	0.87 (3.92)				25
$PhSN(4\text{-}AcC_6H_4)^{\bullet}$	293		8.97	0.90) (3.46)		0.94				25
$C_6D_5SN(4\text{-}AcC_6H_4)^{\bullet}$	293	2.0063	8.97	(3.43)	(1.24)					25
$PhSN(3,5\text{-}Bu^t_2C_6H_3)^{\bullet}$	293	2.0060	9.53	0.76 (3.71)	0.27	0.83 (4.22)				20

(*continued*)

TABLE 4. (*continued*)

Radical	Temp. (K)	*g*-Value	Hyperfine coupling (G)							Ref.
			a(N)	*a*(*o*-H)[b]	*a*(*m*-H)[b]	*a*(*p*-H)[b]	*a*(H)	*a*(^{33}S)	*a*(other)	
$C_6D_5SN(3,5\text{-}Bu^t_2C_6H_3)^\bullet$	293	2.0060	9.52					4.62	5.44 (^{13}C)	20
				(3.73)		(4.23)			10.34 (^{13}C)	
$PhSN(3,5\text{-}Cl_2C_6H_3)^\bullet$	293	2.0061	9.26	0.90		0.90				25
				(3.68)		(3.68)				
$4\text{-TolSNBu}^t{}^\bullet$	289	2.0070	11.70	1.1			1.1 (3H)			40
$4\text{-TolSN}(3,5\text{-}Bu^t_2C_6H_3)^\bullet$	293	2.0060	9.52	0.80	0.26		0.87 (3H)			20
				(3.62)		(4.20)				
$4\text{-TolSNSO}_2(4\text{-}MeC_6H_4)^\bullet$	288	2.0074	8.27	1.9			2.1 (3H)	12.0		31
$4\text{-FC}_6H_4SNBu^t{}^\bullet$	288	2.0070	11.83	0.89					2.22 (F)	24
$3\text{-ClC}_6H_4SNBu^t{}^\bullet$	289	2.0068	11.84	1.09		1.09				40
$3\text{-ClC}_6H_4SN(1\text{-adamantyl})^\bullet$	289	2.0068	11.79							40
$4\text{-ClC}_6H_4SNPr^i{}^\bullet$	289		11.7				9.1 (1H)			40
$4\text{-ClC}_6H_4SNBu^t{}^\bullet$	288	2.0071	11.75	0.93						24,40
$4\text{-ClC}_6H_4SNCHMe(CH{=}CH_2)^\bullet$	378[d]	2.0073	11				11 (1H)			42
$4\text{-ClC}_6H_4SNCMe_2(CH{=}CH_2)^\bullet$	378[d]		11							42
$4\text{-ClC}_6H_4SN\textit{cyclo}\text{-}C_6H^\bullet_{11}$	289		11.6				9.2 (1H)			40
$4\text{-ClC}_6H_4SNCPh^\bullet_3$	293	2.0071	11.81	1.16				6.78		28
$4\text{-ClC}_6H_4SN(1\text{-adamantyl})^\bullet$	289	2.0070	11.74							40
$4\text{-ClC}_6H_4SNCOBu^t{}^\bullet$	297	2.0083	7.57	1.69						30
$4\text{-ClC}_6H_4SNCOPh^\bullet$	297	2.0083	7.16	1.72						30
$4\text{-ClC}_6H_4SNCO(4\text{-}MeOC_6H_4)^\bullet$	297	2.0082	7.38	1.73						30
$4\text{-ClC}_6H_4SNCO(4\text{-}NO_2C_6H_4)^\bullet$	297	2.0084	6.80	1.97						30
$4\text{-ClC}_6H_4SNSO_2(4\text{-}MeC_6H_4)^\bullet$	288	2.0075	8.50	1.8						31
$4\text{-ClC}_6H_4SN(3,5\text{-}Bu^t_2C_6H_3)^\bullet$	293	2.0059	9.58	0.75						20,21
				(3.70)		(4.42)				
$4\text{-ClC}_6H_4SN(2,4,6\text{-}Bu^t_3C_6H_2)^\bullet$	292	2.0067	12.27							21,22
$4\text{-BrC}_6H_4SNBu^t{}^\bullet$	288	2.0072	11.82	1.10						24,40.
$4\text{-BrC}_6H_4SN(1\text{-adamantyl})^\bullet$	289	2.0072	11.76							40
$4\text{-BrC}_6H_4SN(3,5\text{-}Bu^t_2C_6H_2)^\bullet$	293	2.0059	9.56	0.77	0.22					20,21
				(3.71)		(4.38)				

2-$NO_2C_6H_4SNH^•$	323[e]	2.0076								43
2-$NO_2C_6H_4SNPh^•$	298	2.0049	9.48	0.78	0.24	0.78				41
				(3.90)	(1.32)	(4.48)				
2-$NO_2C_6H_4SN(4\text{-}MeC_6H_4)^•$	298	2.0050	9.42	0.68	0.22	0.68				41
				(3.98)	(1.24)	(5.20)				
2-$NO_2C_6H_4SN(4\text{-}MeOC_6H_4)^•$	298	2.0050	9.30	0.68	0.21	0.68				41
				(4.00)	(1.06)	(0.68) (3H)				
2-$NO_2C_6H_4SN(4\text{-}ClC_6H_4)^•$	298	2.0057	9.38	0.72	0.26	0.72				41
				(3.90)	(1.36)	(0.52) (Cl)				
4-$NO_2C_6H_4SNBu^t{}^•$	288	2.0068	11.89	1.07						24
4-$NO_2C_6H_4SNSO_2(4\text{-}MeC_6H_4)^•$	288	2.0073	8.94	1.8						31
4-$NO_2C_6H_4SN(3,5\text{-}Bu^t_2C_6H_3)^•$	293	2.0057	9.64	0.74						20
				(3.81)		(4.55)				
4-$NO_2C_6H_4SN(2,4,6\text{-}Bu^t_3C_6H_2)^•$	292	2.0066	12.30							22
4-$MeOC_6H_4SNSO_2(4\text{-}MeC_6H_4)^•$	288	2.0074	7.90	1.81				12.3		31
2,4-$Cl_2C_6H_3SN(3,5\text{-}Bu^t_2C_6H_3)^•$	293	2.0061	9.59	0.68						20
				(3.85)		(4.55)				
3,5-$Cl_2C_6H_3SNBu^t{}^•$	289	2.0067	11.91	1.10			1.10	5.75	5.80 (^{13}C)	40
3,5-$Cl_2C_6H_3SNCPh_3^•$	293	2.0068	11.88	1.12			1.12	6.41		28
3,5-$Cl_2C_6H_3SN(3,5\text{-}Bu^t_2C_6H_3)^•$	293	2.0057	9.63	0.74	1	0.74				20,21
				(3.87)		(4.52)				
3,5-$Cl_2C_6H_3SN(2,4,6\text{-}Bu^t_3C_6H_2)^•$	292	2.0064	12.25	1.20		1.20				22
2,4,6-$Me_3C_6H_2SNBu^t{}^•$	289	2.0076	12.26					6.70		40
2,4,6-$Me_3C_6H_2SNCPh_3^•$	293	2.0077	12.09					7.40		28
2,4,6-$Bu^t_3C_6H_2SN(2,4\text{-}(NO_2)_2C_6H_3)^•$	298	2.008	8.2							44
$CF_3(Bu^t)NSNBu^t{}^•$	293[f]	2.0060	12.6						2.0 (3F)	33
			0.9							
$Me_3Si(Bu^t)NSNBu^t{}^•$	293[f]	2.0064	12.0					8.34		33
$Bu^n_3Si(Bu^t)NSNBu^t{}^•$	293[f]	2.0064	12.0					8.34		33
$CF_3S(Bu^t)NSNBu^t{}^•$	293[f]	2.0054	12.4							33
$[(EtO)_2PO]Bu^tNSNBu^t{}^•$	293[f]	2.0062	12.25						10.05 (^{31}P)	33
			1.0							

[a] In benzene solvent, unless otherwise stated.
[b] Values for *S*-aryl group; values for *N*-aryl groups are in parentheses,
[c] Coupling to the NO_2 group.
[d] In chlorobenzene,
[e] In toluene.
[f] In cyclopropane.

(i) *g*-Values lie in the range 2.0057–2.0084. This is somewhat larger than the general range of 2.003–2.006 for nitrogen-centred radicals[45] and may be ascribed to some of the unpaired spin density residing at the sulphur atom which has a large spin–orbit coupling of 382 cm^{-1} [46].

The *g*-values are lower than in the corresponding sulphinyl radicals (Section III.B), a trend that has been observed for $R^1SONR^•$ and $RSO_2^•$[15] and is a result of the greater electronegativity of oxygen as compared to nitrogen. Again, this results in a larger proportion of unpaired spin density residing at the sulphur atom in $RSO^•$ as compared to $R^1SNR^{2•}$.

(ii) Aryl groups attached to the sulphur atom lower *g*-values, presumably by removing spin density from sulphur. Electron-withdrawing groups, e.g. CCl_3, at sulphur also lower the observed value of *g*, but the mechanism for this is somewhat different and will be described later (Section II.C.3)

(iii) Aryl groups attached to the nitrogen atom also lower *g*-values. A slight increase in *g*-value is observed for *N*-aryl systems containing electron-withdrawing groups as compared to those containing electron-releasing groups.

(iv) For R^1,R^2 = alkyl, coupling to the α-CH hydrogen atoms can be observed. However, coupling to the α-CH of the *N*-substituent, *ca* 15 G, is greater than the α-CH of the *S*-substituent, *ca* 3 G. Similarly, for R^1,R^2 = aryl coupling to the hydrogen atoms of both *S*- and *N*-aryl rings is observable. For both, the size of the coupling follows the order *ortho*-H ~ *para*-H > *meta*-H, though the magnitude of coupling to the *N*-aryl ring is some five times larger than that to the *S*-aryl ring.

(v) The hyperfine coupling constants to the ^{14}N nucleus lie in the range 7–13 G, a range consistent with nitrogen-centered radicals in a π-electronic ground state[45]. *N*-Alkyl thioaminyls have *a*(N) values that lie to the high end of this range; *N*-aryl thioaminyls lie to the low end. The presence of electron-withdrawing groups in the *N*-Ar ring decreases *a*(N); conversely the same groups in the *S*-Ar ring increase *a*(N). Large bulky *N*-Ar groups, e.g. 2,4,6-$Me_3C_6H_2$, result in *a*(N) values similar to those for *N*-alkyl systems.

(vi) Hyperfine coupling to the ^{33}S nucleus increases as the electron-withdrawing power of the *N*-substituent increases. For *S*-aryl thioaminyls, the *a*(^{33}S) coupling constant appears to decrease slightly as the electron-withdrawing ability of the aryl substituent increases.

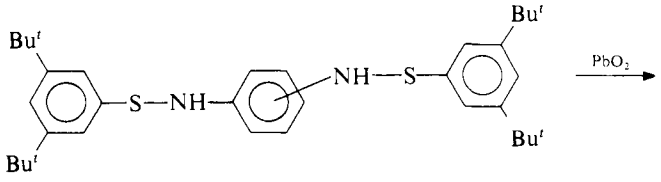
Comparison of the *a*(H) and *a*(N) values for $R^1SNR^{2•}$ with those of the corresponding $R^1ONR^{2•}$ is of some interest. For R^1 = alkyl, $a(H)_{SN} > a(H)_{ON}$ (3.1 G vs 2.5 G)[27]; for R^2 = alkyl, $a(H)_{SN} < a(H)_{ON}$ (15 G vs 21 G)[27]; for R^2 = aryl, *a*(*ortho*-H or *para*-H)$_{ON}$ > *a*(*ortho*-H or *para*-H)$_{SN}$ by ca 1 G[29]. Moreover, *a*(N) is larger for $R^1ONR^{2•}$ than $R^1SNR^{2•}$. All of these observations may be ascribed to a greater spin density on sulphur in $R^1SNR^{2•}$ than on oxygen in $R^1ONR^{2•}$.

Thioaminyl diradicals of structure **21** can be generated from the bis(sulphenamides) **20** (equation 22)[47]. These give ESR spectra analogous to the monoradicals described above, and show negligible interaction between the two spins. Thus, *g*-values of 2.0056–2.0059, and *a*(N) values 9.49–9.61 G are observed. Coupling to the *ortho*- and *para*-hydrogen atoms of the *N*-aryl and *S*-aryl rings of *ca* 4 G and *ca* 0.8 G, respectively, is also found[47].

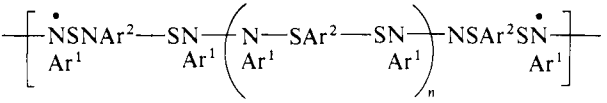
Bis(thio)aminyls **22** (also called sulphenimidyls) are radicals derived from sulphenimides. Table 5 contains the *g*-values and *a*(^{14}N), *a*(^{15}N), *a*(^{33}S) and *a*(H) hyperfine coupling constants for the known acyclic and cyclic radicals of this class†.

RS–N̈–SR
(22)

† Reference 34 contains further data for other cyclic sulphenimidyls. However, the structure of the radicals is uncertain and we have not included the data here.



(20) (22)



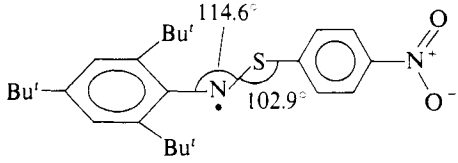
(21)

The g-values and the $a(^{14}N)$ and $a(^{33}S)$ hyperfine coupling constants vary little for large changes in structure. The g-values and $a(^{14}N)$ hyperfine couplings lie to the high end of the ranges observed for the simple thioaminyls, whereas the $a(^{33}S)$ values are to the low end of the corresponding range (Table 4). However, it is clear from the ESR parameters that sulphenimidyl radicals are little different from their thioaminyl counterparts.

Although aminothiyl radicals (**19**) are the sulphur analogues of the well-known nitroxides, there have been remarkably few studies of this system[38,39,49]. The known ESR spectral data are contained in Table 6. The g-values are larger than those for nitroxides (g *ca* 2.006) and this can be attributed to the larger spin–orbit coupling for sulphur than oxygen. The nitrogen hyperfine coupling for dialkylaminothiyls is smaller than that for nitroxides (11 G *vs* 15 G), and that for the iminothiyl smaller than the corresponding iminoxyl (18 G *vs* 32 G). This is readily explained by the relative electronegativities of sulphur and oxygen; the greater electronegativity of oxygen results in greater unpaired spin density at the nitrogen atom.

3. Structure

The [(4-nitrophenyl)thio](2,4,6-tri-*tert*-butylphenyl)aminyl radical (**23**) is isolable as dark brown crystals (from methanol) in 45% yield[22]. This enables a unique opportunity to study the structure of a thioaminyl radical directly. An important feature of the radical is the *trans* co-planarity of the C–S–N–C system. Moreover, the S–N bond length is 160.5 pm, intermediate between the value of an S–N single bond (164–169 pm) and an S=N double bond (155–157 pm). The *S*-Ar ring is co-planar with the C–S–N–C system, and the nitro group also lies in this plane. The *N*-Ar ring, however, is at right angles to the plane containing the ArSNC grouping, presumably due to severe steric interactions.

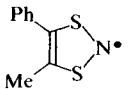
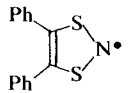
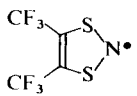
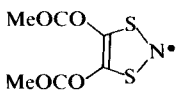
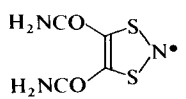
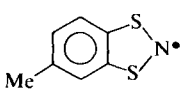
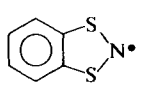
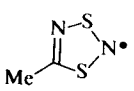


(23)

Interestingly, *ab initio* MO calculations for HSNH• using the double-zeta basis set correctly predicts a *trans* co-planar arrangement of the atoms (**24**) as the most stable conformation[27]. The unpaired electron occupies a π^* molecular orbital. The a(N) and

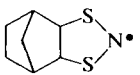
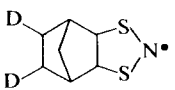
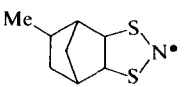
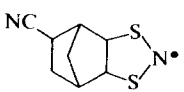
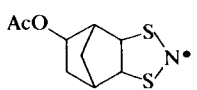
TABLE 5. *g*-Values and hyperfine coupling constants *a*(X) for bis(thio)aminyl (sulphenimidyl) radicals

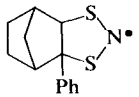
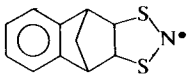
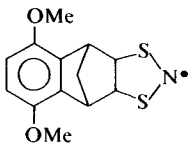
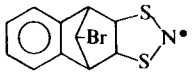
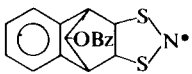
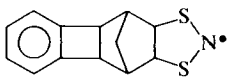
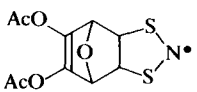
Radical	Temp (K)	*g*-Value	Hyperfine coupling (G)							Ref.
			$a(^{14}N)$	*a*(*o*-H)	*a*(*m*-H)	*a*(*p*-H)	$a(^{33}S)$	$a(^{15}N)$	*a*(other)	
$(Ph_2S)_2N^\bullet$	293[a,b]	2.0075	11.41				3.9			18, 23, 32
$(C_6D_5S)_2N^\bullet$	293[a]	2.0075	11.44				3.9	16.0		18
$(2\text{-TolS})_2N^\bullet$	293[a]	2.0076	11.36							23
$(4\text{-TolS})_2N^\bullet$	293[a]	2.0075	11.45							23
$(4\text{-Bu}^tC_6H_4S)_2N^\bullet$	293[a]	2.0075	11.45	0.48	0.20					23
$(4\text{-FC}_6H_4S)_2N^\bullet$	293[a]	2.0075	11.49							23
$(2\text{-ClC}_6H_4S)_2N^\bullet$	293[a]	2.0074	11.29	0.67	0.21	0.67				23
$(3\text{-ClC}_6H_4S)_2N^\bullet$	293[a]	2.0074	11.40	0.57		0.57				23
$(4\text{-ClC}_6H_4S)_2N^\bullet$	293[a,b]	2.0075	11.37	0.56						23
	288[b]	2.0081	11.3							32
$(2\text{-BrC}_6H_4S)_2N^\bullet$	293[a]	2.0074	11.27	0.67		0.67				23
$(3\text{-BrC}_6H_4S)_2N^\bullet$	293[a]	2.0074	11.40	0.57		0.57				23
$(4\text{-BrC}_6H_4S)_2N^\bullet$	293[a]	2.0076	11.37	0.56	0.22					23
$(4\text{-NO}_2C_6H_4S)_2N^\bullet$	293[a]	2.0073	11.26							23
$(2,4\text{-Me}_2C_6H_3S)_2N^\bullet$	293[a]	2.0076	11.44							23
$(2,3,5,6\text{-Me}_4C_6HS)_2N^\bullet$	288[b]	2.0088	12.0							32
$(2,4,6\text{-Pr}^i_3C_6H_2S)_2N^\bullet$	288[b]	2.0080	12.2							32
$(2,4,6\text{-Bu}^t_3C_6H_2S)_2N^\bullet$	288[b]	2.0080	11.5							32
$(2\text{-Me-4-Cl-C}_6H_3S)_2N^\bullet$	293[d]	2.0076	11.36							23
$(2,3\text{-Cl}_2C_6H_3S)_2N^\bullet$	293[d]	2.0073	11.27	0.70	0.21	0.70				23
$(2,4\text{-Cl}_2C_6H_3S)_2N^\bullet$	293[d]	2.0075	11.29	0.62						23
$(2,5\text{-Cl}_2C_6H_3S)_2N^\bullet$	293[a]	2.0073	11.30	0.70	0.18	0.70				18, 23
$(3,5\text{-Cl}_2C_6H_3S)_2N^\bullet$	293[a]	2.0073	11.40	0.58		0.58	3.90			18, 23
$(2,4\text{-(NO}_2)_2C_6H_3S)_2N^\bullet$	288[b]	2.0076	11.5							32
	293[c]	2.0065	10.71						1.34 (H)	37

	295[d]	2.0064	11.08							36
	295[e]	2.0064	10.71				3.92	15.02		36
	228[b]	2.0064	11.11						0.8 (6F)	36
	298[e]	2.0064					4.07	15.80	0.7 (6F)	36
	294[b]	2.0065	11.01				4.18	15.53		36
	293[f]	2.0064	10.97							36
	293[c]	2.0065	11.33	0.59	0.59	0.59			0.59	37
	293[c]	2.0081	8.20	0.88	0.88 3.75	2.83	4.51 3.51			37
	221[g]	2.0052	10.95 0.64				5.18 3.72		0.64 (3H)	37, 48

(*continued*)

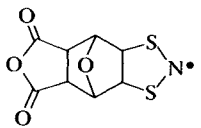
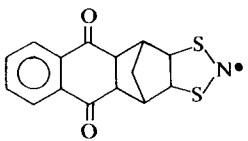
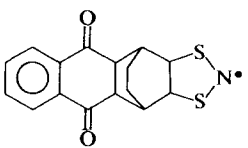
TABLE 5. (*continued*)

Radical	Temp (K)	*g*-Value	Hyperfine coupling (G)							Ref.
			$a(^{14}N)$	*a*(*o*-H)	*a*(*m*-H)	*a*(*p*-H)	$a(^{33}S)$	$a(^{15}N)$	*a*(other)	
	303[b]	2.0065	12.91				2.98	18.31	3.46 (2H)	34, 36
	293[b]		12.94						3.44 (2H)	34
	293[b]		12.92						3.41 (2H)	34
	293[b]		13.04						3.36 (2H)	34
	293[b]		13.01						3.39 (2H)	34

	293[h]		13.01				2.83 (H)	34
	293[b]		12.92				3.18 (2H) 0.32 (1H, 7-*anti*)	34
	295[b]	2.0065	13.05	2.77	18.25		3.19 (2H) 0.31 (1H, 7-*anti*)	34, 35, 37
	293[b]		13.19				2.15 (2H) 2.08 (1H, 7-*anti*)	34
	293[b]		12.76				3.69 (2H) 0.81 (1H, 7-*anti*)	34
	293[b]		12.93				3.49 (2H)	34
	293[b]		13.27				2.88 (2H)	34

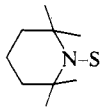
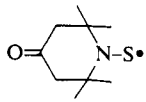
(*continued*)

TABLE 5. (*continued*)

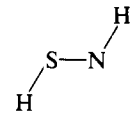
Radical	Temp (K)	*g*-Value	Hyperfine coupling (G)							Ref.
			$a(^{14}N)$	*a*(*o*-H)	*a*(*m*-H)	*a*(*p*-H)	$a(^{33}S)$	$a(^{15}N)$	*a*(other)	
	293[b]		13.14						3.28 (2H)	34
	293[b]		12.95						3.00 (2H)	34
	293[b]		12.98						3.26 (2H)	34

[a]In benzene. [b]In CH_2Cl_2. [c]In toluene. [d]In n-hexane. [e]In CCl_4. [f]In MeOH. [g]In CH_3CN. [h]In *iso*-pentane.

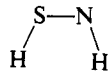
TABLE 6. ESR spectral data of aminothiyl radicals

Radical	Solvent	Temp. (K)	g-Value	a(N)	a(H)	Ref.
$Pr^i_2NS^\bullet$	$Bu^tC_6H_5$	193–213	2.0159	10.9	2.5	38, 39
$Ph_2NS^\bullet$	$Bu^tC_6H_5$		2.017	8.0		38
$Ph_2C{=}NS^\bullet$	$Bu^tC_6H_5$		2.0152	18.16		39
	Ph_2O	363–423	2.0173	11.4		38, 39, 49
	PhI	413–473	2.0171	10.9		49

$a(^{33}S)$ hyperfine coupling constants calculated for **24** are 10.68 and 5.17 G, respectively. These are in remarkable agreement with those for e.g. $Bu^tSNBu^{t\bullet}$ which are 12.28 and 5.93 G, respectively (Table 4). The corresponding values for the *cis* co-planar structure **25** have been calculated as a(N) 10.29 G and $a(^{33}S)$ 3.66 G which fit the data less well. Indeed, the lowest value of $a(^{33}S)$ so far observed is 4.3 G (Table 4) which suggests that all thioaminyls adopt the *trans* co-planar arrangement of atoms.

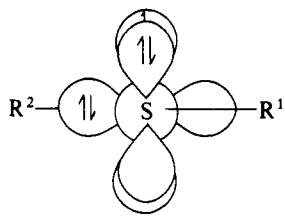


(24)



(25)

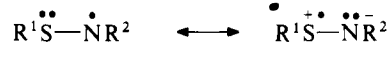
The above observations point to thioaminyls as π-radicals (**26**). Further, the order of *S*-Ar and *N*-Ar hyperfine proton coupling constants, *viz ortho*-H ~ *para*-H > *meta*-H, corroborates this[50]. Confirmation comes from applying simple McConnell-type equations (equations 23 and 24) relating the observed isotropic hyperfine couplings to the π-spin density. Using values of $Q_N = 22$ G and $Q_{33_S} = 23$ G[27], and the experimental hyperfine couplings in Table 4, the π-spin density for both *S* and *N* and also the aryl rings can be calculated for a range of thioaminyl radicals (Table 7). It is clear that 70–90% of the unpaired spin density can be accounted for by a delocalized π-radical at the sulphur and nitrogen atoms. The radical may be considered as a resonance hybrid of **27** and **28**, with **27**



(26)

$$a(X) = Q_x \rho_x^{\pi} \tag{23}$$

$$a(H) = 27\,\rho_c^{\pi} \tag{24}$$



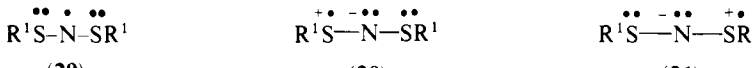
(27) (28)

generally predominating. For many of the radicals in Table 7, the remainder of the spin density resides in either the *S*- or *N*-aryl ring.

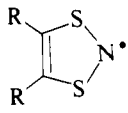
The observed trends in both *g*-values and hyperfine coupling constants are entirely consistent with the above conclusion. Thus, *N*-aryl groups enable delocalization of the unpaired spin in **27** over the π-system. This reduces *g*-values, a(N) and the total spin density at the *S* and *N* atoms. Significantly, thioaminyl (**23**), in which the *N*-aryl ring is orthogonal to the C–N–S–C plane and therefore cannot delocalize the unpaired electron over the ring, has an a(N) value expected for an *N*-alkyl group (Table 4). The smaller coupling to *S*-aryl ring protons and the insensitivity to substituent effects indicates that, in general, structure **27** is nearer to the true structure than **28**.

Powerful electron-withdrawing groups at *N*, e.g. $ArSO_2$, sufficiently stabilize the charged structure **28** that this becomes more representative of the true radical structure for such aminyls. This is reflected in *g*-values that lie to the high end of the range observed, and low values of a(N) together with the highest values of $a(^{33}S)$ for thioaminyls. Table 7 shows that for these radicals the greater part of the spin density resides at the *S*, rather than the *N*, atom. A similar situation almost certainly exists for analogous *N*-acyl thioaminyls, where high *g*-values and low a(N) values suggest **28** is more representative of the radical structure. Unfortunately, complementary $a(^{33}S)$ values are not available to verify this conclusion. Conversely, for electron-withdrawing groups at sulphur, e.g. CCl_3, structure **27** would be expected to reflect the real structure, and the observation that *g* decreases and a(N) increases is consistent with this interpretation.

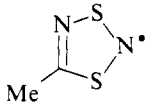
Sulphenimidyl radicals give ESR spectra that are consistent with them having a structure similar to that of thioaminyls and may be considered a resonance hybrid of structures **29** to **31**. Thus sulphenimidyls are also π-radicals. Using equations 23 and 24, S and N π-spin densities may be calculated and these are recorded in Table 7. Like thioaminyls, *ca* 55% of the spin density resides at nitrogen, and *ca* 35% of the spin density is shared between the two sulphur atoms. These spin densities also have been derived by HMO calculation and the values correspond well[18]. The result of this lower spin density per sulphur atom in sulphenimidyls as compared to thioaminyls is that a smaller coupling to the *S*-aryl ring protons is observed [*cf* a(H) *ca* 0.6 G for $(ArS)_2N^{\bullet}$ and *ca* 1 G for $ArS\dot{N}R$]. Interestingly, despite the observation that sulphenimidyls are π-radicals, little delocalization of spin density throughout the ring occurs in cyclic dithiazolyl systems containing carbon–carbon or carbon–nitrogen double bonds, e.g. **32** and **33**. INDO MO



(29) (30) (31)

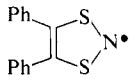
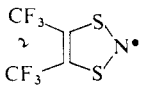
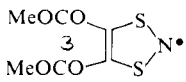
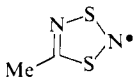
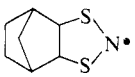
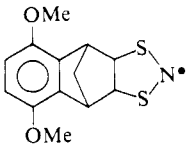


(32)



(33)

TABLE 7. Sulphur, nitrogen and aryl ring π-spin densities for some thioaminyls

Radical	Spin density		
	S	N	Ar
Bu^tSNBu^t•	0.26	0.56	—
$Ph_3CSN(3,5\text{-}Bu^t_2C_6H_3)$•	0.19	0.45	0.45
$C_6D_5SNBu^t$•	0.27	0.54	0.11
$PhSNCPh_3^{\bullet}$	0.30	0.53	0.13
$C_6D_5SNSO_2(4\text{-Tol})$•	0.52	0.38	0.20
$C_6D_5SN(3,5\text{-}Bu^t_2C_6H_3)$•	0.20	0.43	0.54
$4\text{-}TolSNSO_2(4\text{-Tol})$•	0.52	0.38	0.22
$4\text{-}ClC_6H_4SNCPh_3^{\bullet}$	0.29	0.54	—
$4\text{-}MeOC_6H_4SNSO_2$ (4-Tol)•	0.53	0.36	0.13
$3,5\text{-}Cl_2C_6H_3SNBu^t$•	0.25	0.54	0.12
$3,5\text{-}Cl_2C_6H_3SNCPh_3^{\bullet}$	0.28	0.54	0.12
$2,4,6\text{-}Me_3C_6H_2SNBu^t$•	0.29	0.56	—
$2,4,6\text{-}Me_3C_6H_2SNCPh_3^{\bullet}$	0.32	0.55	—
$Me_3Si(Bu^t)NSNBu^t$•	0.36	0.55	—
$Bu^n_3Si(Bu^t)NSNBu^t$•	0.36	0.55	—
$(Ph_2S)_2N^{\bullet}$	0.34	0.52	—
$(C_6D_5S)_2N^{\bullet}$	0.34	0.52	—
$(3,5\text{-}Cl_2C_6H_3S)_2N^{\bullet}$	0.34	0.52	0.13
	0.34	0.49	
	0.35	0.51	
	0.36	0.50	
	0.39	0.50	
	0.26	0.59	
	0.24	0.59	

calculations have been used to determine $a(^{14}N)$ and $a(^{33}S)$ hyperfine coupling constants for structures such as **32**. Reasonable agreement between theory and experiment is obtained, e.g., for **32** (R = MeOCO); calculated values for $a(^{14}N)$ and $a(^{33}S)$ are 11.15 G and 0.47 G whereas observed values are 11.01 G and 4.14 G, respectively, for a structure in which the S–N bond lengths are 172 pm and the SNS bond angle is 110.8°[36].

Powerful evidence that sulphenimidyl radicals, and also thioaminyls, are π-radicals comes from the powder spectra for several sulphenimidyls[35–37]. g-Values and both $a(^{14}N)$ and $a(^{15}N)$ hyperfine coupling constants are anisotropic (Table 8). The isotropic and anisotropic components of these nitrogen hyperfine couplings, which are related to the degree of unpaired spin density in the nitrogen 2s and 2p orbitals, respectively, may therefore be calculated. Using the theoretical 2s and 2p couplings for ^{14}N and ^{14}N, *viz* 552 G and 17 G for ^{14}N and 775 G and 24 G for ^{15}N[17], the unpaired spin densities in the 2s and 2p orbitals can then be determined. The data in Table 8 result in *ca* 55% of the spin density occupying a 2p orbital and only *ca* 2% in the 2s orbital. The corresponding information for sulphur from $a(^{33}S)$ observations is unavailable but would provide complementary and definitive proof of the π-nature of such radicals.

D. Sulphenamide Radical Cations, $[R^1SNR^2R^3]^{+\bullet}$

1. Formation

As might be anticipated, sulphenamide radical cations are generated via electron transfer processes. Thus, direct *in situ* electrolysis of an acetonitrile solution of the sulphenamide using a platinum wire anode generates the corresponding radical cation (**34**)[51] (equation 25). Alternatively, addition of an electron acceptor, e.g. $AlCl_3$ or $TiCl_3$[52], $Ar_3N^{+\bullet}SbCl_6^-$[53], $AgClO_4/I_2$[54], brings about an identical transformation. Cyclic voltammograms for *N,N*-dialkylsulphenamides exhibit one-electron oxidation at 0.7–1.2 V *vs* SCE[53,45]. At fast scan rates, the difference between the peak in the anodic wave and its cathodic counterpart is *ca* 70 mV, and the ratios of the cathodic to anodic peak heights vary between 0.6 and 1[53,55]. Thus, oxidation of the sulphenamides is a one-electron quasi-reversible process.

$$R^1SNR^1R^2 \xrightarrow[-e^\bullet]{\text{Pt anode}} \underset{(\mathbf{34})}{R^1SNR^1R^{2+\bullet}} \qquad (25)$$

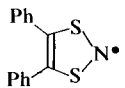
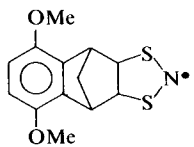
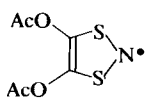
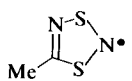
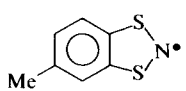
Attempts to generate radical cations of *N*-phenyl sulphenamides have met with little success. Though ESR spectra can be observed in these systems, they are assigned to the radical cations of *N,N*-dialkyldibenzoquinone diimines (**35**)[55]. These are formed via the reactions shown in Scheme 1.

2. g-Values and hyperfine coupling constants

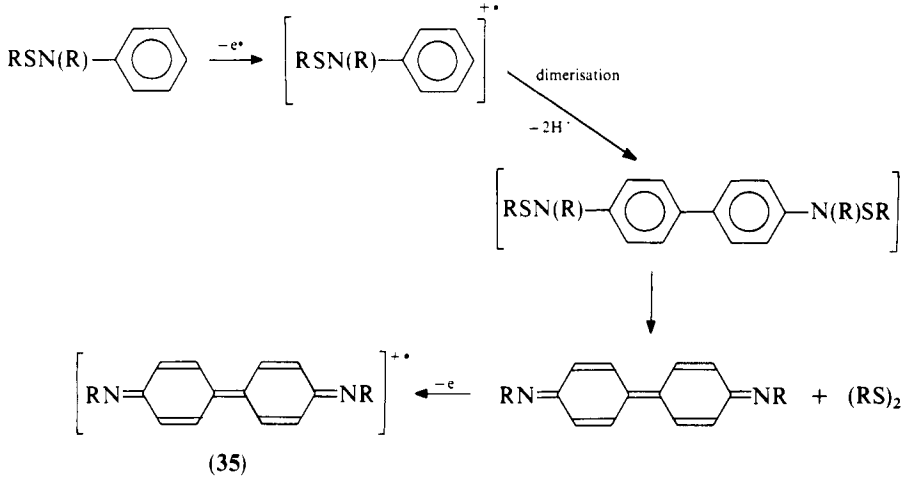
Compared to the number of thioaminyl radicals that have been reported, sulphenamide radical cations are relatively little studied. ESR spectral data for those that have are contained in Table 9, from which the following observations can be made.

(i) g-Values for *N,N*-dialkyl radical cations lie in the range 2.005–2.007 for both *S*-alkyl and *S*-aryl series, which is similar to that for thioaminyl radicals. *N*-Aryl radical cations have significantly lower g-values (*ca* 2.003).

TABLE 8. Anisotropic g-values, and $a(^{14}N)$ and $a(^{15}N)$ hyperfine coupling constants for some sulphenimidyl radicals and the N 2s and 2p spin densities[35]

Radical	g-Values	$a(^{14}N)$	$a(^{15}N)$	a^a_{iso}	a^a_{aniso}	$\%s^a$	$\%p^a$	$p/(s+p)^a$
	2.0140 2.0048 2.0021	2.3 2.3 27.7	−2.8 −2.8 −39.2	10.8 (−14.9)	8.73 (−12.15)	1.96 (1.92)	51.32 (50.63)	0.96 (0.96)
	2.0087 2.0087 2.0021	3.63 3.63 31.88	−4.18 −4.18 −46.38	13.05 (−18.25)	9.41 (−14.06)	2.36 (2.35)	55.35 (58.58)	0.96 (0.96)
	2.0089 2.0089 2.0016	2.40 2.40 27.25		10.68	8.29	1.93	48.74	0.96
	2.0135 2.0043 2.0016	2.30 2.30 27.70		10.8	8.73	1.96	51.32	0.96
	2.0130 2.0014 2.0012	2.1 2.1 28.6		10.9	8.85	1.97	52.06	0.96
	2.0129 2.0051 2.0017	2.25 2.45 28.95		11.22	8.87	2.03	52.15	0.96
$(PhS)_2N^•$	2.0130 2.0077 2.0021	1.88 1.44 30.30		11.21	9.55	2.03	56.15	0.97

[a] Values in parentheses are calculated from $a(^{15}N)$.



(35)

SCHEME 1

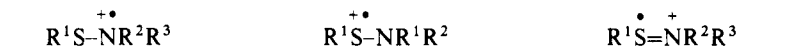
(ii) Nitrogen hyperfine couplings a(N) follow a similar trend; large values, *ca* 14 G, are observed for *S*-alkyl or aryl *N*,*N*-dialkyl radical cations whereas much smaller values (*ca* 10 G) are observed for *N*-aryl systems.

(iii) Relatively large proton hyperfine couplings a(H) are observed to both *N*- and *S*-α-CH hydrogen atoms and, in general, the coupling to *N*-CH is much larger than to *S*-CH. Similarly, little if any coupling is observed to the ring protons of *S*-aryl groups, whereas values of a(H) as large as 4.5 G are seen for coupling to *N*-aryl ring protons.

(iv) For *N*,*N*-disubstituted systems that, in theory, have two identical groups attached to the nitrogen atoms, two *different* α-CH couplings are observed.

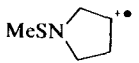
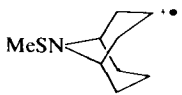
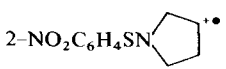
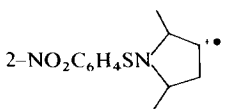
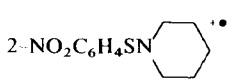
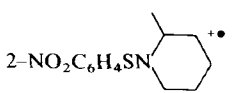
3. Structure

Sulphenamidyl radical cations may be considered to have a structure that is a resonance hybrid of structures **36**–**38**. Structure **38** indicates that some S=N double-bond character exists in these radicals. In MO terms, the unpaired electron occupies a π^* orbital that is localized between the sulphur and nitrogen atoms. This has led several authors to describe this system as a two-centre three-electron bond[51-53]. A consequence of this double-bond character is an increase in the energy barrier to rotation about the S–N bond. Restricted rotation about the S–N bond is known for sulphenamides[60], and it is to be expected that the energy barrier of the derived radical cations will be greater than that for the parent compounds. Assuming that both nitrogen and sulphur use p orbitals to attain π overlap, the structure of the radical cation is **39**, where the unpaired electron is



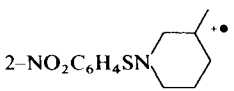
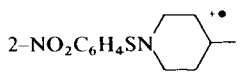
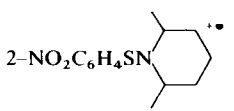
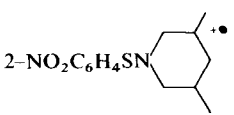
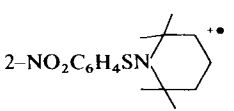
(36) (37) (38)

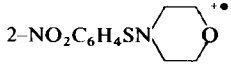
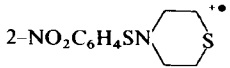
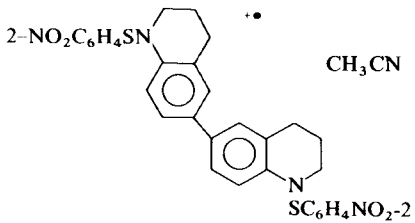
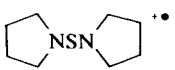
TABLE 9. ESR spectral data for sulphenamide radical cations

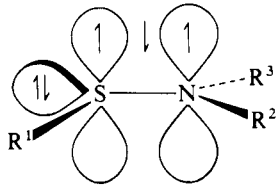
Radical	Solvent	Temp. (K)	g-Value	Hyperfine coupling (G)			Ref.
				a(N)	a(*N–CH*)	a(*S-CH*)	
$MeSNMe_2^{+\bullet}$	$MeNO_2$	273	2.0069	12.1	14.4 (3H) 14.3 (3H)	8.7 (3H)	52
$MeSNEt_2^{+\bullet}$	$MeNO_2$	273	2.0071	14.3	9.9 (2H) 8.6 (2H)	8.6 (3H)	52
	CH_2Cl_2	293		13.8	21.7 (2H) 18.2 (2H)	8.5 (3H)	53
	CH_2Cl_2	293		14.1		8.3 (3H)	53
$PhSNEt_2^{+\bullet}$	CH_3CN			14.7	10.5 (2H) 8.7 (2H)		54
$2\text{-}NO_2C_6H_4SN(CH_2Ph)_2^{+\bullet}$	CH_3CN	253	2.0063	13.4	10.2 (2H) 9.9 (2H) 1.0 (2H) 0.9 (1H)		56
	CH_3CN	298	2.0061	14.3	20.0 (2H) 19.0 (2H)		51
		183	2.0061	14.0	21.5 (1H) 20.3 (1H) 19.7 (1H) 14. 7 (1H)		51
	CH_3CN	298	2.0062	13.6	21.5 (1H) 20.3 (1H)		51
	CH_3CN	243	2.0060	14.0	22.7 (1H) 16.1 (1H) 1.8 (1H) 0.95 (8H)		51, 57
	CH_3CN	298	2.0060	Not assigned			51

(*continued*)

TABLE 9. (*continued*)

Radical	Solvent	Temp. (K)	*g*-Value	Hyperfine coupling (G)			Ref.
				a(N)	*a*(*N*–*CH*)	*a*(*S*-*CH*)	
	CH_3CN	298	2.0061	14.3	22.1 (1H) 16.4 (1H)		51
	CH_3CN	298	2.0061	14.0	22.5 (1H) 17.3 (1H) 1.8 (1H) 0.95 (7H)		51
	CH_3CN	243	2.0062	14.6 14.6	5.5 (1H) 2.7 (1H) 2.4 (1H) 1.9 (1H)		51
	CH_3CN	298	2.0061	14.1	21.9 (1H) 16.6 (1H)		51
	CH_3CN	298	2.0067	12.7	2.0 (2H) 1.0 (3H)		51

	CH_3CN	233	2.0061	13.4	21.7 (1H) 14.6 (1H) 2.8 (1H) 1.3 (1H)	51, 57
	CH_3CN	298	2.0061	13.7	19.7 (1H) 13.4 (1H)	51, 57
$2\text{-}NO_2C_6H_4SN(Me)\ (4\text{-Tol})^{+\bullet}$	CH_3CN	298	2.0031	9.7	9.4 (6H) 4.5 (2H) 1.0 (2H)	56
$2\text{-}NO_2C_6H_4SN(Me)\ (4\text{-}Bu^tC_6H_4)^{+\bullet}$	CH_3CN	298	2.0030	9.5	9.2 (3H) 4.4 (2H) 1.0 (2H)	56
$2\text{-}NO_2C_6H_4SN(Me)\ (4\text{-}EtOCOC_6H_4)^{+\bullet}$	CH_3CN	233	2.0042	10.2	9.6 (3H) 4.15 (2H) 1.0 (2H)	56
	CH_3CN	298	2.0026	5.0 (2N)	5.0 (2H) 2.6 (4H) 1.3 (4H)	58
$Me_2NSNMe_2^{+\bullet}$	$MeNO_2$	293	2.0050	7.5 (2N)	7.5 (12H)	52, 59
$Et_2NSNEt_2^{+\bullet}$	$MeNO_2$	293	2.0056	7.5 (2N)	5.0 (8H)	52, 59
	Bu^nCN	253	2.0055	7.6 (2N)	10.3 (8H)	59



(39)

associated with either or both of the *S* and *N* atoms. Structure **39** has no plane of symmetry, which means that R^2 and R^3 are non-equivalent provided that rotation about the S–N bond is slow.

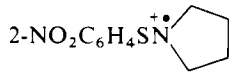
The observation that the methylene protons for all sulphenamide radical cations so far studied (except $[Et_2N)_2S]^{+\bullet}$) have different hyperfine coupling constants suggests that S–N bond rotation is indeed slow, at least on the ESR time scale, and is evidence that the above description of the radical cation is probably correct. Of course, either sulphur or nitrogen may use an sp^3 orbital for π-bond overlap; this would change slightly the structure of **39**, such that either sulphur or nitrogen becomes more pyramidal, but would not change substantially the conclusions reached.

For most radicals, ^{14}N hyperfine coupling constants are *ca* 14 G. Assuming that sulphenamidyls are indeed π radicals and using equation 23 together with a value of $Q_N = 22$ G, the π-spin density at the nitrogen atom is *ca* 64%. Though corresponding $a(^{33}S)$ values have not been reported, by difference this implies 36% of the π-spin density resides at sulphur. This is consistent with the magnitudes of the observed *g*-values, which are of similar magnitude to thioaminyls, and may be attributed to the large spin–orbit coupling of sulphur. Further, the magnitudes of the hyperfine coupling constants to *N*-aryl protons are much larger than to *S*-aryl protons (4.5 G *vs* 1 G). Indeed, for most *S*-aryl compounds studied no coupling to the ring protons has been observed. This difference between *a*(H) for *N*-aryl and *S*-aryl sulphenamidyl cations is somewhat larger than the corresponding difference for thioaminyls (4 G *vs* 1 G). Thus, it would appear that sulphenamidyl cations have an increased spin density at nitrogen (calculated as 64%) compared to thioaminyls (calculated as 55–60%). Moreover, it is clear that *N*-aryl substitution has a significant effect on *g*-values, which drop to *ca* 2.003 from 2.006, and *a*(N), which drop to *ca* 9.7 G from *ca* 14 G. Clearly, substantial spin density is transferred to the aryl ring. Interestingly, from the limited data available it would appear that *g*-values and *a*(N) hyperfine couplings are most reduced by substituents in the *N*-aryl ring that are electron releasing. This suggests that the true structure of the radical cations resembles structure **36** most closely. However, the corresponding trends for *S*-aryl substitution are almost absent. A comparison of $MeSNEt_2^{+\bullet}$ with $PhSNEt_2^{+\bullet}$ indicates that *a*(N) and *a*(NCH) hyperfine coupling constants are virtually unchanged and that no coupling to the *S*-Ph protons is observed. Taken together, these comparisons are consistent with the greater part of the spin density residing at the nitrogen atom in sulphenamide radical cations.

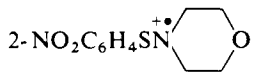
The vexed question as to whether the spin density at the *S* and *N* atoms resides in a pure p orbital or if it resides in an orbital that has some s character cannot be answered from the data currently available. The absence of data detailing the anisotropy in *a*(N) and $a(^{33}S)$ from radical cations in solid state precludes any discussion of this matter. Moreover, the type of interaction between the unpaired spin density and the *N*- or *S*-aryl rings is still unclear. For a π-type interaction *a*(*ortho*-H) ~ *a*(*para*-H) > *a*(*meta*-H), whereas for a σ-type interaction *a*(*meta*-H) > *a*(*ortho*-H) ~ *a*(*para*-H). Unfortunately, the compounds thus far studied are not sufficient for an assignation of the 4.56 and 1.0 G to

the *ortho* and *meta* protons of an *N*-aryl group, or of the 1.0 G and 0.9 G to *ortho*, *meta* or *para* protons of an *S*-aryl group. However, the general lack of coupling to the protons of the *S*-aryl ring may indicate that this ring lies orthogonal to the orbital at sulphur containing the unpaired electron.

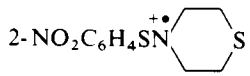
Since sulphenamide radical cations do not possess a plane of symmetry, the methylene protons of $N(CH_2R)_2$ are diastereotopic. Thus, in theory, each methylene proton should exhibit a different hyperfine coupling constant. For freely rotating systems, such as Et or CH_2Ph, such magnetic non-equivalence of all four protons has not been observed. Even with cyclic systems, where rotation about the C–N bond is severely restricted, the methylene protons often exhibit identical hyperfine couplings at room temperature. However, at low temperature the radicals **40** and **41** clearly exhibit couplings to four different protons. Indeed, for radical **42** at room temperature, coupling to only two



(**40**)

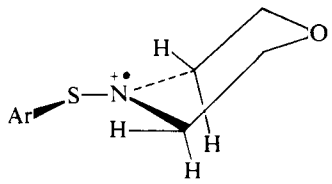


(**41**)



(**42**)

protons is observed. The magnitudes of the observed hyperfine couplings may be explained by the McConnell equation 26. Taking the value of a(H) for $MeSNMe_2^{+\bullet}$ (14.4 G) as the average value of the hyperfine coupling for a freely rotating methyl group, equation 26 may be modified to equation 27. From the observed values of a(H), it is then possible to calculate the corresponding values of θ. Thus, for radical **41** the a(H) values lead to values of θ of 30°, 45°, 72° and 78°, respectively, corresponding to a conformation which is not too dissimilar from that in which the morpholino ring adopts the chair conformation **43**. This identifies the axial protons as those with the larger hyperfine



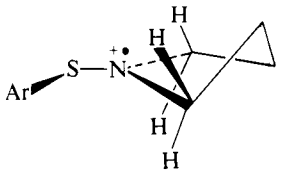
(**43**)

couplings, the equatorial protons lying almost in the plane orthogonal to the π orbital containing the unpaired spin density. Likewise, the hyperfine couplings for radical **40** are consistent with these expected from a structure similar to **44**, with all protons subtending angles θ of *ca* 35°.

$$a(\mathrm{H}) = \rho_{\mathrm{N}}^{\pi} B \cos^2 \theta \tag{26}$$

$$a(\mathrm{H}) = 28.8 \cos^2 \theta \tag{27}$$

The data for the radical cations $(R_2N)_2S^{+\bullet}$ are easily understood in terms of the arguments outlined above. The presence of an extra nitrogen atom over which the radical



(44)

cation may be delocalised results in a lowering of the g-value (less unpaired spin on sulphur) and a decrease in a(N) by a factor of *ca* 2. Moreover, all of the methylene protons appear equivalent. The extra resonance form must reduce the π-bond order between sulphur and each nitrogen atom and therefore result in a lower energy barrier to rotation.

E. The Perthiyl Radical, RSS•

1. Formation

Despite their deceptively simple structure, and also their relationship to the analogous sulphinyl radicals RSO• (Section II.B), the ESR spectroscopy of perthiyl radicals has been the subject of some controversy. The problem resides in the difficulty of unambiguously generating, detecting and assigning the spectra to such radicals. Because of their biological significance, a variety of sulphur-containing compounds including thiols (e.g. cysteine), sulphides (e.g. *N*-acetylmethionine) and disulphides (e.g. cystine) have been subjected to radiolytic (X- and γ-) and photolytic damage. Several types of radical are produced in such circumstances, and one that has been studied in some detail has anisotropic g-values of *ca* 2.004, 2.026 and 2.053, i.e. $g_{ave} = 2.028$[61-68]. This is consistent with a sulphur-centered radical, and in the early studies this radical was assigned a thiyl structure, RS•[61-63]. However, such an assignment is incorrect. Thiyl radicals in general are unlikely to be detected because of the degeneracy of the p-orbitals, and the media in which they are generated are unlikely to provide a sufficiently strong asymmetric interaction to lift this degeneracy[69]. A more practical and definitive consideration for ruling out the RS• assignation is the observation from $a(^{33}S)$ hyperfine coupling constants (see later) that the radicals contain two, non-equivalent sulphur atoms[65]. However, this negative evidence does not identify the observed radical as the perthiyl structure RSS•. As Symons has pointed out, most of the data are consistent with both the perthiyl structure and $RSSR_2^{\bullet}$[67,69]. Since neither are primary radicals but are formed via secondary processes[64,66,70], it has proved exceedingly difficult to assign with confidence the structure of the observed radical. However, Griller and coworkers have attempted to resolve the situation by studying the relatively simple *tert*-butylperthiyl radical, Bu^{t}SS•[71]. By employing a variety of techniques, and a range of substrates with the potential for generating Bu^{t}SS•, they obtained ESR and UV-visible spectra considered to be those of the perthiyl radical. Thus, laser flash photolysis of both *tert*-butyl tetrasulphide and *tert*-butylthiosulphenyl chloride (equations 28 and 29), as well as direct photolysis of *tert*-butyl disulphide in the presence of the triplet sensitizer benzophenone (which is known to result in C–S, rather than the more usual S–S, bond cleavage[72]) (equation 30), all yield the same UV–visible spectrum, with the most intense λ_{max} at *ca* 370 nm but also a less intense maximum at 550 nm. Interestingly, other workers have identified the perthiyl radical as having λ_{max} 380 nm[66,70], though this is true of $RSSR_2^{\bullet}$[67].

$$Bu^tSSSSBu^t \xrightarrow{h\nu} 2\ Bu^tSS^{\bullet} \qquad (28)$$

$$Bu^tSSCl \xrightarrow{h\nu} Bu^tSS^\bullet + Cl^\bullet \quad (29)$$

$$Bu^tSSBu^t \xrightarrow[Ph_2CO]{h\nu} Bu^tSS^\bullet + Bu^{t\bullet} \quad (30)$$

ESR investigation of photolysed frozen toluene solutions of $Bu^tS_4Bu^t$ and Bu^tSSCl give anisotropic g-values 2.002, 2.027 and 2.058, with g_{ave} equal to 2.029[71]. These values bear remarkable similarity to those previously incorrectly ascribed to thiyl radicals (see above) and it would seem that such radicals may well be perthiyl radicals, as assigned by Gordy and coworkers amongst others[64,65]. Other, independent, evidence that perthiyl radicals are responsible for the spectrum with g *ca* 2.025 comes from the work of Roberts, who found that radicals of structure $R_2SSCF_3^\bullet$ and $R_2SSCOR'^\bullet$ have g-values *ca* 2.014[73]. Though one cannot take this evidence as definitive—the presence of electron-withdrawing groups will decrease spin density at sulphur and therefore lower g—taken together with the results for $Bu^tSS^\bullet$ it does suggest that the species having g *ca* 2.025 are indeed perthiyl radicals. Accepting this view, but not disregarding the important comments of Symons[67,69], it would appear that perthiyl radicals may be generated by photolytic and radiolytic methods from a variety of substrates. As well as those outlined above in equations 28–30, γ- and X-radiolysis of thiols[62,65,67] (equation 31), sulphides[61,65] (equation 32) and disulphides[63,64] (equation 33) have all proven successful, as has the photolysis of thiols[66,70] and disulphides[68,70,71] (though for direct photolysis of disulphides S–S bond cleavage is the major process). γ-Radiolysis of sulphenyl chlorides (equation 34) and thiosulphenyl chlorides (equation 35) has also been used[66]. Perthiyl radicals are also formed by the photolysis of thiosulphenyl chlorides[74].

$$RSH \longrightarrow RS^\bullet + H^\bullet \xrightarrow{RSH} RSSHR^\bullet \longrightarrow RSS^\bullet + RH \quad (31)$$

$$RSR' \longrightarrow RS^\bullet + R'^\bullet \xrightarrow{RSR'} RSSRR'^\bullet \longrightarrow RSS^\bullet + RR' \quad (32)$$

$$RSSR' \xrightarrow{+e^\bullet} RSSR'^{\bullet} \xrightarrow{+H^+} RSSHR'^\bullet \longrightarrow RSS^\bullet + R'H \quad (33)$$

$$RSCl \xrightarrow{+e^\bullet} RS^\bullet + Cl^- \longrightarrow R^\bullet + S \xrightarrow{RS^\bullet} RSS^\bullet \quad (34)$$

$$RSSCl \xrightarrow{+e^\bullet} RSS^\bullet + Cl^- \quad (35)$$

2. g-Values and hyperfine coupling constants

The identification of the ESR spectrum of $Bu^tSS^\bullet$ as that with anisotropic g-values of 2.058, 2.027 and 2.002 gives sufficient confidence that other sulphur-containing radicals, generated by a variety of methods, with similar anisotropic g-values also have the perthiyl structure. The ESR spectral data for such species are contained in Table 10. The following features are noteworthy.

(i) Values of g_{ave} are remarkably structure-independent. Only when the –S–S$^\bullet$ radical centre is directly attached to an acyl, phosphoryl or thiophosphoryl centre are the average

TABLE 10. ESR spectral data for perthiyl radicals, RSS•

	Medium	Temp. (K)	g_{ave}	g_1	g_2	g_3	Hyperfine coupling constants (G) $a_{iso}(^{33}S)$	$a_{aniso}(^{33}S)$	a(H)	Ref.
HSS•	H_2S		2.029	2.061	2.024	2.003			*ca* 7	75
MeSS•	Neat	77	2.026	2.057	2.025	1.997				76, 77
	Me_2S_2	77	2.027	2.056	2.025	2.000			7.2 (3H)	67
		77		2.0598					7.6 (3H)	85
EtSS•			2.030	2.063	2.027	1.999				77–79
		77	2.029	2.059	2.026	2.002			8 (1H)	67
Pr^nSS•	Neat	77	2.027	2.054	2.026	2.000				77
Bu^nSS•	Neat	77	2.027	2.058	2.025	1.998				76
	isooctane	213	2.0262							80
Bu^tSS•	Toluene	113	2.029	2.058	2.027	2.002				71, 77
	Toluene	77	2.029	2.059	2.026	2.001				74
$C_5H_{11}SS$•	Neat	77	2.029	2.061	2.025	2.001				77
$C_6H_{13}SS$•	Neat	77	2.029	2.062	2.026	2.000				77
$C_{12}H^n_{25}SS$•	Neat		2.025	2.057	2.022	1.998				76
$H_3\overset{+}{N}CH_2CH_2SS$•		77	2.028	2.058	2.025	2.001				67
	Cysteamine·HCl crystal	295	2.029	2.054	2.027	2.005			9 (1H)	83
$HO_2CCH_2CH_2SS$•		77	2.029	2.061	2.025	2.001			9 (1H)	67
$HO_2CCHMeCH_2SS$•		77	2.028	2.059	2.025	2.000				67

$HO_2CCH(\overset{+}{N}H_3)CH_2SS^{\bullet}$	Cystine·2HCl crystal	298	(a) 2.026	2.053	2.026	2.000	20.6 13.0	14.5 9.2	10(1H)	64
			(b) 2.032	2.067	2.027	2.002	20.3 12.3	16.0 10.0	5(1H)	
	Cystine crystal	77	0.028 2.026	2.062 2.055	2.022 2.024	2.001 2.000			10(1H)	76 67
	Cystine·2HCl crystal	298	2.028	2.052	2.029	2.003			9(1H)	63, 81, 82
	Cysteine·HCl crystal	298	(a) 2.025 (b) 2.028	2.055 2.062	2.023 2.023	1.998 1.999	21.0 13.0	15.4 10.0	11(1H) 5(1H)	65
	Cysteine crystal	295	2.028	2.052	2.025	2.006			9(1H)	83
$HO_2CCH(NHCOMe)CH_2SS^{\bullet}$	Crystal	200–300	2.031	2.063	2.026	2.004	21.8 13.0	14.3 10.1	10(1H)	65
	Crystal	298	2.032	2.064	2.029	2.004			9.5(1H)	61
$HO_2CCH(\overset{+}{N}H_3)CMe_2SS^{\bullet}$	Penicillamine crystal	77	2.028	2.057	2.025	2.001				67
		295	2.028	2.053	2.026	2.004				83, 84
$ClCH_2CHOHCH_2SS^{\bullet}$		77	2.028	2.059	2.025	2.001			8(1H)	67
$HSCH_2(CHOH)_2CH_2SS^{\bullet}$		77	2.029	2.060	2.025	2.001			9(1H)	67
$EtCOSS^{\bullet}$	Cyclopropane	*ca*165	2.024							73
$Bu^tCOSS^{\bullet}$	Cyclopropane	*ca*160	2.024							73
$(EtO)_2P(O)SS^{\bullet}$	Neat	130	2.023	2.040	2.0254	2.0025				68
$(EtO)_2P(S)SS^{\bullet}$	Toluene	130	2.023	2.041	2.0259	2.0024				68
$(Pr^iO)_2P(S)SS^{\bullet}$	Toluene	140	2.023	2.040	2.0257	2.0022				68
$(Bu^sO)_2P(S)SS^{\bullet}$	Toluene	130	2.023	2.041	2.0260	2.0023				68

g-values lowered significantly. Clearly, these groups must be capable of removing some of the spin density from the radical centre.

(ii) Coupling of two ^{33}S nuclei is apparent, and the coupling is anisotropic. One of the sulphur nuclei couples more strongly to the unpaired electron, indicative of greater spin density at that nucleus.

(iii) An essentially isotropic proton hyperfine coupling, a(H), of *ca* 5–10 G to one proton is observed for some radicals with the $RCH_2SS^{\bullet}$ structure. Though this has generally been taken as coupling to one of the CH_2 protons, it has also been considered consistent with the RSSHR$^{\bullet}$ formulation of these radicals[67, 69]. In favour of the former is the quartet observed for $MeSS^{\bullet}$[85], the lack of coupling for the radical derived from pencillamine, $HO_2CCH(\overset{+}{N}H_3)CMe_2SS^{\bullet}$, which has no α-CH_2 protons with which to couple[83], and the presence of the a(H) coupling on replacement of all NH and OH protons by deuterons[83]. In favour of the latter, Symons has reinvestigated the penicillamine radical and observed an anisotropic proton coupling of *ca* 3.3 G which disappears on deuterium replacement[67]. However, the result for $MeSS^{\bullet}$ appears to be unequivocal showing that coupling to the α-CH protons is observed.

Irradiation of cysteine or cystine generates two radicals that display very similar anisotropy in both g and a (^{33}S) (Table 10). These appear to be the same radical experiencing different crystal-field interactions[64, 65].

3. Structure

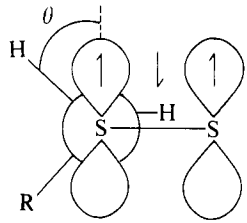
SCF MO calculations for $HSS^{\bullet}$ using an *spd* basis set predicts H–S and S–S bond distances of 133 pm and 202 pm, respectively, with an $H\hat{S}S$ bond angle of 98°[16]. Based on this structure, the UHF method was used to calculate proton, a(H) and sulphur, $a(^{33}S)$, hyperfine coupling constants. The value for a(H) is −4.9 G, and the two $a(^{33}S)$ values are 9.5 G and 16.2 G for the central and terminal sulphur atoms, respectively[16]. These are in fairly good agreement with the experimental values: a(H) for $HSS^{\bullet}$ is *ca* 7 G, and the two isotropic $a(^{33}S)$ hyperfine coupling constants are *ca* 13 G and 20 G (Table 10). The minimum value of g, and the maximum $a(^{33}S)$ coupling are perpendicular to the CSS plane (the plane of the sulphur p orbital) with the direction of the maximum value of g near to that of the S–S bond[64, 65]. It is believed that the $C\hat{S}S$ angle is *ca* 120°[64].

The values of a_{iso} (^{33}S) and a_{aniso} (^{33}S) enable the spin densities of the two sulphur atoms to be determined. These are contained in Table 11 and show unquestionably that the perthiyl radical, like the analogous sulphinyl and thioaminyl radicals, is a π radical. The greater part, *ca* 55% of the unpaired spin resides on the terminal sulphur atom, 37% residing at the central sulphur atom. The value for the central sulphur is similar to that found for thioaminyls but much lower than for the sulphinyl radicals (Sections II. B and II. C). This is in accord with expectations based on the relative electronegativities of oxygen, nitrogen and sulphur.

TABLE 11. Sulphur 3s and 3p spin densities for $RSS^{\bullet}$ radicals

Radical	Spin density							
	Central S				Terminal S			
	3s	3p	3s+3p	p/(s+p)	3s	3p	3s+3p	p/(s+p)
$HO_2CCH(\overset{+}{N}H_3)CH_2SS^{\bullet}$	0.013	0.36	0.37	0.97	0.022	0.55	0.57	0.96
$HO_2CCH(NHCOMe)CH_2SS^{\bullet}$	0.013	0.36	0.37	0.97	0.022	0.51	0.53	0.96

Since perthiyl radicals are π-radicals, it is possible to analyse the values of the hyperfine coupling to the α-CH protons using the McConnell-type equation 9. If we assume that the a(H) value observed for MeSS• is that for a freely rotating methyl group, then a value of 15.2 G for $\rho_S^\pi B$ is obtained. Since the π-spin density at the central sulphur atom is 0.36, B is *ca* 42 G. The observed values of a(H) for one proton lie between 5–11 G, and by implication the other has a value $5 > a(H) > 0$. The radical conformation which best fits these data is **45**, where θ can vary between *ca* 30° and 55°. This results in one of the protons lying almost perpendicular to the π-orbital, for which calculated a(H) values lie between 0 and 2.7 G. This is well below the resolution of most spectra and would remain undetected.



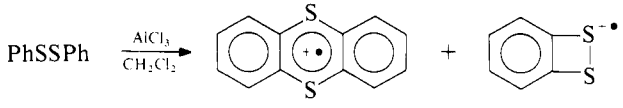
(**45**)

F. The Disulphide Radical Cation, $[R^1SSR^2]^{+\bullet}$

1. Formation

Disulphide radical cations are formed via one-electron oxidation of the parent disulphides; this may be carried out directly, or indirectly from precursor 1, *n*-dithiols and their thioacetals (equation 36). Various methods have been used to effect this oxidation for ESR spectroscopy including dissolution in concentrated sulphuric acid[86–91], low temperature (4–77 K) γ- and X-radiolysis of the disulphides[68,85,92–99], electrochemical oxidation[87,100,101] using a platinum electrode, and mild chemical oxidation using I_2 or Br_2 in nitrobenzene[101] or $AlCl_3$ in dichloromethane or nitromethane[89,91,102–104]. This latter reagent produces well-resolved spectra and may be used for disulphides possessing vertical ionization potential $<ca$ 8 eV[102]. As might be expected, cyclic aryl disulphides have been found to give a direct correlation between the oxidation potential and the calculated energy of the HOMO[101]. In general, aryl disulphides have been studied using chemical methods of oxidation, whereas the alkyl disulphides are subjected to ionizing radiation (though $AlCl_3/CH_2Cl_2$ has been used for alicyclic disulphides[102]). Radical cations of diphenyl disulphide and related compounds have not been observed, because they rearrange to thianthrene and dithiete radical cations (equation 37)[104].

$$\begin{array}{l} R^1SH + HSR^2 \xrightarrow{\text{oxidation}} R^1SSR^2 \xrightarrow{-e^\bullet} [R^1SSR^2]^{+\bullet} \\ \quad\uparrow \\ R^1SCH_2SR^2 \end{array} \qquad (36)$$



(37)

2. g-Values and hyperfine coupling constants

ESR spectral information for disulphide radical cations is contained in Table 12, from which the following salient observations can be made.

(i) g_{ave}- and g_{iso}-values appear to be structure-independent. For dialkyl disulphide radical cations, including those of cyclic systems, the g-values are *ca* 2.020; radical cations of dithietes, which have an extra double bond that can remove spin density from the sulphur atoms, have somewhat smaller values, *ca* 2.015; radical cations that are able to significantly delocalise spin density onto a ring system, e.g. naphthalene-1,8-disulphide, or a dialkylamino group, have g-values < 2.01. Spin density does not appear to delocalise onto neighbouring acyl and thiophosphoryl groups.

(ii) Not surprisingly, g-values for the radical cations of disulphides are larger than those of the sulphenamides, though they are smaller than the corresponding perthiyls.

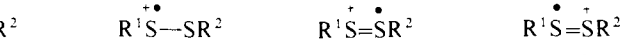
(iii) Coupling is observed to the α-CH protons of the alkyl groups. These are generally observed to be equivalent. Thus $MeSSMe^{+\bullet}$ displays a septet due to six equivalent protons. In some cases of symmetrical acyclic disulphides, e.g. cystine and dithiodiglycolic acid, the four protons give rise to a triplet of triplets. As will be discussed below, this is a conformational effect rather than the non-equivalence of the two alkyl groups. This is most clearly observed in the cyclic systems, where two sets of α-CH_2 proton couplings can be observed. For lipoic acid all three magnetically different α protons exhibit unique hyperfine couplings. The magnetic non-equivalence of the α-CH_2 groups is temperature-dependent (see later).

(iv) Coupling to ring protons of aromatic systems is discernible. Where such positions can be clearly assigned the order of coupling is *para*-H > *ortho*-H > *meta*-H.

(v) In favourable circumstances, coupling to the ^{33}S nuclei at natural abundance can be observed. In one case of a non-symmetrical system, two such $a(^{33}S)$ hyperfine coupling constants are obtained.

3. Structure

Disulphide radical cations can be considered as resonance hybrids of structures **46a–d**, electron loss presumably occurring from a non-bonding 3p orbital[96]. Structures **46c, d**



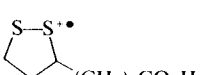
(46a) **(46b)** **(46c)** **(46d)**

indicate some multiple-bond character between the sulphur atoms, and an increased bond strength as compared with the disulphides themselves. To accommodate such a structure, the p orbitals of the sulphur atoms must overlap such that the unpaired electron occupies a π^* orbital. This conclusion leads to a co-planar arrangement of the C–S–S–C system, **47** and **48**, the trans form **47** being favoured[103]. Cyclic systems, of course, are forced to adopt the *cis* arrangement **48**.

(47) **(48)**

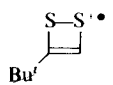
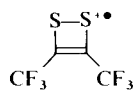
In the absence of anisotropic $a(^{33}S)$ hyperfine coupling constants, which would identify the π nature of the radical, the most convincing arguments for such a structure comes from the anisotropic g-tensors. That g_3 $(=g_z)$ is close to the free-spin g-value indicates

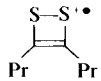
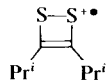
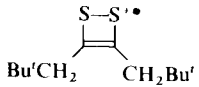
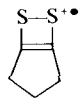
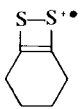
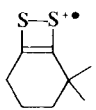
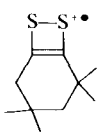
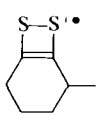
TABLE 12. ESR spectral data for disulphide radical cations, $[R^1SSR^2]^{+\bullet}$

Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling (G) a(H)	$a(^{33}S)$	Ref.
$MeSSMe^{+\bullet}$	Crystal	77	2.018	2.032	2.019	2.004	9.1 (6H)		85
	$CFCl_3$	77	2.018	2.036	2.017	2.002	8.7 (6H)		97, 98
$Pr^iSSPr^{i+\bullet}$	$CFCl_3$	77	2.019	2.035	2.018	2.003	11.0 (2H)		97
$Bu^tSSBu^{t+\bullet}$	$CFCl_3$	77	2.019	2.035	2.018	2.003			94, 97
$C_5H_{11}SSC_5H_{11}^{+\bullet}$	Amorphous Glass	77	2.019	2.035	2.018	2.003			96
$HO_2CCH_2SSCH_2CO_2H^{+\bullet}$	Crystal	4	2.018	2.027	2.023	2.003	12 (2H) 10 (2H)		92
			2.017	2.034	2.016	2.002	15 (2H) 11 (2H)		
$Cystine^{+\bullet}$	Crystal	4	2.022	2.033	2.028	2.005	6.58 (H) 2.8 (2H)		93,105
$PhCH_2SSCH_2Ph^{+\bullet}$	Crystal		2.019	2.034	2.020	2.002	17.7 (2H) 0.7 (2H)		105b
	H_2SO_4		2.0193				3.7 (4H)		89
	$AlCl_3/CH_2Cl_2$	180	2.0183				16.25 (2H) 3.9 (2H)	13.3	102, 106
	H_2SO_4		2.0182				10.0 (4H)		89
	$AlCl_3/CH_2Cl_2$		2.0183				12.3 (1H) 10.6 (1H) 7.6 (1H)		102, 106
	$AlCl_3/CH_3Cl_2$		2.0185				9.5 (4H)		102

(*continued*)

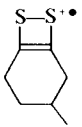
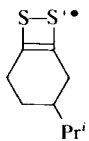
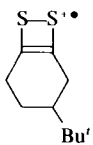
TABLE 12. (*continued*)

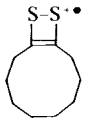
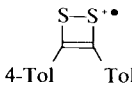
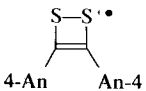
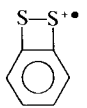
Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling (G) a(H)	$a(^{33}S)$	Ref.
	$AlCl_3/CH_2Cl_2$		2.0183				9.5 (4H)		102
	H_2SO_4		2.018				6.3 (2H)		89
	$AlCl_3/MeNO_2$		2.014						89
	$H_2SO_4/MeNO_2$	100	2.016	2.026	2.020	2.003	2.75 (2H)		90, 91
	H_2SO_4		2.0159				3.3 (1H) 1.8 (3H)		89, 90
	H_2SO_4		2.0155				2.19 (6H)		89
	$AlCl_3/MeNO_2$		2.014						91
	$MeNO_2/H_2SO_4$	100	2.014	2.022	2.016	2.005	2.06 (6H)		91
	H_2SO_4						3.17 (1H)		90
	H_2SO_4						1.35 (6F)		90

	H_2SO_4		2.05 (4H)	90
	H_2SO_4		1.06 (2H)	90
	H_2SO_4		1.55 (4H)	90
	H_2SO_4		5.37 (4H)	90
	H_2SO_4	2.0155	3.04 (4H)	89, 90
	H_2SO_4		2.94 (2H)	90
	H_2SO_4		2.62 (2H)	90
	H_2SO_4		3.57 (1 H) 3.36 (1 H) 2.63 (1 H)	90

(*continued*)

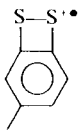
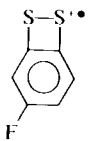
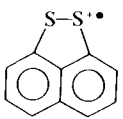
TABLE 12. (*continued*)

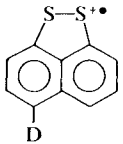
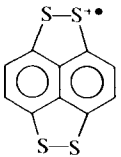
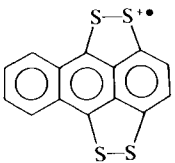
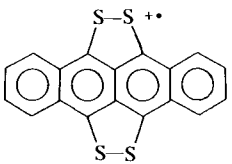
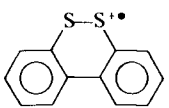
Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling (G) a(H)	$a(^{33}S)$	Ref.
	H_2SO_4						3.76 (2H) 2.30 (2H)		90
	H_2SO_4						3.95 (2H) 2.16 (2H)		90
	H_2SO_4						4.04 (2H) 2.02 (2H)		90
	H_2SO_4						2.80 (2H) 0.85 (2H)		90

	H_2SO_4						2.34 (2H)	90
	H_2SO_4		2.0144				2.75 (1H) 0.90 (4H)	89
	H_2SO_4						3.14 (1H)	90
	$AlCl_3/MeNO_2$ $H_2SO_4MeNO_2$	 100	2.014 2.016	 2.025	 2.019	 2.003		91 91
	$AlCl_3/MeNO_2$ $H_2SO_4/MeNO_2$	 100	2.014 2.014	 2.020	 2.018	 2.003		91 91
	$AlCl_3/MeNO_2$ $H_2SO_4/MeNO_2$	 100	2.013 2.015	 2.023	 2.019	 2.003		91 91
	$AlCl_3/CH_2Cl_2$		2.0150				1.15 (3-H)	104

(*continued*)

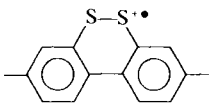
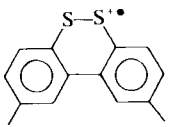
TABLE 12. (*continued*)

Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling (G) a(H)	$a(^{33}S)$	Ref.
	$AlCl_3/CH_2Cl_2$		2.0150				1.15 (3-H and Me)		104
	$AlCl_3/CH_2Cl_2$		2.0160				1.20 (3-H) 3.30 (4-F)		104
	94% H_2SO_4						3.85 (*o*-H) 0.70 (*m*-H) 5.20 (*p*-H)		88
	$MeO(CH_2)_2OMe$		2.0081				4.44 (*o*-H) 0.88 (*m*-H) 5.30 (*p*-H)		87
	$AlCl_3/MeNO_2$		2.0082				4.50 (*o*-H) 0.92 (*m*-H) 5.37 (*p*-H)	7.33	86, 107
	H_2SO_4/CF_3CO_2H		2.0079				4.56 (*o*-H) 0.96 (*m*-H) 5.52 (*p*-H)	7.16	101

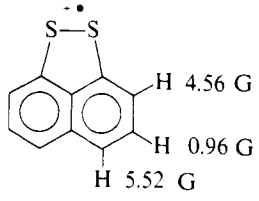
	$AlCl_3/MeNO_2$		4.50 (*o*-H) 0.92 (*m*-H) 5.37 (*p*-H) 0.82 (*p*-D)		86
	CH_3CN	2.0094	1.51	4.37	101
	$C_6H_5NO_2$	2.0086	1.80 (2H) 0.55 (2H) 0.43 (2H)	3.70 4.01	101
	Acetone $C_6H_5NO_2$	2.0064 2.0077	0.55 (8H)	3.30	100 101
	94% H_2SO_4 $AlCl_3/MeNO_2$	2.0112	0.70 (*o*-H) 1.40 (*p*-H) 0.98 (2-H) 0.38 (3-H) 1.83 (4-H) <0.1 (5-H)	10.9	88 86

(*continued*)

TABLE 12. (*continued*)

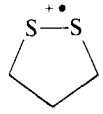
Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling (G) a(H)	$a(^{33}S)$	Ref.
	$AlCl_3/MeNO_2$						1.15 (2-H) 0.40 (Me) 1.97 (4-H) <0.1 (5-H)		86
	$AlCl_3/MeNO_2$						0.98 (2-H) 0.39 (3-H) 2.42 (Me) <0.1 (5H)		86
$PhCOSSCOPh^{+\bullet}$	Crystal	4	2.018	2.032	2.019	2.004			99
$(Pr^iO)_2P(S)SSP(S)(Pr^iO)_2^{+\bullet}$	Freon	77	2.017	2.035	2.014	2.002			68
$Me_2NSSNMe_2^{+\bullet}$	$AlCl_3/CH_2Cl_2$	210	2.0047				7.5 (^{14}N) 7.5 (Me)		103

that the radical cation has relaxed from the orthogonal structure of the parent disulphide[96, 106] to a planar structure[94, 97]. Values for g_x and g_y are then expected to be greater than the free-spin value, with g_x being larger since the field should couple the SOMO with the S–S σ-bonding orbital[94, 97]. Confirmation of the π character of the radical comes from the hyperfine coupling constants for aryl ring protons in, for example, the radical cation of naphthalene-1,8-disulphide (**49**). These show that the 2- and 4-protons have a(H) values of similar magnitude to each other, and that these are much larger than the a(H) value of the 3-proton. As discussed earlier, this is the order expected for a π radical.



(**49**)

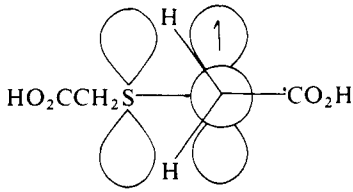
Symmetrical disulphides can be considered to be resonance hybrids in which both **46a** and **46b** (or **46c** and **46d**) contribute equally to the structure. Thus, for the radical cation **49**, the unpaired electron couples of two 2-H protons, two 3-H protons and two 4-H protons. Similarly, the hyperfine splitting for $MeSSMe^{+\bullet}$ is a septet. More convincing evidence comes from the ^{33}S hyperfine splittings. For all symmetrical disulphides only one $a(^{33}S)$ value is observed, even for those systems for which the α-CH protons exhibit two different hyperfine couplings, e.g. **50**.



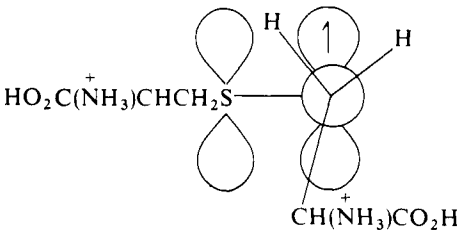
(**50**)

Such structures imply that the maximum unpaired spin density on each sulphur is *ca* 50%, though for aryl systems delocalization onto the ring will reduce this accordingly. Sulphur π-spin densities may be calculated using equation 23 provided a value of $Q_{^{33}S}$ is known. For sulphide radical cations a value of 33.4 G has been determined[108] and, interestingly, a plot of the observed $a(^{33}S)$ values versus the calculated sulphur π-spin density using the HMO method for five cyclic aryl disulphide radical cations yields a value of 33.0 G[101]. Taking this value, which we note in passing is *ca* 50% larger than that used for sulphenamide radical cations (Section II.D), and the experimental $a(^{33}S)$ hyperfine coupling constants observed for other radicals, the sulphur π spin densities in Table 13 may be calculated, together with the aryl ring spin densities.

Since disulphide radical cations are π radicals, coupling to α-CH protons is hyperconjugative in nature; equation 9 then pertains. Taking the observed hyperfine coupling, a(H), for $MeSSMe^{+\bullet}$ as that for a freely rotating methyl group (for which $\langle \cos^2\theta \rangle = \frac{1}{2}$), the value of $\rho_S B$ for disulphide radical cations is 18.2 G. Using this value to calculate θ for those radical cations that give rise to two different α-CH hyperfine coupling constants gives rise to the following conclusions regarding the conformations adopted by such radicals. Dithiodiglycolic acid adopts a conformation similar to **51** (or the equivalent involving rotation of 180° about the C–S bond), whereas cystine adopts conformation **52**. Presumably these differences relate to crystal effects.

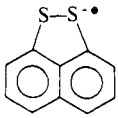
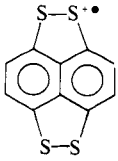
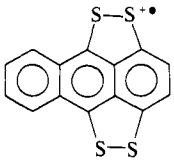
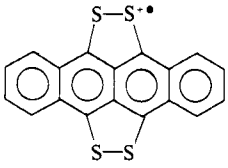
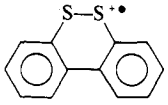


(51)



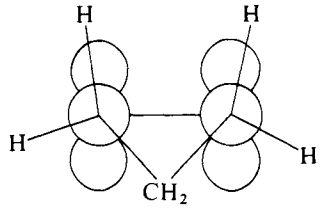
(52)

TABLE 13. Sulphur and aryl ring π-spin densities for disulphide radical cations

Radical	Spin density		
	S^1	S^2	aryl ring
	0.40	0.40	—
	0.22	0.22	0.67
	0.26	0.26	0.49
	0.22	0.24	0.50
	0.20	0.20	0.64
	0.33	0.33	0.24 (0.34)[a]

[a] Calculated.

The cyclic disulphide **50** is constrained to adopt a *cis* co-planar conformation about the S–S bond, and the large proton hyperfine coupling observed for two of the α-CH protons indicates that these must lie in the plane of the π orbital containing the unpaired electron **53**. This results in the two remaining α-CH protons lying close to the plane orthogonal to the π orbital containing the unpaired electron ($\theta = 122°$), and the small observed hyperfine coupling is entirely consistent with this interpretation. On warming, the spectrum of **50** collapses to a quintet, $\langle a(H) \rangle$ *ca* 10 G, the α-CH protons becoming magnetically equivalent by a ring flip of the central methylene group. The energy barrier for this process has been calculated as 8 kJ mol^{-1} [102,106].



(53)

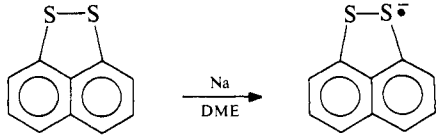
G. The Disulphide Radical Anion, $[R^1SSR^2]^{-\bullet}$

1. Formation

Disulphides occupy a significant position in radiation chemistry and biology, possessing the ability to act as protecting agents against the damaging effects of ionising radiation. In the previous section it was seen that removal of an electron from the disulphide group using X- or γ-radiation results in a disulphide radical cation; trapping of the ejected electron by another disulphide generates the corresponding radical anion. Thus, both types of radical are observed in such irradiations, and this method of generating the disulphide radical anion is the most common (equation 38)[67,82,85,92,94–96,98,99,109–112].

$$R^1SSR^2 \xrightarrow[\substack{\gamma\text{-irradiation} \\ <77\,K}]{\text{X- or}} R^1SSR^{2+\bullet} + e^{\bullet} \xrightarrow{R^1SSR^2} R^1SSR^{2\,\bar{\bullet}} \qquad (38)$$

Two other methods should be mentioned. One electron reduction, using either sodium in dimethoxyethane[87] or $CO_2^{-\bullet}$[3], generates the corresponding radical (e.g. equation 39), and the oxidation of a [1, *n*]-dithiol using Ti(III)–H_2O_2 at pH 7 produces the cyclic disulphide radical anion (equation 40)[3].



(39)

$$HS(CH_2)_nSH \xrightarrow[\substack{\text{Ti(III)} \\ H_2O_2}]{\text{pH 7}} {}^{-}S(CH_2)_nS^{\bullet} \longrightarrow \overline{S(CH_2)_nS}^{\bullet} \qquad (40)$$

$n = 3.4$

2. g-Values and hyperfine coupling constants

Table 14 contains the g-values and proton, a(H), and sulphur $a(^{33}S)$ hyperfine coupling constants for known disulphide radical anions. Clearly, there is less information available than for perthiyl and disulphide radical cations. Nevertheless, the data allow some conclusions to be made.

(i) g-Values in the solid state are anisotropic, though g_{ave} is roughly of similar magnitude to that for disulphide radical cations. However, the radical anion may be distinguished by the axial symmetry of the g-tensor with $g_{\perp}$ *ca* 2.02 and $g_{||}$ *ca* 2.002, which is the free-spin value. The radical cation does not exhibit such symmetry, and $g_{\perp}$ is *ca* 2.002. g-Values appear largely to be structure-independent.

(ii) The proton hyperfine coupling is anisotropic. For example, for cystine the principal values have been reported as 7.49, 9.63 and 9.99 G for two of the protons, and 6.42, 8.56 and 9.63 G for the others[111]. Generally, however, either of two situations pertains. Either all of the α-CH protons are observed to couple with the unpaired electron, or only two of the four α-CH protons couple. This is a conformational problem (see below).

(iii) Coupling to the ^{33}S nucleus has been observed for MeSSMe$^{\bullet-}$ and cystine$^{\bullet-}$. Whereas for MeSSMe$^{\bullet-}$ such coupling has been reported to be largely isotropic, a (^{33}S) *ca* 60 G[85], for cystine two independent investigations have reported significant anisotropy[95,109], e.g. $a_{||} = 64$ G and $a_{\perp} \approx 8$ G[109].

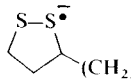
3. Structure

Disulphide radical anions can be thought of as resonance hybrids of **54a,b**. There are two possible locations for the unpaired electrons: either it resides in a sulphur 3d orbital or it resides in the S–S σ^*_{3p} antibonding orbital. Three observations indicate that the electron does not reside in a 3*d* orbital. First, the g tensor is axially symmetric with $g_{\perp} > g_{||}$, and $g_{||} \approx g_{\text{free spin}}$. For several radical anions the direction cosines of $g_{||}$ are essentially those for the S–S bond (Table 15). Moreover, a calculation for the energy gap between the ground state and the first excited state for d-orbital participation using the $g_{||}$ value observed is an order of magnitude too large. However, a similar calculation reproduces the energy gap quite well for a σ^*_p orbital[82]. Secondly, that it is the σ^* antibonding orbital of the S–S bond that is occupied comes from the $a(^{33}S)$ hyperfine coupling. Coupling to a 3d orbital would be an order of magnitude less than that observed and would not clear the signal for the ^{32}S–^{32}S species[95]. Moreover, the direction of maximum ^{33}S coupling is almost coincident with the direction of $g_{||}$, i.e. the direction of the S–S bond. The anisotropy in $a(^{33}S)$ is symmetric about the axis of $g_{||}$, clearly demonstrating that the unpaired electron is in a σ orbital[95, 109]. Third, the naphthalene-1,8-disulphide radical anion is highly localized on sulphur, with little interaction between the unpaired spin and the π system of the aryl rings. Whereas this is concordant with a σ^* orbital, d-orbital participation would be expected to interact strongly with the π system and can therefore be ruled out[87].

$R^1S\text{–}\dot{\bar{S}}R^2$ (**54a**) $\qquad$ $R^1\dot{\bar{S}}\text{–}SR^2$ (**54b**)

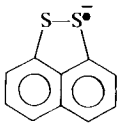
Such an analysis implies that the unpaired electron is shared equally by the two sulphur atoms. This would accord with the experimental observation that for MeSSMe$^{\bullet-}$ all six α-CH protons are equivalent, and that for cystine only one ^{33}S hyperfine coupling is

TABLE 14. ESR spectral data for disulphide radical anions

Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling constants (G) a(H)	a_{iso} (^{33}S)	a_{aniso} (^{33}S)	Ref.
$MeSSMe^{\bullet-}$	Crystal	77	2.013	2.020	2.020	2.000	5.0 (6H)	*ca* 60		85
$C_5H_{11}SSC_5H_{11}^{\bullet-}$	THF	77	2.016	2.022	2.022	2.003				96
$PhCH_2SSCH_2Ph^{\bullet-}$	Crystal		2.014	2.021	2.018	2.003	9.3 (2H), 5.4 (2H)			105b
$HO_2CCH_2SSCH_2CO_2H^{\bullet-}$	Crystal	4	2.013	2.021	2.017	2.001	8 (2H)			92
Cystine$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.013	2.019	2.019	2.002	8.5 (2H)			110
	Crystal	77	2.013	2.018	2.018	2.002	8.5–10 (2H), 6–8 (2H)	27	18.5	82, 109
	Crystal	77	2.0125	2.0178	2.0174	2.0024	9.09 (2H), 8.21 (2H)			111
	Crystal	4	2.016	2.022	2.021	2.005	9.56 (1H), 9.03 (1H), 5.28 (1H), 3.92 (1H)			112
	Crystal	77	2.013	2.018	2.018	2.002		31.9	15.8	95
	Crystal	77					10.3 (1H), 10.3 (1H), 7.18 (1H) 7.18 (1H)			105a
Homocystine$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.013	2.019	2.019	2.002	8.5 (2H)			110
	H_2O		2.0132				6.8 (4H) 1.0 (2H)			3
	H_2O		2.0129				7.8 (1H), 4.35 (2H) 1.45 (2H)			3
	D_2O–CD_3OD (4:1)	77	2.011	2.020	2.012	2.002	10 (1H)			110
	H_2O		2.0133				6.3 (4H)			3

(*continued*)

TABLE 14. (*continued*)

Radical	Matrix	Temp. (K)	g_{iso} or g_{ave}	g_1	g_2	g_3	Hyperfine coupling constants (G) a(H)	a_{iso} (^{33}S)	a_{aniso} (^{33}S)	Ref.
	$MeOCH_2CH_2OMe$		2.0110				0.4 (2H)			87
PhCOSSCOPh$^{\bullet-}$	Crystal	4	2.009	2.014	2.010	2.004				99
Alcohol dehydrogenase$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.013	2.019	2.019	2.002	9.5 (2H)			110
Glutathione$^{-\bullet}$	D_2O–CD_3OD (4:1)	77	2.012	2.017	2.017	2.002				110
α-Chymotrypsin$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.012	2.021	2.014	2.002	8.0 (2H)			110
α-Lactolbumin$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.014	2.020	2.020	2.002	9.5 (2H)			110
Conalbumin$^{-\bullet}$	D_2O–CD_3OD (4:1)	77	2.014	2.020	2.020	2.002				110
Insulin$^{\bullet-}$	D_2O–CD_3OD (4:1)	77	2.014	2.020	2.020	2.002	9.0 (2H)			110

Venom$^{\bar{\bullet}}$ (Formosan cobra)	D_2O–CD_3OD (4:1)	77	2.014	2.020	2.020	2.002	7.5 (2H)	110
Oxytocin$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.014	2.020	2.020	2.002	8.0 (2H)	110
Lysozyme$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.014	2.024	2.017	2.002	9.0 (2H)	110
Glutathione reductase$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.014	2.024	2.015	2.002	8.0 (2H)	110
Lipoamide dehydrogenase$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.014	2.024	2.015	2.002	8.0 (2H)	110
Thyroglobulin$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.013	2.018	2.018	2.002		110
Superoxide dismutase$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.013	2.018	2.018	2.002		110
Albumin$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.013	2.018	2.018	2.002		110
Ribonuclease$^{\bullet}$	D_2O–CD_3OD (4:1)	77	2.013	2.019	2.019	2.002		110

TABLE 15. Direction cosines for $g_{||}$ and the disulphide bond in some disulphide radical anions

Radical	$g_{||}$			S–S			Ref.
	a'	*b*	*c*	*a'*	*b*	*c*	
PhCOSSCOPh$^{\bullet-}$	0.642	−0.256	−0.723	0.535	−0.458	−0.709	99
Cystine$^{\bullet-}$	0.610	0.707	0.358	0.526	0.740	0.419	112
$HO_2CCH_2SSCH_2CO_2H^{\bullet-}$	0.79	0.00	0.62	0.84	0.00	0.55	92

observed, but each line has an intensity of *ca* 0.4% (i.e. twice the intensity of a radical containing only one sulphur atom) of the ^{32}S spectrum. This equivalence for $a(^{33}S)$ for the two sulphur atoms confirms the symmetry of the radical.

Calculation of the sulphur 3s and 3p spin densities for the cystine radical anion, as described in earlier sections, results in the conclusion that the s character of the orbital containing the unpaired electron is *ca* 3% and the p character *ca* 63%[95,109]. Thus, the orbital has almost entirely p character (Figure 6), though the contribution of the 3p orbitals is somewhat greater than the 50% anticipated. This has been interpreted in terms of an increased dipolar field experienced by one ^{33}S nucleus due to the electron spin on the neighbouring sulphur atom[95,109]. The situation is confused by the report for MeSSMe$^{\bullet-}$ that the $a(^{33}S)$ hyperfine coupling constants are largely isotropic, varying between 56 and 64 G[85]. This indicates that the isotropic coupling is *ca* 60 G, corresponding to *ca* 12% spin density in the sulphur 3s orbital, and the anisotropic coupling is *ca* 2–3 G, corresponding to *ca* 10% spin density in the sulphur 3p orbital. However, the data for cystine$^{\bullet-}$ are more accurate and the conclusions derived from them ought to be considered more reliable.

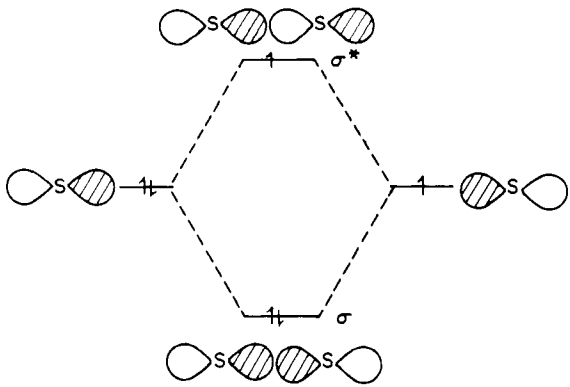
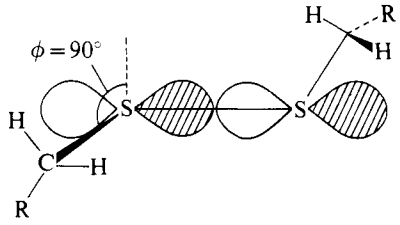


FIGURE 6. Schematic MO representation of the σ bonding of disulphide radical anions

The anisotropy in the *g*-tensor provides an indication of the dihedral angle (φ) between the C_1–S_1S_2 plane of one alkyl group and the C_2–S_2S_1 plane of the other. Since $g_1 = g_2$ (i.e. $g_\perp$) and $g_\perp > g_{||}$, symmetry dictates that $\varphi = 90°$. This is the dihedral angle found in the parent disulphide[96,106]. If $\varphi \neq 90°$ then $g_1 \neq g_2$. For most disulphides in Table 14, $g_1 = g_2$, so most have φ close to 90°. Significantly, for lipoic acid, which is a cyclic disulphide, the molecular structure constrains φ to be no more than *ca* 60°, and for this radical anion axial symmetry is lost[110].

The proton hyperfine coupling constants are largely isotropic, which indicates that they mainly arise from hyperconjugative processes[95,105]. This allows the conformation of the C–S bond to be determined using equation 9. Assuming that the value of a(H) for $MeSSMe^{\bullet}$ is that for a freely rotating methyl group, $\rho_S B = 10$ G. Thus the relatively large value of the hyperfine coupling constants observed for two of the protons, 8–10 G, implies that these protons lie in or close to the plane of the σ^* orbital. This results in the other protons having a(H) values *ca* 2.5 G. All of the couplings in Table 14 can be accommodated by slight conformational variations of this model or by adopting $\rho_S B = 12$ G[105]. Thus the data point to a structure similar to **55** for a disulphide radical anion.



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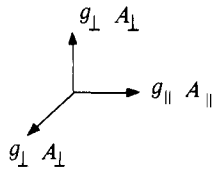
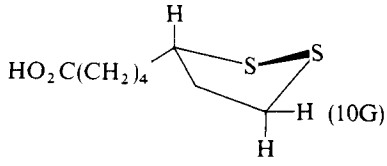


Interestingly, the large coupling observed in the solid state spectrum of lipoic acid must be due to the in-plane proton in **56**; the other two α-CH protons are almost orthogonal and will have couplings close to zero.



(56)

III. THE NMR SPECTRA OF SULPHENIC ACIDS AND DERIVATIVES

A. Proton and Carbon-13 Chemical Shifts and Coupling Constants

1. Introduction

Sulphenyl groups are modestly electron-withdrawing by the inductive effect and have a deshielding effect on adjacent alkyl groups. Table 16 gives substituent effects for some sulphenyl groups, SX. The electron-withdrawing ability falls in the order, sulphonyl- > sulphinyl > sulphenyl.

The –SR groups (R = alkyl, aryl) are weakly electron-withdrawing by the inductive effect but resemble –OR groups in being resonance electron-supplying. This contrasts with sulphinyl groups –S(O)R which are resonance electron–withdrawing[15]. The electron-supplying resonance effect is almost completely suppressed by the presence of an electron-withdrawing group X in –SX. The –SCl group is similar in inductive electron-withdrawing power to Cl (σ_ICl, 0.37–0.50[116]; σ_ISCl, 0.40[115]) but by contrast to Cl has an almost negligible resonance effect (σ_R^0Cl, −0.18 to −0.365; σ_R^0SCl, 0.08[115]). For the

TABLE 16. Some substituent constants for SX and related groups

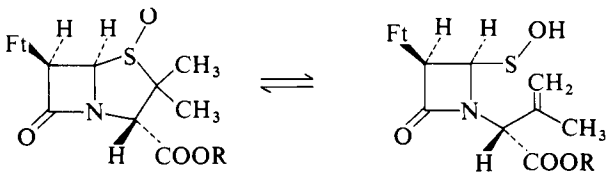
SX	σ_m	σ_p	Ref.	σ_I	σ_R^0	σ_p^+	Ref.
SCH_3	0.14	0.06	117	0.13	−0.16		115
						−0.55	118
$SCOCH_3$	0.39	0.44	119	0.41			116
					±0.08		120
$SN(CH_3)_2$	0.12	0.09	115	0.15	−0.06		115
$SOCH_3$	0.21	0.17	115	0.25	−0.08		115
$SSCH_3$	0.22	0.13	121				
SCl	0.44	0.48	115	0.40	0.08		115

majority of sulphenyl derivatives the simple inductive–only effect is reflected in rather monotonous ^1H and ^{13}C NMR chemical shift patterns.

2. *Sulphenic acids*

Although sulphenic acids, RSOH, have been known since 1912[122] there exist only a small number of well-characterized examples[123]. The first sulphenic acid to be characterized by NMR spectroscopy was 2-(2-methylpropane) sulphenic acid ('*t*-butylsulphenic acid')[124] prepared by pyrolysis of *t*-butyl sulphoxide. The CH_3 protons in the acid appeared 0.03 ppm to low frequency of the sulphoxide methyl protons in non-aromatic solvents, but were deshielded by 0.1 to 0.33 ppm in aromatic solvents. The shift in the aromatic solvents was attributed to π complexation between the acid and the solvent[124]. The acidic OH proton was not detected. The ^1H NMR spectrum of *t*-butylsulphenic acid has also been recorded in CCl_4[125, 126] where the methyl group resonance appears at δ 1.31 ppm. The acid proton chemical shift was not reported. Resonances in the ^{13}C NMR spectrum at δ 28.45 and 50.99 ppm were tentatively assigned to *t*-butylsulphenic acid and it was argued[125] that this was reasonable as the quaternary carbon in *t*-butylthiol appears at δ 41.12 ppm and oxygen in a β-position deshields by about 10 ppm[127, 128].

The acidic proton was observed in the ^1H NMR spectrum of the azetidinone sulphenic acids **58**, obtained by refluxing the penicillin sulphoxide esters **57** in ethyl acetate for ten minutes[129] (equation 41). The acid protons of **58a**, **58b** and the α,β-unsaturated sulphenic acid isomer of **58b** appeared at δ 7.25–7.56 ppm in $CDCl_3$ solution and were exchangeable with D_2O. The ^1H NMR spectrum of **58a** was also reported [129] to be almost identical (essentially superimposable) with that of the related sulphinyl chloride[130], RS(O)Cl, which is a little surprising in view of the strongly electron-withdrawing nature of the –SOCl group. The azetidinone ring CH protons appear at δ 5.6 and 5.9 ppm (J = 4.5 Hz) in **58a** and are not further deshielded by the SOCl group.



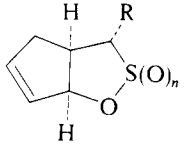
(57) (58) (41)

Ft = phthalimido, R = *p*-$NO_2C_6H_4CH_2$, **58a**; CH_3, **58b**

3. Sulphenic esters

There have been no systematic studies of the ^1H and ^{13}C NMR spectra of sulphenic esters, RSOR[1].

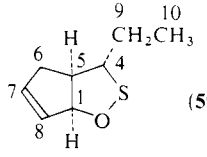
The ^1H and ^{13}C NMR spectra of a series of bicyclic 1,2-oxathiolanes, **59**, have been reported as part of a study of derivatives of 2-thiabicyclo[2,2,1]hept-5-ene[131]. The complete ^1H NMR spectrum of one sulphenate ester **59c** is given in Table 17 and the ^{13}C NMR shifts of a series of **59** are recorded in Table 18.



(**59**)

(**a**) R = H; (**b**) R = CH_3;
(**c**) R = CH_2CH_3; (**d**) R = $CH_2CH_2CH_3$
n = 0,1,2.

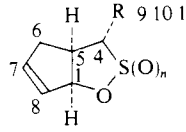
TABLE 17. ^1H NMR chemical shifts for the 1,2-oxathiolane **59c** in $CDCl_3$ at MHz[131]



(**59c**)

Chemical shift δ(ppm), J(Hz) in parentheses							
H-1	H-4	H-5	H-6	H-7	H-8	H-9	H-10
5.3 ($J_{1,8}$ = 2.3 $J_{1,5}$ = 6.9 $J_{1.6en}$ = 2.2)	3.3 ($J_{4,5}$ = 2.0 $J_{4,9}$ = 5.6)	2.9 ($J_{5,6en}$ ~ 5.3 $J_{5,6ex}$ ~ 7.5)	2.7*en* ($J_{6ex,6en}$ = 14.5 $J_{6en,}$ = 2.0 $J_{6en,7}$ = 2.2) 2.3*ex* ($J_{6ex,8}$ = 2.2)	6.1 ($J_{7,8}$ = 5.5)	5.7	1.8 ($J_{9,10}$ = 8)	0.9

TABLE 18. ^{13}C NMR chemical shifts for the 1,2 oxathiolanes **59** in $CDCl_3$[131]



(**59**)

		δ(ppm)								
R	n	C-1	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
H	0	95.6	45.0	43.9	39.7	137.9	128.2			
CH_3	0	95.6	56.7	53.1	38.7	136.6	128.3	19.9		
CH_2CH_3	0	95.0	64.8	51.0	39.3	136.7	128.1	27.2	12.8	
$CH_2CH_2CH_3$	0	95.6	63.0	51.7	39.3	136.9	128.5	36.4	21.9	13.8
CH_2CH_3	1[a]	101.8	79.9	46.3	40.0	136.3	129.2	23.7	12.4	
		98.4	77.7	43.0	36.8	133.9	130.1	20.8	13.1	
CH_2CH_3	2	87.9	63.3	42.5	38.1	137.2	127.6	21.9	11.3	

[a] Mixture of *endo* and *exo* diastereoisomers; isomers not identified.

From the electron-withdrawing ability, $-SO_2O > -SOO > SO$, it would be expected that the α-carbon and protons (CH-4) in **59c** ($n=0$) would be less shielded than in the corresponding sulphinate and sulphonate ($n=1,2$, respectively) analogues. The proton NMR data are not available, but Table 18 allows comparison of C-4 for the three R = ethyl compounds. Surprisingly, the α- deshielding of C-4 decreases in the order $SOO > SO > SO_2O$. A similar trend is observed for the α^1 carbon chemical shifts. The strongly deshielding effect of the SOO groups is independent of the *exo/endo* stereochemistry, but one (unassigned) isomer has a slightly stronger effect than the other. In the absence of other data an explanation of these effects is not available; however, it is likely that the anomaly is a consequence of the anisotropic electronic properties of the SOO group[15].

4. Disulphides

Di- and polysulphides RS_nR^1 (R = alkyl, aryl, H; $n \geqslant 2$) have been reasonably well studied by ^1H and ^{13}C NMR spectroscopy. In particular, the disulphides RSSR have been examined for their interesting dynamic properties (see Section III.C.2) and as precursors of thiosulphinates and thiosulphonates.

There have also been scattered studies on hydrosulphides RS_nH (also called sulphanes). A series of aryl hydrodisulphides was prepared by Tsurugi and coworkers[132] specifically for ^1H NMR studies. Marcus and Miller in 1964[133] had found that the ^1H chemical shift of the SH proton in benzene thiols correlated with the Hammett σ values of *meta* and *para* substituents ($\rho = -21.8$ for a 60 MHz instrument with SH resonance frequency plotted against σ). Subsequently Marcus, Reynolds and Miller[134] predicted that the equivalent ρ-value for aryl hydrodisulphides would be between −5.7 and −8.5. Tsurugi[132] set out to test that prediction. The SH shifts obtained[132] are given in Table 19, together with those for some related compounds obtained by Langer and Hyne[135]. As can be seen from Table 19, the predictions of Miller and coworkers were not borne out as there is no correlation at all between the SH chemical shift and the normal σ constants. Tsurugi[132], however, noted a reasonable correlation ($r = 0.993$) between σ_R and $\Delta\nu_{SSH}$ ($\rho = +15.8$ for a 60 MHz instrument with $\Delta\nu_{SSH}$ in Hz plotted against σ_R) but no satisfactory explanation was offered for this supposed inverse substituent effect. They concluded, however, that the S–S

TABLE 19. ^1H chemical shifts for the SH proton in some aryl hydrodisulphides, XC_6H_4SSH

X	δ^1H(ppm)	Ref.
p-OC_2H_5	3.47[a]	132
p-OCH_3	3.48[a]	132
p-$C(CH_3)_3$	3.37[a]	132
p-CH_3	3.38[a]	132
	3.39[b]	135
H	3.35[a]	132
	3.38[b]	135
p-F	3.47[a]	132
p-Br	3.40[a]	132
p-Cl	3.47[b]	135
p-NO_2	3.58[b]	135
o-NO_2	3.19[b]	135

[a] Extrapolation to infinite dilution in CCl_4.
[b] In CS_2 at 1.0 mol per litre.

bond does not transmit conjugation and permits only very little inductive transmission. Langer and Hyne[135] in a study encompassing higher sulphanes PhS_nH ($n<7$) re-interpreted the data in terms of the anisotropic shielding effects of the aromatic ring. It was suggested[135] that the SH proton in thiophenols is within the paramagnetic (deshielding) cone of the benzene ring whereas the corresponding proton in hydrodisulphides is constrained to move on, or close to, the 'zero effect' surface. In this way the –SSH proton would be subject to much less deshielding, and compared with arylhydropolysulphides it is the thiophenols that could be considered anomalous. The proposed anisotropic effect is illustrated in Figure 7.

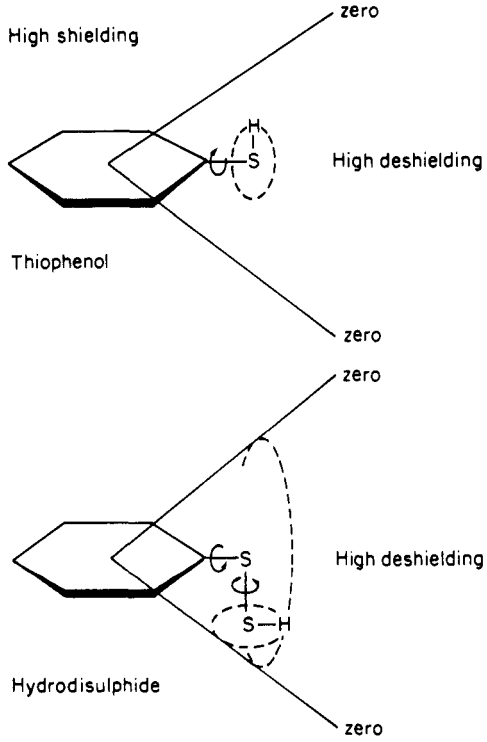


FIGURE 7. Anisotropy effects in aromatic sulphides and disulphides

Even without the perturbing effect of the aromatic ring the comparison between the RSH and RSSH proton shifts is not straightforward[136,137]. Table 20 gives ^1H NMR data for some alkylhydrodisulphides and their thiol analogues. It can be seen that –SSR is consistently more deshielding than –SR. Additionally for the hydrodisulphides, the unexpected shielding by electron-supplying groups is manifested in a linear dependence of δ^1H_{SSH} on the Taft σ^* constant, with the *t*-BuSSH resonance being 0.45 ppm to low frequency of the MeSSH resonance[136]. An opposite dependence on σ^* (electron supply shifts SH to high frequency) was observed for the corresponding thiols[133]. In that case a modified σ^*-value was used[133] ($\sigma^* + 0.29n$, where n is the number of α-C–C bonds) so that the anisotropic and electronic effects of the α-C–C bond could be accounted for. In the hydrodisulphides the extra sulphur atom shields the SH proton from the alkyl group.

TABLE 20. ^{1}H NMR chemical shifts of some alkylhydrodisulphides[136]

Compound	δ^1H (ppm)[b]	δ^1H (ppm) SH of RSH[133]
CH_3SSH[a]	3.04 s, SSH; 2.47 s, CH_3	0.98
CH_3CH_2SSH	2.80 s, SSH; 1.37 t, CH_3; 2.70 q, CH_2	1.16
$(CH_3)_2CHSSH$	2.65 s, SSH; 1.31 d, CH_3; 2.90 sep CH	1.35
$(CH_3)_3CSSH$	2.59 s, SSH; 1.35 s, CH_3	1.61
$PhCH_2SSH$[137]	2.70 s	1.96

[a] Unstable; one component in a mixture.
[b] In CCl_4, δ^1H SH extrapolated to infinite dilution.

Hydrogen bonding appears to be important in determining the SH proton chemical shifts in hydropolysulphides[132,135,136] so most values are quoted at infinite dilution or at low concentration[135]. The SH proton in *p*-$NO_2C_6H_4SSH$ is markedly concentration-dependent[135] varying by 0.15 ppm (8–10 Hz) between 1.0 mol per litre and infinite dilution. Through intramolecular hydrogen bonding, the chemical shift of *o*-$NO_2C_6H_4SSH$ is almost concentration-independent[135].

There have been several detailed studies of ^{1}H and ^{13}C NMR chemical shifts of disulphides[138–141] but these have generally been comparative with thiosulphinates[15] and thiosulphonates. The assumption, on which chemical shift discussions were based, was that the disulphides behave in a regular and predictable way, based on the electron-withdrawing properties of the –SSR group. Some confirmation of this view is seen in the results given in Table 21, where the ^{13}C NMR chemical shifts are given for a number of alkyl disulphides. The shielding parameters α–δ are defined as the difference in chemical shift between a carbon atom and the same carbon atom of the corresponding alkane[142]. The shielding constants are quite appropriate to a moderately electron-withdrawing group[142] although there are some small variations with increasing steric effects of the alkyl group.

TABLE 21. ^{13}C chemical shifts and shielding parameters for some disulphides[140]

Compound	δ^{13}C(ppm)[a] (shielding parameter)			
	α	β	γ	δ
CH_3SSCH_3	22.04 (24.14)			
$CH_3CH_2SSCH_2CH_3$	32.82 (26.92)	14.50 (8.6)		
$CH_3CH_2CH_2SSCH_2CH_2CH_3$[b]	41.26 (25.66)	22.56 (6.46)	13.12 (−2.48)	
$CH_3CH_2CH_2CH_2SSCH_2CH_2CH_2CH_3$[b]	38.97 (25.77)	31.37 (6.37)	21.68 (−3.32)	13.67 (−0.47)
$(CH_3)_2CHSSCH(CH_3)_2$	41.14 (25.04)	22.60 (7.0)		
$(CH_3)_3CSSC(CH_3)_3$	45.63 (20.43)	30.51 (6.21)		
$(CH_3)_2CHCH_2SSCH_2CH(CH_3)_2$[b]	48.60 (24.3)	28.21 (3.01)	21.78 (−2.52)	
$(CH_3)_3CCH_2SSCH_2C(CH_3)_3$[b]	55.96 (24.46)	30.31 (2.41)	28.83 (−2.67)	

[a] 5–15% w/w $CDCl_3$ solutions; 22.5 MHz.
[b] From Reference 141.

There is an apparently large difference in ^{13}C chemical shift behaviour between the sulphenate esters and their oxidized analogues where the α and α' deshielding follows the order SOO > SO > SO_2O, and the disulphides, where the α deshielding decreases as

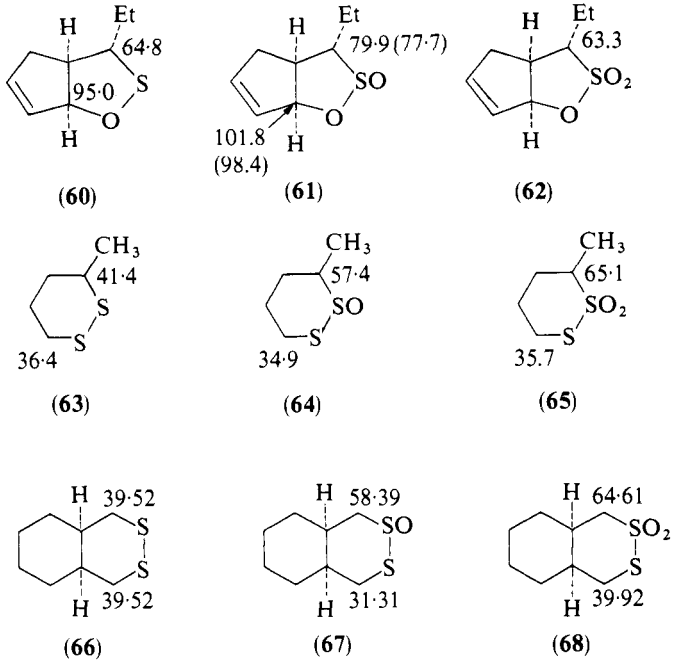


FIGURE 8. The ^{13}C NMR chemical shifts of three series of sulphenyl sulphinyl and sulphonyl compounds. Data for **60–62** from Reference 131, **63–65** from Reference 138 and **66–68** from Reference 139

expected in the order $SO_2S > SOS > SS$[138,139] but the α' deshielding follows the order $SO_2S > SS > SOS$[138,139]. These trends are illustrated in Figure 8. There are only extremely limited data available and more study is required to establish the generality of these observations.

The proton NMR spectra of disulphides containing at least one alkyl or benzyl group are unexceptional. At ambient temperature no effects of restricted rotation about the S–S bond are observed and the shielding effect reflects the moderately electron-withdrawing nature of the SSR groups. Some typical ^1H NMR chemical shifts for alkyl disulphides and related compounds are given in Table 22. Predictably, the shielding by –SSR is almost identical to that of –SSH (Table 20). Useful charts of ^1H and ^{13}C NMR chemical shift ranges of many organosulphur compounds including disulphides are available[144].

TABLE 22. ^1H NMR chemical shifts of some alkyl disulphides

Compound	δ ^1H (ppm)	Ref.
$C_6H_5CH_2SSCH_2C_6H_5$	3.60, s, CH_2	140
$C_6H_5CH_2SSC_6H_5$	3.91, s, CH_2; 7.1–7.6 ar-H	143
$(CH_3)_3CCH_2SSCH_2C(CH_3)_3$	2.76, s, CH_2; 1.02, s, CH_3	140
$(CH_3)_3CCH_2SSC_6H_5$	2.80, s, CH_2; 1.0, s, CH_3; 7.1–7.6 arH	140
$C_6H_5SSCH_3$	2.39, s, CH_3	138
$C_6H_5SSCH_2CH_3$	2.71, q, CH_2; 1.29, t, CH_3	138

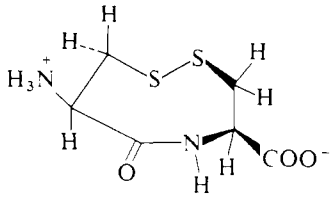
Diaryl disulphides have been the subject of much interest, owing to the possibility of observing restricted rotation about either the S–S or S–C bonds. That is covered in Section III.C.2. During the course of these studies some detailed chemical shift and coupling information has been produced. Table 23 gives ^{1}H NMR chemical shifts and coupling constants for a representative number of diaryl disulphides. The ^{13}C NMR spectra of several diaryl disulphides have been reported. The aromatic additivity constants for PhSSAr have been measured as +8.2, *ipso*; +0.2, *ortho*; −1.3, *meta* and −1.7 ppm *para*[151] and these follow the usual additivity rules[152,153]. The ^{13}C NMR chemical shifts of some diaryl disulphides are given in Table 24.

Whereas the chemical shift values for 4-$CH_3C_6H_4SSC_6H_4CH_3$-4 and 4-$BrC_6H_4SSC_6H_4Br$-4[146] correlate very well with the calculated values [151–153], the shifts for the 4-$ClC_6H_4SSC_6H_4Cl$-4[146] are suspiciously close to those for the parent diphenyl disulphide and differ by −5.7 ppm from the calculated shift (133.3) for the *para* (4) carbon nucleus.

The assignment of chemical shifts in $C_6H_5SSC_6H_5$ was aided by spin–lattice relaxation time (T_1) measurements[151]. The measured T_1 values are given in Table 25. It was argued[151] that the quaternary carbon C-1 has, as usual, a long relaxation time and that *para* (4) carbons relax faster than *ortho* and *meta* carbons[154]. In the same study[151] Pappalardo and colleagues compared the chemical shift trends of $C_6H_5SSC_6H_5$, $C_6H_5SeSeC_6H_5$ and $C_6H_5TeTeC_6H_5$. The results together with the relaxation times are given in Table 25. The Pauling electronegativity falls in the order S > Se > Te. Thus the low frequency C-1 carbon shift in the order S < Se < Te is in accord with crude electronegativity (and 'heavy atom') expectation of effects. However, the C-2,6 and C-4 shifts are to lowest frequency for the S derivative, which is explained in terms of an effective resonance supply of electrons by sulphur that is not efficient for tellurium.

Although the NMR analysis of biological systems and peptides are outside the scope of this review, there are one or two model studies that reflect the nature of the S–S bond in disulphides.

In cyclic dipeptides, containing an S–S linkage, the solution conformation can be investigated by NMR spectroscopy. For example the ^{1}H NMR spectrum of L-cysteinyl-L-cysteine[155], **69**, was analysed using the iterative program LAOCOON[156]. The conformation in the solid state has been determined by X-ray crystallography[157]. The structure is as shown in **69**, with a P-helical structure about the SS bond and a *cis* peptide unit.



(69)

The P- and M-helical descriptions for –S–S– bonds are given in Figure 9. In the example of **69**, potential energy calculation[158] had led to the prediction that two conformations had equally low energy and that these conformations differed mainly in the conformation about the S–S bond. Unfortunately, chemical shifts and coupling constants would be almost identical for the two conformers. The two ABX multiplets in **69** were analysed and the coupling constants were subjected to a Karplus-type analysis[159]. The results, given in Table 26, showed that the solution NMR spectrum was highly compatible

TABLE 23. ^{1}H NMR chemical shifts and coupling constants for some diaryl disulphides

Compound	δ ^{1}H (ppm)					J (Hz)						Solvent	Ref.
	H-2	H-3	H-4	H-5	H-6	J_{23}	J_{24}	J_{25}	J_{26}	J_{34}	J_{35}		
$C_6H_5SSC_6H_5$	7.298	7.032	6.963			7.673	1.171	0.501	1.945	7.365	1.566	CS_2	145
	7.500	7.277	7.200			7.523	1.419	0.534	2.037	7.212	1.616	$CDCl_3$	145
	7.427	7.187	7.113			7.844	1.214	0.539	2.118	7.497	1.515	$(CD_3)_2CO$	145
	7.438	7.214	7.128			8.00	1.17	0.58	2.13	7.52	1.58	CCl_4	146
4-$CH_3C_6H_4SSC_6H_4CH_3$-4	7.297	7.023				7.93		0.33	1.93		2.25	CCl_4	146
4-$ClC_6H_4SSC_6H_4Cl$-4	7.361	7.251				8.53		0.38	2.41		2.41	CCl_4	146
4-$BrC_6H_4SSC_6H_4Br$-4	7.298	7.385				8.57		0.35	2.55		2.38	CCl_4	146
2-$NO_2C_6H_4SSC_6H_4NO_2$-2[a]		7.44	7.61	7.90								$CDCl_3$	147
4-$NC_5H_3SSC_5H_3N$-4[b]	8.50											CD_3OD	148
2-$NC_5H_3SSC_5H_3N$-2[c]		8.361	7.053	7.530	7.558							$CDCl_3$	149
(2,4,6 Bu^t$C_6H_4S)_2$[d]	1.67 (CH_3)	7.45	1.30 (CH_3)	7.20	1.01 (CH_3)						2.1	$CDCl_3$	150

[a] J_{34} 8.179; J_{35} 1.421; J_{36} 0.337; J_{45} 7.057; J_{46} 0.783; J_{56} 8.108 Hz.
[b] At 20 °C;
[c] J_{34} 4.421; J_{35} 1.558; J_{36} 0.774; J_{45} 7.640; J_{46} 1.069; J_{56} 7.571 Hz at 38 °C
[d] At 0 °C.

TABLE 24. ^{13}C NMR chemical shifts of some diaryl disulphides

Compound	δ ^{13}C (ppm)				Solvent	Ref.
	C-1	C-2,6	C-3,5	C-4		
$C_6H_5SSC_6H_5$	137	129	127.5	127.1	$CDCl_3$	151
4-$ClC_6H_4SSC_6H_4Cl$-4	137.0	128.9	127.45	127.0	$CDCl_3$	146
4-$CH_3C_6H_4SSC_6H_4CH_3$-4	133.75	129.6	128.3	137.1	$CDCl_3$	146
4-$BrC_6H_4SSC_6H_4Br$-4	135.5	128.8	131.6	121.2	$CDCl_3$	146

TABLE 25. ^{13}C chemical shifts and spin lattice relaxation times of 1 M diphenyl dichalcogenides in $CDCl_3$[151]

Compound	δ (ppm) T_1 (s) in parentheses			
	C-1	C-2,6	C-3,5	C-4
$C_6H_5SSC_6H_5$	137	129.6	127.5	127.1
	(50)	(6.4)	(6.4)	(5.0)
$C_6H_5SeSeC_6H_5$	130.9	131.5	129.1	127.6
	(50)	(6.8)	(6.8)	(3.7)
$C_6H_5TeTeC_6H_5$	108.0	137.6	129.2	128.0
	(50)	(5.7)	(5.7)	(2.8)

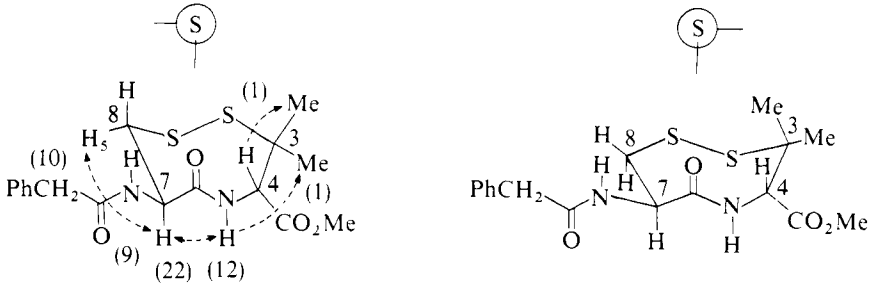
FIGURE 9. The P- and M-helical conformations of disulphides. The P-helix has a positive dihedral angle

with the X-ray structure, but no definite information could be extracted concerning the nature of the S–S bond conformation[155].

In a much more recent study Baxter, Scott and coworkers[160] have been able to determine the helical sense of the related dipeptide **70** and show that in solution it has the P-helical structure I, shown in Figure 10. The coupling constants and chemical shift assignments are given in Table 27. Once these were established the relative proximities of the protons were determined from the NOE difference spectra. It was assumed that the spectrum was that of a single conformer as the barrier to interconversion of P- and M-helical forms is expected to be in the range 50–90 kJ mol^{-1}[161]. Under those conditions the two conformations would give separate spectra. The NOE difference values are shown on Figure 10. A careful analysis showed that for the compound in solution only a rigid P-helical structure is consistent with these data. The solid-state structure was very similar[160]. It was also pointed out that in the majority of biological compounds studied so far the P-helical form predominates.

TABLE 26. Comparison of experimental and calculated coupling constants for the cyclic dipeptide **69**[155]

N-terminal redidine	Dihedral angles[157] from X-ray (deg)	Calculated J (Hz)	Experimental J (Hz)
H_A–C–C–H_X	196	11.0	12.1
H_B–C–C–H_X	71	2.7	3.5
C-terminal residue			
H_A–C–C–H_X	−65	1.3	4.4
H_B-C-C-H_X	170	11.4	9.7



(70)

FIGURE 10. P-helical (I) and M-helical (II) conformations for **70**. The perspectives viewed along the S–S bonds of each conformation are shown above the formulae. The principal NOEs observed in the ^{1}H NMR spectrum are indicated on conformer I. Figures in parentheses are the % enhancement values measured in the difference NOE experiment (8 mM solution in $CDCl_3$ at 25 °C)

5. Sulphenamides

Despite particular NMR interest in the dynamic properties of sulphenamides[113] there have been very few ^{1}H or ^{13}C NMR studies devoted to chemical shift or coupling constants. The ^{1}H NMR shifts of some sulphenamides are given in Table 28.

It is clear that the chemical shift of the groups bound to nitrogen in sulphenamides is affected by the nature of the groups on sulphur. The predictable effect of electron-withdrawing groups on sulphur, shifting *N*-methyl groups to high frequency, is observed. The proton NMR N-CH_3 resonance in $CH_3SN(CH_3)_2$ is at δ 2.69 ppm[162] and appears at δ 3.07 ppm in $CH_3OSN(CH_3)_2$[163] and δ 3.23 ppm in $Cl_3CSN(CH_3)_2$[162]. There are insufficient data to comment on how varying the groups on nitrogen affects the SCH resonance chemical shifts.

^{13}C NMR shifts for a closely related series of *N*-(2-nitrophenylthio)alicylic amines, **71**, have been reported and are given in Table 29.

The radical cation derivatives of **71** have already been discussed (Section II.D) and conformational aspects were considered important in interpreting the spectra. The

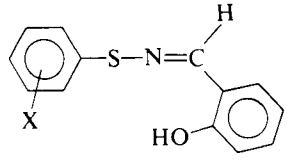
TABLE 27. Proton chemical shifts and coupling constants for compound **70** in different solvents[160]

	$CDCl_3$[a] (ppm)	$(CD_3)_2SO$[a] (ppm)	$\Delta\delta$ (ppm)[b]	Coupling constants (in Hz in $CDCl_3$)[c]
3-*pro S* CH_3	1.44	1.44	0.00	s
3-*pro R* CH_3	1.48	1.48	0.00	s
8-*pro R* H	2.84	2.90	0.06	14.0, 11.2
8-*pro S* H	3.35	3.14	−0.21	14.0, 5.2
Phenylacetyl CH_2	3.57	3.31	−0.26	s
OCH_3	3.74	3.69	−0.05	s
7-H	4.56	4.68	0.12	11.2, 7.0, 5.2
4-H	4.89	4.76	−0.13	11.1
Cysteinyl NH	6.39	8.40	2.01	7.0
Penicillaminyl NH	6.64	8.81	2.17	11.1

[a] 8 mM solutions at 25 °C.
[b] A negative sign denotes a shift to lower frequency in $(CD_3)_2SO$.
[c] s denotes a singlet.

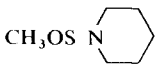
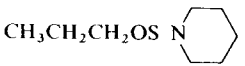
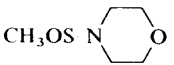
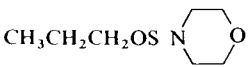
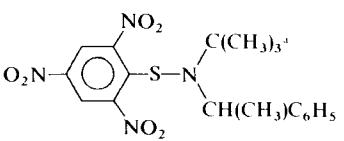
^{13}C NMR spectra were used to estimate conformational preferences in **71**. In most cases there was only one set of resonances, but in one case, **74**, namely *cis*-2,6-$(CH_3)_2$, there were two conformations in an approximately 2:1 ratio. The starting piperidine was the pure *cis* isomer, so configurational effects were not responsible. On the basis of the large difference in C-3,5 shifts for each conformer (5.2 ppm) and the small difference between the methyl resonances (2.0 ppm), it was suggested that in one conformation the 2-nitrophenyl group was equatorial and in the other it was axial. The chemical shifts of the piperidine C-3,4,5 ring carbon atoms are within 1 ppm of the parent piperidine resonances and the C-2,6 carbon atoms in **71** are deshielded by 6–9 ppm relative to the parent piperidine. Thus the effect of the sulphur diminishes very rapidly.

The transmission of substituent effects through sulphur in some *N*-salicylidenearene-sulphenamides, **72**, has been measured by Davis and coworkers[165]. The effect of varying X on the ^1H NMR chemical shift of the imidoyl and hydroxyl protons was measured. A plot of δ_{CH} against σ^+ for **72** in CCl_4 gave a reasonable straight line ($r = 0.990$) with a ρ-value of −0.357. The better fit with σ^+ than with σ was rationalized in terms of through conjugation between the aromatic groups involving p–π and d–π bonding using both the sulphur p and d orbitals. This effect was particular to sulphenamides; oxidation to sulphinamides or sulphonamides resulted in an insensitivity of the imidoyl proton to variation in X. A plot of δ_{OH} against σ for **72** in CCl_4 gave a straight line ($r = 0.944$) with ρ being +0.22. It was suggested[165] that intramolecular hydrogen bonding from the imidoyl



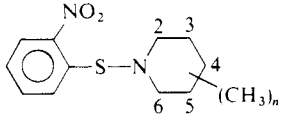
(**72**)

TABLE 28. ^{1}H NMR shifts of some sulphenamides

Compound	δ ^{1}H (ppm) J(Hz) in parentheses	Solvent	Ref.
$ClSN(CH_3)_2$	3.11 ($N-CH_3$) ($^1J_{^{13}C\ H}$ 138.7)	50% in $CDCl_3$	162
$CH_3SN(CH_3)_2$	2.69 ($N-CH_3$) ($^1J_{^{13}C-H}$ 134.7); 2.20 (SCH_3)	neat	162
$Cl_3CSN(CH_3)_2$	3.23 ($N-CH_3$) ($^1J_{^{13}C\ H}$ 137.2)	neat	162
$C_6H_5SN(CH_3)_2$	2.69 ($N-CH_3$) ($^1J_{^{13}C-H}$ 135.5)	50% in $CDCl_3$	162
	1.54 m (CH_2); 3.38 m($N-CH_2$); 3.66 s (OCH_3)	CCl_4	163
	1.55 m (CH_2); 3.36 m($N-CH_2$); 0.85 t (CH_3); 3.85 t($O-CH_2$)	CCl_4	163
	3.36 m (NCH_2); 3.55 m (OCH_2); 3.69 s (OCH_3)	CCl_4	163
	3.31 m (NCH_2); 3.56 m (OCH_2); 0.36 t (CH_3); 1.55 m (CH_2); 3.75 t (OCH_2)	CCl_4	163
$CH_3OSN(CH_3)_2$	3.07 s (NCH_3); 3.68 (OCH_3)	CCl_4	163
	major: 1.44s ($C(CH_3)_3$); 1.61 d, (6.8Hz) (CH_3); 4.49q (6.8Hz)$CHCH_3$; 6.92s (C_6H_5); 8.13s ($C_6H_2(NO_2)_3$) minor: 1.16s ($C(CH_3)_3$): 1.57d (CH_3); 7.20s (C_6H_5); 8.55s ($C_6H_2(NO_2)_3$	$CDCl_3$	164

[a] Mixture of two diastereoisomers in a ratio 3/1.

TABLE 29. ^{13}C NMR chemical shifts for sulphenamides, **71**, in $CDCl_3$ [51]

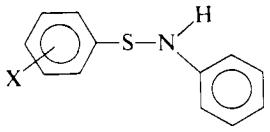


(**71**)

Methyl substitution	δ (ppm)					
	C-2	C-3	C-4	C-5	C-6	CH_3
2-CH_3	58.5	34.7	23.5	27.2	56.7	19.4
3-CH_3	63.4	32.0	32.4	26.0	55.8	19.2
4-CH_3	55.8	35.4	29.8	35.4	55.8	21.8
cis-2,6-$(CH_3)_2$ [a]	60.6	31.2	25.1	31.2	60.6	19.3
	60.3	36.4	24.1	36.4	60.3	21.3
3,5-$(CH_3)_2$ [b]	62.9	31.0	41.3	31.0	62.9	19.1
	62.6	28.5	37.8	28.5	62.6	18.1
2,2,6,6-$(CH_3)_4$	59.8	41.2	17.4	41.2	59.8	31.3; 25.2

[a] Mixture of two conformers, ratio 1:0.56 upper: lower.
[b] Mixture of *cis* and *trans* isomers (ratio not given).

nitrogen to the hydroxyl proton was being observed. Electron supply to the nitrogen increased the hydrogen bonding and consequently deshielded the OH proton. In this way an electron-supplying substituent causes a high-frequency shift so that ρ is positive. The simple sulphenamides **73** were also studied by the ^1H NMR method[165]. The ρ-value for **73** (in CCl_4) when δ_{NH} was plotted against σ was -0.185, suggesting that there is



(**73**)

transmission of substituent effects through the sulphur–nitrogen bond when sulphur is attached to an sp^2-hybridized nitrogen, but little if any when attached to an sp^3-hybridized nitrogen. It was suggested[165] that (p–d)π bonding between sulphur and nitrogen is dependent on the hybridization of the nitrogen lone pair, although this was difficult to explain in view of the dynamic NMR results in which substituent effects had been measured[2]. The ^{15}N–H coupling constant has been used to explore the (p–d)π bonding hypothesis in a number of heteroatom–nitrogen compounds, including sulphenamides[166]. The $^1J_{NH}$ coupling constants measured were 80.6 Hz for $CF_3S^{15}NH_2$ and 99.1 Hz for $(CF_3S)_2{}^{15}NH$. In terms of the phenomenological equation of Binsch and coworkers[167] (equation 42), CF_3SNH_2 should be almost tetrahedral (approximately 28% s) and $(CF_3S)_2NH$ should be planar about nitrogen (approximately 36%s). It was suggested, however, that equation 42 is not applicable where the electronegativity of the

heteroatom is markedly different from that of carbon (the group electronegativity of SCF_3 is very high at 3.38[168]). An alternative explanation was advanced involving the group electronegativity of X in XNH_2 and X_2NH and the isovalent hybridization hypothesis[169]. That hypothesis states[169] that s character concentrates in bonds that are directed towards electropositive substituents. As the electronegativity of X increases, so the s character is directed into the NH bonds, leading to an increase in J_{NH}. Cowley[166] found a very good correlation between substituent group electronegativity and J_{NH}. It was concluded that this correlation does not preclude the existence of an N–S (p–d)π bonding component, but it was unnecessary to invoke such bonding to explain the NMR data.

$$\%s \text{ character at nitrogen} = 0.43\, J_{^{15}NH} - 6 \tag{42}$$

The question of the nature of the N–S bond remains unanswered by ^1H or ^{13}C NMR.

6. *Sulphenyl halides*

The reactions of sulphenyl chlorides have been well studied[170, 171] but the NMR spectra of these compounds has elicited very little interest. The ^1H NMR spectra of four sulphenyl chlorides have been reported[172] showing that the SCl group is quite strongly deshielding (Table 30)

TABLE 30. The ^1H NMR spectra of some sulphenyl chlorides[172] in $CDCl_3$

Compound	δ (ppm) J(Hz)
CH_3SCl	2.90
CH_3SSCl	2.74
CH_3CH_2SCl	1.44 (t); 3.15 (q) (7.1)
CH_3CH_2SSCl	1.45 (t); 3.04 (q) (7.3)

The most interesting studies of sulphenyl chlorides have been those designed to probe for the existence of sulphenylium ions, RS^+, which had been proposed but not directly observed[173]. The first preliminary report[174] showed that the ^1H NMR spectrum of CH_3SCl in liquid SO_2 was highly temperature-sensitive, moving from δ 2.83 to 3.61 ppm as the temperature was decreased from $-10\,^\circ C$ to $-80\,^\circ C$. On addition of BF_3 the CH_3SCl resonance splits into two equal components and at low temperature ($-80\,^\circ C$) becomes invariant with equal singlet peaks at 3.22 and 4.06 ppm when $[BF_3]/[CH_3SCl] > 0.5$. The same effect was observed on addition of SbF_5 and, in the preliminary communication, it was reported that BCl_3 had no effect, but in the full paper[175] this was corrected and BCl_3 was reported to have the same effect as BF_3. These observations are incompatible with simple ionisation of RSCl and are best interpreted in terms of the alkyl (alkylthio) (chloro) sulphonium ions shown in equation 43.

$$2RSCl + BF_3 \rightleftharpoons R-\overset{+}{S}=\overset{Cl}{\overset{|}{S}}\diagdown R \tag{43}$$

As the temperature was increased the two singlets from $CH_3SS(CH_3)Cl^+$ coalesced, and the coalescence temperature could be reduced by addition of chloride ion[174, 175] suggesting a bimolecular mechanism.

Similar ions were observed when sulphenyl chlorides were mixed with disulphides in SO_2 in the presence of Lewis acids[176]. The equilibrium is expressed in equation 44.

$$CH_3SCl + CH_3SSCH_3 + BF_3 \rightleftharpoons CH_3-\overset{+}{S}(SCH_3)-SCH_3 + BF_3Cl^- \qquad (44)$$

B. Multinuclear NMR Studies of Sulphenic Acid Derivatives

The most obvious nucleus for study in sulphenic acid derivatives would appear to be the sulphur nucleus. Unfortunately, like sulphides in general the unsymmetrical electronic environment around the quadrupolar sulphur results in line widths greater than 1 kHz and precludes observation or accurate measurement of chemical shifts[177, 178].

The ^{14}N NMR shifts of two sulphenamides were measured in 1978[179], seven ^{15}N NMR spectra were recorded in 1984[180] and a further one in 1985[181]. Two different chemical shift standards were used. Table 31 gives the nitrogen NMR shifts from these studies relative to nitromethane, in accordance with current practice[178]. The sulphenamide nitrogen appears to low frequency in the S–N single bond region[179].

Dorie and Gouesnard had measured the ^{15}N chemical shifts of the seven sulphenamide derivatives to probe the hybridization at nitrogen[180]. By comparison with ^{15}N NMR shifts of secondary amines, and using comparisons previously evaluated[183], it was suggested that the degree of sp^3 character at nitrogen may decrease in the order[180] sulphonamides > sulphinamides > sulphenamides.

The ^{19}F NMR spectra of CH_3OSF and C_2H_5OSF have been reported (δ +261 and 212.7 ppm, respectively, relative to $CFCl_3$)[184]. The ^{19}F NMR spectra of some fluorophosphoranes, $RSPF_4$, have also been reported[185].

The ^{29}Si NMR spectra of some silylsulphenamides $RSN(SiMe_3)_2$ all showed resonances at about $+10 \pm 2$ ppm appropriate to an N–Si bond[186].

TABLE 31. Nitrogen NMR chemical shifts of some sulphenamides, relative to CH_3NO_2

Compound	δ (ppm)[a] (W)[b]	Solvent	Ref.
$C_6H_5SN(CH_3)_2$	−354.6 (700Hz)	Neat	179[c]
$C_6H_5SN(CH_2CH_3)_2$	−350.6 (720Hz)	Neat	179[c]
	−335.1	Neat	181[d]
	−334.4	$CDCl_3$	181
$ClSN(CH_3)_2$	−304.2	Neat	180[d]
$ClSN(CH_2CH_3)_2$	−274.7	Neat	180
$ClSN(CH(CH_3)_2)_2$	−249.7	Neat	180
$ClSN(CH_3)CH_2C_6H_5$	−292.8	Neat	180
$(CH_3)_2NSN(CH_3)_2$	−327.2	Neat	180
$(CH_3CH_2)_2NSN(CH_2CH_3)_2$	−304.9	Neat	180
$((CH_3)_2NSN(CH(CH_3)_2)_2$	−289.9	Neat	180

[a] ^{14}N and ^{15}N chemical shifts are interchangeable[178].
[b] Width at half height.
[c] Measured relative to NH_4^+; δ −259.6 ppm relative to CH_3NO_2[182] used in the conversion.
[d] Measured relative to CH_3NO_2.

C. DNMR of Sulphenic Acid Derivatives

1. Introduction

The sulphur atom in S(II) derivatives is generally agreed to be configurationally stable[187, 188] so that DNMR studies on sulphenic acid derivatives are concerned with the measurement of rotational changes about S–X bonds. In addition, if the heteroatom X can undergo configurational change (e.g. nitrogen) then complex changes involving both rotation and inversion can be studied.

In effect two main classes of compounds have been examined by DNMR: disulphides and sulphur–nitrogen compounds. In the following section we discuss, in some detail, the rotational processes in disulphides, but as the sulphur–nitrogen DNMR is covered in detail elsewhere in this volume[113] only a very brief outline is included here.

2. DNMR of disulphides

It has been recognised for a long time that disulphides are 'bent' with a barrier to rotation about the S–S bond[189, 190]. The normal CS–SC dihedral angle is about 90°[190] so that the low-energy conformations of disulphides are chiral by virtue of the chiral axis. However, the rotation barrier is generally so low that disulphides exist as a racemic mixture of rapidly equilibrating enantiomers at normal temperatures[191] (equation 45).

(45)

What were claimed to be the first direct and unambiguous measurements of the S–S bond rotation barrier were made by studying the temperature dependence of the NMR spectra of some benzyl disulphides[192]. The benzylic CH_2 protons in derivatives $C_6H_5CH_2SSR$ can only be diastereotopic if there is restricted rotation of the type shown in equation 45 or if the benzyl group preferentially adopts a gauche conformation about the S–S bond. The latter possibility was considered to be highly unlikely. The appearance of an AB quartet for the benzylic protons as $C_6H_5CH_2SSR$ compounds were cooled was therefore attributed to restricted S–S bond rotation[192] as shown in Figure 11. The free-energy barriers to this S–S bond rotation were calculated from total line-shape analysis and the values for several benzyl disulphides are given in Table 32. The supposedly higher barriers for $R = CF_3$ and CCl_3 were attributed to the strongly inductive electron-withdrawing nature of those substituents. The barrier was also observed to increase with increasing steric bulk of R. On balance a *cis* transition state was favoured[192] (path a, Figure 11). However, the barriers measured by Frazer and coworkers[192] are similar to those calculated[193] for *trans* rotation in dimethyl disulphide, which are between 26 and 33 kJ mol^{-1}, depending on the level of refinement of the MO calculations. *Trans* rotation is also favoured in a report on molecular mechanics calculations on disulphides[194] in which the *cis* pathway always had higher energy that the *trans*. The question of the mode of rotation about the disulphide bond is mentioned again later in this section.

No other data are available for simple acyclic aliphatic disulphides. These systems seem to warrant further investigation in view of the interesting suggestion, first raised in 1960[195] and reiterated in 1972[196], that a correlated 'cogwheel' motion is expected for the methyl groups in di(*t*-butyl) disulphide.

There have been two reports of DNMR studies on heteroatom-substituted disulphides. The first[197] was concerned with S–S bond rotation in diethoxy disulphide

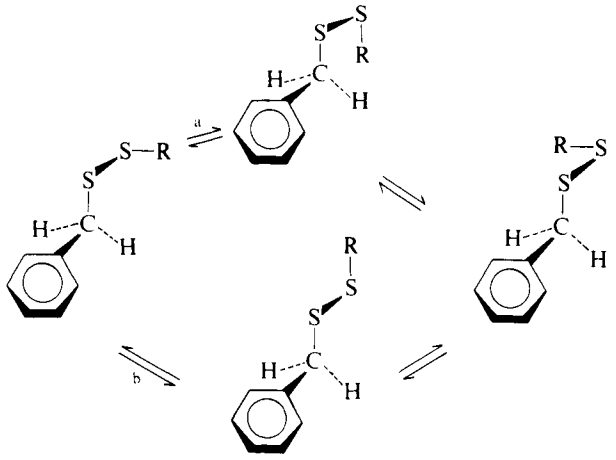


FIGURE 11. *Cis* and *trans* rotation about the S–S bond in benzyl disulphides

$CH_3CH_2OSSOCH_2CH_3$, in which the methylene protons were diastereotopic at 30° but collapsed to an A_2X_3 quartet by 100°. A line-shape analysis and Arrhenius plot gave an activation energy of 36.1 ± 7.1 kJ mol^{-1}, which is very similar to the values obtained by Frazer[192] for $\Delta G^{\neq}$ for S–S bond rotation. The other report[198] on heteroatom disulphides compared the stereochemistry of bis(amino)sulphides and disulphides, $(R_2N)_2S$ and $(R_2N)_2S_2$, where R = CH_3, CH_2CH_3 and $CH(CH_3)_2$. The temperature dependence of the proton NMR spectra of $((CH_3CH_2)_2N)_2S$ and $(((CH_3)_2CH)_2N)_2S$ was interpreted in terms of restricted rotation about the S–N bond. Rapid inversion at nitrogen, or planar geometry at nitrogen, was postulated. The values of $\Delta G^{\neq}$ for these compounds were 42.8 and 47.8 kJ mol^{-1}, respectively[198]. The corresponding disulphides have more complex stereochemical behaviour as restricted rotation about the S–S bond is also possible. For $((CH_3CH_2)_2N)_2S_2$ the methylene protons were not all isochronous at 30 °C, but appeared as two distinct methylene quartets, separated by less than 1 Hz. This spectrum was analysed as overlapping A_2X_3 and C_2Y_3 spectra. At −120 °C the spectrum was even more complex and was analysed as overlapping ABX_3 and CDY_3 spectra. The barrier for this dynamic process was calculated[198] to be 41.8 kJ mol^{-1} and that for the isopropyl derivative was 46.5 kJ mol^{-1}. The similarity between the barriers for the disulphides and sulphenamides led the authors to suggest that S–N rotation was being observed in both cases[198]. It is not certain that is the case as the S–S barriers for disulphides are also in the range 30–40 kJ mol^{-1} for aliphatic acyclic systems[192, 197].

The conformations of cyclic systems containing S–S units have been well-studied, but lie outside the scope of this review. Leading references for systems containing one S–S unit are found in papers by Bestmann, Snyder and coworkers[199], Lüttringhaus[191] and also Pappalardo[200], who has references to work on compounds with two and three disulphide bridges. Bushweller and coworkers[201] examined the twist-to-chair conformational changes in some *s*-tetrathiane ring systems.

There have been a number of reports of DNMR studies on diphenyl disulphides. The first and most comprehensive account by Kessler and Rundel[202] appeared in 1968. They studied a range of substituted diphenyl disulphides by ^{1}H NMR spectroscopy and analysed in detail the expected consequences of restricted S–S and S–Ar rotation. Their assumption[202] was that the phenyl ring planes were perpendicular to the C-*ipso*, SS plane.

TABLE 32. Rotational barriers for compounds $C_6H_5CH_2SSR$[192]

R	Solvent	T_c (°C)	$\Delta\nu$ (Hz)	$\Delta G^{\ddagger}$[a] (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
CCl_3	CH_2=CHCl/$C_6H_5CH_3$	−83	16	39.3		
	CS_2	−87	4	38.4		
	CH_2=CHCl	−87	17	38.1		
	CH_2=CHCl/[b]$C_6H_5CH_3$			39.3	38.1	−6.7
$C(C_6H_5)_3$	$CS_2/C_6H_5CH_3$	−95	19	36.8		
CF_3	CH_2=CHCl/C_6H_5/CH_3	−104	4.5	34.7		
C_6Cl_5	$CS_2/C_6H_5CH_3$	−108	30[b,c]	33.4		
C_6F_5	$CS_2/C_6H_5CH_3$	−109	40[c]	33.0		
C_6H_5	CH_2=CHCl	−115	15	32.2		
$C(CH_3)_3$	CH_2=CHCl	−113	15	33.0		
	CH_2=CHCl[a,b]			32.6	28.4	−28
$CH_2C_6H_5$	CH_2=CHCl/$CHCl_2F$	−128	15	30.1		
	CH_2=CHCl/[b]$CHCl_2F$			29.2	27.6	−10.9

[a] From coalescence temperature, J_{AB} 12.0-13.0 Hz.
[b] By total line-shape analysis.
[c] Approximately; the solution froze.

More recent X-ray crystallographic studies[203–205] and CNDO/2 calculations[145] both favour the extended conformations with the phenyl rings approximately in the same plane as the C-*ipso* SS plane.

The rotations discussed by Kessler and Rundel[202] are shown in Figure 12. Restricted rotation about a (S–S), or b (S–Ar), is insufficient to render the 2,2′,6,6′ set inequivalent as long as the substituents on those individual, identically substituted carbon atoms only bear isochronous protons (e.g. 2,2′,6,6′ substituted by H or CH_3 or $C(CH_3)_3$). Rotation, slow on the NMR time scale, about both S–S and S–Ar bonds, under the above conditions gives rise to two non-equivalent sets comprising 2,2′ and 6,6′. The same is true if the equilibrium conformation of the phenyl rings is 90° to those shown in Figure 12. When groups CX_2Y are placed on 2,2′,6 and 6′, the NMR spectra can become more complex. Assuming the conformations shown in Figure 12, the following analysis obtains. Slow rotation about both S–S and S–Ar bonds gives rise to *four* sets of resonances; each X group in CX_2Y becomes diastereotopic and the 2,2′ and 6,6′ positions are non-equivalent. Now, fast rotation about the S–S bond makes the 2,2′,6 and 6′ positions equivalent, leaving the X_2 groups diastereotopic. Fast rotation about S–Ar renders the X_2 groups isochronous. The opposite situation is true if the phenyl rings are in the CSS planes in the low-energy conformations. There are still four anisochronous sets when both S–S and S–Ar rotations are slow on the NMR time scale. However, fast rotation about the S–S bond now renders the X_2 groups in CX_2Y isochronous leaving the 2,2′ and 6,6′ positions anisochronous. Fast rotation about the S–Ar bonds now brings about exchange of the 2,2′ and 6,6′ positions. Deviations from dihedral angles of 0° or 90° open even more possibilities. There is therefore considerable complexity in the dynamic behaviour of 2,2′,6,6′ tetraethyldiphenyl disulphide and similar compounds. Using modern NMR spectroscopic techniques, such as 2-D NMR, it should be possible to disentangle both the

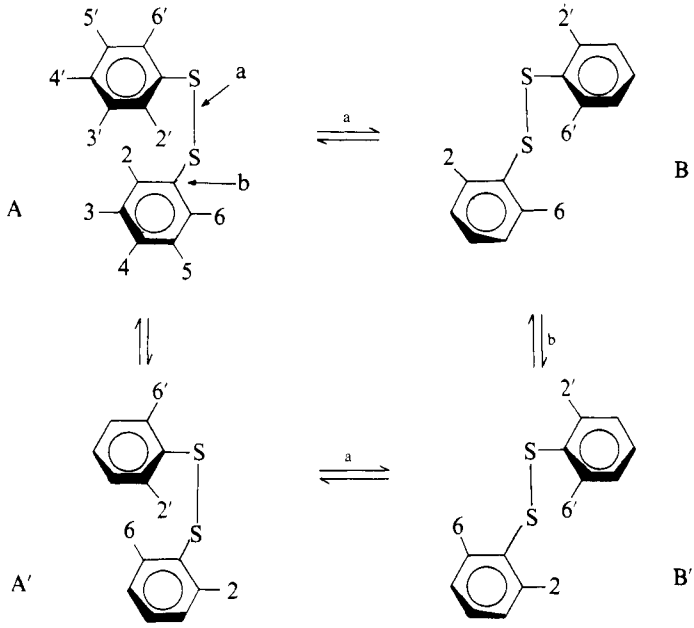
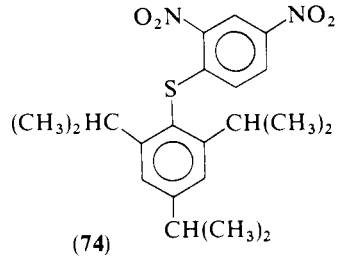


FIGURE 12. Dynamic processes in diphenyl disulphides

ground state conformations *and* the respective S–S and S–Ar bond rotation barriers. Kessler and Rundel[202] had only the benefit of simple ^{1}H DNMR.

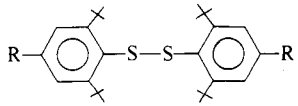
For the tetraethyl derivative an ABX_3-type spectrum appeared at $-55°C$ and the multiplet was analysed as $J_{AX} = J_{BX} = 7.6$ Hz and $J_{AB} = 13.2$ Hz. This was interpreted as fast rotation about the S–S bond and slow rotation about the S–Ar bond[121]. The approximate barrier to S–Ar rotation was estimated at 49 kJ mol^{-1} for the tetraethyl derivative and 53 kJ mol^{-1} for the tetraisopropyl derivative. These values are somewhat lower than the unambiguous S–Ar rotation barrier in compound **74** which was found[187] to be 63 kJ mol^{-1}.



(**74**)

The spectra of the *t*-butyl compounds **75** gave two separate *t*-butyl resonances at around ambient temperature[90] which coalesced to one on heating. The activation data for **75** are given in Table 33. The data were interpreted as being values for S–S rotation. Certainly the barriers for both S–Ar and S–S rotation in these examples must have a lower limit of the measured $\Delta G^{\ddagger}$.

TABLE 33. Measured[201] activation free energies for disulphides **75**



(**75**)

R	Aromatic protons			*t*-Butyl groups		
	$\Delta\nu$ (Hz)	T_c (°C)	$\Delta G^{\ddagger}$ (kJ mol^{-1})	$\Delta\nu$ (Hz)	T_c (°C)	$\Delta G^{\ddagger}$ (kJ mol^{-1})
H				39	39	64.8
CH_3	14.0	31	65.6	37.8	39	64.8
$N(CH_3)_2$	8.0	18	63.5	35.0	37	64.8
$C(CH_3)_3$	14.8	40	67.7	39.0	54	68.1

It was also found that *ortho* monosubstituted disulphides had temperature-independent spectra, consistent with fast rotation about the S–S and S–Ar bonds[202].

In general, the conclusions of Kessler and Rundel[202] are reasonable and the work is widely quoted, but it would be very desirable to use modern NMR techniques to confirm which dynamic processes are occurring, and establish their relative energies.

Pappalardo and coworkers[145, 148, 149] have made extensive studies on diphenyl disulphides using a variety of techniques such as dipole moment measurement, CNDO/2 calculations and ^{1}H NMR. The CNDO/2 calculations[145] favour a *trans* rotation about the S–S bond with a barrier height of about 60 kJ mol^{-1} compared with greater than 250 kJ mol^{-1} for the *cis* rotation. The barrier to S–Ar rotation was calculated[145] at 239 kJ mol^{-1} although the curve was very shallow about the minimum, allowing appreciable thermal oscillations. The *trans* rotation about S–S bonds (in open-chain compounds) now seems to be generally accepted[206].

Pappalardo has also recorded spin–lattice relaxation times for diphenyl disulphide[151, 207] as shown in Table 10. It was concluded on the basis of a thorough analysis that conformational motions about the S–Ar bond occur at a rate comparable to that of overall molecular reorientation.

3. DNMR of sulphenamides

This subject is covered by Kost and Raban[113] and has been previously reviewed by Kost and Raban[114]. The problem is similar in some ways to that of the disulphides in that two possible processes could contribute to dynamic NMR behaviour: nitrogen inversion and S–N bond rotation. This is illustrated in Figure 13.

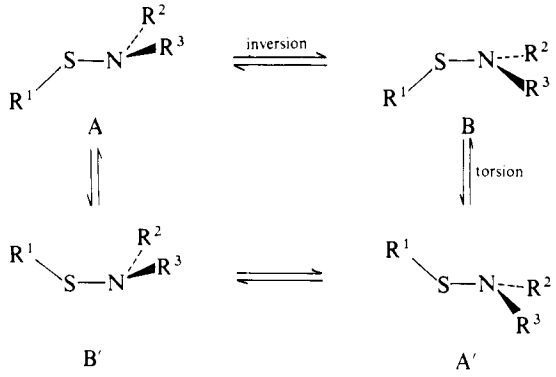


FIGURE 13. Dynamic processes in sulphenamides

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **5**

Synthesis of sulphenic acids and esters

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Edited by S. Patai

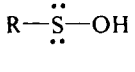
I. INTRODUCTION

Sulphenic acids and their esters belong to a family of organic sulphur compounds in which the sulphur atom is simultaneously connected with the carbon and oxygen atoms. Among organic oxoacids of sulphur, sulphenic acids are the least stable compounds and for this reason they are considered in many cases as elusive reactive intermediates. Up to now, only a limited number of sulphenic acids possessing special structural features have been isolated in a pure state and characterized. On the other hand, sulphenic acid esters are well known as isolable, albeit reactive, derivatives. Synthetic methods for the preparation of sulphenic acids and esters are briefly reviewed in both the old and new editions of Houben-Weyl devoted to organic sulphur compounds.

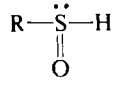
The aim of the present chapter is to provide the reader with a comprehensive and systematic survey of the methods which can be applied for synthesis of both unstable and stable sulphenic acids or their salts as well as sulphenic acid esters. An attempt has been made to cover the recent literature on this subject, practically until the end of 1988.

II. SYNTHESIS OF SULPHENIC ACIDS

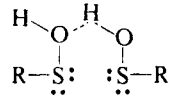
Sulphenic acids may exist in two tautomeric forms, **1a** and **1b**. Bruice and Sayigh[1] investigated the solution infrared spectra of anthraquinone-1-sulphenic acid and reached the conclusion that it exists as the O-protonated form **1a**. The same conclusion was reached by Penn and Block[2] from microwave spectroscopy studies of methanesulphenic acid. The IR spectra of stable 2-oxoazetidine-4-sulphenic acid[3] and 9-triptycenesulphenic acid[4] indicate that these acids have also the structure **1a**. However, Shelton and Davis[5a, b] in their early paper ascribed the IR absorptions of *t*-butanesulphenic acid at 3400 and 2600 cm^{-1} to the presence of both forms **1a** and **1b**, respectively. Very recently, Davis and his coworkers[6] have investigated the structure of *t*-butanesulphenic acid and benzenesulphenic acid using a modified flash vacuum pyrolysis (FVP) apparatus allowing IR measurements at low temperatures and drew similar conclusions. Moreover, the same authors, based on the studies of all sulphenic acids generated by FVP, proposed an explanation of the high reactivity and instability of this class of compounds. According to Davis[6] the formation of the hydrogen bonded dimer **2** is the main factor which lowers the energy of activation for the thiosulphinate formation. Therefore, the stability of a few sulphenic acids that have been isolated and characterized so far can be explained in terms of steric, electronic and intramolecular hydrogen-bonding effects which prevent the formation of dimer **2**.



(**1a**)



(**1b**)

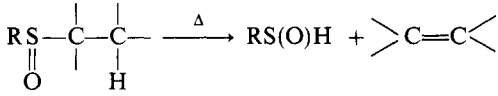


(**2**)

Equations 1–8 indicate in summary fashion principal methods for the synthesis of sulphenic acids.

$$RSH \xrightarrow{[O]} RS(O)H \tag{1}$$

$$RSX \xrightarrow[HO^-/H_2O]{H_2O\ or} RSOH \text{ or } RSO^- + X^- \tag{2}$$



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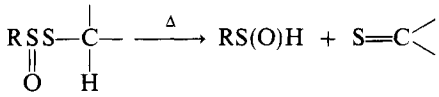
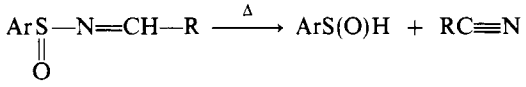
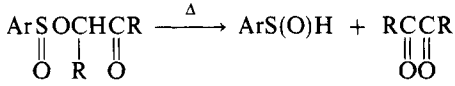


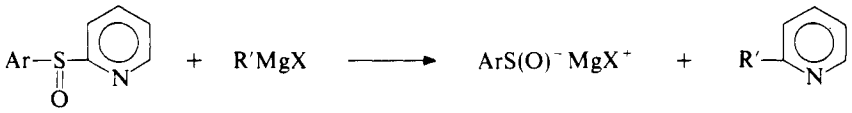
(4)



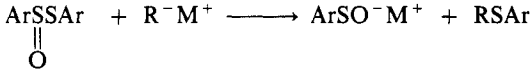
(5)



(6)



(7)



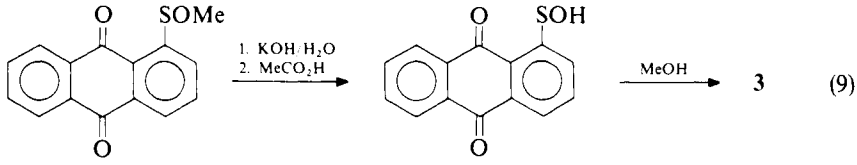
(8)

The first equation shows a very simple way to generate sulphenic acids starting from the corresponding thiols. So far, however, only few papers applying this approach have been published in the chemical literature. On the other hand, the reaction shown in equation 2 found much wider application and, among other things, it has been successfully used for the preparation of the first stable sulphenic acid. Thermolysis of sulphoxides (equation 3) constitutes the most versatile method for generating unstable sulphenic acids. In recent years, in addition to the sulphoxide thermolysis, several E_i-type eliminations have been discovered that also result in the formation of sulphenic acids. For example, Block[7] showed that alkyl thiosulphinates undergo easily thermolytic decomposition to give sulphenic acids (equation 4). Davis and collaborators[8] have found that *N*-arenesulphinylimines give arenesulphenic acids and the corresponding nitriles when heated at 80 °C (equation 5). The formation of aromatic sulphenic acid salts in the reaction of aryl arenethiosulphinates with organometallic reagents has been reported by Vinkler and coworkers[9] in 1970. More recently, the salts of arenesulphenic acids were found to be formed in the reaction of pyridyl sulphoxides with Grignard reagents[10] (equation 7). The formation of aromatic sulphenic acids by thermal decomposition of sulphinates derived from α-hydroxy ketones has also been reported[11]. A more detailed discussion of syntheses of stable and unstable sulphenic acids will be given below.

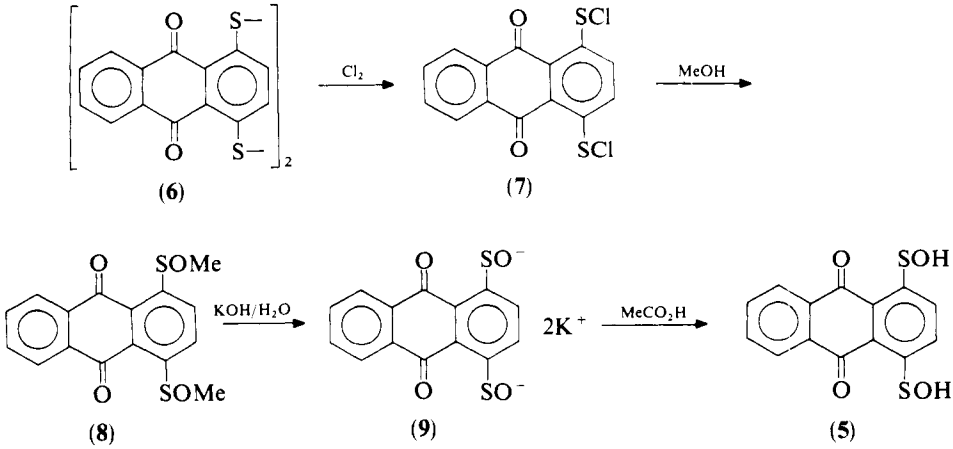
A. Synthesis of Stable Sulphenic Acids

Anthraquinone-1-sulphenic acid **4**, the first stable member of this class of compounds, was isolated by Fries[12] as early as 1912. This acid was prepared by hydrolysis of the methyl sulphenate **3** using strong potassium hydroxide solution followed by the liberation of the free sulphenic acid **4** with acetic acid (equation 9). The original synthesis of **4** by Fries was later confirmed by Jenny[13]. It is interesting to note that the structural

assignments to **4** done by Fries based on the empirical formula, means of preparation and reformation of the ester **3** on treatment with methanol have been supported by the spectroscopic studies of Bruice and Sayigh[1].



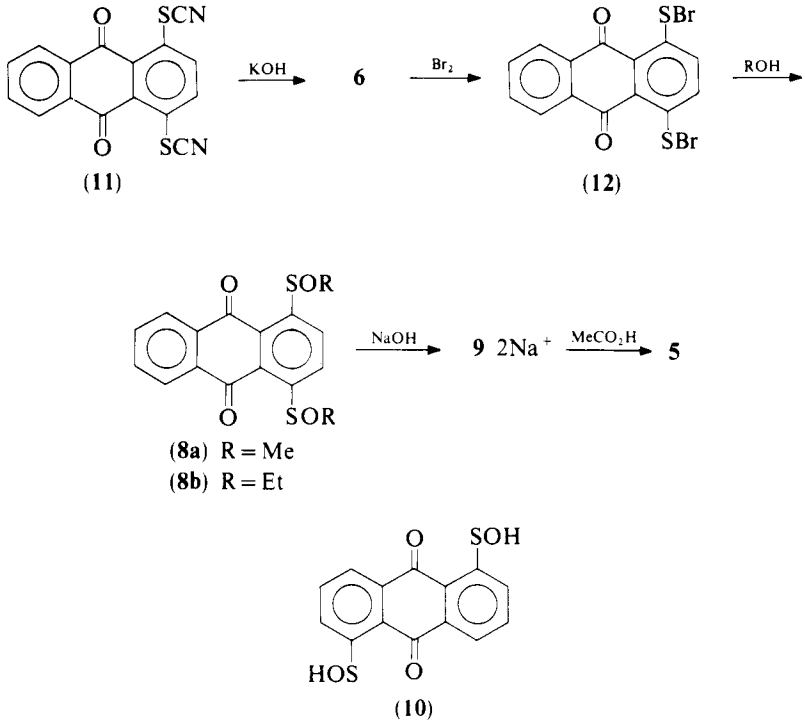
Bruice and Markiv[14] described the synthesis of the second stable sulphenic acid, anthraquinone-1,4-disulphenic acid (**5**), shown in Scheme 1. This synthesis begins with polysulphide **6**, which was chlorinated under anhydrous conditions in the presence of aluminium chloride as a catalyst to give anthraquinone-1,4-disulphenyl chloride (**7**). The reaction of **7** with methanol in benzene solution in the presence of traces of pyridine afforded dimethyl anthraquinone-1,4-disulphenate (**8**). The latter was converted to disulphenic acid **5** in 22–26% yield according to the original procedure of Fries[12].



SCHEME 1

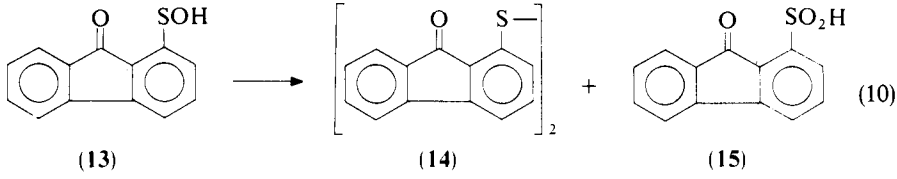
An independent synthesis of the acid **5** and its 1,5-analogue **10** has been reported by Jenny[15,16] (Scheme 2). In this case, polysulphide **6** was generated from the corresponding thiocyanate **11** by treatment with aqueous solution of potassium hydroxide. Bromination of **6** gave anthraquinone-1,4-disulphenyl bromide (**12**), which was refluxed with methanol or ethanol affording the sulphenate esters **8a** and **8b**, respectively. These esters were finally converted into the desired sulphenic acid **5** according to the procedure of Fries. The synthesis of anthraquinone-1,5-disulphenic acid **10** was accomplished in a similar way.

In this context, it is interesting to point out that the synthesis of the closely related fluorenone-1-sulphenic acid **13** failed[17]. Most probably the free acid **13** and its salts show

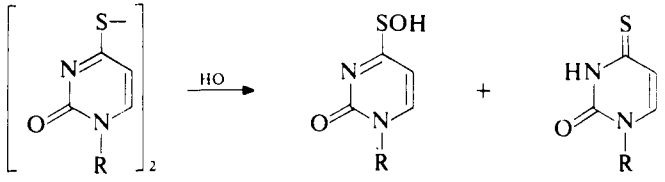


SCHEME 2

a great tendency to disproportionate to the corresponding disulphide **14** and sulphinic acid **15** (equation 10).



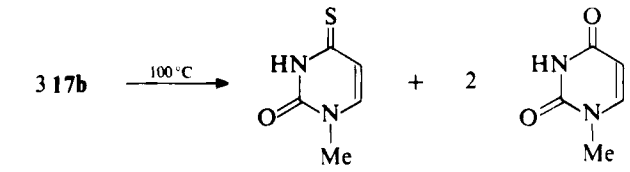
Hydrolysis of bis(1-β-ribofuranosyl-4-thiouracil)-disulphide **16a** and a simple *N*-methyl analogue **16b** has been found to produce almost quantitatively the stable sulphenic acids **17a** and thiones **18** (equation 11)[18]. 1-Methyluracil-4-sulphenic acid **17b** was isolated and fully characterized as its silver salt. The solutions of the free acid **17b** are relatively stable at room temperature at pH = 2. However, heating these solutions at 100 °C at pH = 1 for 1 hour causes a complete decomposition (equation 12).



(16) (17) (18)

(a) R = β-D-ribosyl
(b) R = Me

(11)



(18) (19)

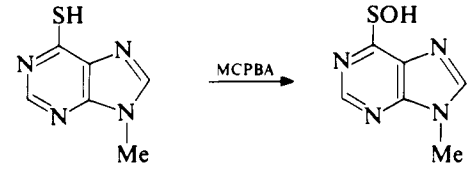
(12)

Uridine-4-sulphenic acid **17a** was identified by its UV spectrum, which was similar to that of the acid **17b**.

Recently, the synthesis of the sulphenic acids **21**, **23** and **25** derived from 6-thiopurine **20**, 9-methylthiopurine **22** and 4-mercapto-1*H*-pyrazolo-[3,4,*d*]-pyrimidine **24** (equations 13–15) was reported[19]. They were obtained from the parent thiols by oxidation with *m*-chloroperbenzoic acid and purified as the silver salts. Although the free sulphenic acids could not be isolated in a pure state, their properties were examined in solutions.

(20) (21)

(13)

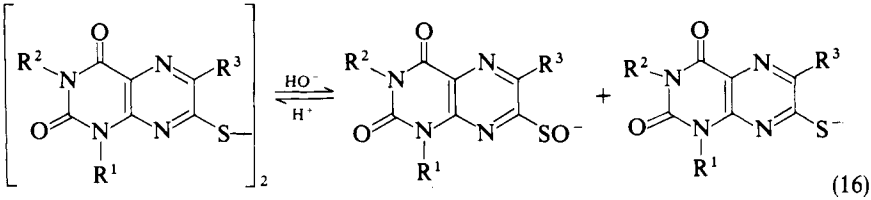


(22) (23)

(14)

(24) (25) (15)

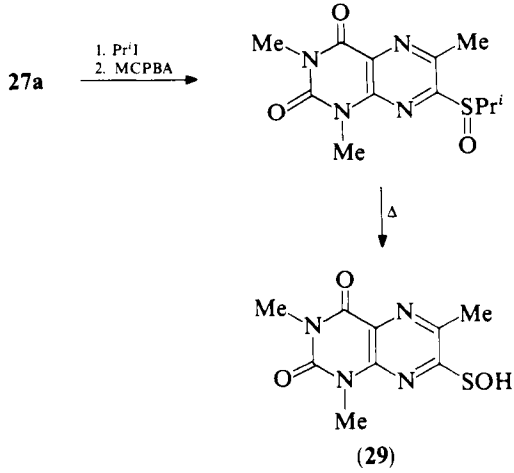
Heckel and Pfleiderer[20] have also prepared a series of stable lumazine-7-sulphenates **27** by nucleophilic cleavage of the disulphide bond taking place on dissolution of dilumazin-7-yl disulphides **26** in alkaline medium. This reaction is reversible and acidification of the solutions after hydrolysis produces the starting disulphides **26** in almost quantitative yield (equation 16).



(26) (27) (28) (16)

(a) $R^1 = R^2 = R^3 = Me$
(b) $R^1 = R^2 = Me$, $R^3 = H$
(c) $R^1 = Me$, $R^2 = R^3 = H$
(d) $R^1 = R^3 = H$, $R^2 = Me$

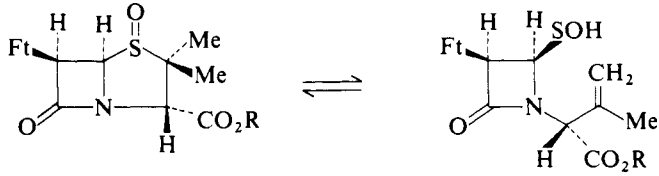
The analytically pure 1,3,6-trimethyllumazine-7-sulphenic acid **29** was prepared by thermal decomposition of the isopropyl sulphoxide obtained from **27a** as shown in Scheme 3.



(29)

SCHEME 3

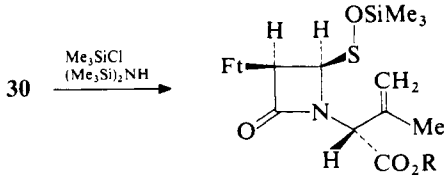
It was mentioned above that thermolysis of sulphoxides represents a general method for the synthesis of sulphenic acids. This method was applied for the synthesis of the stable azetidinone sulphenic acids **31**[3] (equation 17). Thus, heating the ester **30a** in ethyl acetate for 10 min results in the formation of the sulphenic acid **31a** in 20% yield. Evaporation of the solvent to dryness and recrystallization of the residue gave the starting ester **30a** (60%) and the pure sulphenic acid **31a** in 10% yield. When the penicillin sulphoxide esters **30a** and **30b** were refluxed in benzene with 100% excess of a mixture of trimethylsilyl chloride and hexamethyldisilazane, the trimethylsilyl sulphenates **32** were formed in a nearly quantitative yield[21] (equation 18). Their hydrolysis in chloroform solution with moist air leads to the sulphenic acids **31**. When the reaction shown in equation 18 is performed in the presence of small amounts of triethylamine, the isomeric trimethylsilyl sulphenate (**33b**) and the sulphenic acid **33a** are obtained.



(17)

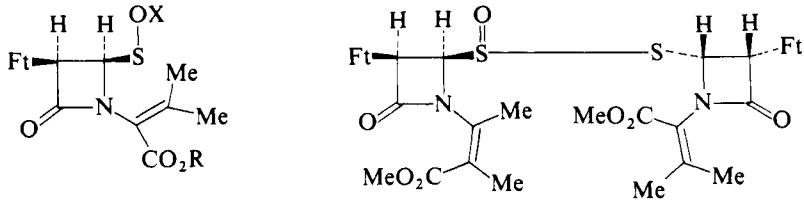
(30) (31)

(**a**) R = *p*-$NO_2C_6H_4CH_2$ Ft = Phthalimido
(**b**) R = Me



(32)

(18)



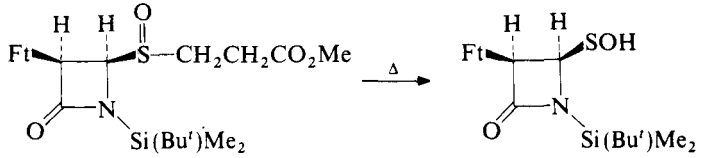
(33) (34)

(**a**) X = H
(**b**) X = $SiMe_3$

Both sulphenic acids **31b** and **33a** are unstable even in a solution. The former undergoes a spontaneous annelation to the penicilline sulphoxide ester **30a**, thus reverting the electrocyclic process by which it was obtained, while the latter eliminates water to give the corresponding thiosulphinate **34**[22].

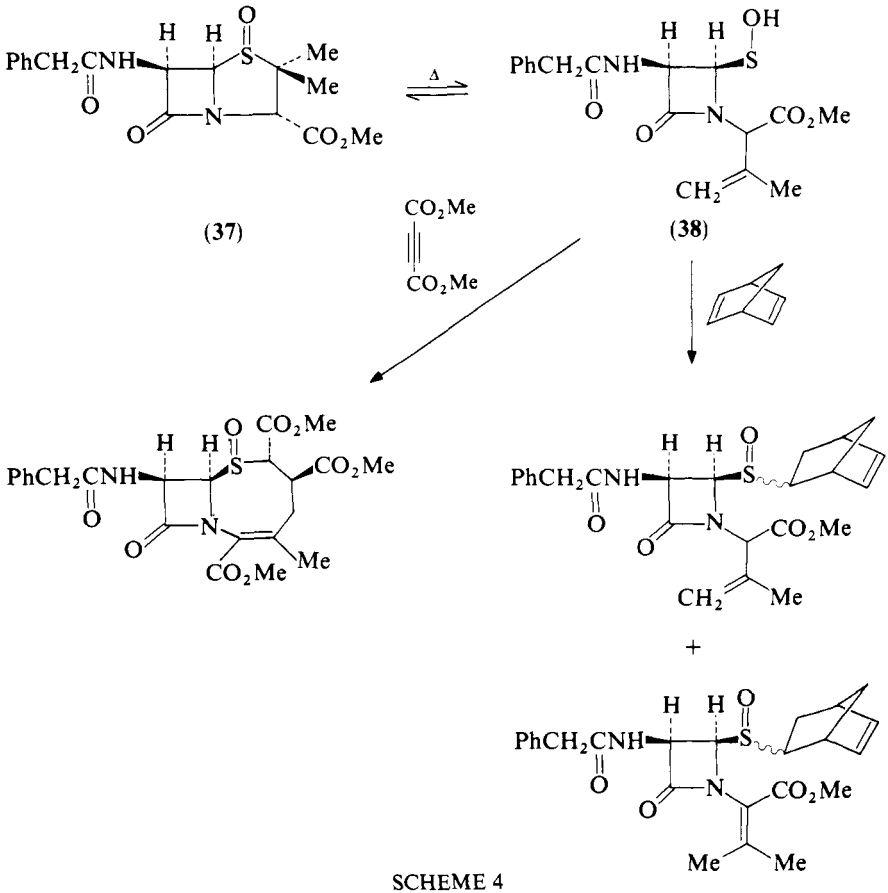
More recently, the synthesis of the sulphenic acid **36** exhibiting an unusually high thermal stability has been described by Bachi and Gross[23]. This acid was obtained in 79%

yield from the sulphoxide **35** on heating in benzene at 60 °C for 24 hours (equation 19). The acid **36** was found to be remarkably stable. For example, no trace of decomposition was detected after 6 months storage at 0 °C or after refluxing in benzene for 24 hours. However, it decomposed on heating in xylene at 130 °C. According to Bachi and Gross this striking stability results from steric hindrance of the bulky *t*-butyldimethylsilyl group which prevents a self-condensation of **36** to the corresponding thiosulphinate.



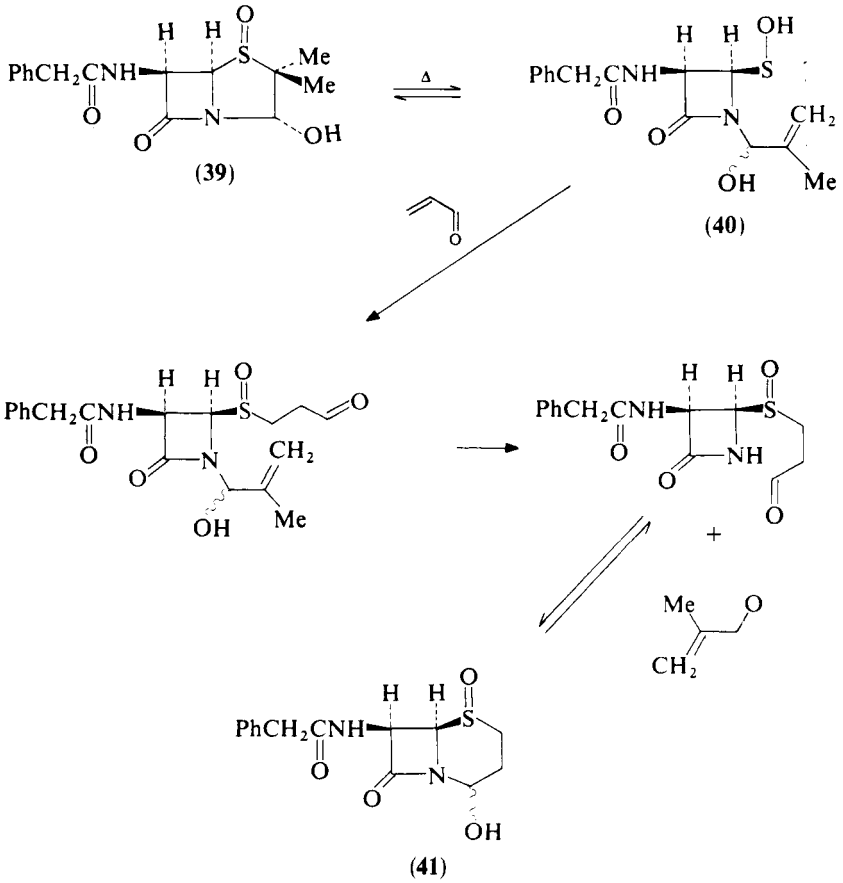
(35) (36) (19)

Barton and his coworkers[24] obtained the sulphenic acid **38** which could be trapped either by norbornadiene or by dimethyl acetylenedicarboxylate (Scheme 4).



SCHEME 4

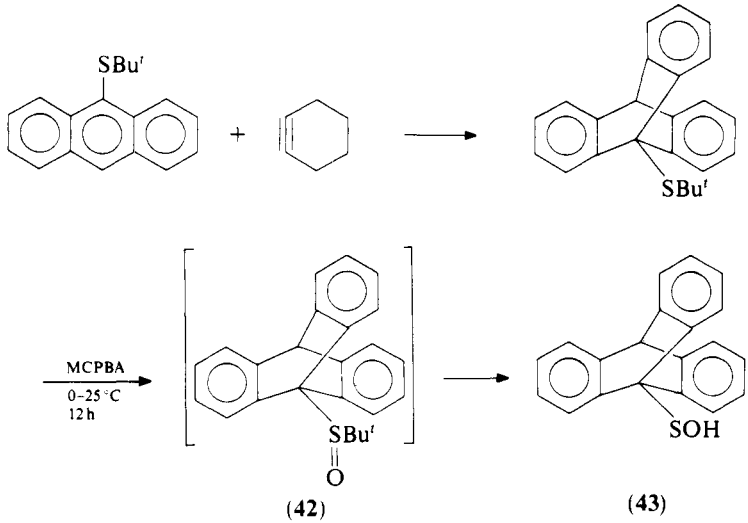
It was also found that 3-hydroxyphenam-*S*-oxide **39** gives, on heating, the sulphenic acid **40** which undergoes a trapping reaction with acroleine to give the hydroxycepham **41** isolated as a mixture of diastereoisomers (Scheme 5). In the absence of the external trapping agent the sulphenic acid **40** adds to the internal double bond affording back a penicilline sulphoxide[25,26].



SCHEME 5

Nakamura[4] reported recently that 9-(*t*-butylsulphinyl)triptycene **42** undergoes very easily an E_i-type elimination affording the stable 9-triptycenesulphenic acid **43** whose stability may be attributed to the steric nature of a triptycene skeleton. The synthesis of **43** is presented in Scheme 6.

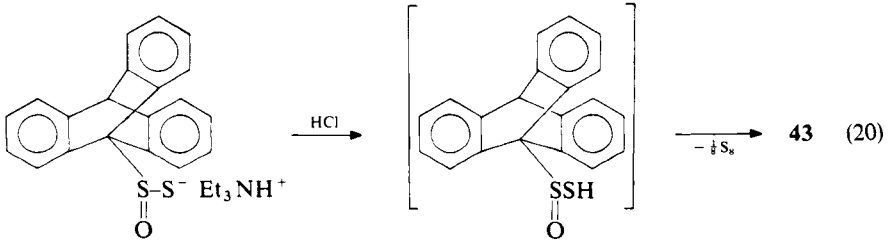
Triptycenesulphenic acid **43** was also obtained by Mikołajczyk and coworkers[27] as a product of sulphur elimination from triptycenethiosulphinic acid **44** generated from its triethylammonium salt upon acidification (equation 20). The conversion of the triethyl-



(42) (43)

SCHEME 6

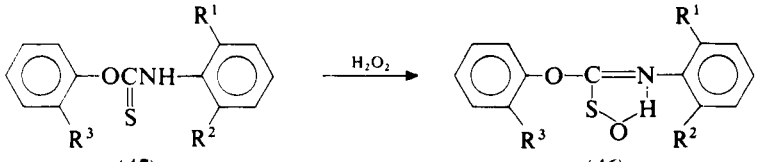
ammonium salt of **44** to **43** may also be achieved by using triphenylphosphine as a desulphurization agent.



43 (20)

(44)

An interesting group of stable sulphenic acids was obtained by Walter and Bode[28] by oxidation of aromatic esters of *N*-arylthiocarbamic acids **45**. These authors found that treatment of **45** with an equivalent amount of hydrogen peroxide in a methanol/methylene chloride solution at 40 °C for a few hours gives the corresponding sulphenic acids **46** in satisfactory yields (Table 1). In this case the acids **46** are stabilized by hydrogen bond formation as shown in equation 21.



(21)

(45) (46)

TABLE 1. Synthesis of sulphenic acids **46** by oxidation of thiocarbamic acid O-aryl esters **45**

R^1	R^2	R^3	Reaction time (h)	Yield (%)	M.p. (°C)
Me	Me	Ph	6	57	118–120
Et	Et	Ph	8	48	135–142
Pr^i	Pr^i	Ph	15	48	55–58
Me	Me	Me	5	33	103.5–105
Me	Me	Br	7	48	115–117

B. Synthesis of Unstable Sulphenic Acids

Unstable sulphenic acids greatly exceed in number the stable sulphenic acids discussed above. Such unstable sulphenic acids can be generated by all the methods described by equations 1–8. Generally, these sulphenic acids are not formed to detectable levels in solution during generation. However, Shelton and Davis[5b] in their pioneering work in 1967 have shown that they can be trapped by alkynes or activated alkenes (equations 22 and 23). Since that time trapping of sulphenic acids has been widely used to demonstrate their presence as transient intermediates in various reactions.

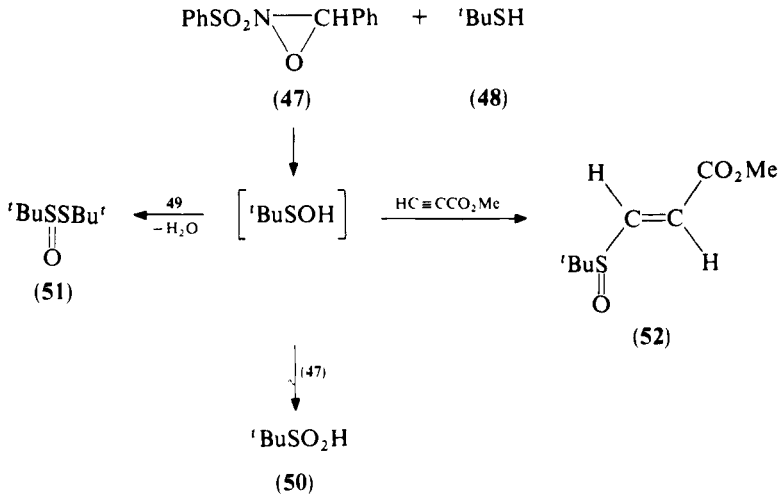
$$RSOH + RC{\equiv}CR \longrightarrow RSC(=O)CH{=}CHR \quad (22)$$

$$RSOH + CH_2{=}CHCO_2R \longrightarrow RSCH_2CH_2CO_2R \quad (23)$$

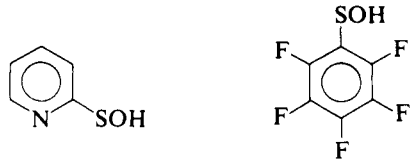
1. *Oxidation of thiols*

The first direct evidence for the involvement of sulphenic acids in the oxidation of thiols was provided by Davis and Billmers[29] in 1981. These authors found that a fast addition of one equivalent of 2-(benzenesulphonyl)-3-phenyloxaziridine (**47**) to two equivalents of *t*-butanethiol (**48**) results in an immediate reaction in which the oxidizing agent was completely consumed and the corresponding sulphinic acid **50** (80% yield) and the thiosulphinate **51** (6% yield) as well as the sulphoximine, $PhSO_2N{=}CHPh$, were formed. That *t*-butanesulphenic acid **49** is an intermediate in this reaction was clearly demonstrated by trapping experiments with methyl propiolate. Thus, Davis and Billmers found that slow addition of oxaziridine **47** to a solution of thiol **48** and methyl propiolate gives vinyl sulphoxide **52** in 25–47% yield (Scheme 7).

Davis and Jenkins[30] have also found that oxidation of 2-mercaptopyridine and pentafluorobenzenethiol with **47** gives 2-pyridinesulphenic acid **53** and pentafluorobenzenesulphenic acid **54** as the first unstable intermediates.

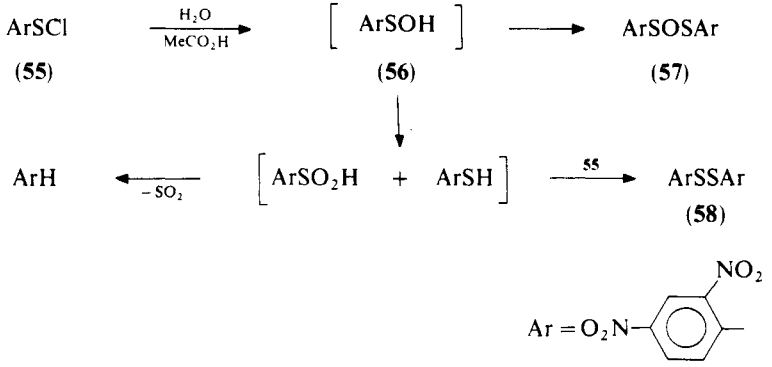


SCHEME 7



2. Hydrolysis of sulphenyl derivatives

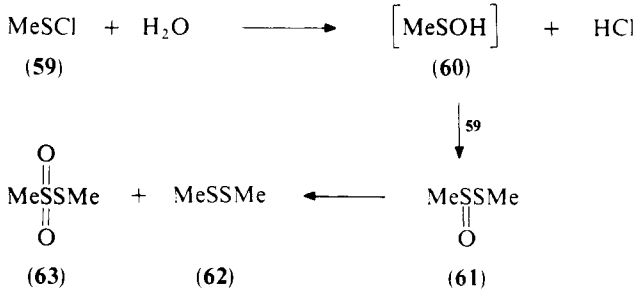
As early as 1956 Kharasch and coworkers[31] investigated the hydrolysis of 2,4-dinitrobenzenesulphenyl chloride **55** as a possible route to 2,4-dinitrobenzenesulphenic acid **56**. In fact, hydrolysis of **55** occurred readily in aqueous acetic acid with quantitative



SCHEME 8

release of the chloride anion. However, instead of **56** several other products were isolated. Among them, 2,4-dinitrobenzenesulphenic anhydride **57** and 2,4-dinitrophenyl disulphide **58** were the major products. The formation of all compounds was rationalized on the basis that the sulphenic acid **56** is the primary, unstable hydrolysis produet (Scheme 8).

In 1959 Douglass[32] reported that the reaction of methanesulphenyl chloride **59** with water leads to dimethyl disulphide **62** and *S*-methyl methanethiosulphonate **63**. He proposed a mechanism which involves the formation of methanesulphenic acid **60** as the first intermediate that reacts further with **59** to give methyl methanethiosulphinate **61**. The latter undergoes disproportionation to the final products **62** and **63** (Scheme 9).

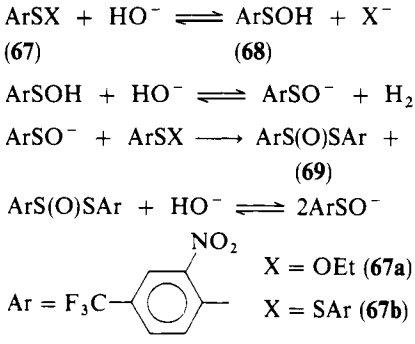


SCHEME 9

Similarly, the formation of dichlorosulphine **66** on hydrolysis of trichloromethanesulphenyl chloride **64** was explained[33] by assuming trichloromethanesulphenic acid **65** to be formed on the reaction pathway (equation 24).

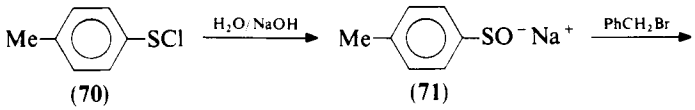
$$\underset{(64)}{Cl_3CSCl} \xrightarrow[-HCl]{H_2O} \underset{(65)}{[Cl_3CSOH]} \xrightarrow{-HCl} \underset{(66)}{Cl_2C{=}S{=}O} \qquad (24)$$

Base-catalyzed hydrolysis of ethyl 2-nitro-4-trifluoromethylbenzenesulphenate **67a** leads to the corresponding sulphenate anion via the sulphenic acid **68** as the primary product. The mechanism proposed by Hogg and Stewart[34, 35] for this raction involves a nucleophilic attack of hydroxide anion at sulphur in **67** followed by reversible formation of the thiosulphinate **69**. This, in turn, reacts with hydroxide anion. All the reactions involved are shown in Scheme 10. Interestingly, hydrolysis of bis-2-nitro-4-trifluoromethyl disulphide **67b** follows the same mechanism but it is 100 times faster.

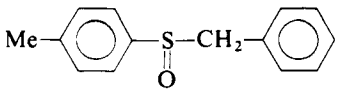


SCHEME 10

Alkaline hydrolysis of *p*-toluenesulphenyl chloride **70** was found[9] to afford sodium *p*-toluenesulphenate **71** that was trapped with benzyl bromide producing benzyl *p*-tolyl sulphoxide as a sole product (equation 25).



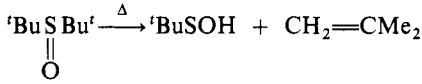
(70) (71)



(25)

3. *Thermolysis of sulphoxides*

The thermal decomposition of di-*t*-butyl sulphoxide **72**, first reported by Shelton and Davis[5a], results in the formation of *t*-butanesulphenic acid **49** and isobutylene (equation 26). This acid exhibits a particular stability among the simple alkanesulphenic acids.

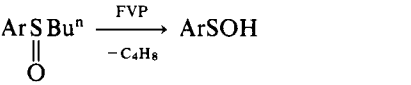


(72) (49) (26)

Although it was found that other aryl and alkyl sulphoxides containing a β-hydrogen atom may be pyrolysed to give sulphenic acids, the rather high temperature (100–200 °C) required for this reaction to proceed at a convenient rate precludes the studies of the labile sulphenic acids. This drawback may easily be overcome by use of flash vacuum pyrolysis (FVP). Davis and his coworkers[30, 36] demonstrated that this technique allows one to prepare large concentrations of arene- and alkanesulphenic acids (equations 27 and 28).

(27)

(**49**) R = Bu^t
(**60**) R = Me
(**73**) R = Ph
(**74**) R = 2, 6Me$_2$C$_6$H$_3$

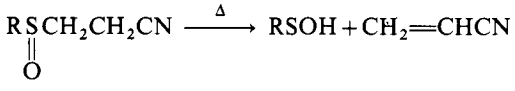


(28)

(**53**) Ar = C_6H_4N
(**54**) Ar = F_5C_6
(**75**) Ar = *p*-$O_2NC_6H_4$

The FVP technique was also applied successfully by Block's group[2] to generate methanesulphenic acid **60** from *t*-butyl methyl sulphoxide.

Jones and coworkers[37] found that thermolysis of β-cyanosulphoxides **76** occurs at much lower temperatures and represents a convenient method for generating a variety of sulphenic acids (equation 29).

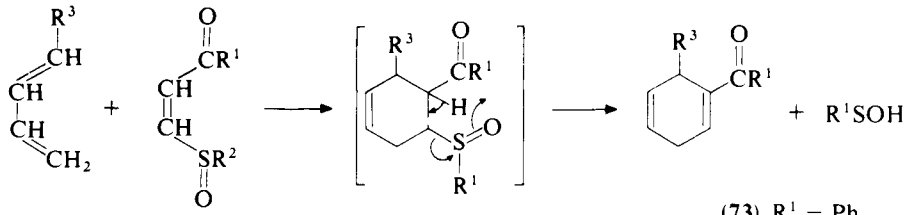


(29)

(**76**)

(**60**) R = Me
(**73**) R = Ph
(**77**) R = EtO_2CCH_2

Formation of ethanesulphenic acid **78** and benzenesulphenic acid **73** was observed[38] to occur in the thermal cycloaddition of β-sulphinyl-α,β-unsaturated ketones **79** to butadienes **80**. The Diels–Alder adducts formed in the first step eliminate sulphenic acids to give 1,4-cyclohexadiene derivatives as shown in equation 30.

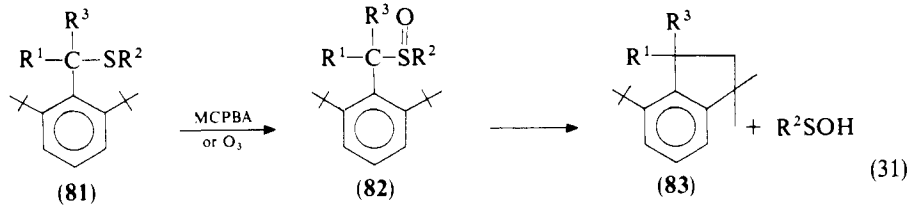


(**80**) (**79**) R^3 = H or Me

(**73**) R^1 = Ph
(**78**) R^1 = Et

(30)

An unusually fast cleavage of a sulphur–carbon bond in the sterically crowded sulphoxides **82** was found by Okazaki and coworkers[39]. When the starting sulphides **81** were oxidized in dichloromethane at −78 °C and then gradually warmed to room temperature, indane **83** was obtained and not the expected sulphoxides **82** (equation 31). The latter undergo decomposition at *ca* 0 °C as evidenced by ^{1}H-NMR studies and gave *t*-butanesulphenic acid **49** and phenylmethanesulphenic acid **84**. The formation of both acids was additionally confirmed by isolation of the corresponding thiosulphinates.



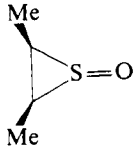
(**81**) (**82**) (**83**)

(**a**) $R^1 = R^2 = {}^t$Bu, R^3 = H
(**b**) R^1 = Ph, $R^2 = PhCH_2$, R^3 = H

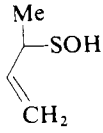
(**49**) $R^2 = {}^t$Bu
(**84**) $R^2 = PhCH_2$

(31)

An interesting rearrangement of the strained *trans*-2-butaneepisulphoxide **85** involving the intermediate formation of the allylic sulphenic acid **86** has been observed by Baldwin and his group[40].



(85)



(86)

Sodium or potassium salt of methanesulphenic acid **60** was generated by O'Connor and Lyness[41] on treatment of dimethyl sulphoxide with sodium or potassium. This reaction afforded also methylsulphinyl carbanion, methane and dimethyl sulphide according to equations 32–34. The sodium and potassium salts of **60** so obtained were stable for several days at room temperature in the reaction mixture. Alkylation of these salts with alkyl bromides and iodides gave the corresponding sulphoxides.

$$\underset{\underset{\underset{O}{\|}}{MeSMe}}{} + 2M \longrightarrow MeSO^- + Me^-M^+ \qquad (32)$$

$$\underset{\underset{\underset{O}{\|}}{MeSMe}}{} + Me^-M^+ \longrightarrow \underset{\underset{\underset{O}{\|}}{MeSCH_2^-M^+}}{} + CH_4 \qquad (33)$$

$$\underset{\underset{\underset{O}{\|}}{MeSMe}}{} + 2M \longrightarrow MeSMe + M_2O \qquad (34)$$

$$M = Na, K$$

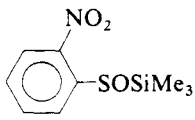
4. Decomposition of N-alkylidene arenesulphinamides

The title compounds were found by the group of Davis[8] to undergo a concerted, thermal rearrangement to arenesulphenic acids and nitriles according to the general equation 35. Sulphenic acids **88** were trapped by methyl propiolate or ethyl acrylate. When *N*-benzylidene 2-nitrobenzenesulphinamide **87c** was heated in the presence of trimethylsilyl chloride, trimethylsilyl 2-nitrobenzenesulphenate **89** was formed in high yield[42]. It can be very easily converted into the free acid **88c** or its salts.

$$\underset{\underset{\underset{O}{\|}}{ArSN{=}CHR}}{} \xrightarrow[24\,h]{80-115\,^\circ C} ArSOH + RCN \qquad (35)$$

(87)

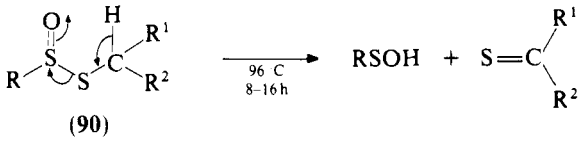
(88) (**a**) Ar = *p*-ClC_6H_4
(**b**) Ar = *m*-$NO_2C_6H_4$
(**c**) Ar = *o*-$NO_2C_6H_4$
(**75**) Ar = *p*-$NO_2C_6H_4$



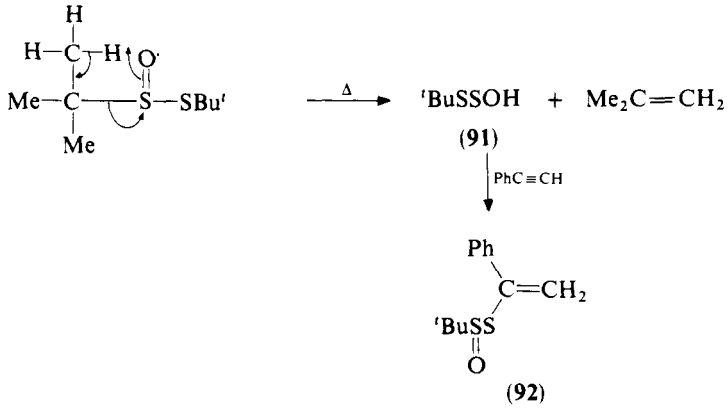
(89)

5. Decomposition of dialkyl thiosulphinates

Dialkyl thiosulphinates **90** decompose thermally to sulphenic acids under considerably milder conditions than those required for thermolysis of sulphoxides (equation 36). In this way Block and O'Connor[43] were able to generate a series of alkanesulphenic acids which were trapped by alkynes or alkenes. It is interesting to note that the thermal decomposition of *t*-butyl *t*-butanethiosulphinate affords *t*-butanethiosulphoxylic acid **91** (equation 37). The intermediacy of the latter was unequivocally confirmed by trapping experiments with phenylacetylene resulting in the thiosulphinate **92**.



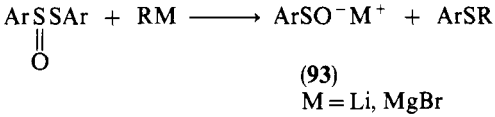
(90) (36)



(92) (37)

6. Reaction of thiosulphinates with organometallic reagents

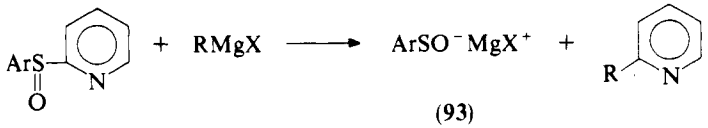
Vinkler and Klivenyi[9,44] reported that arenesulphenates are formed when aromatic thiosulphinates are subjected to action of phenyllithium or Grignard reagents (equation 38). The above authors examined the chemistry of these sulphenates in detail. Thus, their treatment with benzyl bromide gives benzyl aryl sulphoxides, while heating a solution of the sulphenates causes disproportionation to sulphinic acid salts and mercaptides. Oxidation of lithium benzenesulphenate by air leads to lithium benzenesulphinate.



(93) (38)
M = Li, MgBr

7. Reaction of pyridyl sulphoxides with Grignard reagents

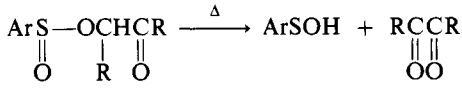
An interesting synthesis of arenesulphenates **93** involving the reaction of aryl pyridyl sulphoxides **94** with Grignard reagents was reported by Oae and Furukawa[10] (equation 39).



(93) (39)

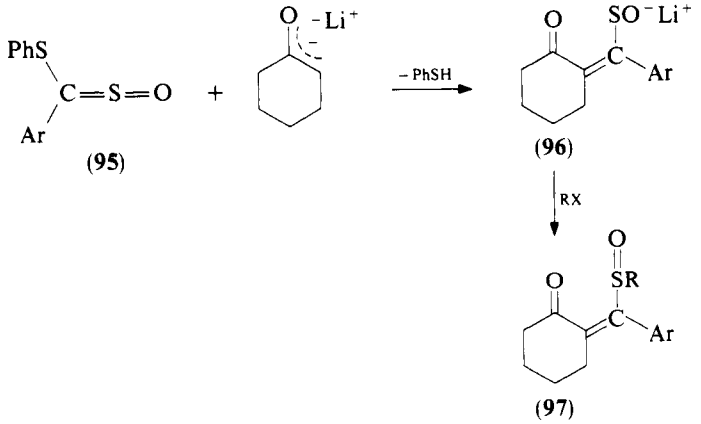
8. *Miscellaneous methods*

Arenesulphenic acids may also be generated by thermal decomposition of arenesulphinates **94** derived from α-ketoalcohols[11] (equation 6).



(94) (6)

Addition of lithium cyclohexanone enolate to sulphine **95** was found[45] to give the sulphenate anion **96** which, upon alkylation, was transformed into the corresponding 1-aryl-3-oxo-1-alkenyl sulphoxide **97** (equation 40).



(95) (96) (97) (40)

III. SYNTHESIS OF SULPHENIC ACID ESTERS

A. Reaction of Sulphenyl Halides with Alcohols and Phenols

The oldest and most general synthesis of sulphenic acid esters consists of the condensation of sulphenyl halides with an appropriate alcohol or phenol. This reaction was reported for the first time by Fries[12] as early as 1912 and was discussed in the first part of this chapter in connection with the synthesis of anthraquinone-1-sulphenic acid **4** and anthraquinone disulphenic acids **5** and **10** (see Schemes 1 and 2).

Some years later, Vorländer[46] reported that the reactions of triphenylmethanesulphenyl chloride **98** with methanol in the presence of potassium hydroxide and with phenol in the presence of pyridine afforded the corresponding sulphenates **99** and **100** (equation 41).

$$\underset{\textbf{(100)}}{Ph_3CS{-}OPh} \xleftarrow[C_5H_5N]{PhOH} \underset{\textbf{(98)}}{Ph_3CSCl} \xrightarrow[KOH]{MeOH} \underset{\textbf{(99)}}{Ph_3CS{-}OMe} \qquad (41)$$

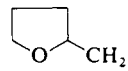
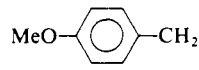
Later on, Fava and coworkers[47] used the same procedure to prepare a series of aromatic sulphenates.

Esters of the unstable trichloromethanesulphenic acid (**65**) attracted much attention. In 1935 *O*-aryl trichloromethanesulphenates **101** were first prepared by Connolly and Dyson[48] by condensing trichloromethanesulphenyl chloride **64** with sodium salts of phenols (equation 42). The reaction of **64** with various aliphatic alcohols in the presence of pyridine allowed one to prepare *O*-alkyl trichloromethanesulphenates[49-51] (equation 43 and Table 2).

$$\underset{\textbf{(64)}}{Cl_3CSCl} + ArONa \xrightarrow[-NaCl]{} \underset{\textbf{(101a-d)}}{Cl_3CS{-}OAr} \qquad (42)$$

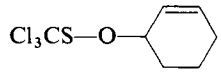
$$\underset{\textbf{(64)}}{Cl_3CSCl} + ROH \xrightarrow{C_5H_5N} \underset{\textbf{(101e-p)}}{Cl_3CS{-}OR} \qquad (43)$$

TABLE 2. Synthesis of trichloromethanesulphenates **101**, Cl_3CSOR, from trichloromethanesulphenyl chloride **64** and alcohols or phenols, ROH[a]

Sulphenate **101**	R	Yield (%)	Ref.
a	Ph		48
b	4-MeC_6H_4		48
c	2-ClC_6H_4		48
d	3,5-$Me_2C_6H_3$		48
e	Me	69, 77	49, 50
f	*n*-Pr	47, 52	49, 50
g	*i*-Pr	53, 41	49, 50
h	*n*-Bu	40	49
i	*i*-Bu	58	49
j	$CH_2{=}CH{-}CH_2$	55	49, 50
k	$H_2C{=}CH(CH_2)_3$	58	49
l		88, 48	49, 50
m			51
n	$ClCH_2CH_2$	59	50
o	$CH_3(CH_2Cl)CH$	54	50
p	$(ClCH_2)_2CH$	57	50

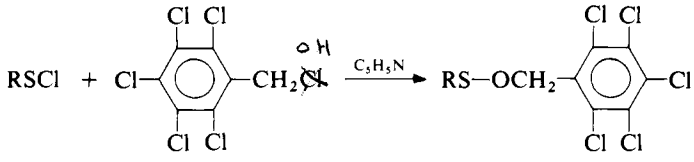
[a] In **101a-d** Na salts of phenols were used; in **101e-p** pyridine was used as HCl acceptor.

Zefirov and Abdulaveeva[52] were able to obtain the cyclic, unsaturated sulphenate **102**.



(102)

The reaction of perhalogenated sulphenyl chlorides **103** with pentachlorobenzyl alcohol **104** using pyridine as a hydrogen chloride acceptor, as a useful method for the preparation of the sulphenates **105** (equation 44), was the subject of a patent[53].



(103) **(104)** **(105)** (44)

(a) $R = Cl_2FC$ **(e)** $R = F_2CHClFC$
(b) $R = Cl_2CHCl_2C$ **(f)** $R = ClCH{=}CCl$
(c) $R = ClF_2C$ **(h)** $R = Cl_2C{=}CR$
(d) $R = F_3C$

In another patent[54] the synthesis of *O*-alkyl trifluoromethanesulphenates **107** (equation 45) as well as the sulphenates **108** and **109** was described.

$$F_3CSCl + ROH \xrightarrow{C_5H_5N} F_3CSOR \qquad (45)$$

(106) **(107)**

$(F_3CSOCH_2)_2$ $(CF_3)_2FCSOMe$

(108) **(109)**

O-Ethyl ethanesulphenate **111** as a first representative of simple aliphatic sulphenates was reported by Meuwsen and Gebhardt[55] in 1937 when **110** was treated with sodium ethoxide (equation 46).

$$EtSSCN + EtONa \longrightarrow EtSOEt + NaSCN \qquad (46)$$

(110) **(111)**

O-Ethyl *t*-butanesulphenate **113** results from the reaction of *t*-butanesulphenyl iodide **112** and sodium ethoxide[56] (equation 47).

$$^tBuSI + EtONa \longrightarrow {}^tBuSOEt + NaI \qquad (47)$$

(112) **(113)**

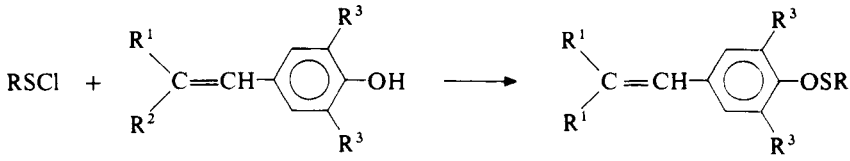
However, an early attempt[32] to prepare *O*-methyl methanesulphenate by reacting methanesulphenyl chloride **59** with methanol failed. More recently, *O*-alkyl methanesulphenates **114** were obtained[57] in 40–70% yield in the reaction of **59** with lithium

alkoxides in dimethoxyethane at −40 to −60 °C (equation 48).

$$\underset{\textbf{(59)}}{\text{MeSCl}} + \text{ROLi} \longrightarrow \underset{\textbf{(114)}}{\text{MeS—OR}} \qquad (48)$$

R = *t*-Bu, n-C_5H_{11}, *sec*-C_5H_{11}

A wide family of the sulphenic acid esters of general formula **117** was synthesized[58] by treatment of alkanesulphenyl chlorides **115** with the metal derivatives of phenols **116** (equation 49).



(49)

(115) **(116)** **(117)**

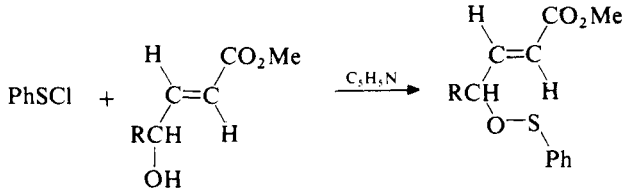
R = Me, Et, CH_2=CH
$R^1 = R^2 = H$, CN, CO_2H, NO_2, CO_2R, $CONR_2$
R^3 = alkyl

In contrast to alkanesulphenates, sulphenic acid esters derived from aromatic sulphenic acids are more stable and have been known since 1925 when Lecher[59] obtained *O*-methyl benzenesulphenate **118** from benzenesulphenyl chloride and sodium methoxide. In a similar way alkyl *p*-toluenesulphenates **119** were also prepared [60a,b].

MeOSPh **(118)** ROSTol-*p* **(119)**

(a) R = Me
(b) R = $PhCH_2$

Very recently, a series of *O*-allyl benzenesulphenates **122** containing an electron-withdrawing group at the conjugated position was reported by Tanikaga and Kaji[61] to be formed by condensation of benzenesulphenyl chloride **120** with methyl (2*E*)-4-hydroxy-2-alkenoates **121** (equation 50). These esters **122** exist as a mixture of two isomers.

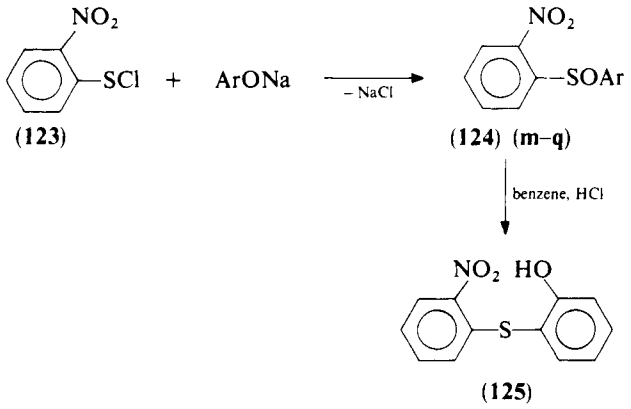


(50)

(120) **(121)** **(122)**

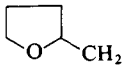
R = Et, Pr, C_5H_{11}, C_8H_{17}

In 1936 Smiles[62] found that the reaction of 2-nitrobenzenesulphenyl chloride **123** with sodium phenoxides gives the corresponding sulphenates **124** (equation 51). Moreover, he also found that these esters undergo rearrangement to the sulphides **125** on heating in benzene in the presence of hydrogen chloride. Later on, Kharasch[63] described in his patent other *O*-alkyl 2-nitrobenzenesulphenates **124** (see Table 3).



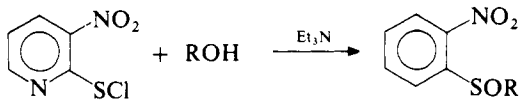
(51)

TABLE 3. Synthesis of 2-nitrobenzenesulphenates **124**, 2-$O_2NC_6H_4SOR$, from 2-nitrobenzenesulphenyl chloride **123** and alcohols or phenols, ROH

Sulphenate **124**	R	Yield[a] (%)	Ref.
a	Me	77	63
b	Me		64
c	n-Pr	52	63
d	*i*-Pr	41	63
e	*t*-Bu	27	63
	t-Bu		64
f	CH_2=$CHCH_2$	55	63
g	$MeOCH_2CH_2$	62	63
h	$PhOCH_2CH_2$	56	63
i		48	63
j	$ClCH_2CH_2$	60	63
k	CH_3CH—CH_2Cl	54	63
l	$ClCH_2CHCH_2Cl$	57	63
m	2,4-Dimethylphenyl		62
n	3,5-Dimethylphenyl		62
o	2-Chloro-3,5-dimethylphenyl		62
p	2,6-Dichloro-3,5-dimethylphenyl		62
q	2-Methyl-5-chlorophenyl		62
r	*p*-$AnCH_2$		51

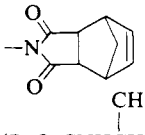
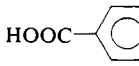
[a] Yields for sulphenates **124 m**–**r** are not given.

3-Nitro-2-pyridinesulphenyl chloride **126** reacts smoothly with hydroxy compounds, including various alcohols and hydroxy acids, to give the corresponding sulphenates **127**[65] (equation 52, Table 4).



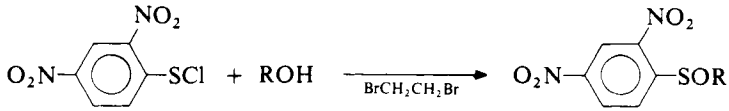
(126) (127) (a–h) (52)

TABLE 4. Synthesis of 3-nitro-2-pyridinesulphenates **127**, from alcohols and hydroxyacids

Sulphenate **127**	R[a]	Yield (%)	M.p (°C)
a	Me	78	95–96
b	Et	71	58–60
c	$CH_2CH_2N(C_2H_5)_2$	54	176–178
d		70	190–192
e	$^tBuO_2CNHCHCOOH$	72	122–124
f	$-CH_2O_2CNHCHCOOH \cdot DCHA$	58	92–94
g		68	173–174
h	$PhCH_2CHCOOH \cdot DCHA$	72	158–159

[a] DCHA indicates the dicyclohexylamine salt.

2,4-Dinitrobenzenesulphenates **129** were obtained by Perold and Snyman[66] and by Kharasch and coworkers[67] from the sulphenyl chloride **128** (equation 53, Table 5). The presence of pyridine greatly facilitated the reaction and permitted the conversion even of tertiary alcohols into **129**. Other tertiary amines such as triethylamine, quinoline and acridine also catalyse the reaction of **128** with alcohols[68].

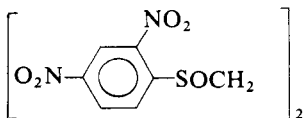


(128) (129) (53)

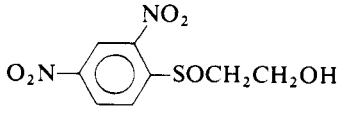
The reaction of **128** with glycols gives mono- or diesters depending on the ratio of the reactants and on the reaction conditions. For instance, a high yield of the diester **130** was obtained when a 2:1 ratio of **128** and ethylene glycol was used. With large excess of glycol, 75% of the monoester **131** and 21% of the diester **130** were produced.

TABLE 5. Synthesis of 2,4-dinitrobenzenesulphenates **129**, 2,4-$(NO_2)_2C_6H_3OR$, from 2,4-dinitrobenzenesulphenyl chloride **128** and alcohols, ROH

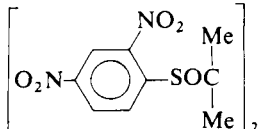
Sulphenate **129**	R	Yield (%)	Ref.
a	Methyl	55	67
b	Ethyl	85	67
c	n-Propyl	85	67
d	*i*-Propyl	90	67
e	n-Butyl	85	67
f	*s*-Butyl	80	67
g	*t*-Butyl	80	67
h	n-Amyl	85	67
i	*i*-Amyl	85	67
j	*t*-Amyl	85	67
k	Octyl	90	67
l	Lauryl	85	67
m	Cyclohexyl	85	67
n	Cholesteryl	80	67
o	L-Menthyl	85	67
p	Benzyl	95	67
q	Allyl	14	68
r	Phenylallyl	35	68
s	α-Phenylethyl	93	68
t	α,α-Dimethylpropargyl	80	68
u	Diphenylmethyl	29	68
v	2-Cyclohexenyl	Not given	52
w	Cyclooctyl	60	70
x	Cyclododecyl	62	70



(130)



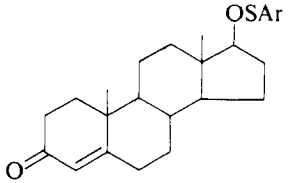
(131)



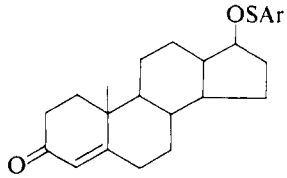
(132)

Pinacol and **128** used in a 1:2 ratio gave 33% of the diester **132** and 36% of 2,4-dinitrophenyl disulphide. However, an attempt to isolate the corresponding monoester was unsuccessful.

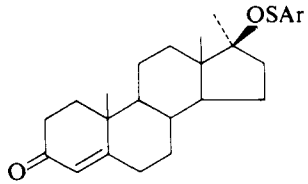
Langford and Kharasch[71] applied the pyridine-catalysed reaction of **128** for the preparation of the sulphenates **133–136** derived from testosterone, 12-nor-testosterone, 17-α-methyltestosterone and 11-α-hydroxyprogesterone.



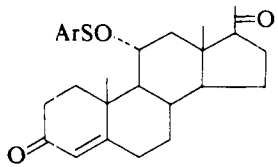
(133)



(134)

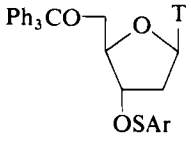


(135)

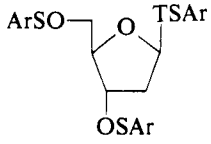


(136)

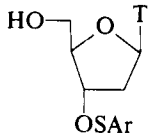
Another interesting class of sulphenates is that derived from nucleosides. Letsinger and coworkers[72] were able to synthesize 2,4-dinitrobenzenesulphenates (**137–139**) shown below.



(137)



(138)

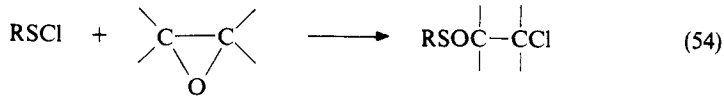


(139)

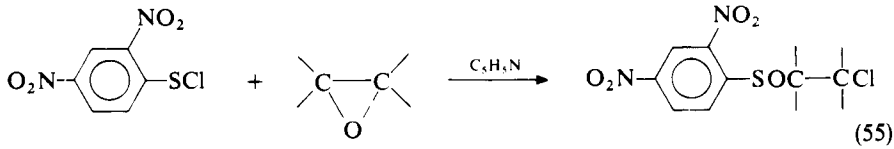
Ar = 2,4-$(NO_2)_2C_6H_3$
T = Thymidyl

B. Reaction of Epoxides with Sulphenyl Chlorides

A general approach to the synthesis of β-chloroalkylsulphenates has been developed by Peters and Kharasch[73]. It involves the reaction of sulphenyl chlorides with epoxides (equation 54). The authors investigated the reaction of 2,4-dinitrobenzenesulphenyl chloride **128** with ethylene oxide, propylene oxide, cyclohexene oxide, styrene oxide and *cis*- and *trans*-stilbene oxide. It was found[73,74] that the addition of pyridine promotes the reaction of **128** with epoxides and leads to β-chloroalkyl 2,4-dinitrobenzenesulphenates **140** (equation 55). The only exception was stilbene oxide, which was unreactive.



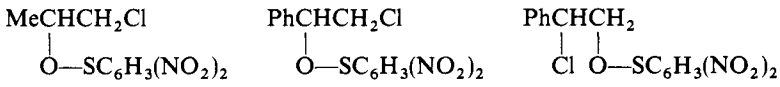
(54)



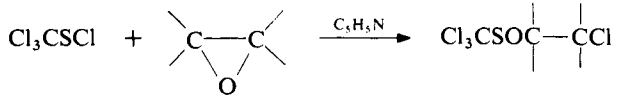
(55)

(128) (140)

Treatment of propylene oxide with **128** gave only one regioisomeric product having the structure of **140b**. However, with styrene oxide a mixture of both regioisomers **140d** and **140d'** was obtained. Later on, Langford and Kharasch[74,75] described the synthesis of β-chloroalkyl trichloromethanesulphenates **141** (equation 56, Table 6).

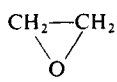
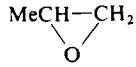
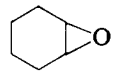
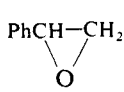


(140b) (140d) (140d')



(64) (141) (56)

TABLE 6. Synthesis of β-chloroalkyl sulphenates **140** and **141** from sulphenyl chlorides **128** and **64** and epoxides

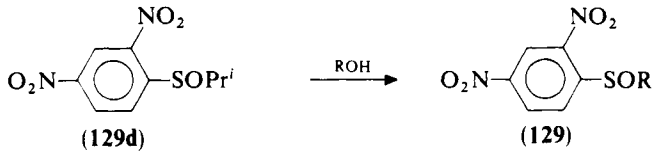
Sulphenyl chloride	Epoxide	Product	Yield	Ref.
128		**140a**	50	73, 74
64		**141a**	85	74, 75
128		**140b**	30	73, 74
64		**141b**	83	74, 75
128		**140c**[a]	78	73
64		**141c**[a]	74	75
128		**140d**+**d'**	Not given	73, 75
64		**141d**	74	74, 75

[a] *trans* isomer.

C. Transesterification of Sulphenates

Reaction of sulphenates with alcohols as a synthetic method (equation 57) has found only limited application. For the first time such a type of nucleophilic exchange at the sulphenyl sulphur atom was reported by Kharasch and his coworkers[67] who found that *O*-isopropyl 2,4-dinitrobenzenesulphenate **129d** gave the esters **129a** and **129b** on heating with methanol and ethanol, respectively, in the presence of hydrogen chloride (equation 58).

$$RSOR^1 + R^2OH \longrightarrow RSOR^2 + R^1OH \quad (57)$$



(129d) (129) (58)

(a) R = Me
(b) R = Et

Recently, Braverman and Reisman[51] described the reaction between *O*-benzyl trichloromethanesulphenate **101w** and alcohols in the presence of acids; this reaction was found to occur with the exclusive cleavage of the sulphur–oxygen bond affording the transesterification products (equation 59).

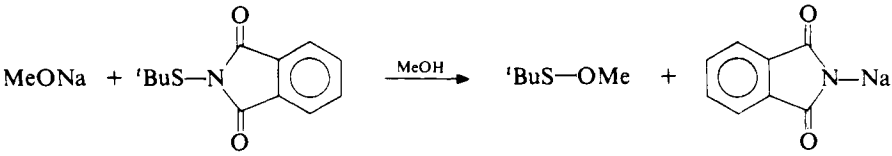
$$Cl_3CS{-}OCH_2Ph \xrightarrow{ROH/H^+} Cl_3CS{-}OR + PhCH_2OH \qquad (59)$$

(**101w**) (**101**)

A similar exchange of the aryloxy groups in *O*-aryl trichloromethanesulphenates has been described by Fava[47].

D. Reaction of Alkoxides with *N*-*t*-Butylthiophthalimide

An interesting synthesis of sulphenates was described in 1970 by Barton and Page[76] which involves the reaction of *N*-*t*-butylthiophthalimide (**142**) with alkoxides. For instance, treatment of **142** with sodium methoxide gave *O*-methyl *t*-butanesulphenate **143** in 46% yield (equation 60).

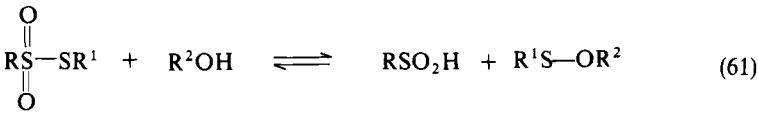


(**142**) (**143**) (60)

In a similar way, *O*-ethyl *t*-butanesulphenate **113** and *O*-*t*-butyl *t*-butanesulphenate (**144**) were obtained.

E. Reaction of Thiosulphonates with Alcohols

Thiosulphonic acid esters **145** react with alcohols to give sulphenic acid esters according to general equation 61. Boldyriev and coworkers[77], who described this reaction, found that it is strongly influenced by tertiary amines. Thus, when 2,4-dinitrophenyl benzenethiosulphonate **145** was heated in boiling ethanol for 70 h the corresponding *O*-ethyl 2,4-dinitrobenzenesulphenate **129b** was formed in 8% yield only. However, when this reaction was performed in the presence of pyridine, the ester **129b** was isolated in 68% yield.

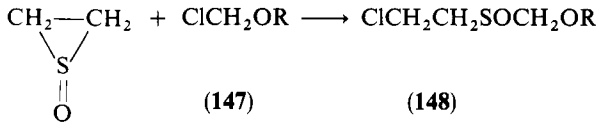


(**145**) (61)

F. Reaction of Chloroethers with Thiiran-*S*-oxide

Vilsmaier and Hloch[78] reported that treatment of thiiran-*S*-oxide **146** with chloroethers **147** results in the formation of α-alkoxymethyl esters of 2-chloroethanesulphenic

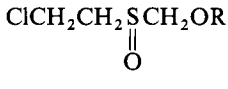
acid **148** and not of the isomeric sulphoxides **149** (equation 62).



(62)

(146) (147) (148)

(a) R = Me (70% yield)
(b) R = ^{n}Pr (70% yield)
(c) R = ^{i}Bu (75% yield)



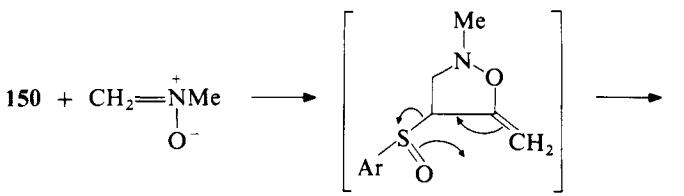
(149)

G. Esterification of Sulphenic Acids

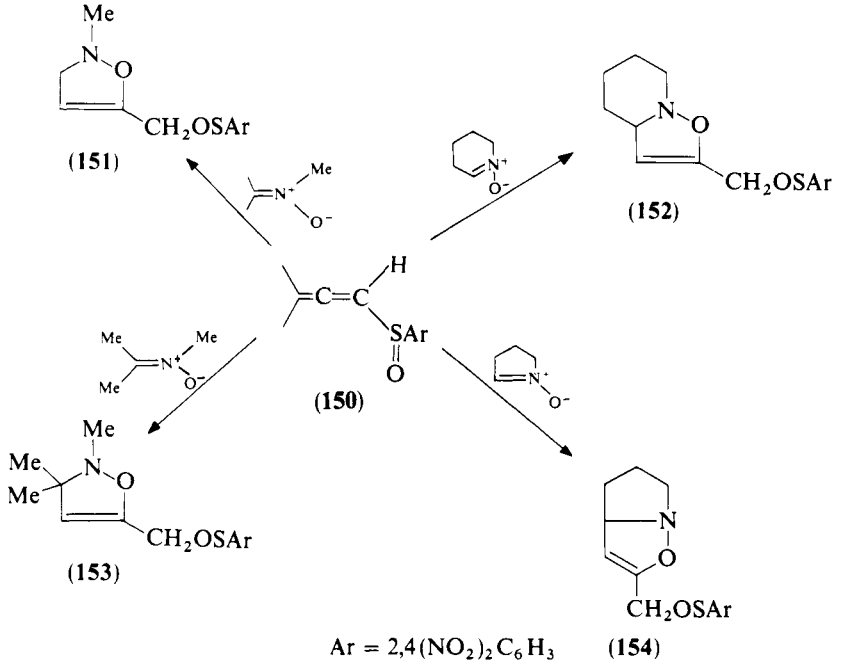
This reaction has only historical value. Fries[12] in his paper in 1912 on the synthesis of anthraquinone-1-sulphenic acid **4** noted that this acid can be converted into the methyl ester **3** by simple treatment with methanol. Until now, there are no other reports on this reaction.

H. Cycloaddition of Allenyl Sulphoxides to Nitrones

Very recently, a new and original procedure for the synthesis of sulphenates has been reported by Padwa and his group[79]. They found that tandem [3+2]-cycloaddition of allenyl sulphoxides **150** to acyclic and cyclic nitrones and [2+3]-sigmatropic rearrangement gave sulphenates in yields above 90%. The examples shown in Scheme 11 illustrate the generality of this approach. The mechanism of the formation of the sulphenates **151–154** involves an initial dipolar cycloaddition of a nitrone across the more activated allene π bond followed by a well-known sigmatropic rearrangement of the allylic sulphoxide to a sulphenate (equation 63).

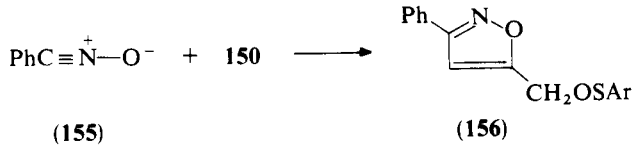


(63)



SCHEME 11

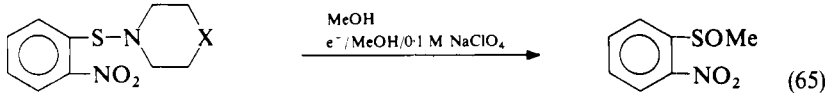
It is interesting to note that the sulphoxide **150** undergoes a cycloaddition with phenylnitrile oxide **155** to give the sulphenate ester **156** in 90% yield (equation 64).



(64)

I. Miscellaneous Methods

O-Methyl 2-nitrobenzenesulphenate **124a** was prepared by electrolysis of the corresponding sulphenamide **157** in methanol solution[80] (equation 65).



(65)

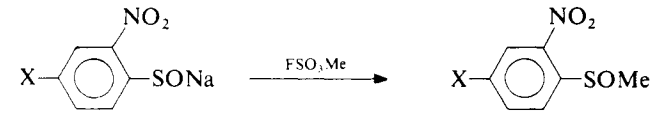
X = O
X = S

Rosenberg and Mutterties[81] reported that difluorosulphurane **158** upon treatment with B_2O_3 is converted into the sulphenic acid ester **159** (equation 66).

$$[(CF_3)_2CH]_2SF_2 \xrightarrow{B_2O_3} (CF_3)_2CHS{-}OCH(CF_3)_2 \qquad (66)$$

(158) **(159)**

Finally, it should be noted that sulphenates can be obtained[35] from sulphenic acid salts and 'hard' electrophilic reagents like methyl fluorosulphonate, dimethyl sulphate or trimethylsilyl chloride (see equation 67).



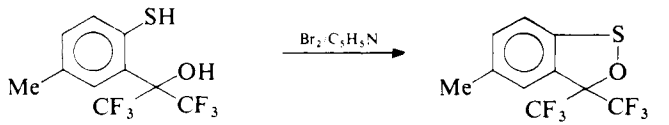
(67)

(68) **(160)**

X = CF_3

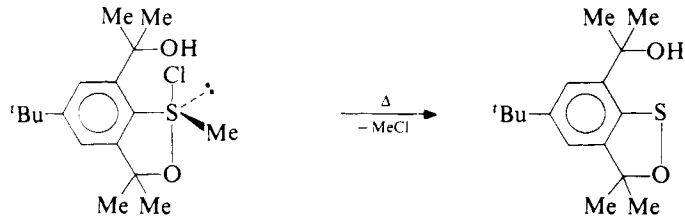
J. Synthesis of Cyclic Sulphenates (Sultenes)

Preparation of cyclic sulphenic acid esters (sultenes) requires special methods and for this reason the number of cyclic sulphenates prepared so far is very limited. Astrologes and Martin[82] found that bromination of aromatic mercaptoalcohol **161** at −50 °C in carbon tetrachloride in the presence of pyridine affords the sultene **162** (equation 68) in 85% yield. The ester **162** is thermally stable at room temperature but reacts rapidly with water to give the products of disproportionation of the sulphenic acid formed. Martin and Lau[83] also reported the synthesis of the first, simple aliphatic sultene **164**, a compound both thermally and hydrolytically stable. It was prepared by heating chlorosulphurane **163** at 80 °C under reduced pressure for one day (equation 69).



(68)

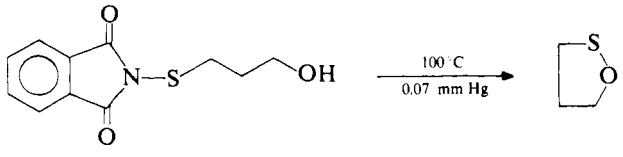
(161) **(162)**



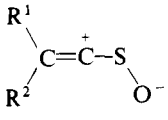
(69)

(163) **(164)**

In 1981 Whitman and Davis[84] as well as Harpp's group[85] provided evidence that pyrolysis of *N*-(3-hydroxypropylthio)-phthalimide **165** gives the parent heterocyclic sultene, 1,2-oxathiolane **166** (equation 70). Schaumann and Behrens[86] showed that 1,3-dipolar cycloaddition of thioketene-*S*-oxides **167** to azomethines **168** results in the formation of 1,2,4-oxathiazolidines **169** in *ca* 70% yield (equation 71).

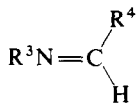


(165) (166) (70)

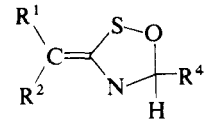


(167)

+



(168)



(169) (71)

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **6**

Synthesis of sulphenyl halides and sulphenamides

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

This chapter describes the synthesis of two classes of bivalent organosulphur compounds, namely sulphenyl halides and sulphenamides. Both of them may be formally derived from sulphenic acids by replacement of the hydroxy group in these acids by halogen and by the amino group, respectively.

$$R\ddot{S}\text{–}NR'_2 \longleftarrow R\ddot{S}\text{–}OH \longrightarrow R\ddot{S}\text{–}X$$

However, in contrast to the very unstable parent sulphenic acids, sulphenyl halides are fairly stable compounds. In particular, sulphenyl chlorides are easily available and used as valuable reagents in organic synthesis.

Sulphenamides show also a good chemical stability. Generally, secondary sulphenamides are more stable than the primary ones.

Since the synthetic approaches to sulphenyl halides and sulphenamides cannot be treated together, this chapter is divided into two practically independent main parts. The first summarizes the methods for synthesis of sulphenyl halides, the second deals with the synthesis of sulphenamides and some closely related compounds.

II. SYNTHESIS OF SULPHENYL HALIDES

The first sulphenyl chloride ever synthesized was trichloromethanesulphenyl chloride **1**, obtained by Rathke in 1870 by the iodine-catalyzed chlorination of carbon disulphide (equation 1)[1].

$$CS_2 \xrightarrow[I_2\ cat.]{Cl_2} Cl_3CSCl + S_2Cl_2 \qquad (1)$$

(1)

A multitude of sulphenyl fluorides, chlorides, bromides and iodides have been obtained by a number of different methods. Most of the syntheses were described in the literature before 1980 and for this reason they were reviewed in several reviews. The most important are in Kühle's book, *The Chemistry of the Sulfenic Acids*[2], and the appropriate chapters in Houben-Weyl[3].

The aim of the following section is to provide an up-to-date overview of methods of synthesis of sulphenyl fluorides, chlorides, bromides and iodides. Within each class, the subsections should enable the reader to find more easily the required type of compound.

A. Synthesis of Sulphenyl Fluorides

So far, practically no stable sulphenyl fluorides have been obtained. A few examples isolated or detected spectroscopically belong mainly to the perfluoroorganic series. The methods, analogous to those applied for the synthesis of sulphenyl chlorides and bromides (see the following sections) involving fluorination of organic sulphides, disulphides or thiols, cannot be applied for the synthesis of sulphenyl fluorides since they lead only to highly fluorinated sulphur derivatives[2].

The chloride–fluoride exchange in certain sulphenyl chlorides, however, made it possible to obtain some highly unstable sulphenyl fluorides. Thus, trichloromethanesulphenyl fluoride **2**[4] and trifluoromethanesulphenyl fluoride **4**[5,6] were obtained when the corresponding sulphenyl chlorides **1** and **3** were treated with activated potassium fluoride (equations 2 and 3). However, the sulphenyl fluoride **2** was detected only spectroscopically because it isomerized spontaneously to dichlorofluoromethanesulphenyl chloride (equation 2). The fluoride **4** underwent dimerization above 0 °C and had to be stored below 0 °C. Trifluoromethanesulphenyl fluoride **4** was also obtained from the chloride **3** by using mercury(II) or silver(I) fluorides[5,6]; the yields were almost quantitative. Silver(I) fluoride was also used for the synthesis of perfluoropropanesulphenyl fluoride. However, in this case the reaction conditions were drastic and the yield was very low (~5%)[7].

$$Cl_3CS\text{–}Cl \xrightarrow{KF} Cl_3CS\text{–}F \longrightarrow Cl_2FCS\text{–}Cl \qquad (2)$$

(1) **(2)**

$$\underset{\textbf{(3)}}{F_3CS\text{–}Cl} \xrightarrow{KF} \underset{\textbf{(4)}}{F_3CS\text{–}F} \tag{3}$$

A very unstable methanesulphenyl fluoride **6** has been obtained from methanesulphenyl chloride **5** in the reaction either with potassium fluoride (equation 4)[8] or with silver fluoride (equation 5)[9]. In each case the desired sulphenyl fluoride **6** formed underwent decomposition to different compounds shown in equations 4 and 5.

$$\underset{\textbf{(5)}}{MeS\text{–}Cl} \xrightarrow[100\,^\circ C]{KF} \underset{\textbf{(6)}}{MeS\text{–}F} \xrightarrow[-HF]{} H_2C{=}S \xrightarrow{MeSF} MeSSCH_2F \tag{4}$$

$$\underset{\textbf{(5)}}{MeS\text{–}Cl} \xrightarrow{AgF} \underset{\textbf{(6)}}{MeS\text{–}F} \longrightarrow MeSF_3 + MeSSMe \tag{5}$$

An interesting dichloro-difluoroaminomethanesulphenyl fluoride **8a** has been obtained from the corresponding sulphenyl chloride **7** by chloride–fluoride exchange using silver(II) fluoride (equation 6)[10]. The bromine trifluoride/mercury(II) fluoride system has also been used to achieve the chloride–fluoride exchange in chlorodifluoromethanesulphenyl chloride **9** (equation 7)[11].

$$\underset{\textbf{(7)}}{F_2NCCl_2S\text{–}Cl} \xrightarrow[25\,^\circ C]{AgF_2} \underset{\textbf{(8a)}}{F_2NCCl_2S\text{–}F} \tag{6}$$

$$\underset{\textbf{(9)}}{\begin{matrix} F_2CS\text{–}Cl \\ | \\ Cl \end{matrix}} \xrightarrow{BrF_3/HgF_2/90^\circ C} \underset{\textbf{(10)}}{\begin{matrix} F_2CS\text{–}F \\ | \\ Cl \end{matrix}} \tag{7}$$

A successful approach to the synthesis of sulphenyl fluorides involves the pyrolysis of difluorosulphuranes, e.g. bis-(heptafluoroisopropyl)-difluorosulphurane **11** (equation 8)[12].

$$\underset{\textbf{(11)}}{(F_3C)_2\overset{\overset{F}{|}}{\underset{F\ F\ F}{C\text{–}S\text{–}C}}(CF_3)_2} \xrightarrow{\Delta,\ 200\,^\circ C} \underset{\textbf{(12)}}{(F_3C)_2\underset{F}{C\text{–}S\text{–}F}} + SF_4 + \underset{F\ F}{F_3CC\text{–}CCF_3} \tag{8}$$

Finally, photochemical addition of tetrafluorohydrazine to dihalogenothiocarbonyls **13** gives *N*,*N*-difluoroamino-dihalo-methanesulphenyl fluorides **8** (equation 9)[13].

$$\underset{\textbf{(13)}}{2\,Hal_2C{=}S} + F_2NNF_2 \xrightarrow{h\nu} \underset{\textbf{(8)}}{\begin{matrix} & & Hal \\ & & | \\ F_2N & C & SF \\ & & | \\ & & Hal \end{matrix}} \tag{9}$$

(**a**) Hal = Cl
(**b**) Hal = F

B. Synthesis of Sulphenyl Chlorides

1. Alkane- and arenesulphenyl chlorides

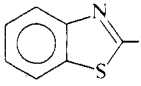
a. Chlorination of organic disulphides. Chlorination of disulphides is undoubtedly the most important, versatile and convenient method of preparing sulphenyl chlorides. Chlorine or sulphuryl chloride are used interchangeably as chlorinating agents. In some cases, milder reagents are applied, e.g. methyl-trichlorosulphurane. Several representative examples of sulphenyl chlorides obtained from disulphides are collected in Table 1.

$$RSSR \xrightarrow{\text{chlorination}} RSCl \qquad (10)$$

Lower alkanesulphenyl chlorides are rather unstable. For example, methanesulphenyl chloride must be distilled at relatively low temperature; it undergoes decomposition within 1–2 days even when stored in a refrigerator[15]. Alkanesulphenyl chlorides are coloured (red to yellow) liquids, having a very characteristic smell. Arenesulphenyl chlorides are coloured (orange-yellow) liquids or solids. Some of them, especially those bearing electron-withdrawing substituents in the aromatic ring (e.g. 2,4-dinitrobenzenesulphenyl chloride[23]), are quite stable even in the presence of water.

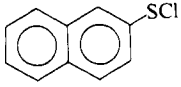
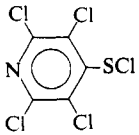
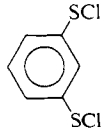
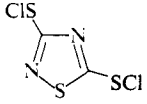
b. Chlorination of thiols. This method may be considered as a modification of the former one, for two reasons. First, the reaction of thiols with chlorinating agents results in the intermediary formation of the corresponding disulphides (by oxidation of the thiols), which are subsequently chlorinated to give sulphenyl chlorides (equation 11). Second, almost the same chlorinating agents are used and the same or very similar sulphenyl chlorides can be prepared by both methods. However, there are sometimes possibilities of

TABLE 1. Synthesis of sulphenyl chlorides by chlorination of organic disulphides

Sulphenyl chloride	Chlorinating agent	Solvent/Temp. (°C)	Yield (%)	Ref.
MeSCl	SO_2Cl_2	$Cl_2CHCHCl_2$/−20 to −15	*a*	14
MeSCl	Cl_2	neat/−15 to −20	75	15
EtSCl	Cl_2	neat/−20 to −15	*a*	16
CF_3SCl	Cl_2/UV	neat/20–25	100	17
n-PrSCl	Cl_2	neat/−60 to −50	*a*	16
i-PrSCl	Cl_2	neat/−60 to −50	*a*	16
n-BuSCl	Cl_2	neat/−60 to −50	*a*	16
$CF_3OCFClCF_2SCl$	Cl_2	neat	83	18
Cl_2CFCF_2SCl	Cl_2	neat/190	82	18
$ClS(CH_2)_3SCl$	Cl_2			19
$ClSCCl_2SCl$	Cl_2	CCl_4/−10	56	20
PhSCl	Me–SCl_3	CH_2Cl_2/−25	56	21
2-$NO_2C_6H_4SCl$	Cl_2/I_2	CCl_4/50–60	97	22
2,4-di-$NO_2C_6H_3SCl$	Cl_2/oleum	CCl_4/20	71–96	23
2-NO_2-4-OMe–C_6H_3SCl	Cl_2	CH_2Cl_2/20	43	24
4-NCO–C_6H_4SCl	Cl_2	CCl_4/0–10	82	25
4-$Cl_2C{=}NC_6H_4SCl$	SO_2Cl_2	SO_2Cl_2/20	50	26
	Cl_2	CCl_4/20	100	27

[a] Not given.

TABLE 2. Synthesis of sulphenyl chlorides by chlorination of thiols

Sulphenyl chloride	Chlorinating agent	Solvent/Temp. (°C)	Yield (%)	Ref.
MeSCl	Cl_2	$CCl_4/-15$	*a*	28
F_3CSCl	Cl_2	-22	72	17
F_2CHCF_2–S–Cl	Cl_2	-30 to -40	67	29
$(F_3C)_2C$–S–Cl	Cl_2	$CH_2Cl_2/20$–45	57	30
t-BuSCl	NaOCl	pentane/20	100	31
PhSCl	Cl_2	$CCl_4/0$–10	100	32
4-MeC_6H_4S–Cl	Cl_2	$CCl_4/0$–10	85	33
4-ClC_6H_4SCl	Cl_2	$CCl_4/0$	100	34
	Cl_2	$CHCl_3/20$	*a*	35
	Cl_2		100	36
$ClS(CH_2)_2SCl$	SO_2Cl_2	$CH_2Cl_2/20$	100	37
	Cl_2	$CCl_4/0$	~100	38
	Cl_2	$CH_2Cl_2/-50$	74	39

[a] Not given.

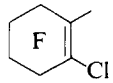
side reactions consisting in the chlorination of other reactive centres in the thiol molecule. To avoid this the solution of a thiol in an inert solvent is added to the chlorinating agent, leading to the direct formation of the desired sulphenyl chloride. Some selected examples of sulphenyl chlorides obtained by this method are collected in Table 2.

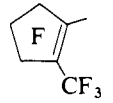
$$2\,RSH \xrightarrow{[Cl]} [RSSR] \xrightarrow{[Cl]} RSCl \qquad (11)$$

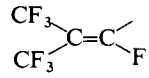
c. Chlorination of sulphides. Chlorolysis of sulphides, as a method of synthesis of sulphenyl chlorides, has a very limited application and is restricted to special cases which will be presented below.

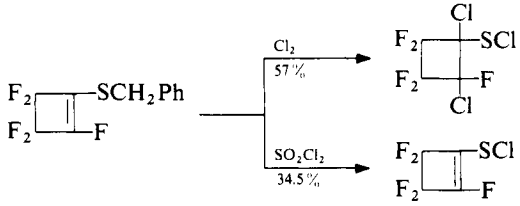
Benzyl aryl sulphides[40a] and benzyl perfluoroalkenyl sulphides[40b] can be easily converted by chlorine or sulphuryl chloride into sulphenyl chlorides with elimination of benzyl chloride (equations 12 and 12a). However, when benzyl trityl sulphide **14** is chlorinated with dichloroiodobenzene, the reaction takes a different course and phenylmethanesulphenyl chloride **15** and trityl chloride are produced (equation 13)[41].

$$RSCH_2Ph \xrightarrow[\text{or } SO_2Cl_2]{Cl_2} RSCl + ClCH_2Ph \qquad (12)$$

R =  yield 61%

R =  yield 78%

R =  yield 57%



(12a)

$$Ph_3CSCH_2Ph \xrightarrow{PhICl_2} PhCH_2SCl + Ph_3CCl \qquad (13)$$

(14) **(15)**

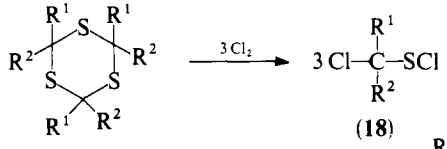
Chlorolysis of other alkyl or aryl sulphides usually leads to a mixture of products or to the products of overchlorination[2,3]. However, chlorolysis of cyclic sulphides has been successfully applied for the synthesis of ω-chloroalkanesulphenyl chlorides (equation 14)[42-44].

$$(CH_2)_nS \xrightarrow{[Cl]} Cl\text{-}(CH_2)_n\text{-}SCl \qquad (14)$$
$$n = 2, 3, 4$$

Chlorination of dithioacetals results also in the formation of sulphenyl chlorides. For example, methyl methylthiomethyl sulphide **16**, when treated with chlorine (equation 15), produces methanesulphenyl chloride in 90% yield in addition to chloromethyl methyl sulphide[45]. Chlorination of 1,3,5-trithiane or its C-alkylated derivatives **17** gives α-chloroalkanesulphenyl chlorides **18** in poor yields (equation 16)[46,47]. The use of a large excess of chlorine transforms 1,3,5-trithiane **17a** into dichloromethanesulphenyl chloride **19** in 85% yield (equation 17)[48].

$$MeSCH_2SMe \xrightarrow{Cl_2} MeSCl + MeSCH_2Cl \qquad (15)$$

(16)



(17) **(18)**

R^1, R^2 = H, Me, Et, Pr
yields 10–38%

(16)

(17a)

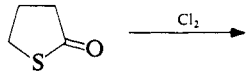
$$\xrightarrow[-3\,HCl]{6Cl_2} 3\,Cl_2CHSCl \quad (19) \qquad (17)$$

Another reaction leading to sulphenyl chlorides is the chlorolysis of thioloesters. Although simple alkyl thiolocarboxylates proved to be unsuitable for this purpose[49], bis-thioloesters **20** serve as good substrates for bis-sulphenyl chlorides **21** (equation 18)[50, 37]. Thiolactones behave in a similar way[44, 51], e.g. γ-butyrothiolactone **22** gives 3-chlorocarbonylpropanesulphenyl chloride **23** in 67% yield (equation 19)[51]. Chlorination of the thiophosphorylthiomethyl isocyanate **24** gives rise to the interesting functionalized sulphenyl chloride **25** (equation 20)[52].

$$\underset{\underset{O}{\|}}{MeCS}\text{–}(CH_2)_n\text{–}\underset{\underset{O}{\|}}{SCMe} \xrightarrow[\text{or } SO_2Cl_2,^{37}]{Cl_2,^{50}} ClS\text{–}(CH_2)_n\text{–}SCl \qquad (18)$$

(20) **(21)**

$n=1$—product isolated as a cyclohexene adduct[50]
$n=2$—yield 98%[37]



(22) **(23)**

(19)

$$(MeO)_2\underset{\underset{S}{\|}}{P}SCH_2NCO \xrightarrow{Cl_2} ClSCH_2NCO + (MeO)_2\underset{\underset{S}{\|}}{P}Cl \qquad (20)$$

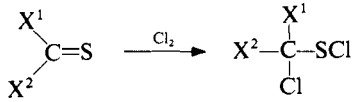
(24) **(25)**

d. Chlorination of thiocarbonyl compounds. The first example, already mentioned at the beginning of this chapter (equation 1), is the reaction of carbon disulphide with chlorine affording trichloromethanesulphenyl chloride **1**[1]. This compound has become a very important industrial product and is nowadays produced on a large scale[2]. Also several other sulphenyl chlorides are obtained from this compound. For instance, trifluoromethanesulphenyl chloride **3** can be directly obtained from **1** by fluorination with sodium fluoride in high-boiling solvents[53] (cf. equation 2) or with hydrogen fluoride over a catalyst (equation 21)[54].

$$Cl_3CSCl \xrightarrow[\text{or HF, cat.}]{NaF} F_3CSCl \qquad (21)$$

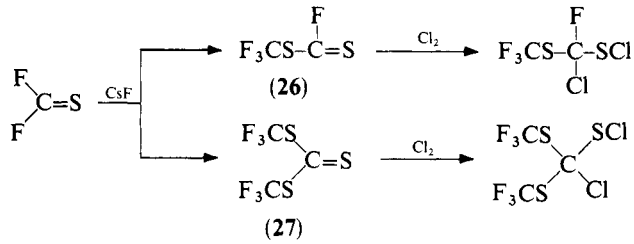
(1) **(3)**

Thiophosgene and analogues add chlorine to produce a variety of perhalogenomethanesulphenyl chlorides (equation 22)[55–57]. The dimer **26** and trimer **27** of thiocarbonyl difluoride have also been transformed by chlorine into sulphenyl chlorides (equation 23)[58].



(22)

(**a**) $X^1 = X^2 = Cl$[55]
(**b**) $X^1 = Cl$, $X^2 = F$[56]
(**c**) $X^1 = X^2 = F$[57]

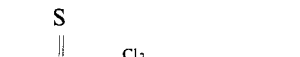


(23)

(**26**)

(**27**)

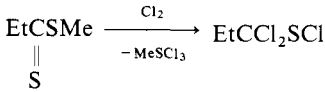
Dithiocarbonates **28a** and chlorocarbothionates **28b** undergo reaction with chlorine to give α-alkoxy- or α-aryloxy-α,α-dichloromethanesulphenyl chlorides **29** (equation 24)[49, 59]. Similarly dithiocarboxylates **30** give α,α-dichloroalkanesulphenyl chlorides **31** on treatment with chlorine (an example shown in equation 25)[49].



(24)

(**28**) (**29**)

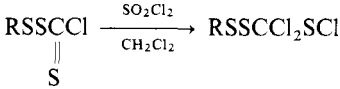
(**a**) R = Me, Y = SMe, yield 53%[49]
(**b**) R = Ph, Y = Cl, yield 74%[59]



(25)

(**30**) (**31**)

Chlorination of dithio-thiocarbonyl chlorides **32** results in the formation of very interesting dithio-dichloromethanesulphenyl chlorides **33** in which the disulphide moiety remains untouched (equation 26)[20].



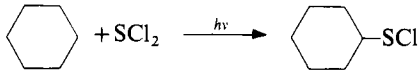
(26)

(**32**) (**33**)

R = MeCO, yield 35%
R = ClCO, yield 85%
R = Cl_3C, yield 90%
R = Cl_5C_2, yield 50%

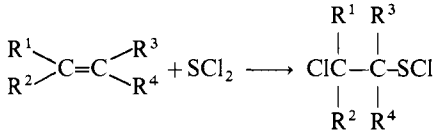
Among thioketones, only hexafluorothioacetone gives on chlorination the corresponding sulphenyl chloride[30]; other thioketones undergo desulphuration.

e. Application of sulphur dichloride. Sulphur dichloride reacts with alkanes under UV-light catalysis to give sulphenyl chlorides according to a free-radical mechanism, e.g. equation 27[60].



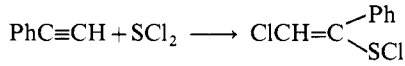
(27)

Sulphur dichloride adds easily to C–C multiple bonds, to give 2-chlorosubstituted sulphenyl chlorides **34** (equation 28, Table 3). Alkynes react with sulphur dichloride in a similar way yielding 2-chloroalkenesulphenyl chlorides, e.g. equation 29[67].



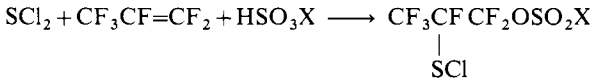
(28)

(34)



(29)

When sulphur dichloride is reacted with perfluoropropene **35** in the presence of a halosulphonic acid **36**, 1-halosulphonyloxy-perfluoropropane-2-sulphenyl chlorides **37** are formed among other products. The yield of **37** depends on the HSO_3X to S_2Cl_2 ratio, being highest when this ratio is 3:1 (equation 30)[68].



(30)

(35) **(36)** **(37)**

X = F, yield: 75%
X = Cl, yield: 34%

f. Other methods. As a result of photolysis of a mixture of tetrafluorohydrazine and thiophosgene, dichloro-*N*,*N*-difluoroamino-methanesulphenyl chloride is formed[69] in yields from 0 to 29.4%, depending on experimental conditions (equation 31; compare the

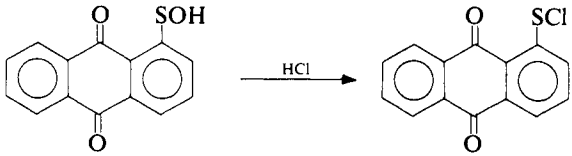
TABLE 3. Sulphenyl chlorides by the addition of sulphur dichloride to alkenes (equation 28)

R^1	R^2	R^3	R^4	Yield of **34** (%)	Reference
H	H	H	H	—	61
H	H	CN	Me	36, 50	62, 63
Cl	H	Cl	Cl	26	64
Cl	Cl	H	CH_2Cl	86	65
$(ClCH_2CH_2O)_2P{=}O$	H	H	H	—	66

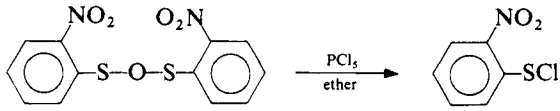
different result[13] of the same reaction shown in equation 9).

$$F_2NNF_2 + Cl_2C{=}S \xrightarrow{UV} F_2NCCl_2SCl + \text{other products} \tag{31}$$

In some cases sulphenic acids[70] or their anhydrides[71] proved to be sufficiently stable to serve as substrates for sulphenyl chloride syntheses (equations 32 and 33).



(32)



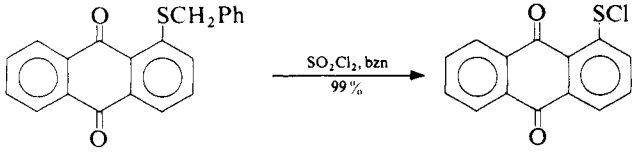
(33)

Sulphenic esters[71, 72] and sulphenamides[32, 73] can also be transformed into sulphenyl chlorides.

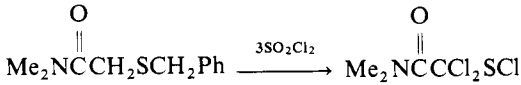
2. Alkane- and arenesulphenyl chlorides bearing other functional groups in the molecule

a. Oxo-sulphenyl chlorides. Chlorination of oxo-alkane- and oxo-arene disulphides and thiols gives the corresponding oxo-sulphenyl chlorides. Some representative examples are collected in Table 4. It is worth noting that most of these compounds are unstable and have not been isolated, though they have been proven to be formed in high yields.

Similar sulphenyl chlorides can also be obtained by chlorolysis of the corresponding benzyl sulphides (equations 34[80] and 35[81]), thiolactones (see compound **23**, equation 19)[51] or other sulphides, e.g. a derivative of aminopenicillanic acid (equation 36)[82].

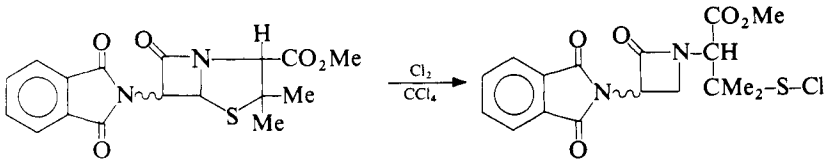


(34)



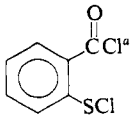
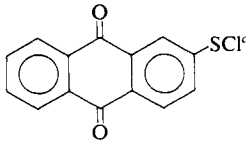
(35)

Sulphur dichloride reacts easily with CH-acidic (mono or dicarbonyl) compounds to produce sulphenyl chlorides (equations 37 and 38)[83, 84]; bis-sulphenyl chlorides are obtained in special cases (equation 39)[85].



(36)

TABLE 4. Oxo-sulphenyl chlorides from organic disulphides or thiols

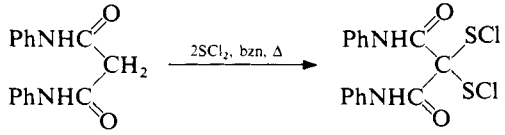
Sulphenyl chloride	Halogenating agent	Solvent/Temp. (°C)	Yield (%)	Ref.
$EtCCH(Me)SCl$[a] (O)	Cl_2	CH_2Cl_2/−80 to −70	69[b]	74
$HCC(Me)_2SCl$[a] (O)	Cl_2			75
$Cl{-}CCH_2CH_2SCl$[a] (O)	Cl_2	CCl_4/−30	90[b]	76
$EtOCCH_2CH_2SCl$[a] (O)	Cl_2	CCl_4/−35	80[b]	76
$EtOCCH(CH_2SCl)NHCPh$[a] (O, O)	Cl_2	$CHCl_3$/−20	77[b]	77
	Cl_2	CCl_4		78
	Cl_2	$CHCl_3$/20–25	90	79

[a] From disulphide.
[b] Not isolated.
[c] From thiol.

$$Me_2CHCCHMe_2 \xrightarrow[50\%]{SCl_2,\ AlCl_3,\ cat.} Me_2CHCCMe_2SCl \quad (37)$$

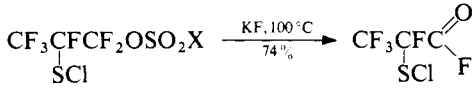
$$R_2CHCHO \xrightarrow[CH_2Cl_2]{SCl_2,\ 5\ ^\circ C} R_2C(CHO)SCl \quad (38)$$

R = Me, yield 69%[84]
R = Et, yield 24%



(39)

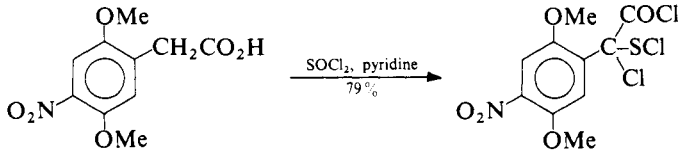
An interesting compound—1-fluorocarbonylperfluoroethanesulphenyl chloride **38**—has been obtained from halosulphonyloxy sulphenyl chlorides **37** (equation 40; for the synthesis of **37** see equation 30)[68].



(40)

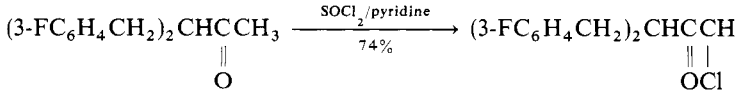
(37) (38)

Certain arylaliphatic acids, e.g. **39**, and ketones, e.g. **41**, react with thionyl chloride in the presence of amines to give α-chloro-α-chlorosulphenylcarboxylic acid chlorides **40**[86, 87] and α-chloro-β-oxosulphenyl chlorides **42**[88], respectively (equations 41 and 42).



(41)

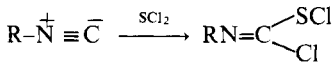
(39) (40)



(42)

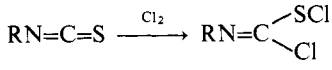
(41) (42)

b. Iminomethanesulphenyl chlorides and related compounds. The addition of sulphur dichloride to isonitriles takes place at the terminal carbon atom to form iminochloromethanesulphenyl chlorides **43** (equation 43)[89]. This type of sulphenyl chloride can be obtained more easily by chlorination of isothiocyanates. This reaction allows also the synthesis of bis-sulphenyl chlorides **44** from the corresponding bis-isothiocyanates (equations 44, 45 and Table 5)[89, 90].



(43)

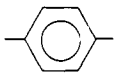
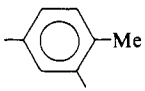
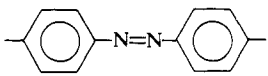
(43)



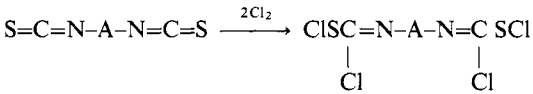
(44)

(43)

TABLE 5. Iminomethanesulphenyl chlorides **43** and bis-iminomethanesulphenyl chlorides **44** from isothiocyanates and chlorine

R or A	Yield (%)	Reference
Me–	31	89
i-Pr–	54	89
n-C_4H_9–	54	89
cyclohexyl-	61	89
Ph–	97	89
4-ClC_6H_4–	73	89
PhC(O)–	12	89
PhC(O)–	68	90
4-$ClC_6H_4C(O)$–	70	89
PhC(=NPh)–	*a*	89
Me_2NSO_2–	*a*	89
4-$ClC_6H_4SO_2$–	*b*	89
	*a*	89
	*a*	89
	*a*	89

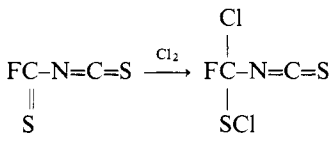
[a] Not given.
[b] Characterized as derivative.



(45)

(44)

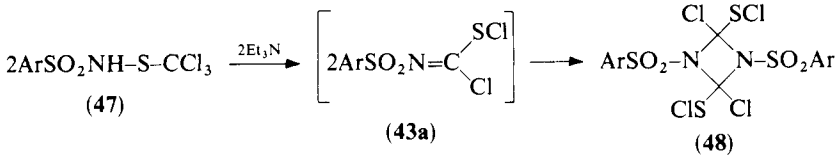
Fluorothiocarbonyl isothiocyanate **45** behaves differently, since only the thiocarbonyl group undergoes selective chlorination to give isocyanatomethanesulphenyl chloride **46** (equation 46)[91].



(46)

(45) **(46)**

N-sulphonylimino-chloromethanesulphenyl chlorides **43a**, obtained from the corresponding sulphonyl-sulphenamides **47**, serve as substrates for diazetidine-bis-sulphenyl chlorides **48** (equation 47)[92].



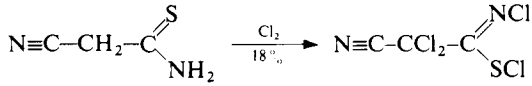
(47)

(43a)

(48)

(47)

Cyanothioacetamide and chlorine react to give *N*-chloroiminomethanesulphenyl chloride in low yield (equation 48)[93].

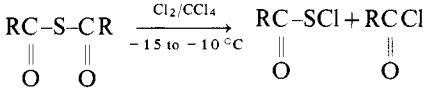


(48)

3. Acylsulphenyl chlorides and related compounds

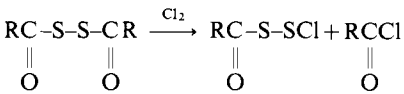
Four different approaches have been described for the synthesis of acylsulphenyl chlorides **49**. They are presented in equations 49, 50–52 and discussed below, and acylsulphenyl chlorides thus obtained are collected in Table 6.

a. Chlorination of diacyl sulphides (method A)[94, 95]. Diacyl sulphides give on chlorination acylsulphenyl chlorides **49** and acyl chlorides (equation 49). Purification of the product, i.e. separation from the acid chloride formed, constitutes a severe problem. For this reason, practically only acetylsulphenyl chloride **49a** is accessible by this method without special problems[94, 95]. It should be stressed that chlorination of diacyl disulphides does not result in the expected symmetrical cleavage of the molecule, but proceeds with the splitting of the C–S bond which results (equation 49a) in the formation of acetylthiosulphenyl chloride **50**[94] (compare Section II.B.7.a).



(49)

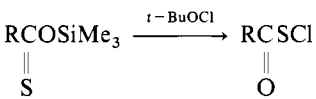
(49)



R = Me, Ph (50)

(49a)

b. Chlorination of O-trimethylsilyl thiocarboxylates **51** *(method B)*[96]. This method can be used for the synthesis of non-volatile aroylsulphenyl chlorides (e.g. **49b** and **49c**) since volatile by-products can be simply removed by evaporation (equation 50).



(51) (49)

(50)

c. Chlorination of thiocarboxylic acids (method C)[97]. This method has been applied only for the synthesis of trifluoroacetylsulphenyl chloride **49d** (equation 51).

$$CF_3C(=O)SH \xrightarrow{Cl_2,\ -78\,^\circ C} CF_3C(=O)SCl \qquad (51)$$

(49d)

d. Chlorination of diphenyltin bis-thiocarboxylates **52** *(method D)*[98]. Diphenyltin bis-thiocarboxylates **52** react with *N*-chlorosuccinimide to give acylsulphenyl chlorides in reasonable yields. It is interesting and useful that the diphenyltin dichloride formed can be reconverted to **52** by reaction with potassium or piperidinium thiocarboxylate (equation 52).

$$(RC(=O)S)_2SnPh_2 \xrightarrow{4\ NCS} RC(=O)SCl + Cl_2SnPh_2 \qquad (52)$$

(52) **(49)**

$$RC(=O)S^-\ M^+$$

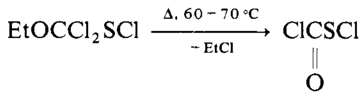
TABLE 6. Synthesis of acylsulphenyl chlorides **49**

Symbol	Sulphenyl chloride	Method	Chlorination conditions	Yield (%)	Ref.
49a	MeC(O)SCl	A	Cl_2/CCl_4, −15 to −10 °C	50	94, 95
49b	4-$MeC_6H_4C(O)SCl$	B	*t*-BuOCl, −78 °C	78	96
49c	4-$ClC_6H_4C(O)SCl$	B	*t*-BuOCl, −78 °C	73	96
49d	$F_3CC(O)SCl$	C	Cl_2, −78 °C	98	97
49e	PhC(O)SCl	D	NCS, $CH_2Cl_2/CHCl_3$, −20 °C	40	98
49f	2-$MeC_6H_4(O)SCl$	D	NCS	41	98
49b	4-$MeC_6H_4C(O)SCl$	D	NCS	43	98
49g	3-$ClC_6H_4C(O)SCl$	D	NCS	50	98
49c	4-$ClC_6H_4C(O)SCl$	D	NCS	55	98
49h	4-$MeOC_6H_4C(O)SCl$	D	NCS	57	98
49i	n-$C_{17}H_{35}$-C(O)SCl	D	NCS	53	98

e. Carbonylsulphenyl chlorides. Careful hydrolysis of trichloromethanesulphenyl chloride **1** with a strictly equivalent amount of water in the presence of sulphuric acid gives chlorocarbonylsulphenyl chloride **53** (equation 53)[99]. The same sulphenyl chloride is obtained by thermolysis of ethoxydichloromethanesulphenyl chloride **54** (equation 54)[100]. The sulphenyl chloride **53** was used as a substrate for the synthesis of fluorocarbonylsulphenyl chloride **55** (equation 55)[101, 102] and alkoxycarbonylsulphenyl chlorides **56** (equation 56)[103, 104], the latter being used for protecting the cysteine SH-group in peptide synthesis[104].

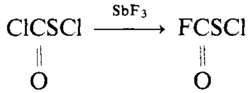
$$Cl_3CSCl \xrightarrow[45-50\,^\circ C,\ 85\%]{H_2O/H_2SO_4} ClC(=O)SCl \qquad (53)$$

(1) **(53)**



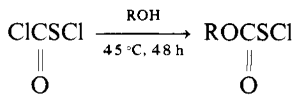
(54)

(54) (53)



(55)

(53) (55)



(56)

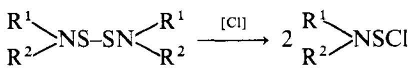
(53) (56)

R = n–Bu[103]; *t*–Bu, CH_2Ph[104]

4. Aminosulphenyl chlorides

In this section the synthesis of *N*-aminosulphenyl chlorides, i.e. compounds in which the chlorosulphenyl moiety is attached to the nitrogen atom, will be described. This topic has been recently reviewed[3b]. The term 'aminosulphenyl chlorides' covers all kinds of N–S–Cl compounds, irrespective of the other substituents at the nitrogen atom such as alkyl or aryl groups, sulphonyl, phosphoryl and other groupings. It is useful to divide this section into three parts, depending on the method of synthesis of the title products.

a. Aminosulphenyl chlorides via chlorination of bis-amino disulphides. Bis-(dialkyl-amino) disulphides and bis-(alkyl-arylamino) disulphides undergo easy chlorination with chlorine or sulphuryl chloride to give the corresponding aminosulphenyl chlorides **57** in good to high yields (equation 57)[105, 106].

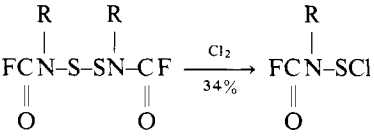


(57)

(57)

R^1	R^2	Yield (%)	Ref.
Et	Et		105a
–CH(Me)–$(CH_2)_4$–CH(Me)–		65	105b
F_3C–C(=)–CF_3		94	105c
c–C_6H_{11}	CHO	90	105d
–C(=O)–$(CH_2)_2$–C(=O)–		98	105e
2,4-$Cl_2C_6H_3$	CF_3	87	106

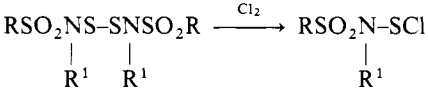
N-fluorocarbonylaminosulphenyl chlorides **59** are also obtained by chlorination of the corresponding bis-(fluorocarbonylamino)disulphides **58** (equation 58)[107].



(58)

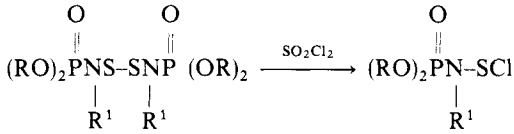
(58) **(59)**

The same reaction has been applied for the synthesis of sulphonamide-*N*-sulphenyl chlorides **60**[108] and phosphoroamide-*N*-sulphenyl chlorides **61**[109] (equations 59 and 60, respectively).



(59)

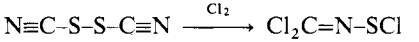
(60)



(60)

(61)

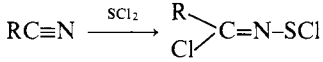
Chlorination of dicyano disulphide gives the product to which the structure of dichloromethylimine-*N*-sulphenyl chloride **62**[110] has been ascribed (equation 61). The same product is formed when acetyl and trimethylsilyl isothiocyanates are reacted with chlorine[110] (for another direction of the chlorination of isothiocyanates see Section II.B.2.b, Table 5).



(61)

(62)

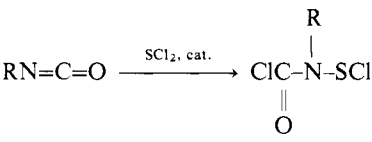
b. Sulphur dichloride procedure. Sulphur dichloride undergoes addition to C–N multiple bonds to give the appropriate aminosulphenyl chlorides. Thus, activated nitriles give chloroimino-*N*-sulphenyl chlorides **63** (equation 62)[111] while alkyl and cycloalkyl isocyanates afford *N*-chlorocarbonyl-*N*-aminosulphenyl chlorides **64** (equation 63)[112].



(62)

(63)

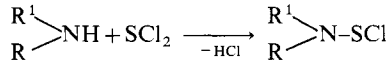
R = Cl, CCl_3, $MeSO_2$



(63)

(64)

Secondary amines react readily with sulphur dichloride in the presence of a hydrogen chloride acceptor to give the corresponding aminosulphenyl chlorides **57** (equation 64)[113].

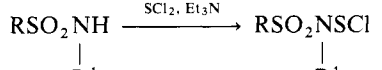


(64)

(57)

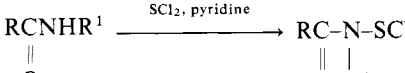
R, R^1 = alkyl, aryl, trifluoromethyl

Sulphonamide *N*-sulphenyl chlorides **60** (already presented in equation 59) may also be prepared by treatment of sulphonamides with sulphur dichloride in the presence of hydrogen chloride acceptors (equation 65)[114]. *N*-Alkyl carboxylic acid amides[112], their *N*-trimethylsilyl derivatives and *N*-trimethylsilyl ureas[115b] behave similarly and give, with sulphur dichloride, carboxamide-*N*-sulphenyl chlorides, e.g. **65** (equation 66)[112]. Cyclic thiophosphoroamide-*N*-sulphenyl chlorides **66** have been prepared in a similar way (equation 67)[116].



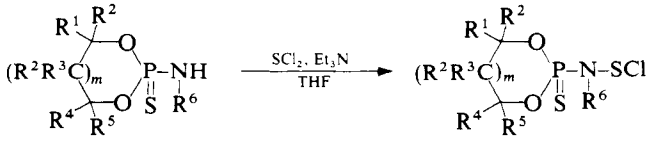
(65)

(60)



(66)

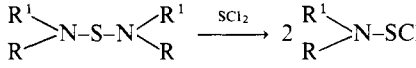
(65)



(67)

(66)

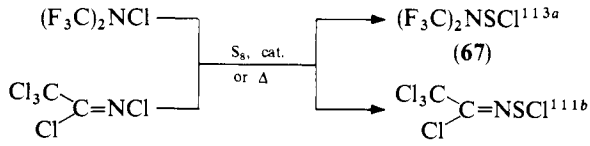
Bis-(dialkylamino) sulphides react with sulphur dichloride to produce aminosulphenyl chlorides **57** in high yields (equation 68)[117].



(68)

(57)

c. Other methods. Activated *N*-chloroamines and *N*-chloroimines incorporate elemental sulphur and give aminosulphenyl chlorides (equation 69)[111b, 113a].



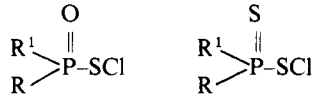
(69)

(67)

(68)

5. *Phosphoranesulphenyl chlorides*

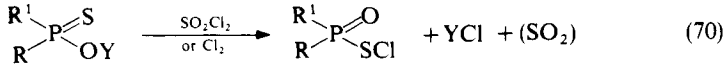
This section deals with the synthesis of sulphenyl chlorides in which the chlorosulphenyl function '—SCl' is connected directly to a phosphorus atom. This subject has been exhaustively reviewed up to 1978 by Gusar[118]. There are two main groups of these compounds: oxophosphoranesulphenyl chlorides **69** and thioxaphosphoranesulphenyl chlorides **70**. Since the syntheses of each of them require different approaches, they will be discussed in separate subsections.



(69) **(70)**

a. Oxophosphoranesulphenyl chlorides **69**. The first example of this type of compound was *O,O*-diethyloxophosphoranesulphenyl chloride **69c**, synthesized in 1956 by chlorination of *O,O*-diethyl phosphorothioic acid[119]. Later on, several other methods were also devised. All the methods are listed below and selected examples of oxophosphoranesulphenyl chlorides **69** are collected in Table 7.

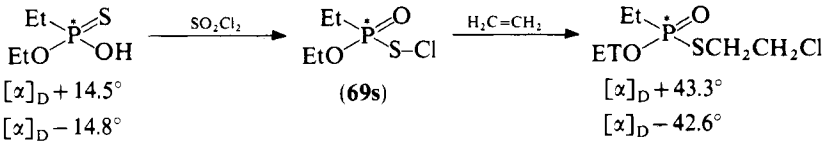
Method A. Phosphorus monothioacids **71** (phosphorothioic **71a**, phosphonothioic **71b** and phosphinothioic **71c**) or their salts react with sulphuryl chloride or chlorine to give oxophosphoranesulphenyl chlorides (equation 70)[119,120]. This reaction has been widely used for the synthesis of a broad variety of sulphenyl chlorides **69** (see Table 7). It was also applied for the preparation of optically active sulphenyl chlorides which were trapped with ethylene without isolation, e.g. equation 71[121]. Other optically active sulphenyl chlorides, e.g. **69q**, have been used without isolation for the synthesis of optically active phosphorochloridothionates **72** (equation 72)[122].



(70)

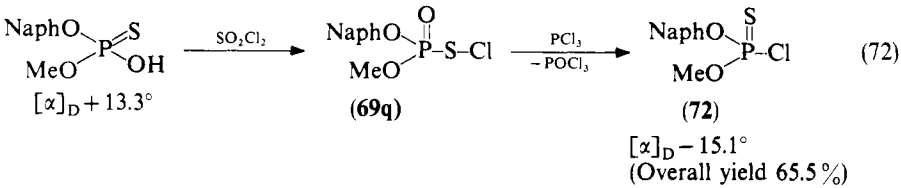
(71) **(69)**

Y = H, metal
(**a**) R = R¹ = *O*-alkyl, *O*-aryl
(**b**) R = *O*-alkyl, *O*-aryl; R¹ = alkyl, aryl
(**c**) R = R¹ = alkyl, aryl



(71)

(69s)

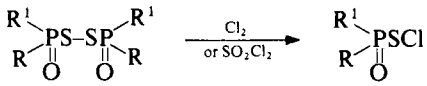


(72)

TABLE 7. Oxophosphoranesulphenyl chlorides **69**

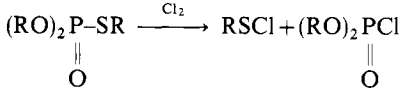
Symbol	Sulphenyl chloride	Method of synthesis	Yield (%)	Remarks	Ref.
69a	(EtO) (Cl)P(O)–SCl	C			133
69b	$(MeO)_2P(O)$–SCl	C	89		127
69c	$(EtO)_2P(O)$–SCl	A	70–80		119, 120
		B	76–90		120, 123
		C	50–90		126, 127
69d	$(n\text{-}PrO)_2P(O)$-SCl	A	60		120
		C	80		127
69e	$(i\text{-}PrO)_2P(O)$–SCl	A	47		120
69f	$(n\text{-}BuO)_2P(O)$–SCl	A	66		120
		B	70		123
		C	70–80		126, 127
69g	(neo-Pent $O)_2P(O)$–SCl	A	84		134
69h	(EtO) (*i*-PrO)P(O)–SCl	A		$[\alpha]_D + 3.85°$	135
69i	(EtO) (BuO)P(O)–SCl	A		$[\alpha]_D - 4.73°$	135
69k	 P(O)–SCl *cis* or *trans*	C	98		129, 130
69l	 P(O)–SCl	A	100		136
69m	 P(O)–SCl	C		not purified	122
69n	(EtO) (PhO)P(O)–SCl	C	50		127
69o	$(PhO)_2P(O)$–SCl	C	65		127
69p	$(Me_3SiO)_2P(O)$–SCl	C		not isolated	131
69q	(MeO) (1-NptO)P(O)–SCl	A		not isolated	122
69r	(Et_2N) (EtO)P(O)–SCl	C	40		127
69s	(EtO)EtP(O)–SCl	A	70		137
		A		opt. active	121
		C			138
69t	(BuO)EtP(O)–SCl	A	55		137
69u	(MeO) (*i*-Pr)P(O)–SCl	A			139, 122
69v	(MeO) (*t*-Bu)P(O)–SCl	A	96	$[\alpha]_D - 164°$	140
69w	(*i*-PrO)MeP(O)–SCl	A		not isolated	122
69x	(t-Bu)PhP(O)–SCl	A		not isolated	139

Method B. Bis(phosphoryl) disulphides **73** are easily cleaved by chlorinating agents to give **69** in good yields (equation 73)[120, 123]. In this context, it should be mentioned that chlorolysis of alkyl phosphorothiolates **74** is accompanied by the cleavage of the sulphur–phosphorus bond and gives alkanesulphenyl chlorides and chlorophosphates[124] and not sulphenyl chlorides **69** (equation 74, see also equation 20). On the other hand,

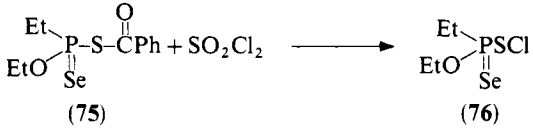


(73) **(69)** (73)

however, *O*-ethyl *S*-benzoyl ethylphosphonoselenonate **75** reacts with sulphuryl chloride to yield the selenoxaphosphoranesulphenyl chloride **76** (equation 75)[125].

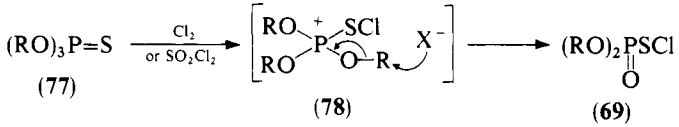


(74)



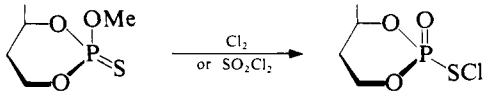
(75)

Method C. Reaction of trialkyl phosphorothionates **77** with chlorine or sulphuryl chloride gives oxophosphoranesulphenyl chlorides **69** in high yields[126, 127]. The reaction was proven to proceed via a phosphonium salt **78** (equation 76)[128].

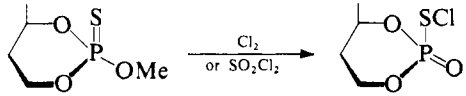


(76)

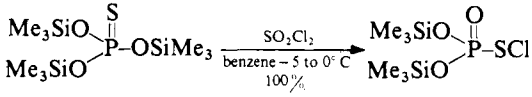
This method was found to be the most general and convenient route to various types of oxophosphoranesulphenyl chlorides. For example, it has been used for the synthesis of diastereoisomeric cyclic oxophosphoranesulphenyl chlorides **69k** (equations 77a and 77b)[129, 130]. Also P-amino analogues of sulphenyl chlorides (e.g. **69r**, Table 7) have been synthesized in this way[127]. Another interesting example which deserves special mention is *O,O*-bis-(trimethylsilyl)oxophosphoranesulphenyl chloride **69p** obtained by chlorolysis of tris-(trimethylsilyl)phosphorothionate **79** (equation 77c)[131].



trans-(**77k**) (90%) *trans*-(**69k**) (87%) (77a)

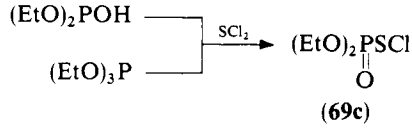


cis-(**77k**) (97%) *cis*-(**69k**) (93%) (77b)



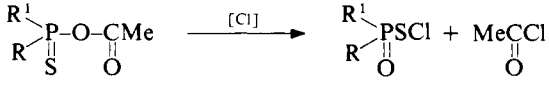
(**79**) (**69p**) (77c)

Method D. Sulphur dichloride reacts with dialkyl phosphites or trialkyl phosphites with elimination of hydrogen chloride or alkyl chlorides, respectively, to afford oxophosphoranesulphenyl chlorides as major products (equation 78). The latter are always contaminated with some by-products, mainly with thiopyrophosphates[132].



(69c) (78)

Method E. Recently, a new method of synthesis has been reported which involves the reaction of chlorine or sulphuryl chloride with the mixed anhydrides **80** derived from phosphorus thioacids and acetic acid (equation 79). The reaction proceeds below ambient temperature in neutral solvents and gives oxophosphoranesulphenyl chlorides in almost quantitative yields[141].



(80) (69) (79)

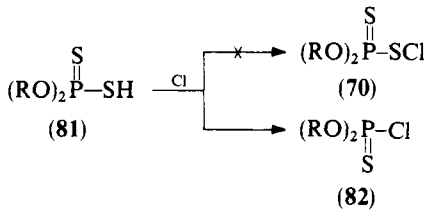
The stability of the sulphenyl chlorides **69** depends on the nature of substituents around the phosphorus and decreases in the following order:

phosphoro: $(RO)_2P$ > phosphono: $\begin{matrix} RO \\ R^1 \end{matrix}\!\!>\!P$ > phosphino: $\begin{matrix} R \\ R^1 \end{matrix}\!\!>\!P$

(see equation 70). Phosphoro-derivatives are usually quite stable; dialkoxyphosphoryl derivatives can be distilled under vacuum. They undergo, however, decomposition when stored, even at low temperatures. A very stable compound is *O,O*-dineopentyl-oxophosphoranesulphenyl chloride **69g**, which can be kept in the refrigerator without decomposition for over one year[134].

Phosphono-derivatives extrude sulphur on heating and phosphino-derivatives lose sulphur at 20°C, being moderately stable at 0 °C[118].

b. Thioxaphosphoranesulphenyl chlorides **70**. The methods described in the previous section are generally not suitable for the synthesis of thioxaphosphoranesulphenyl chlorides **70**. For example, chlorination of phosphorodithioic acids **81** does not provide **70**; instead, phosphorothionochloridates **82** are formed (equation 80)[118,141]. Nevertheless, several other methods have been developed which enable one to obtain the desired derivatives **70** in satisfactory yields. All these procedures are listed below and the thioxaphosphoranesulphenyl chlorides **70** thus obtained are collected in Table 8.

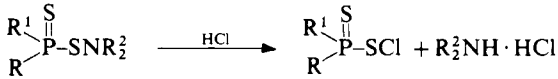


(81) (82) (80)

Method A. Thioxaphosphoranesulphenamides **83** react easily with hydrogen chloride, introduced into the reaction medium, to give thioxaphosphoranesulphenyl chlorides **70** in good yields (equation 81)[142–146]. However, this reaction does not always give reproducible results and difficulties often arise in the purification of products.

TABLE 8. Thioxaphosphoranesulphenyl chlorides **70**

Symbol	Sulphenyl chloride	Method of synthesis	Yield (%)	Remarks	Ref.
70a	$(MeO)_2P(S)$–SCl	C	90		149
70b	$(EtO)_2P(S)$–SCl	A	73		142, 146
		B	100		147
70c	$(n\text{-}PrO)_2P(S)$–SCl	A	65		143
70d	$(i\text{-}PrO)_2P(S)$–SCl	A	80		143
		B	100		147
		C	87		149
70e	$(n\text{-}BuO)_2P(S)$–SCl	A	60		143
70f	$(i\text{-}BuO)_2P(S)$–SCl	A	60		143
70g	$(neo\text{-}PentO)_2P(S)$–SCl	B	100		147
		C	90		149
70h	(l-MenthylO)(EtO)P(S)–SCl	B		diastereoisomers $[\alpha]_D - 89.5°$ $[\alpha]_D + 54.1°$	141
70i	(EtO)PhP(S)–SCl	A			144
70k	$(i\text{-}PrO)PhP(S)$–SCl	A	60		144
70l	$Me_2P(S)$–SCl	A		unstable,	145
70m	$Et_2P(S)$–SCl	A		identified	145
70n	$n\text{-}Pr_2P(S)$–SCl	A		as products	145
70o	$n\text{-}Bu_2P(S)$–SCl	A		of the reaction with	145
70p	$(PhCH_2)_2P(S)$–SCl	A			145
70q	$Ph_2P(S)$–SCl	A		thiols	145

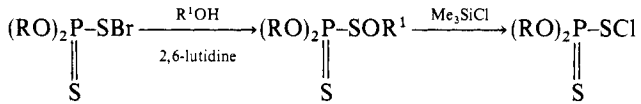


(81)

(**83**) (**70**)

Method B. This method is based on the same chemical transformation as Method A. However in this case hydrogen chloride is formed *in situ* by the reaction of chlorotrimethylsilane with an equivalent amount of ethanol. Such conditions enable one to obtain **70** in quantitative yields and in a pure state[147].

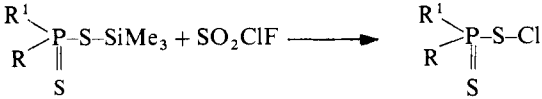
Method C. This method consists in the reaction of alkyl thioxaphosphoranesulphenates **84**, easily available from thioxaphosphoranesulphenyl bromides **85** (for the preparation of **85** see Section II.C.4) and alcohols, with chlorotrimethylsilane (equation 82). Sulphenyl chlorides **70** obtained according to this procedure are separated from the reaction mixture by simple removal of the solvent and the silyl ether formed[148,149].



(82)

(**85**) (**84**) (**70**)

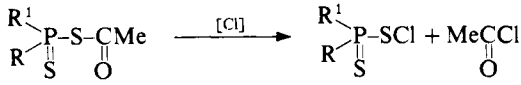
Method D. When silyl esters of phosphorodithioic acids **86** are treated with sulphuryl chloride-fluoride **87**, thioxaphosphoranesulphenyl chlorides **70** are formed in moderate yields[141].



(83)

(86) **(87)** **(70)**

Method E. In a full analogy with Method E of the synthesis of oxophosphoranesulphenyl chlorides (Section II.A.5.a, equation 79), it was found that chlorination of the mixed dithiophosphoric acetic anhydrides **88** gives **70** in almost quantitative yields (equation 84)[141].



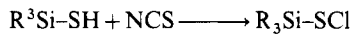
(84)

(88) **(70)**

Thioxaphosphoranesulphenyl chlorides **70** are less stable than the corresponding oxaphosphoranesulphenyl analogues. Nevertheless, some of them are stable enough to be purified by distillation.

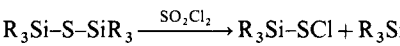
6. *Silanesulphenyl chlorides*

Silanesulphenyl chlorides **90** have been synthesized either by treatment of triorganosilanethiols **89** with *N*-chlorosuccinimide (NCS, equation 85)[150] or by chlorination of hexaorganodisilathianes **91** with sulphuryl chloride (equation 86)[151,152].



(85)

(89) **(90)**

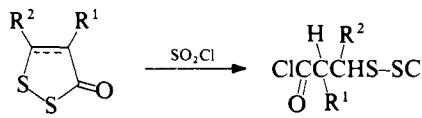


(86)

(91) **(90)**

7. *Thiosulphenyl chlorides*

This section deals with the sulphenyl chlorides in which the SCl moiety is bonded to a sulphur atom connected with a carbon or placed at the end of the polysulphide chain. The synthesis and reactions of this class of compounds have been reviewed[3c] and recently over 70 examples have been listed in the minireview by Moltzen and Senning[153]. Therefore, in this section only the general methods of synthesis and selected examples of thiosulphenyl chlorides will be presented.



(87)

(92)

TABLE 9. ω-Chlorocarbonyl-thiosulphenyl chlorides **92**[154]

Compound	Reaction temperature (°C)	Yield (%)
$ClC(O)CH_2CH(Me)\text{-}S_2\text{-}Cl$	−35	78
$ClC(O)CH(Me)CH_2\text{-}S_2\text{-}Cl$	−35	70
$ClC(O)CH(Cl)CH_2\text{-}S_2\text{-}Cl$	50	90
$ClC(O)C(Me)(Cl)CH_2\text{-}S_2\text{-}Cl$	0	85
$ClC(O)CH=CH\text{-}S_2\text{-}Cl$	60	50
$ClC(O)CH=C(Me)\text{-}S_2\text{-}Cl$	20	79
$ClC(O)C(Me)=CH\text{-}S_2\text{-}Cl$	20	68

a. Chlorolysis of acyl disulphides. Chlorolysis of 1,2-dithiolanones and 1,2-dithiol-4-enones proceeds smoothly under various conditions with splitting the S–C(O) bond and formation of ω-chlorocarbonyl thiosulphenyl chlorides **92** (equation 87 and Table 9)[154]. In the case of open-chain acyl disulphides both the S–S and S–C(O) bonds are competitively cleaved. The ratio of both directions depends on the place of attack of the chlorinating agent which in turn depends on the relative nucleophilicity of each sulphur atom[154]. Thus, acylthiosulphenyl chlorides **50** are formed when diacyl disulphides are treated with chlorine (see equation 49a)[94].

b. Reaction of thiols with sulphur dichloride. Thiols react easily with sulphur dichloride to give thiosulphenyl chlorides (equation 88)[155–159]. Among compounds synthesized in this way there are some very interesting and unusual derivatives. For example, methanebis(thiosulphenyl chloride) **93** is prepared from methanedithiol **94** (equation 89)[158]. Perfluoropentenethiosulphenyl chloride **95** has been obtained from the enethiol form of perfluoropentanethione **96** (equation 90)[157].

$$RSH + SCl_2 \longrightarrow RSSCl \qquad (88)$$

R = alkyl, aryl, perfluoroorganyl groups

$$HSCH_2SH + SCl_2 \xrightarrow{-80\ ^\circ C} ClSSCH_2SSCl \qquad (89)$$

(**94**) (**93**)

$$\begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!C=C(SH)\text{-}C_2F_5 \xrightarrow[45\%]{SCl_2,\ -40\ ^\circ C} \begin{matrix} CF_3 \\ CF_3 \end{matrix}\!\!>\!C=C<\!\!\begin{matrix} C_2F_5 \\ SSCl \end{matrix} \qquad (90)$$

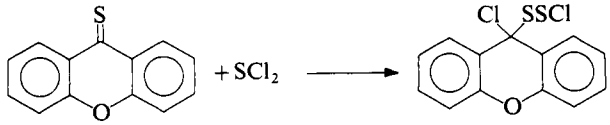
(**96**) (**95**)

c. Reaction of sulphur dichloride with thiocarbonyl compounds. Thiophosgene and sulphur dichloride give trichloromethanethiosulphenyl chloride **97** (equation 91)[160].

$$Cl_2C=S + SCl_2 \xrightarrow{I_2} Cl_3CSSCl \qquad (91)$$

(**97**)

Reaction of suitably substituted aliphatic and aromatic thiones with sulphur dichloride in dry carbon disulphide affords the corresponding α-chloro thiosulphenyl chlorides, isolated, however, in a crude state only, e.g. **98** (equation 92)[161].



(92)

(98)

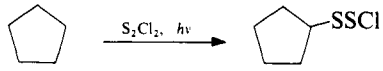
d. Insertion of sulphur into the S–Cl bond. Perchloro- and fluorochloroalkanesulphenyl chlorides react with elemental sulphur in the presence of triethyl phosphate to give the corresponding thiosulphenyl chlorides **99** (equation 93)[162–164].

$$R^x\text{–S–Cl} \xrightarrow[(EtO)_3PO]{S_8} R^x\text{–S–S–Cl} \quad (93)$$

(**99**)

$R^x = CCl_3$ (**97**)[163]
$R^x = FCl_2C$[162]
$R^x = C_2Cl_5$, yield 73%[164]

e. Disulphur dichloride procedures. Alkanes and cycloalkanes react with disulphur dichloride under UV irradiation to give the corresponding thiosulphenyl chlorides, e.g. **100** (equation 94)[165].



(94)

(**100**)

C–H acidic compounds give thiosulphenyl chlorides[63,83] on treatment with disulphur dichloride, e.g. equation 95. This reaction is analogous to that with sulphur dichloride—see equations 37 and 38.

$$Me_2CHCN \xrightarrow{S_2Cl_2} NCC(Me)_2SSCl \quad (95)$$

Disulphur dichloride adds to C–C multiple bonds. For example, perfluoroisobutene gives in this reaction 2-chlorooctafluoroisobutanethiosulphenyl chloride **101** (equation 96)[166], and perfluoroketene **102** affords 1-chlorocarbonyl-hexafluoropropanethiosulphenyl chloride **103** (equation 97)[167].

$$(CF_3)_2C{=}CF_2 \xrightarrow[20\,^\circ C]{S_2Cl_2} ClCF_2\text{—}C(CF_3)_2SSCl \quad (96)$$

(**101**)

$$(CF_3)_2C{=}C{=}O \xrightarrow[20\ C]{S_2Cl_2, MeCN, -10^\circ \text{ to } 0\ C} (CF_3)_2CSSCl\,C(O)Cl \quad (97)$$

(**102**) (**103**)

f. Polythio-sulphenyl chlorides. These compounds may be obtained in a similar way as thiosulphenyl chlorides described above. The most common and useful methods are

the reactions of hydro-polysulphides with sulphur dichloride or disulphur dichloride (equation 98)[155,168].

$$\begin{array}{l} \mathrm{ArSSSH} \xrightarrow{S_2Cl_2} \mathrm{ArS{-}S{-}S{-}S{-}SCl} \\ \quad\downarrow SCl_2 \\ \mathrm{ArS{-}S{-}S{-}SCl} \end{array} \qquad (98)$$

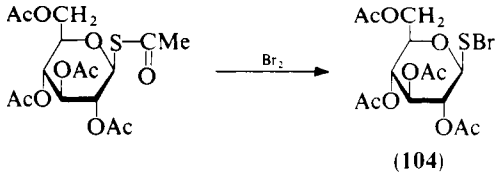
C. Synthesis of Sulphenyl Bromides

Sulphenyl bromides may be, in general, synthesized by the same methods as sulphenyl chlorides. However, they are usually less stable and therefore less common. Nevertheless, at least four different types of sulphenyl bromides exist which will be discussed in separate subsections.

1. Alkane- and arenesulphenyl bromides

Sulphenyl bromides of this type are available by identical methods as the analogous sulphenyl chlorides. For this reason, only general equations will be presented. Selected examples of the sulphenyl bromides obtained are listed in Table 10. Thus, alkane- and arenesulphenyl bromides can be synthesized by bromination of disulphides[23,169] or thiols[28,170] (equation 99). Bromination of benzyl sulphides [80,171] and thiolesters leads also to the formation of sulphenyl bromides, e.g. a sugar derivative **104** (equation 100)[172].

$$\begin{array}{l} \mathrm{RSSR} \\ \mathrm{RSH} \end{array} \xrightarrow{[Br]} \mathrm{RSBr} \qquad (99)$$



(100)

(104)

TABLE 10. Alkane- and arenesulphenyl bromides

Sulphenyl bromide	Substrate	Brominating agent	Yield (%)	Ref.
$2\text{-}NO_2\text{-}4\text{-}Cl\text{-}C_6H_3SBr$	$(2\text{-}NO_2\text{-}4\text{-}ClC_6H_3S)_2$	$Br_2/CHCl_3$	—	169
$2,4\text{-}(NO_2)_2C_6H_3SBr$	$(2,4\text{-}(NO_2)_2C_6H_3S)_2$	$Br_2/AlBr_3$	69	23
	$2,4\text{-}(NO_2)_2C_6H_3SCH_2Ph$	Br_2/CCl_4	86	80
$2\text{-}NO_2C_6H_4SBr$	$2\text{-}NO_2C_6H_4SO_2H$	excess HBr	—	178
MeSBr	MeSH	Br_2/CCl_4	75	28
C_6Cl_5SBr	C_6Cl_5SH	Br_2/n-hexane	—	170
Br_3CSBr	Se=C=S	Br_2/H_2O	—	173
BrClFCSBr	ClFC=S	Br_2	81	174
BrF_2CSBr	F_2C=S	Br_2	55	174
Cl_3CSBr	Cl_3CSCl	HBr	90–95	176
$(CF_3)_2C(Br)SBr$	$(F_3C)_2C$=S	Br_2	86	179
$RCBr_2SBr$	RC(S)SR	Br_2	—	175
Ph_3CSBr	Ph_3CSCl	NaBr/MeCN	50	177

Reaction of bromine with thiocarbonyl compounds leads to the formation of α-bromosulphenyl bromides[173,174] or dibromo sulphenyl bromides, e.g. **105** (equation 101), arising from dithiocarboxylic esters[175].

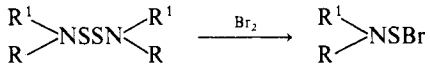
$$\underset{\underset{\text{S}}{\|}}{\text{RCSR}} \xrightarrow{\text{Br}_2} \underset{\textbf{(105)}}{\text{RCBr}_2\text{SBr}} \qquad (101)$$

Certain sulphenyl chlorides may be transformed into the corresponding bromides (e.g. **106**) when treated with hydrogen bromide[176] or sodium bromide[177]; see equation 102.

$$\underset{\textbf{(106)}}{\text{Ph}_3\text{CSCl}} \xrightarrow{\text{NaBr/MeCN}} \text{Ph}_3\text{CSBr} \qquad (102)$$

2. *Aminosulphenyl bromides* ***107***

This class of compounds has been obtained by bromination of the corresponding bis-amino disulphides (equation 103)[105a,106].



$$\xrightarrow{\text{Br}_2}$$

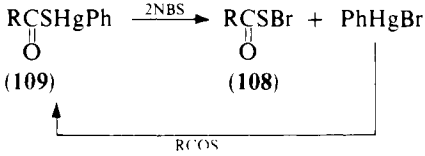
(107) (103)

R	R^1	Reference
Et	Et	105a
	$-(CH_2)_5-$	105a
	$-(CH_2)_2S(CH_2)_2-$	105a
2,5-$Cl_2C_6H_3-$	CF_3	106

3. *Acylsulphenyl bromides* ***108***

Sulphenyl bromides of this type have been known only since 1982, when the first paper of Kato's group appeared[180]. Until now, the same group have developed several other methods of the synthesis of acylsulphenyl bromides which are specified below, and all examples published are listed in Table 11. Acylsulphenyl bromides **108** are stable for 2–3 h at room temperature. They decompose when heated over their melting point or exposed to sunlight.

a. Bromination of phenylmercury thiocarboxylates (Method A). Phenylmercury thiocarboxylates **109** react with *N*-bromosuccinimide (NBS) to give acylsulphenyl bromides **108** in good yields[180]. It is advantageous that phenylmercury bromide formed is almost quantitatively reconverted into the starting material **109** by the reaction with thiocarboxylate salt (equation 104).



(104)

b. Bromination of silver thiocarboxylates Method B). Silver salts of arylthiocarboxylic acids when treated with bromine or NBS also afford **108** in moderate yields (equation 105)[181].

$$RC(=O)SAg \xrightarrow{Br_2 \text{ or NBS}} RC(=O)SBr + AgBr \quad (105)$$

(108)

$$(RCS)_2SnPh_2 \xrightarrow{\text{NBS, or } Br_2} RCSBr \quad (106)$$

(52) **(108)**

c. Bromination of diphenyltin bis-thiocarboxylates (Method C). Treatment of diphenyltin bis-thiocarboxylates **52** with NBS or bromine gives **108** in good yields (equation 106). The bromination proceeds in the same way as the chlorination, described in equation 52[98]. It should be added that the analogous treatment of diphenyltin bis-dithiocarboxylates **110** enabled Kato and coworkers[182] to obtain the thioacylsulphenyl bromides **111** which are the first representatives of this class of compounds (equation 107). Thioacylsulphenyl bromides proved, however, to be too unstable to allow their purification by t.l.c. or column chromatography. Their structure was, therefore, established by their conversion into acyl thioacyl disulphides.

TABLE 11. Synthesis of acylsulphenyl bromides **108**

Symbol	Sulphenyl bromide	Method	Bromination conditions	Yield (%)	Ref.
108a	*t*-BuC(O)–SBr	D	NBS/−23°C	70	96
108b	PhC(O)–SBr	A	NBS	85	180
		B	Br_2 or NBS	57–61	181
		C	Br_2 or NBS	83	98
		D	NBS/−78°C	70	96
108c	3-$MeC_6H_4C(O)$–SBr	A	NBS	83	180
108d	4-$MeC_6H_4C(O)$–SBr	A	NBS	83	180
		B	Br_2 or NBS	36–61	96
		D	NBS/−78°C	52	96
108e	3-$ClC_6H_4C(O)$–SBr	A		81	180
		B		50–71	181
		C		73	96
108f	4-$ClC_6H_4C(O)$–SBr	A		77	180
		B		24	181
		D		62	96
108g	4-$MeOC_6H_4C(O)$–SBr	A		86	180
		B		40	181
108h	2-$O_2NC_6H_4C(O)$–SBr	B		8	181
108i	3-$O_2NC_6H_4C(O)$–SBr	B		4	181
108k	4-$O_2NC_6H_4C(O)$–SBr	B		23	181

$$(RCS)_2SnPh_2 \xrightarrow[-15\ ^\circ C]{NBS,CH_2Cl_2} RCSBr \qquad (107)$$

(110) (111)

R = Ph, *p*-Tol, *p*-An, *p*-ClC_6H_4

d. Bromination of O-silyl thiocarboxylates (Method D). This method affords acylsulphenyl bromides in high yields[96]. It enabled one to obtain for the first time an aliphatic acylsulphenyl bromide, namely **108a** (Table 11).

$$RCOSiMe_3 \xrightarrow{NBS} RCSBr \qquad (108)$$

(108)

Trifluorothioacetic acid may be brominated directly to give trifluoroacetylsulphenyl bromide in 98% yield[97].

4. Phosphoranesulphenyl bromides

The unstable *O,O*-diethyloxophosphoranesulphenyl bromide **112a** was found to be formed by the action of bromine on triethylthionophosphate (equation 109a)[126]. Recently, a new method (equation 109b) based on the bromination of mixed phosphorothioic-acetic anhydrides **80** has been reported which affords sulphenyl bromides **112** of higher purity and stability than those prepared by other methods[141].

$$(EtO)_3P{=}S + Br_2 \longrightarrow (EtO)_2PSBr \qquad (109a)$$

(112a)

$$RR^1P(S)\text{–}O\text{–}CMe(=O) \xrightarrow{Br_2} RR^1PSBr(=O) + MeCOBr \qquad (109b)$$

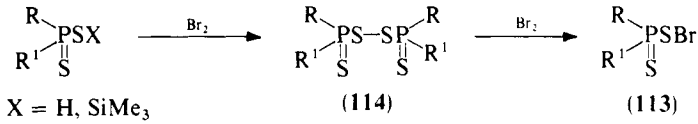
(80) (112)

Surprisingly, thioxaphosphoranesulphenyl bromides **113** appeared to be reasonably stable compounds—they may be isolated in a pure state, but decompose at room temperature within a few days. They were obtained for the first time by Michalski and coworkers in 1982[148]. All the methods of their synthesis are presented below, and details are collected in Table 12.

a. Bromination of phosphorodithioic acids and their derivatives (Method A). A simple reaction of elemental bromine with phosphorodithioic acids leads to the formation of the sulphenyl bromides **113** in very high yields[148,149]. The reaction proceeds (equation 110) via the disulphides **114**, which can be used advantageously as starting materials. It is interesting to point out that chlorination proceeds in a different way and cannot be applied for the synthesis of thioxaphosphoranesulphenyl chlorides (compare Section II.B.5.b, equation 80). The bromides **113** are also formed in quantitative yields by the action of bromine on silyl esters.

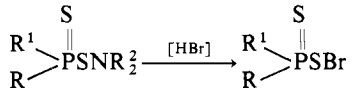
TABLE 12. Synthesis of thioxaphosphoranesulphenyl bromides **113**

Sulphenyl bromide	Method	Yield (%)	Ref.
$(MeO)_2P(S)$–SBr	A	84.3	148, 149
$(i\text{-}PrO)_2P(S)$–SBr	A	98	148, 149
	B	100	147
$(neo\text{-}PentO)_2P(S)$–SBr	A	97	148, 149
	B	100	147
$(PhO)_2P(S)$–SBr	A	98	148, 149
	C	60	183
$(MeO)t\text{-}BuP(S)$–SBr	A		148
$(p\text{-}TolO)_2P(S)$–SBr	C	80	183
$(p\text{-}MeOC_6H_4O)_2P(S)$–SBr	C	72	183
$(p\text{-}Cl\text{-}C_6H_4O)_2P(S)$–SBr	C	50	183
$(c\text{-}HexO)_2P(S)$–SBr	C	81	183



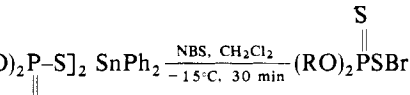
X = H, $SiMe_3$ (110)

b. Cleavage of thioxaphosphoranesulphenamides (Method B). Treatment of sulphenamides **83** with hydrogen bromide, formed *in situ* from bromotrimethylsilane and ethanol, affords **113** (equation 111) in very high yields[147].



(**83**) (**113**) (111)

c. Bromination of diphenyltin dithiophosphates (Method C). This procedure[183] for the preparation of **113** (equation 112) resembles that used for the synthesis of acylsulphenyl halides (Section II.B.3.d, equation 52 and Section II.C.3.c, equation 106, Reference 98).



(**113**) (112)

D. Synthesis of Sulphenyl Iodides

Sulphenyl iodides are the least stable members of the family of sulphenyl halides. They have been often postulated as intermediates (e.g. Reference 184) without having been characterized. Aside from the question of stability, sulphenyl iodides seem to be biologically important. Tobacco mosaic virus forms a stable sulphenyl iodide, and other proteins were found to do so as well[185].

The first sulphenyl iodide **115** was prepared in 1939 by Rheinboldt and Motzkus[186], who treated mercury *tert*-butyl mercaptide with iodine in ether. The preparation of **116** was later improved by using silver mercaptide instead of **115**[185]; see equation 113.

$$t\text{-BuS–Hg–SBu-}t \xrightarrow{I_2} t\text{-BuSI} \qquad (113)$$

(115) **(116)**

A very stable sulphenyl iodide **117** was synthesized in 1954 (equation 114)[171]. However, it must be considered as an untypical example due to its salt-like character.

(114)

(117)

Later on, triphenylmethanesulphenyl iodide **118** was obtained (equation 115) and proven to be stable at −80 °C under nitrogen, and at room temperature in a solution in the absence of light[177]. The sulphenyl iodide **119** derived from 2-mercapto-2-methylpropanoic acid has been trapped at −40 °C by *p*-chlorothiophenol (equation 116)[187].

$$Ph_3CSCl + NaI \longrightarrow Ph_3CSI \qquad (115)$$

(118)

crystallized at −80 °C
yield 40%

$$\begin{matrix} Me \\ | \\ HSCCO_2H \\ | \\ Me \end{matrix} + I_2 \xrightarrow[-40\ ^\circ C]{EtOH} \left[\begin{matrix} Me \\ | \\ ISCCO_2H \\ | \\ Me \end{matrix} \right] \qquad (116)$$

(119)

The first sulphenyl iodide of a typical structure that has been isolated as a pure, stable, crystalline solid was **120** (equation 117), described by Field and White[188]. The solid iodide remains unchanged at ambient conditions for over ten weeks but it is quite reactive in solution.

$$HSCMe_2CH(NHCbz)CONHC_6H_4Cl\text{-}p \xrightarrow[\substack{CH_2Cl_2,\,H_2O \\ 94\text{–}100\%}]{I_2}$$

$$ISCMe_2CH(NHCbz)CONHC_6H_4Cl\text{-}p \qquad (117)$$

(120)

m.p. 110 (dec.)

Recently, Kato and collaborators succeeded in the synthesis of several acylsulphenyl iodides **121**, which were shown to be stable for a few hours at room temperature both in

the solid state and in solution[189]. The following synthetic procedures have been reported:

A. Reaction of phenylmercury thiocarboxylates **109** with iodine[189].

$$\underset{\textbf{(109)}}{RCSHgPh} \xrightarrow{I_2} \underset{\textbf{(121)}}{RCSI} + PhHgI \qquad (118)$$

B. Reaction of silver thiocarboxylates with iodine[181].

$$\underset{\textbf{(121)}}{RCSAg} \xrightarrow{I_2} RCSI + AgI \qquad (119)$$

C. Reaction of diphenyltin bis-thiocarboxylates **52** with iodine[98].

$$\underset{\textbf{(52)}}{(RCS)_2SnPh_2} \xrightarrow{I_2} \underset{\textbf{(121)}}{2\,RCSI} \qquad (120)$$

For spectral investigations of sulphenyl iodides, see Reference 190. Acylsulphenyl iodides **121** are listed in Table 13.

Interestingly, thioxaphosphoranesulphenyl iodides **122** have also been synthesized (equation 21) by Kato's group from diphenyltin dithiophosphates[183]. However, they have not been isolated due to their instability, but identified as products of their reaction with dithiocarboxylic acids.

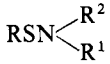
$$[(RO)_2PS]_2SnPh_2 \xrightarrow{N\text{-iodosuccinimide}} \underset{\textbf{(122)}}{2\,(RO)_2PSI} \qquad (121)$$

TABLE 13. Synthesis of acylsulphenyl iodides **121**

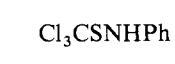
Sulphenyl iodide	Method	Yield (%)	Ref.
PhC(O)–SI	A	72	189
	B	60	181
	C	45	98
4-$MeC_6H_4C(O)$–SI	A	79	189
	B	40	181
4-$MeOC_6H_4C(O)$–SI	A	73	189
	B	20	181
4-$ClC_6H_4C(O)$–SI	A	64	189
4-$O_2NC_6H_4C(O)$–SI	B	12	181

III. SYNTHESIS OF SULPHENAMIDE DERIVATIVES

Sulphenamide derivatives of the general structure **123** constitute a group of organic sulphur compounds containing simultaneously the single sulphur–carbon and sulphur–nitrogen bonds. They have been known since 1983 when Rathke reported[191] the synthesis of the stable trichloromethanesulphenanilide **124**.



(**123**)

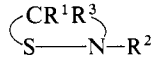


(**124**)

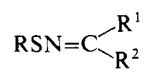
Since the beginning of the 1940s sulphenamides have been used extensively in industry, in the vulcanization of rubber, and more recently as pesticides, fungicides and bacteriocides[192,193]. In recent years also much interest has been focused on the chemistry of this class of sulphur compounds as their importance in organic synthesis has been recognized.

The methods for the synthesis of sulphenamide derivatives published until 1984 have been briefly reviewed by Schubart in a new edition of the sulfur volume of 'Houben-Weyl'[3d]. Earlier, the synthesis of sulphenamide derivatives was also discussed in a few reviews on the chemistry of sulphenamides[194–199] and more recently by Davis and Nadir[200a] and Craine and Raban[200b] in their review articles on the synthesis and properties of sulphenamides. The aim of this part of the present chapter is to provide an up-to-date survey of the methods which may be applied for the synthesis of sulphenamide derivatives. The term sulphenamide used here covers any nitrogen derivative of sulphenic acid in which the sulphenyl sulphur is simultaneously bound to the nitrogen and carbon atoms. Therefore, we will discuss below the synthesis of acyclic and cyclic sulphenamides **123** and **124**, acyclic and cyclic sulphenimines **125** and **126** and di- and tri-[alkane(arene)sulphen]imides **127** or **128**.* Since the synthesis of cyclic sulphenamides **124** and sulphenimines **126** is based on many special procedures, it was necessary to separate the synthesis of these groups of the sulphenamide derivatives from those of acyclic ones. For this reason, in the first part of this review all the general methods of the synthesis of acyclic sulphenamides **123** and di- and tri-[alkane(arene)]sulphen]-imides **127** and **128** will be summarized. In the second one, the preparation of sulphenimine derivatives **125** will be discussed. The last part will present the synthetic procedures leading to heterocyclic systems **124** and **126** starting from acyclic sulphenyl derivatives.

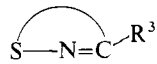
(**123**)



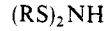
(**124**)



(**125**)



(**126**)



(**127**)

(**128**)

*These types of compounds (**127** and **128**) are called in the chemical literature: di(tri)sulphenylamines, (di)-alkyl(aryl)thiosulphenamides or bis-(tris)-sulphenimides (see for example Ref. 200b). For the sake of simplicity we will use in this section the term 'sulphenimides'.

A. Synthesis of Sulphenamides and Di- and Tri-[alkane(arene)sulphen]imides

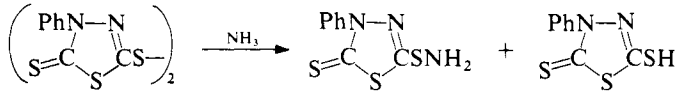
1. Primary sulphenamides

Unsubstituted sulphenamides **129** are usually markedly less stable than their mono and disubstituted analogues. Although many primary sulphenamides are known, only a few could be isolated as stable substances. The synthesis of these stable sulphenamides will be discussed below.

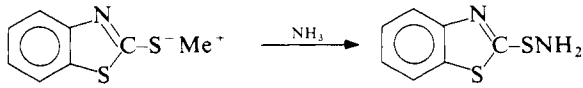
$$RSNH_2$$

(129)

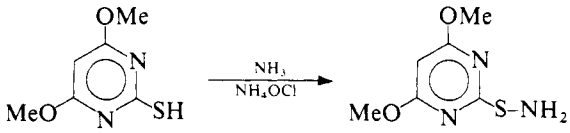
a. Heterocyclic primary sulphenamides. Phenyldithiothiazolesulphenamide **130** is the first heterocyclic sulphenamide which has been reported in the chemical literature. As early as 1896 Busch reported[201] that phenyldithiothiazole disulphide **131** was converted to the stable sulphenamide **130** upon treatment with ammonia (equation 122). In 1949 Carr and coworkers[202] described the preparation of unsubstituted 2-benzothiazole-2-sulphenamide **132**, which is formed in the direct oxidative condensation of ammonia and a metallic thiazolylmercaptide **133** in aqueous solution (equation 123). Much later, modification of this procedure was reported by Sartori and Golloch[203]. This approach was found to be useful for the preparation of pyrimidinesulphenamide **134** starting from the corresponding 2,4-dimethoxy-6-pyrimidinethiol **135** (equation 124)[204].



(131) (130) (122)

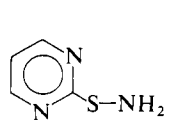


(133) (132) (123)

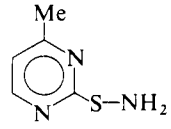


(135) (134) (124)

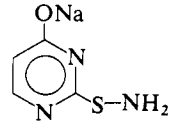
More recently, 2-pyrimidine sulphenamide **136**, 4-methyl-2-pyrimidinesulphenamide **137**, sodium 2-sulphenamido-6-methylpyrimidine-4-olate monohydrate **138**, 2-pyridinesulphenamide **139**, 4-methylpyridinesulphenamide **140** and 2-(pyridyloxide) sulphenamide **141** were prepared in moderate yields by the reaction of chloroamine with the sodium salts of the corresponding heterocyclic thiols[205].



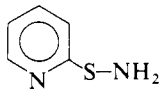
(136) (40%)



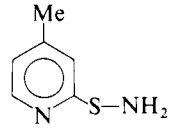
(137) (42%)



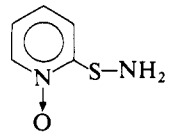
(138) (58%)



(139) (55%)

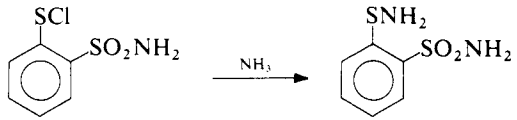


(140) (46%)



(141) (40%)

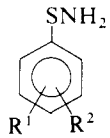
b. Primary arenesulphenamides. As early as 1912 Zincke and Farr[206] prepared 2-sulphonamidobenzenesulphenamide **142** by treatment of the sulphenyl chloride **143** with ammonia (equation 125).

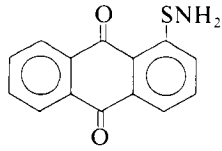


(125)

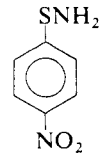
(143) (142)

This approach was applied[207] for the synthesis of anthraquinone-1-sulphenamide **144**, 4-nitrobenzenesulphenamide **145** and 2-nitro-4-chlorobenzenesulphenamide **146**. Much later, the synthesis of **145** and **146** was reported in a patent[208], which describes also, although without any experimental details, the synthesis of mono- and disubstituted benzenesulphenamides **147–158** as well as naphthalenesulphenamides **159–161**.

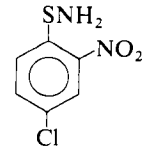




(144)

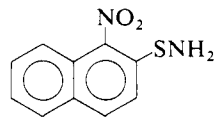


(145)

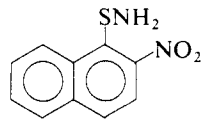


(146)

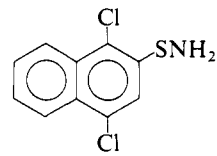
No.	R^1	R^2
(147)	3-NO_2	H
(148)	2-NO_2	H
(149)	2-CN	H
(150)	4-MeCO	H
(151)	4-OCOEt	H
(152)	2-NO_2	4-NO_2
(153)	2-Cl	5-Cl
(154)	4-Cl	2-NO_2
(155)	4-Cl	3-MeCO
(156)	2-Me	4-NO_2
(157)	4-Et	4-NO_2
(158)	2-NO_2	4-Bu-t



(159)

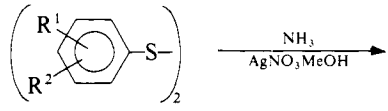


(160)



(161)

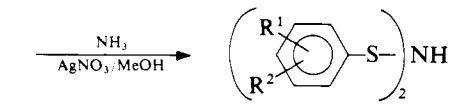
A few primary benzenesulphenamides (**147**, **162** and **163**) were recently prepared in 62–94% yield by the metal-assisted reaction of aromatic disulphides **164** with ammonia (equation 126)[209]. It is interesting to note that this method yields di(arenesulphen)imides **165** or **166** when the groups attached to sulphur are more electron donating than the 3,4-dichlorophenyl group (equation 127). Ammonolysis of 2-chloronaphthalene-1-sulphenylchloride **167** with a 25% ammonia solution was found[210] to give the corresponding primary sulphenamide **168** which, upon treatment with concentrated hydrochloric acid, was reconverted into the starting sulphenyl chloride **167**. However, treatment with diluted hydrochloric acid gave di-(2-chloronaphthylsulphen)-imide **169** (equation 128). Saturation of an ethereal solution of pentafluorobenzenesulphenyl chloride **170** with ammonia at 0°C gave a mixture of the primary sulphenamide **171** and the corresponding di-(pentafluorobenzenesulphen)-imide **172** in 55% and 21% yield, respectively (equation 129)[203]. Tris(pentafluorobenzenesulphen)-imide **173** was obtained[203] in 63% yield by the condensation of sulphenamide **172** with sulphenyl chloride **170** in the presence of triethylamine (equation 130). 2-Nitrobenzenesulphenamide **148** was prepared[211] in 72% yield by the ammonolysis of 2-nitrophenyl benzenethiosulphonate **174** (equation 131).



(126)

164

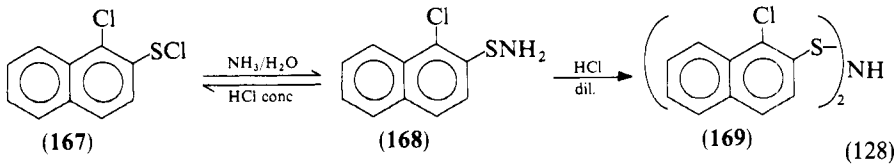
(**a**)	$R^1 = 3\text{-Cl}$	$R^2 = 4\text{-Cl}$	(**147**)	$R^1 = 3\text{-NO}_2$	$R^2 = H$
(**b**)	$R^1 = 3\text{-NO}_2$	$R^2 = H$	(**162**)	$R^1 = 3\text{-Cl}$	$R^2 = 4\text{-Cl}$
(**c**)	$R^1 = 4\text{-NO}_2$	$R^2 = H$	(**163**)	$R^1 = 4\text{-NO}_2$	$R^2 = H$



(127)

(**d**) $R^1 = R^2 = 4$ (**165**) $R^1 = R^2 = H$

(**e**) $R^1 = 4\text{-Cl}$, $R^2 = H$ (**166**) $R^1 = 4\text{-Cl}$, $R^2 = H$



(**167**) (**168**) (**169**)

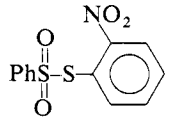
(128)

$$C_6F_5SCl \xrightarrow[\text{ether/°C}]{NH_3} C_6F_5SNH_2 + (C_6F_5S)_2NH \qquad (129)$$

(**170**) (**171**) (**172**)

$$\mathbf{172} + \mathbf{170} \xrightarrow{Et_3N} (C_6F_5S)_3N \qquad (130)$$

(**173**)



(174)

$$\xrightarrow{NH_3} \mathbf{148} + PhSO_2H \qquad (131)$$

c. Primary alkanesulphenamides. The first example of the stable primary alkanesulphenamide, triphenylmethanesulphenamide **175**, was described as early as 1919 by Vorländer and Mittag[212]. They found that treatment of triphenylmethanesulphenyl chloride **176** with ammonia affords **175** in good yield (equation 132). Recently, this sulphenamide was prepared in 97.8% yield by a modification of the original procedure in which a solution of the recrystallized sulphenylchloride **176** in methylene chloride was slowly added to the vigorously stirred, cold NH_4OH/H_2O (29% NH_4OH) solution[213]. The reaction of trifluoromethanesulphenyl chloride **3** with ammonia at $-45\,^{\circ}C$ was found[214] to give the corresponding sulphenamide **177** in almost quantitative yield (98%). When this reaction was carried out with an excess of sulphenyl chloride **3**, di-(trifluoromethanesulphen)-imide **178** was isolated in ~70% yield and no $(CF_3S)_3N$ was detected[214] (equation 133). In 1963 it was found[215] that trichloromethanesulphenyl chloride **1** reacts with ammonia according to equation 134. For the product of this reaction the structure of 3,6-dichloro-1,4,2,5-dithiadiazine **180** (equivalent to **179** where $n=2$) was assigned. Later on, it was unequivocally shown[216] that the product of this reaction has the structure of 2,3,7,8-tetrachloro-5,10,11,12-tetrathia-1,4,6,9-tetraazatricyclo-[5.3.1.1]-dodeca-3,8-diene **181** (equivalent to **179** where $n=4$).

$$Ph_3CSCl \xrightarrow[NH_4OH/H_2O]{NH_3} Ph_3CSNH_2 \qquad (132)$$

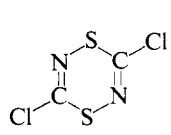
(176) (175)

$$CF_3SCl \longrightarrow \begin{cases} CF_3SNH_2 \\ (177) \end{cases} \quad \begin{cases} (CF_3S)_2NH \\ (178) \end{cases} \qquad (133)$$

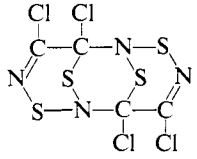
(3)

$$Cl_3CSCl + nNH_3 \xrightarrow{-HCl} (ClCNS)_n \qquad (134)$$

(1) (179)



(180)



(181)

An obvious way to explain the formation of **180** or **181** is to assume that the sulphenamide **182** is formed as the primary product of the reaction between trichloromethanesulphenyl chloride **1** and ammonia (equation 135). Its decomposition according

to equation 136 gave the monomer **179** ($n=1$), which then oligomerizes to form **180** or **181**. This rationalization was later supported by Hass and Lorenz[217], who synthesized and fully characterized sulphenamide **182**. It is interesting to note that the corresponding di-(trichloromethanesulphen)-imide **183** and tris-(trichloromethanesulphen)-imide **184** were prepared and isolated as stable species[218]. In sharp contrast to the reaction of trichloromethanesulphenyl chloride **1** with ammonia, the analogous reaction of pentachloroethanesulphenyl chloride **185** takes place very easily, giving the simple substitution product that is pentachloroethanesulphenamide **186** in 53% yield[219] (equation 137) which was found to be amazingly stable and easy to handle.

$$\underset{\textbf{(1)}}{Cl_3CSCl} + NH_3 \longrightarrow \underset{\textbf{(182)}}{Cl_3CSNH_2} \tag{135}$$

$$\textbf{182} \longrightarrow \textbf{179} + 2HCl \tag{136}$$

$$\underset{\textbf{(183)}}{(Cl_3CS)_2NH} \qquad \underset{\textbf{(184)}}{(Cl_3CS)_3N}$$

$$\underset{\textbf{(185)}}{Cl_3CCCl_2SCl} \xrightarrow{NH_3} \underset{\textbf{(186)}}{Cl_3CCCl_2SNH_2} \tag{137}$$

Haas and Lorenz also reported that chlorofluoromethanesulphenyl chlorides **187** react with ammonia to yield the corresponding sulphenamides **188** (equation 138)[220]. The latter undergo further condensation to di-(chlorofluoromethanesulphen)-imides **189** in the presence of pyridine in pentane at $-60\,^{\circ}C$ (equation 139).

$$\underset{\textbf{(187)}\ \textbf{(a)}\ n=1;\ \textbf{(b)}\ n=2}{CCl_{3-n}F_nSCl} \xrightarrow{NH_3} \underset{\textbf{(188)}}{CCl_{3-n}F_nSNH_2} \tag{138}$$

$$\textbf{188} + \textbf{187} \xrightarrow[-60\,^{\circ}C/\text{pentane}]{\text{Pyridine}} \underset{\textbf{(189)}}{(CCl_{3-n}F_nS)_2NH} \tag{139}$$

Tris-(chlorofluoromethanesulphen)-imides were prepared[220] by the reaction of the primary sulphenamides **188** with two moles of a sulphenyl chloride **187** in pentane using triethylamine as a hydrogen chloride acceptor (equation 140).

$$\textbf{188} + 2\,\textbf{187} \xrightarrow[Et_3N]{} \underset{\textbf{(190)}}{(Cl_{3-n}F_nS)_3N} \tag{140}$$

2. *Secondary and tertiary sulphenamides*

a. Synthesis from sulphenyl halides. The most common method for preparing secondary and tertiary sulphenamides first applied by Rathke[191] involves condensation of a

sulphenyl halide with a primary or secondary amine. This reaction is represented by the general equation 141. Hydrogen halogenide generated in this reaction is removed by a base B. Usually, an excess of the reacting amine is used, sometimes a base such as triethylamine is added to the reaction mixture. Very often, the removal of trace amounts of amine hydrohalogenides formed in this synthesis is difficult. This constitutes an important drawback of this procedure because the presence of amine hydrohalogenides markedly lowers the chemical stability of the desired sulphenamide.

$$RSX + R^1R^2NH \xrightarrow{B} RSNR^1R^2 + B{\cdot}HCl \qquad (141)$$

Generally, arenesulphenyl chlorides are used as a starting material in the preparation of secondary and tertiary arenesulphenamides **191–195** (equation 142 and Table 14) and the use of 2-nitrobenzenesulphenyl chloride **196** for the identification of amines was reported as early as 1939[221].

$$ArSCl + R^1R^2NH \longrightarrow ArSNR^1R^2 \qquad (142)$$
$$\textbf{(191)–(195)}$$

TABLE 14. Synthesis of secondary and tertiary arenesulphenamides, $ArSNR^1R^2$, from arenesulphenyl chlorides and primary and secondary amines

No.	Ar	R^1	R^2	Yield	Ref.
191a	Ph	Me	Me	77	206
191b	Ph	Et	Et	70	224
192a	2-$NO_2C_6H_4$	H	Me	*a*	206
192b	2-$NO_2C_6H_4$	H	Ph	*a*	206
192c	2-$NO_2C_6H_4$	H	4-MeC_6H_4	*a*	206
192d	2-$NO_2C_6H_4$	H	2-$NO_2C_6H_4$	*a*	206
192e	2-$NO_2C_6H_4$	H	α-$C_{10}H_7$	*a*	206
192f	2-$NO_2C_6H_4$	H	β-$C_{10}H_7$	*a*	206
192g	2-$NO_2C_6H_4$	H	2-$MeOC_6H_4$	*a*	221
192h	2-$NO_2C_6H_4$	H	4-BrC_6H_4	*a*	221
192i	2-$NO_2C_6H_4$	H	4-ClC_6H_4	*a*	221
192j	2-$NO_2C_6H_4$	H	2-MeC_6H_4	*a*	221
192k	2-$NO_2C_6H_4$	H	3-MeC_6H_4	*a*	221
192l	2-$NO_2C_6H_4$	H	Et	*a*	221
192m	2-$NO_2C_6H_4$	H	Pr	*a*	221
192n	2-$NO_2C_6H_4$	H	Bu	*a*	221
192o	2-$NO_2C_6H_4$	H	*c*-C_6H_{11}	*a*	221
192p	2-$NO_2C_6H_4$	Me	Me	*a*	221
192r	2-$NO_2C_6H_4$	Et	Et	*a*	221
192s	2-$NO_2C_6H_4$	Me	Ph	*a*	221
193a	4-$NO_2C_6H_4$	H	Me	*a*	221
193b	4-$NO_2C_6H_4$	H	Ph	*a*	221
193c	4-$NO_2C_6H_4$	H	4-MeC_6H_4	*a*	225
193d	4-$NO_2C_6H_4$	H	α-$C_{10}H_7$	*a*	225
193e	4-$NO_2C_6H_4$	H	β-$C_{10}H_7$	*a*	225
193f	4-$NO_2C_6H_4$	H	4-$NO_2C_6H_4$	*a*	225
194a	2-NO_2-4-Cl-C_6H_3	H	2-NO_2-4-ClC_6H_3	*a*	205
195a	C_6Cl_5	Me	Me	90	226

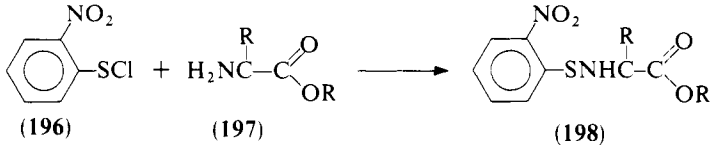
[a] Not given.

TABLE 15. Synthesis of *N*-2-nitrobenzenesulphenyl derivatives **198** of aminoacids **197**

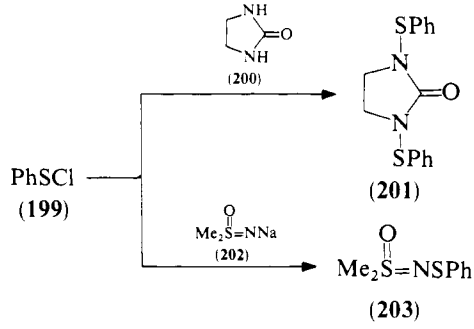
No.	Aminoacid	Yield of **198** (%)	Ref.
a	Glycine ethyl ester	*a*	222
b	*d,l*-Leucine ethyl ester	*a*	222
c	*l*-Alanine	83	223
d	*l*-Valine	65	223
e	*l*-Valine methyl ester	89	223
f	*l*-Valine *p*-nitrophenyl ester	72	223
g	*l*-Phenylalanine	90	223
h	*l*-Phenylalanine methylester	65	223
i	*l*-Leucine	70	223
j	*l*-Asparagine	78	223
k	*l*-Glutamine	60	223
l	*l*-Threonine	60	223
m	*l*-Proline DCHA[b]	45	223
n	*l*-Hydroxyproline DCHA[b]	50	223
o	*l*-Tryptophan DCHA[b]	50	223
p	*l*-Tyrosine DCHA[b]	62	223
q	*l*-Isoluecine	70	223
r	*l*-Methionine DCHA[b]	54	223

[a] Not given.
[b] DCHA = dicyclohexylammonium salt.

Moreover, the use of 2-nitrobenzenesulphenyl chloride **196** for the protection of the amino function of aminoacids **197** was reported by Abderhalden and Riesz[222] (equation 143). This application of sulphenyl chloride **196** was later extended by the work of Zervas and coworkers[223] (see Table 15). Reactions of arenesulphenyl chlorides with the N–H acidic compounds were used for the preparation of a few not so common sulphenamide derivatives. Thus, treatment of benzenesulphenyl chloride **199** with cyclic urea **200** afforded disulphenamide **201** in 75% yield[228]. The sodium salt of dimethylsulphoximine **202** when reacted with **199** gave the sulphenamide **203** in 96% yield[229] (equation 144).



(143)



(144)

With aliphatic sulphenyl halides the reaction occurs in a more complex way. For example, methanesulphenyl chloride **204a** gives, with an excess of dialkylamine at −60 °C, besides the expected sulphenamide **205**, gem-diamine **206** and methyl di- and trisulphides[229] (equation 145). Ethanesulphenyl chloride **204b** with dimethylamine yielded the sulphenamide **207** together with diethyl disulphide and trisulphide, but no gem-diamine could be detected[230] (equation 146). On the other hand, the reaction of the sulphenyl iodide **116** with primary and secondary amines at −20 °C gives the corresponding sulphenamides **208** in yields above 50% (equation 147)[186]. A series of *N*-methyl alkanesulphenanilides **209** was prepared by addition of the sulphenyl chlorides **204a–d** in a chloroform solution to a two-phase system consisting of *N*-methylaniline, ether, sodium hydroxide and water (equation 148)[231]. It was found that in the reaction of 2-acetamidoethanesulphenyl chloride **210** and alkanesulphenyl chlorides **204d–e** with a variety of amines, lower basicity and a higher substitution of the aliphatic amine facilitate the synthesis and purification of the corresponding sulphenamides **211** and **212–214** (equations 149 and 150)[232].

$$\underset{\textbf{(204a)}}{MeSCl} + HNR^1R^2 \longrightarrow \underset{\textbf{(205)}}{MeSNR^1R^2} + \underset{\textbf{(206)}}{CH_2(NR^1R^2)_2} + Me_2S_2 + MeS_3Me \quad (145)$$

$$\underset{\textbf{(204b)}}{EtSCl} + Me_2NH \longrightarrow \underset{\textbf{(207)}}{EtSNMe_2} + Et_2S_2 + Et_2S_3 \quad (146)$$

$$\underset{\textbf{(116)}}{t\text{-BuSI}} + R^1R^2NH \longrightarrow \underset{\textbf{(208)}}{t\text{-BuSNR}^1R^2} \quad (147)$$

(a) $R^1 = H,\ R^2 = Me$
(b) $R^1 = H,\ R^2 = Me$
(c) $R^1 = R^2 =$ 

$$\underset{\textbf{(204)}}{RSCl} + PhNHMe \xrightarrow[CHCl_3/Et_2O/H_2O]{NaOH} \underset{\textbf{(209)}}{RSNPh} \quad (148)$$

(a) R = Me
(b) R = Et
(c) R = *i-Pr*
(d) R = *t*-Bu

$$\underset{\textbf{(210)}}{AcNHCH_2CH_2SCl} + R^1R^2NH \longrightarrow \underset{\textbf{(211)}}{AcNHCH_2CH_2SNR^1R^2} \quad (149)$$

(a) $R^1 = H,\ R^2 = 4\text{-}MeO_2CC_6H_4$
(b) $R^1 = H,\ R^2 =$ benzothiazyl
(c) $R^1 = R^2 = Et$
(d) $R^1 + R^2 = (CH_2)_5$
(e) $R^1 + R^2 = (CH_2)_2O(CH_2)_2$
(f) $R^1 + R^2 =$ benzimidazoyl
(g) $R^1 + R^2 =$ *o*-phthaloyl
(h) $R^1 = H,\ R^2 = p\text{-}TolSO_2$

$$RSCl + R^1R^2NH \longrightarrow RSNR^1R^2 \qquad (150)$$

(204) **(212)** (a) $R = Et$, $R^1 + R^2 = (CH_2)_5$

(b) $R = Et$ (b) $R = Et, R^1 = R^2 = Et$

(d) $R = t\text{-Bu}$ **(213)** $R = Bu\text{-}n, R^1 + R^2 = (CH_2)_5$

(e) $R = n\text{-Bu}$ **(214)** (a) $R = t\text{-Bu}, R^1 + R^2 = (CH_2)_5$

(b) $R = t\text{-Bu}, R^1 = R^2 = Et$

(c) $R = t\text{-Bu}, R^1 = H, R^2 = Ph$

Reaction of trihalogenomethanesulphenyl chlorides **215** with primary and secondary amines as well as with the N–H acidic compounds has recently been intensively investigated because the products of this reaction, the corresponding sulphenamides **216** formed usually in yields above 70%, have been recognized as effective plant-protection agents[3d,194] (equation 151).

$$CX^1_{3-n}X^2_nSCl + R^1R^2NH \longrightarrow CX^1_{3-n}X^2_nSNR^1R^2 \qquad (151)$$

(215) **(216)**

b. Synthesis from sulphenyl thiocyanates. A synthesis of sulphenamides, which is mechanistically similar to the reaction of sulphenyl halogenides with amines, involves the reaction of amines with sulphenyl thiocyanates **217** (equation 152).

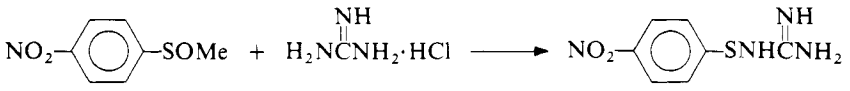
$$RS\text{-}SCN + R^1R^2NH \longrightarrow RSNR^1R^2 \qquad (152)$$

(217) **(218)**

(a) $R = Et$
(b) $R = Pr$
(c) $R = t\text{-Bu}$
(d) $R = Hexyl$

A few *N,N*-dialkylsulphenamides **218** have been prepared[233] in yields ranging from 30% to 68% by adding thiocyanate **217** to a cold solution of two equivalents of a secondary aliphatic amine. However, this procedure cannot be applied for the preparation of primary sulphenamides.

c. Synthesis from arenesulphenates. For the first time the synthesis of sulphenamide derivatives from sulphenic esters and amines was reported in the patent literature[234]. It was found that the reaction of *O*-methyl *p*-nitrobenzenesulphenate **219a** with guanidine hydrochloride gave the corresponding sulphenamide **220** in 77% yield (equation 153).



(219a) **(220)** (153)

Later on, this reaction was also observed by Abbott and Stirling[235] in their study on the interception of arenesulphenates arising from a rearrangement of sulphoxides. Soon thereafter, *O*-methyl benzenesulphenate **219b** was used[236] to prepare a series of sulphenamides (Table 16). Sulphenamides **221** are obtained in high yields from primary and

TABLE 16. Synthesis of benzenesulphenamides, $PhSNR^1R^2$, from sulphenate **219b** and amines, aminosilanes and aminoboranes, RNR^1R^2

R	R^1	R2	Yield (%)	Ref.
H	H	Me	63	236
H	H	Et	87	236
H	H	n-Pr	65	236
H	H	*i*-Pr	66	236
H	H	n-Bu	44	236
H	H	*i*-Bu	50	236
H	H	*s*-Bu	61	236
H	H	*t*-Bu	85	236
Me_3Si	Me	Me	75	236
Me_3Si	Et	Et	70	236
Me_3Si	Me_3Si	Me	22	236
H	Me_3Si	Et	64	236
H	Me_3Si	Pr	80	236
Ph_2B	Me	Me	50	237
$(Et_2N)B$	Et	Et	55	237
$Ph(Et_2N)B$	Et	Et	74	237
$Ph(Et_2N)B$	n-Bu	n-Bu	69	237
$(t\text{-}BuNH)_2B$	*t*-Bu	H	74	237

secondary amines (equation 154) or *N*,*N*-dialkylaminosilanes **222**. However, when *N*-alkylaminotrimethylsilanes **223** were used, a mixture of *N*-alkyl sulphenamides **224** and *N*-alkyl-*N*-trimethylsilyl sulphenamides **225** was formed (equation 155)[236].

$$\text{PhSOMe (219b)} \xrightarrow[\text{Me}_3\text{SiNR}^1\text{R}^2\ (222)]{\text{R}^1\text{R}^2\text{NH}} \text{PhSNR}^1\text{R}^2\ (221) \qquad (154)$$

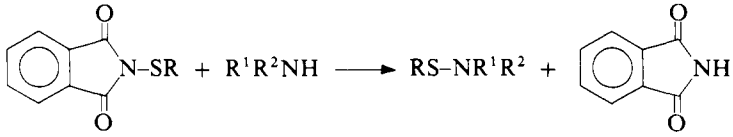
$$\text{219} + \text{Me}_3\text{SiNHR (223)} \longrightarrow \begin{cases} \text{PhSNHR} + \text{Me}_3\text{SiOR} \quad (224) \\ \text{PhSN(R)SiMe}_3 \quad (225) \end{cases} \qquad (155)$$

A few benzenesulphenamides **221** were also prepared in good yields and under mild conditions by reacting *O*-methyl benzenesulphenate **219b** with aminoboranes **226** (equation 156, Table 16).

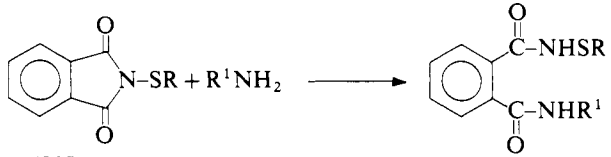
$$\underset{(219b)}{\text{PhSOMe}} + \underset{(226)}{\text{R}^3\text{R}^4\text{B–NR}^1\text{R}^2} \longrightarrow \underset{(221)}{\text{PhSNR}^1\text{R}^2} + \text{R}^3\text{R}^4\text{BOMe} \qquad (156)$$

d. Synthesis from thiophthalimides. Thiophthalimides **227**, which may be considered as a group of very reactive sulphenamide derivatives, undergo displacement when treated with a variety of nucleophiles. The use of primary or secondary amines leads to the

formation of sulphenamides (equation 157)[238,239]. Very good yields (81–100%) and mild reaction conditions are characteristic for this general synthesis of sulphenamides. Of interest is that when R is a bulky group (isopropyl, cyclohexyl, *t*-butyl) thiophthalimides **227** react with amines in a different way and afford the *N*-thio-*N'*-diamides **228** according to equation 158.



(227) R = Et, Bu, CH_2Ph, Ph; R^1, R^2 = H, alkyl, aryl (157)



(227) R = *i*-Pr, *t*-Bu, cyclohexyl

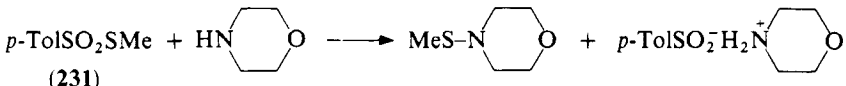
(228) R^1 = Me, *i*-Pr, Bu, allyl, CH_2Ph, cyclohexyl, $C_{18}H_{37}$ (158)

e. Synthesis from thiosulphonates. Dunbar and Rogers have investigated the reaction of thiosulphonates **229** with primary and secondary amines (equation 159)[211]. They determined the equilibrium constants for the reaction of several *S*-alkyl and *S*-aryl thiosulphonates **229** and found that, as the electronegative character of R increases, the formation of sulphenamides is facilitated.

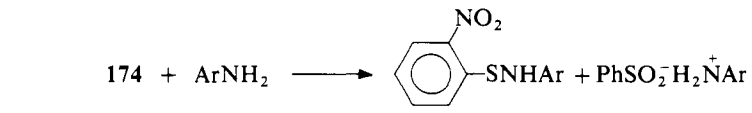
$$ArSO_2SR + 2R^1R^2NH \rightleftharpoons ArSO_2^- H_2\overset{+}{N}R^1R^2 + RSNR^1R^2 \qquad (159)$$

(229)

Taking into account these results they were able to prepare the sulphenamide **230** and a few *N*-arene-2-nitrobenzenesulphenamides **232** from the thiosulphonates **231** and **174**, respectively (equations 160 and 161).



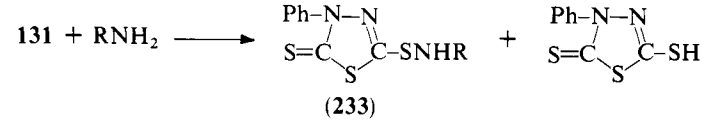
(231) (230) (160)



(232) (161)

f. Synthesis from disulphides. As early as 1946 Busch reported [201] that *N*-methyl and *N*-ethyl phenyldithiothiazolesulphenamides **233a–b** are formed from disulphide **131** and

methyl- and ethylamine (equation 162). In the patent literature this procedure was claimed to be of general scope[202]. Recently, a convenient one-step synthesis of sulphenamides has been developed by Davis and coworkers[209]. They found that disulphides **234** react rapidly and cleanly with primary or secondary amines in the presence of a metal salt such as silver nitrate or mercuric chloride to produce the corresponding sulphenamides (equation 163). The yields are generally high (see Table 17) and the procedure works best for aromatic disulphides and less well for aliphatic disulphides. An advantage of this procedure is that sulphenamides containing reactive functional groups such as a hydroxyl or a C–C double bond can be prepared.



(162)

(233)

(a) R = Me
(b) R = Et

$$RSSR + MX + 2R^1R^2NH \longrightarrow RSNR^1R^2 + RSM + R^1R^2\overset{+}{N}H_2X^- \qquad (163)$$

(234)

$$MX = AgNO_3, \quad AgOAc, \quad HgCl_2$$

TABLE 17. Synthesis of sulphenamides, $RSNR^1R^2$, from disulphides RSSR and amines, HNR^1R^2

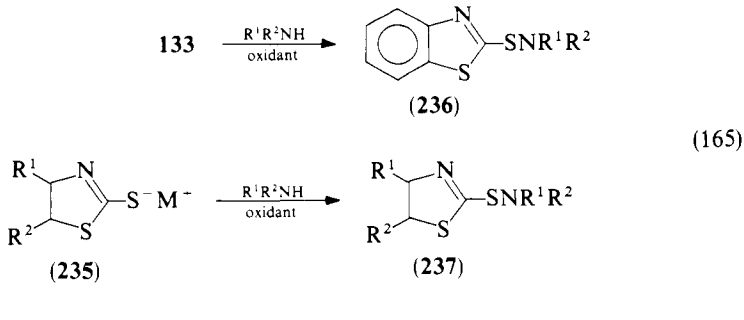
R	R^1	R^2	Conditions	Yield (%)	Ref.
Me	$-(CH_2)_5-$		AgOAc	43	209
Et	$-(CH_2)_5-$		AgOAc	30	209
Pr	Et	Et	$LiNEt_2$	69	240
Pr	Pr	Pr	$LiNPr_2$	75	240
Pr	*i*-Bu	*i*-Bu	$LiNBu^i_2$	96	240
Pr	Bu	H	LiNHBu	92	240
Bu	$-(CH_2)_5-$		AgOAc	40	209
i-Pr	$-(CH_2)_5-$		AgOAc	45	209
$PhCH_2$	*i*-Pr	H	H	97	209
$PhCH_2$	Et	Et	H	58	209
Ph	Et	H	$AgNO_3$	75	209
Ph	*i*-Pr	H	$AgNO_3$	73	209
Ph	Allyl	H	$AgNO_3$	80	209
Ph	Et	Et	$LiNEt_2$	79	240
Ph	*i*-Bu	H	LiNHBu-*i*	91	240
p-ClC_6H_4	Ph	H	$AgNO_3$	75	209
p-BrC_6H_4	Ph	H	$AgNO_3$	70	209
m-$NO_2C_6H_4$	Et	H	$AgNO_3$	90	209
m-$NO_2C_6H_4$	Allyl	H	$AgNO_3$	75	209
m-$NO_2C_6H_4$	CH_2CH_2OH	H	$AgNO_3$	75	209
m-$NO_2C_6H_4$	Ph	H	$AgNO_3$	82	209
m-$NO_2C_6H_4$	S-Bu	S-Bu	$AgNO_3$	90	209
o-$NO_2C_6H_4$	Et	H	$AgNO_3$	87	209
p-$NO_2C_6H_4$	Ph	H	$AgNo_3$	60	209

Another facile synthesis of *N,N*-dialkylpropanesulphenamides and benzenesulphenamides starting from symmetrical disulphides was reported by Ikehira and Tanimoto[240]. It involves the reaction of primary or secondary lithium alkyl amines with a disulphide in THF (equation 164). Since starting materials are relatively inexpensive and easily available and the yields of sulphenamides are satisfactory (see Table 17), this procedure is of great preparative value.

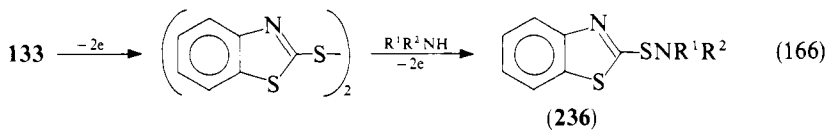
$$RSSR + LiNR^1R^2 \longrightarrow RSNR^1R^2 + LiSR \qquad (164)$$

$$R = Ph$$
$$R = Pr$$

g. Synthesis from thiols. Carr and coworkers[202] were the first to show that thiazolyl mercaptides **133** and **235** react with amines in the presence of an oxidizing agent to afford the corresponding sulphenamides **236** or **237**, respectively (equation 165). Later on, this approach was extended for the preparation of sulphenamides **238** and **239**[241]. As oxidizing agents iodine in aqueous potassium iodide solution (Method I), air-diluted chlorine(II) and sodium hypochlorite(III) were used (for details see Table 18). Very recently, a series of benzothiazole-2-sulphenamides **236** was prepared by the electrolytic cross-coupling reaction of 2-mercaptobenzothiazole **133** with various amines (equation 166, Table 19)[242]. An interesting method of synthesis of sulphenamides **240**, in which thiols are used as substrates, has been reported by Saegusa and collaborators[243] who found that copper(I) salts effectively catalyse the reaction of azides **241** with thiols giving sulphenamides **240**, primary amines and disulphides (equation 167). The yields in this reaction depend primarily upon the nature of the thiol. In the case of alkanethiols, sulphenamides **240** are the main products (64–77% yield), while in the case of aromatic thiols only primary amines and disulphides were isolated as the reaction products.



(165)



(166)

TABLE 18. Synthesis of thiazole-2-sulphenamides, T-SNR^{1}R^2, from thiazole thiols, T-SH, and amines, HNR^{1}R^2

Thiazole	R^1	R^2	Method	Yield (%)	Ref.
Benzothiazole	Me	H	II	68	202
Benzothiazole	Me	Me	I	39	202
Benzothiazole	Me	Et	I	79	202
Benzothiazole	Et	Et	I	55	202
Benzothiazole	Pr	H	I	77	202
Benzothiazole	Bu	H	I	64	202
Benzothiazole	CH_2CH_2OH	H	I	a	202
Benzothiazole	*c*-C_6H_{11}	H	I	96	202
Benzothiazole	Ph	H	I	95	202
6-Nitrobenzothiazole	*c*-C_6H_{11}	H	III	*a*	202
8-Chlorobenzothiazole	$-(CH_2)_2O(CH_2)_2-$		I	58.5	241
8-Chlorobenzothiazole	*t*-Bu	H	I	64.5	241
8-Chlorobenzothiazole	*i*-Pr	H	I	92.6	241
8-Chlorobenzothiazole	CMe_2CH_2OH	H	I	36.8	241
4-Methylthiazole	*c*-C_6H_{11}	H	I	73	202
4-Ethylthiazole	*c*-C_6H_{11}	H	I	77	202
4,5-Dimethylthiazole	*c*-C_6H_{11}	H	I	95	202
4,5-Dimethylthiazole	*i*-Pr	H	I	80	202

[a] Not given.

TABLE 19. Benzothiazolyl-2-sulphenamides **236** prepared by electrolysis of 2-mercaptobenzothiazole with amines[245]

R	R^1	Yield (%)
Pr	H	98
i-Pr	H	93
t-Bu	H	90
$-(CH_2)_2O(CH_2)_2-$		97
$-(CH_2)_5-$		96
$-(CH_2)_4-$		92
Et	Et	89
i-Pr	*i*-Pr	25

$$\underset{\textbf{(241)}}{RN_3} + R^1SH \xrightarrow{Cu(I)} \underset{\textbf{(240)}}{RNHSR^1} + RNH_2 + (R^1S)_2 \qquad (167)$$

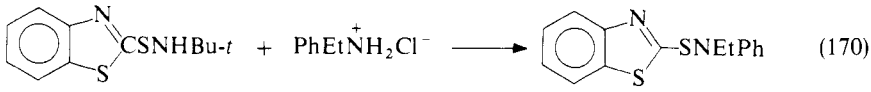
(**a**) $R = CH_2CO_2Bu-t$ $R^1 = Bu-t$, $PhCH_2$
(**b**) $R = CO_2Bu-t$ $R^1 = Ph$

Direct condensation of cyclohexanethiol with *N*-chlorophthalimide was reported to give the sulphenamide **242** in 60% yield (equation 168)[244].

(242) (168)

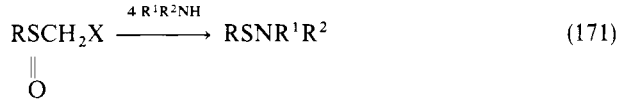
h. Miscellaneous methods. In the patent literature there are some reports on the synthesis of sulphenamides based on a transamination reaction. Thus, heating benzothiazole-2-sulphenamide **132** or **236** with dicyclohexylamine results in the formation of the product of transamination **243** in 93% yield (equation 169)[245]. Reaction of benzothiazole-2-*N*-*tert*-butylsulphenamide **244** with *N*-ethylaniline hydrochloride affords the sulphenamide **245** in 93% yield (equation 170)[246].

(132) R = H
(236) R = Me
(243) (169)



(244) (245) (170)

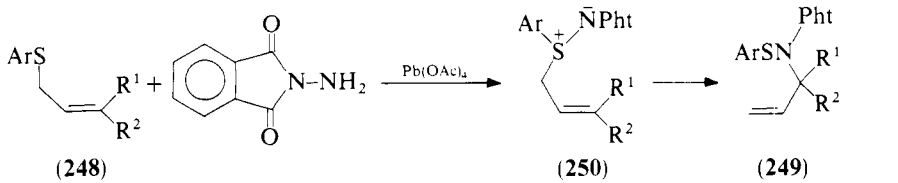
Treatment of α-halomethyl aryl(methyl) sulphoxides **246** with morpholine, piperidine or diethylamine was reported[247] to give the corresponding sulphenamide **247** in nearly quantitative yields (equation 171). Reaction of *N*-nitrenes, generated *in situ* from *N*-aminophthalimide, with allyl aryl sulphides **248** was found to give *N*-allyl-*N*-phthalimidoyl sulphenamides **249** via the ylide **250** which undergoes a [2,3]-sigmatropic rearrangement (equation 172)[248].



(171)

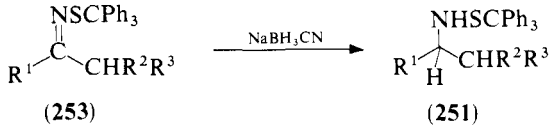
(246)
(a) R = *p*-Tol, X = Br
(b) R = *p*-Tol, X = Cl
(c) R = Me, X = Cl

(247)
R^1R^1 = morpholino
R^1R^2 = piperidino
$R^1 = R^2$ = Et

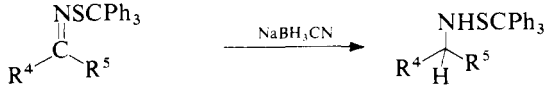


(248) (250) (249) (172)

Very recently, a few triphenylmethanesulphenamides **251** and **252** were prepared by reduction of tritylsulphenimine **253** or **254** using sodium cyanoborohydride and trifluoroacetic acid at pH = 3–6 in THF (equation 173)[213]. Alkylation of the lithiated tritylsulphenimines **253** at −20 °C produced the corresponding sulphenamides **255** in 48–63% yield (equation 174)[213].

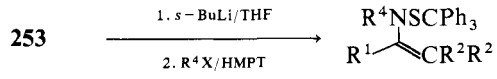


(253) (251)



(254) (252)

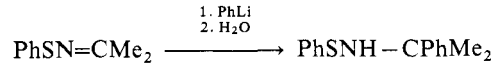
(173)



(255)

(174)

2-Phenyl-2-aminopropylbenzenesulphenamide **256** was obtained in 60% yield by addition of phenyllithium to an ethereal solution of *N*-isopropylidenebenzenesulphenimine **257** at 0 °C (equation 175)[249].



(257) (256)

(175)

B. Synthesis of Acyclic Sulphenimines

1. Synthesis from primary sulphenamides

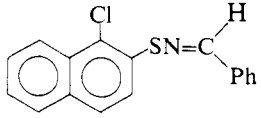
Primary sulphenamides are capable of reacting with carbonyl compounds as aminating reagents to form the corresponding Schiff bases (equation 176). This reaction constitutes the oldest method which has been applied for the synthesis of acyclic sulphenimines. Busch[201] in 1896 found that heating the sulphenamide **130** with benzaldehyde gave *N*-benzylidenesulphenimine **258** (equation 177).

(176)

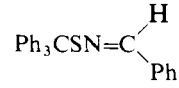
(258)

(177)

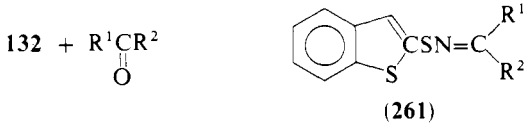
Later, Zincke prepared[250] in the same way benzylidenesulphenimine **259** and Vorländer[212] benzylidenesulphenimine **260**. Condensation of primary sulphenamide **132** with carbonyl compounds gave high yields of benzylidene-2-benzothiazolylsulphenimines **261** (equation 178)[251].



(259)



(260)

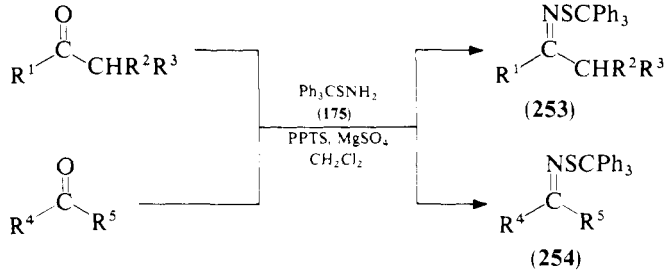


(178)

(261)

	R^1	R^2
(a)	H	Ph
(b)	H	$2\text{-}NO_2C_6H_4$
(c)	H	$4\text{-}NO_2C_6H_4$
(d)	H	$p\text{-}MeOC_6H_4$
(e)	H	CH=CHPh
(f)	Me	Me
(g)	$-(CH_2)_5-$	
(h)	$-(CH_2)_4-$	
(i)	$-CH_2-CH_2-$	

Branchaud[213] prepared a series of tritylsulphenimines **253** and **254** by reacting sulphenamide **175** with a variety of carbonyl compounds in CH_2Cl_2 with anhydrous magnesium sulphate as a drying agent and pyridinium *p*-toluenesulphonate (PPTS) as a catalyst (equation 179; see Tables 20 and 21).



(253)

(254)

(179)

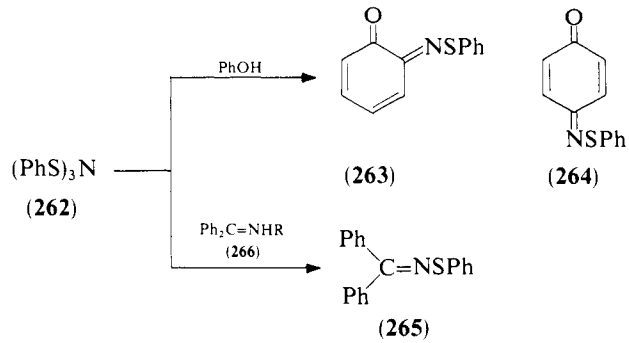
Barton and coworkers reported that the reaction of tris-(benzenesulphen)-imide **262** with phenol gave the mixture of isomeric sulphenimines **263** and **264**[252], while the reaction with hydrazones **266** afforded in 45% yield sulphenimine **265** (equation 180)[253].

TABLE 20. Synthesis of tritylsulphenimines **253** from carbonyl compounds[213]

Symbol	R^1	R^2	R^3	Yield (%)
253a	H	Me	H	96
253b	H	C_8H_{17}	H	98
253c	Me	H	H	98
253d	Me	Me	H	97
253e		$-(CH_2)_4-$	H	96
253f		$-(CH_2)_4-$	Me	98
253g	Me	CO_2Me	H	100
253h	Me	CO_2Et	H	100
253i	Me	$(CH_2)_2OSiMe_2Bu\text{-}t$	H	70

TABLE 21. Synthesis of tritylsulphenimines **254** from carbonyl compounds[213]

Symbol	R^4	R^5	Yield (%)
254a	H	CH=CHMe	92
254b	H	$CH=CMe_2$	92
254c	H	Ph	98
254d	H	*p*-$MeOC_6H_4$	89
254e	Me	Ph	59



(180)

Triphenyl phosphine reacts[253] with sulphenimide **262** in the presence of aromatic aldehydes affording the corresponding *N*-arylidenebenzenesulphenimines **266** in good yields (61–78%) (equation 181).

$$\mathbf{262} + Ph_3P + ArCHO \longrightarrow \underset{\mathbf{(266)}}{PhSN{=}CHAr} \qquad (181)$$

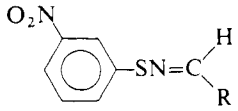
2. Synthesis from disulphides

Davis and coworkers have developed a versatile one-step synthesis of sulphenimines based on metal-assisted reaction of aromatic and aliphatic disulphides with ammonia and carbonyl compounds (equation 182)[209, 254]. When aromatic disulphides are used this procedure works well with aldehydes (yields in 60–97% range), less well with ketones (yields in 30–60% range) and fails with diaryl ketones. Sterically hindered aliphatic ketones were found to give also low yields or fail to react (e.g. camphor). The sulphenimines **267–271** listed below were prepared using this method. In the case of aliphatic disulphides, sulphenimines can be prepared according to this procedure only when the disulphide alkyl groups are unbranched and an aromatic residue is attached to the carbonyl carbon. The yields of the sulphenimines **272–275** prepared in this way are generally low (17–30%).

$$RSSR + R^1CR^2 + MX + NH_3 \longrightarrow RSN{=}C\begin{matrix}R^1\\R^2\end{matrix} + MSR + NH_4X + H_2O \quad (182)$$

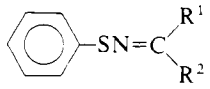
(O)

$MX = AgNO_3, HgCl_2$



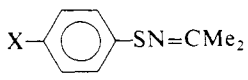
(**267**)

	R
(**a**)	Me
(**b**)	*i*-Pr
(**c**)	Ph
(**d**)	4-$NO_2C_6H_4$
(**e**)	4-$MeOC_6H_4$



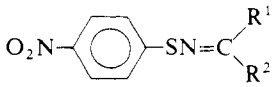
(**268**)

	R^1	R^2
(**a**)	Me	Me
(**b**)	Me	Et
(**c**)	Me	*i*-Pr
(**d**)	Me	Ph
(**e**)	$-(CH_2)_5-$	



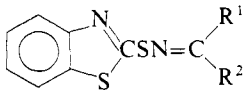
(**269**)

	X
(**a**)	H
(**b**)	Cl
(**c**)	Br
(**d**)	NO_2



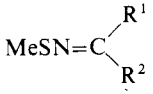
(**270**)

	R^1	R^2
(**a**)		$-(CH_2)_5-$
(**b**)	H	4-$Me_2NC_6H_4$



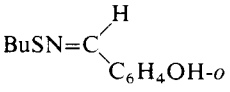
(**271**)

	R^1	R^2
(**a**)	Me	Me
(**b**)	H	Ph
(**c**)	$-(CH_2)_5-$	

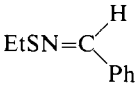


(272)

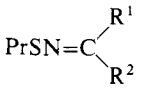
	R^1	R^2
(a)	H	Ph
(b)	H	2-HOC_6H_4



(273)



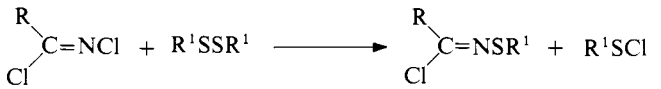
(274)



(275)

	R^1	R^2
(a)	H	Ph
(b)	H	2-HOC_6H_4
(c)	Me	Ph

A few α-chlorosulphenimines **276** were prepared by the reaction of *N*-chloro formimidoyl chlorides **277** with dimethyl disulphide and diphenyl disulphide (equation 183)[255].

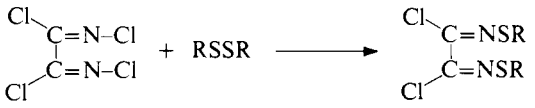


(183)

(277) (276)

	R	R^1	Yield (%)
(a)	Cl	Me	87
(b)	Cl	Ph	90
(c)	CCl_3	Me	84
(d)	CCl_3	Ph	83
(e)	CN	Me	63
(f)	CN	Ph	81
(g)	CCl_2CN	Me	94
(h)	CCl_2CN	Ph	72

Bifunctional *N*-chloro formimidoyl chlorides **278** and **279** react in an analogous way to form sulfenimines **280** and **281** (equations 184 and 185)[255].



(184)

(278) (280)

(a) R = Me (62%)

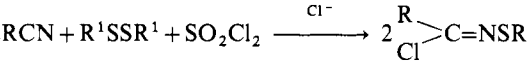
(b) R = Ph (54%)

(279) (281)

(a) R = Me (47%)
(b) R = Ph (60%)

(185)

Comparable yields of **276** are obtained when sulphuryl chloride is added to a mixture of the nitrile and disulphide in the presence of catalytic amounts of chloride anion (equation 186)[255].

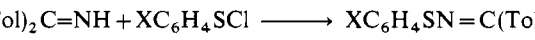


(276)

(186)

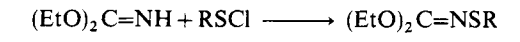
3. Synthesis from sulphenyl chlorides

Davis and Kluger[256] reported the synthesis of two sulphenimines **282** which were prepared by condensation of unsubstituted *p*-tolueneimine with sulphenyl chlorides (equation 187). Condensation of sulphenyl chlorides with iminocarbonates **283**, monothioiminocarbonates **284** and dithioiminocarbonates **285** in the presence of pyridine afforded the corresponding sulphenimine derivatives **286–288** (equations 188–190)[257]. An interesting conversion of the cephalosporine amine **289** into the corresponding sulphenimine derivative **290** was reported by Gordon and collaborators (equation 191)[258].



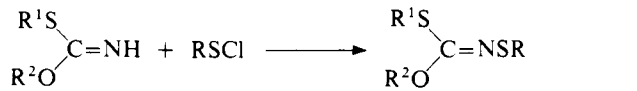
(282)
(a) X = H
(b) X = NO_2

(187)



(283) (286)
(a) R = 2-$NO_2C_6H_4$
(b) R = 2,4-$(NO_2)_2C_6H_3$
(c) R = *i*-Pr

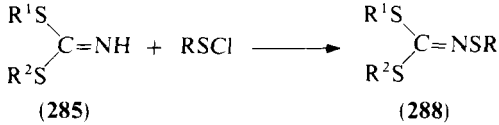
(188)



(284) (287)

(189)

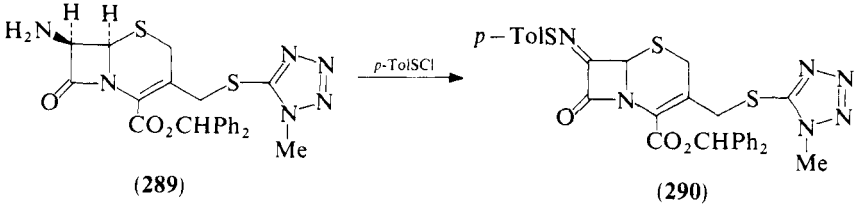
	R	R^1	R^2
(a)	2-$NO_2C_6H_4$	Me	Me
(b)	2,4-$(NO_2)_2C_6H_3$	Me	Me
(c)	2-$NO_2C_6H_4$	Ph	Me



(190)

(285) (288)

	R	R^1	R^2
(a)	2-$NO_2C_6H_4$	$PhCH_2$	$PhCH_2$
(b)	2-$NO_2C_6H_4$	$PhCH_2$	*i*-Pr
(c)	2-$NO_2C_6H_4$	Me	Et
(d)	2-$NO_2C_6H_4$	Me	*i*-Pr
(e)	2-$NO_2C_6H_4$	Me	$PhCH_2$

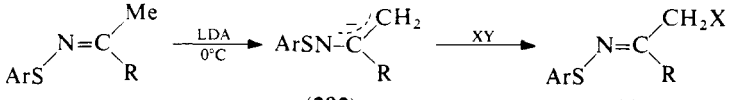


(289) (290)

(191)

4. Miscellaneous methods

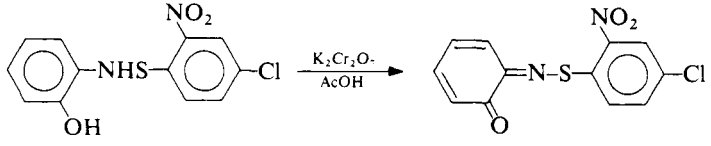
A number of sulphenimines **291** were prepared by reaction of the sulphenimine anion **292** with electrophiles such as alkyl halides, carbonyl compounds and aryl disulphides. In each case new α-substituted sulphenimine derivatives **291** were formed in good yields[259] (equation 192). It was reported[260] that oxidation of sulphenamide **294** with potassium dichromate in acetic acid gave sulphenimine **295** (equation 193). A chromium complex of sulphenimine **296** was prepared by an analogous oxidation of the corresponding sulphenamide **297** (equation 194)[261]. The preparation of sulphenimine **298** was based on a similar oxidation procedure[262].



(192)

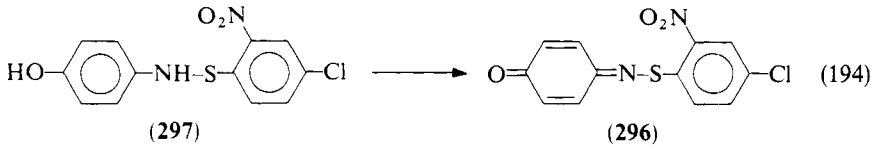
(293) (292) (291)

R = Me, Et X = Me, $PhCH_2$, Ph_2COH PhS

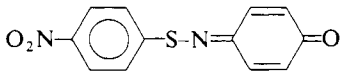


(193)

(294) (295)

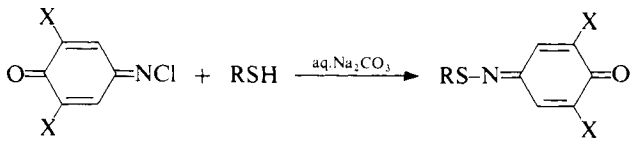


(297) (296) (194)



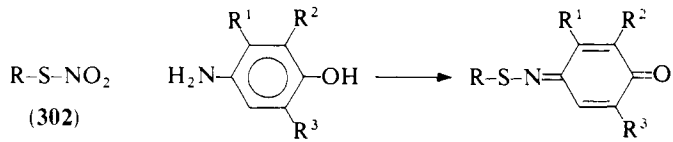
(298)

A few quinonesulphenimines **299** were prepared[263] by reaction of *N*-chloroquinoneimines **300** with a variety of aromatic thiols dissolved in sodium carbonate solution (equation 195). Recently, the synthesis of quinonesulphenimines **301** was reported which involves the reaction of *t*-alkyl thionitrates **302** with *p*-aminophenols **303** (equation 196)[264].



(300) (299) (195)

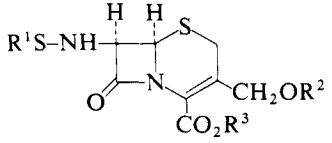
	X	R
(a)	H	Ph
(b)	Cl	CH_2Ph
(c)	Cl	Ph
(d)	Cl	-$AcNHC_6H_4$
(e)	Br	EtOC(S)–



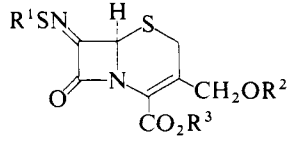
(302) (303) (301) (196)

	R	R^1	R^2	R^3
(a)	*t*-Bu	H	H	H
(b)	*t*-Bu	Me	H	H
(c)	*t*-Bu	H	Me	Me
(d)	*t*-Bu	H	Cl	Cl
(e)	*t*-Amyl	H	H	H
(f)	*t*-Heptyl	H	H	H
(g)	*s*-Bu	H	Cl	Cl

Oxidation of cephalosporinesulphenamides **304** with reagents such as manganese dioxide, trichloroisocyanuric acid, *N*-chlorosuccinimide and *t*-butyl hypochlorite was found by Kobayashi and coworkers[265] to give the corresponding sulphenimines **305** in 68–86% yield (equation 197). These authors[265] also described the synthesis of sulphenimine **305b** in 54% yield by treatment of sulphinamide **306** with thionyl chloride in quinoline at 0 °C.

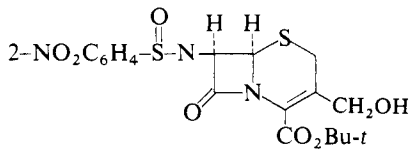


(304)



(305) (197)

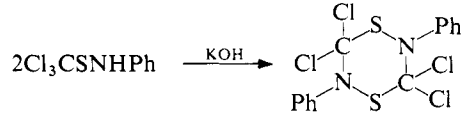
	R^1	R^2	R^3
(a)	Ph	H	*t*-Bu
(b)	2-$NO_2C_6H_4$	H	*t*-Bu
(c)	4-$NO_2C_6H_4$	H	*t*-Bu
(d)	2,4-(NO_2)-C_6H_3	H	*t*-Bu
(e)	Cl_5C_6	H	*t*-Bu
(f)	2-$NO_2C_6H_4$	OAc	$CHPh_2$



(306)

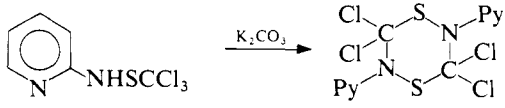
C. Synthesis of Cyclic Sulphenamides and Sulphinimines

Cyclic sulphenamides have been known since 1873 when Rathke[191] observed that trichloromethanesulphenanilide **124** formed, on treatment with potassium hydroxide solution, a new compound for which the structure of the cyclic sulfenamide **307** was later assigned (equation 198)[266].



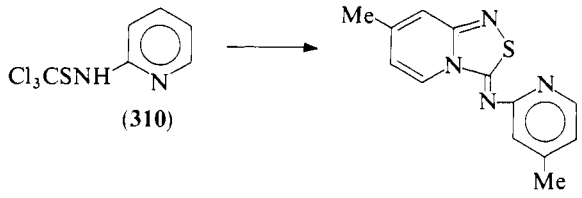
(124) (307) (198)

Under the same conditions *N*-pyridyl trichloromethanesulphenamide **308** was found to give the cyclic sulphenamide **309** in 12% yield (equation 199)[267].



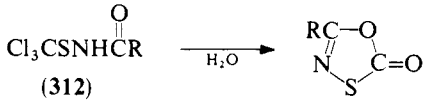
(308) (309) (199)

It was also shown that sulphenamide **310** is able to undergo ring-closure reaction to form the bicyclic sulphenimine derivative **311** (equation 200)[268].



(310) (311) (200)

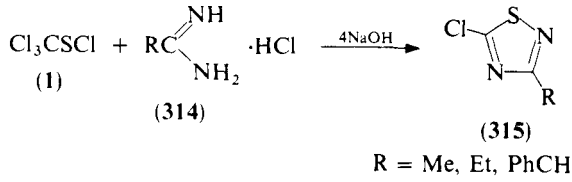
N-Acyl trichloromethanesulphenamides **312** undergo an easy cyclization to 1,3,4-oxathiazol-2-ones **313** on heating with a mixture of an organic acid and water (equation 201)[269].



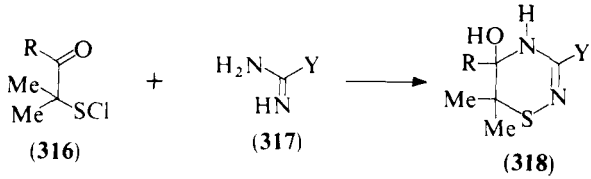
(312) (313) (201)

	R	Yield (%)
(a)	Ph	89
(b)	*m*-Tol	87
(c)	*p*-Tol	87
(d)	2,4-$Me_2C_6H_3$	85
(e)	2,5-$Me_2C_6H_3$	85
(f)	2-ClC_6H_4	81
(g)	3,5-$Cl_2C_6H_3$	69
(h)	2.4-$Cl_2C_6H_3$	92
(i)	3-Cl-4-Me-C_6H_3	98
(j)	3-$NO_2C_6H_4$	89
(k)	α-Naphthyl	74
(l)	$-(CH_2)_6-$	82

Trichloromethanesulphenyl chloride **1** reacts with hydrochlorides of amidines **314** in the presence of four equivalents of sodium hydroxide to give a 5-chloro-3(aryl or alkyl) 1,2,4-thiadiazole system **315** in 40–70% yield (equation 202)[270]. Reactions of β-ketosulphenyl chloride **316** with amidines or *S*-alkylthioureas **317** produce other cyclic sulphenimine systems **318** (equation 203)[271]. Several cyclic sulphenamide derivatives were prepared by the ring-closure reactions of chlorocarbonylsulphenyl chloride **319** with other bifunctional reactants. Thus, primary amides **320** undergo *N*-sulphenylation and simultaneous ring closure with **319** to form S-substituted 1,3,4-oxathiazole-2-ones **313** (equation 204)[272]. *N,N'*-Disubstituted ureas **321** react with **319**, not in the enol form but in the keto form, which results in the formation of 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-diones **322** (equation 205)[273]. An alternative synthesis of **322** is the addition of sulphenyl chloride **319** to carbodiimides **323** followed by hydrolysis of the intermediate 3-chloro-5-oxathiadiazolinium chlorides **324** (equation 205a)[273].



(202)

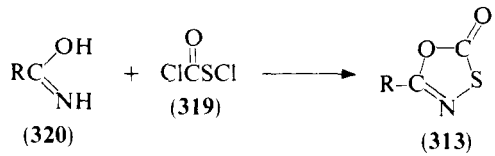


(203)

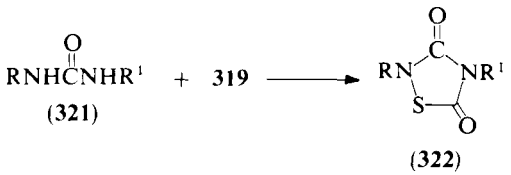
(a) R = H
(b) R = Me

(a) Y = Me
(b) Y = Ph
(c) Y = SMe
(d) Y = SBu

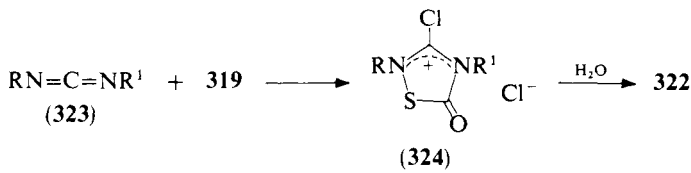
(a) R = H, Y = Me
(b) R = H, Y = Ph
(c) R = H, Y = SMe
(d) R = H, Y = SBu
(e) R = *i*-Pr, Y = Me



(204)

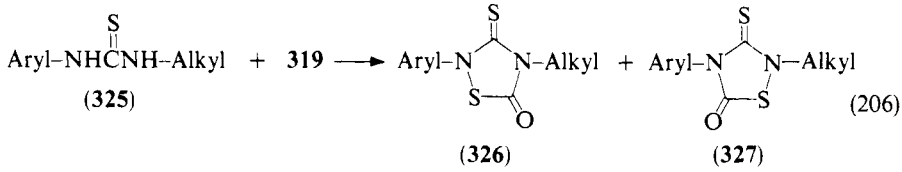


(205)

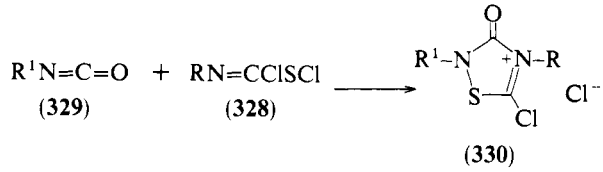


(205a)

In contrast to equation 205, the reaction of *N*-alkyl-*N'*-arylthioureas **325** with **319** leads to a mixture of isomers **326** and **327** in which the cyclic sulphenamide component **326** strongly predominates (equation 206)[272]. Some heterocyclic systems, which may be considered as cyclic sulphenamide(imide) derivatives, were obtained when iminochloromethanesulphenyl chlorides **328** were reacted with certain compounds containing the C–N multiple bond. Thus, with isocyanates **329** they form sparingly soluble but very reactive 3-oxo-thiadiazolinium chlorides **330** (equation 207)[273]. Hydrolysis of the latter

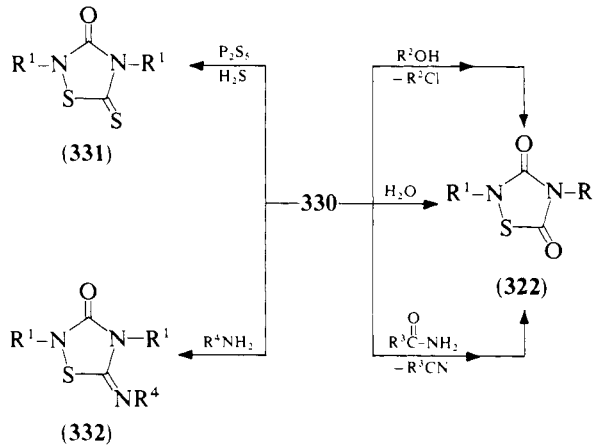


(206)



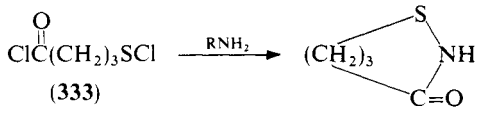
(207)

yields 1,2,4-thiadiazolidine-3,5-diones **322**, which also result from the reaction of **330** with alcohols (elimination of chloroalkane) or with primary amides (elimination of the nitrile). In the reaction of **330** with hydrogen sulphide or with phosphorus pentasulphide, the corresponding 3-oxo-5-thioxo-1,2,4-thiadiazolidines **331** are formed. Aminolysis of **330** with primary aliphatic or aromatic amines leads to 5-imino-3-oxo-1,2,4-thiadiazolidines **332** (Scheme 1)[273].



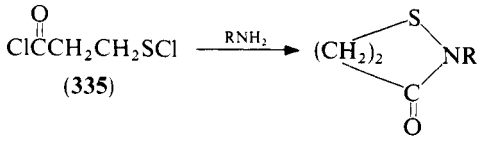
SCHEME 1

Condensation of 3-chloroformylpropanesulphenyl chloride **333** with ammonia and primary amines was reported to give the 1,2-thiazin-2-one system **334** in high yield (equation 208)[274]. Analogous condensations of sulphenyl chlorides **335** and **336** gave the cyclic sulphenamides **337** and **338**, respectively (equations 209 and 210)[275, 276]. Aromatic bifunctional sulphenyl chlorides **339** react in the same way to give the cyclic sulphenamides **340** (1,2-benzisothiazolin-3-ones) (equation 211)[277–279]. A general synthesis of 2-substituted 1,2-benzisothiazolin-3-ones via cyclization of N-substituted 2-methoxycarbonylbenzenesulphenamides has been reported by Grivas[280]. He used as a starting material dimethyl 2,2′-dithiobenzoate **341** which, with bromine, chlorine or sulphuryl chloride,



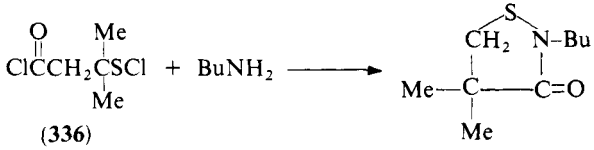
(333) (334) (208)

R = H or Ph,Me,Bu

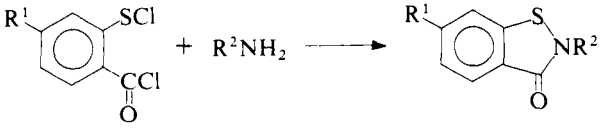


(335) (337) (209)

R = H,Me,Bu,Ph



(336) (338) (210)

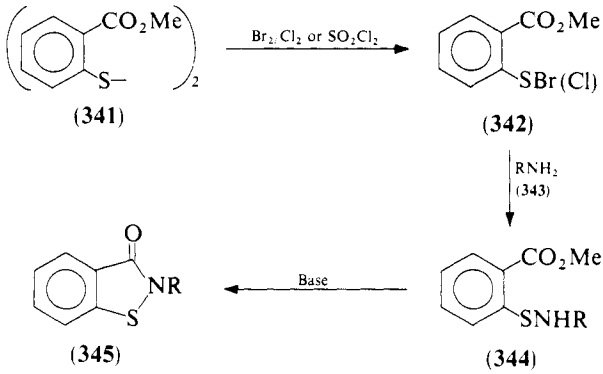


(339) (340) (211)

	R^1	R^2
(a)	$CO-C_6H_4-NO_2$	H
(b)	Cl	Bu
(c)	NO_2	H

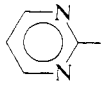
gave sulphenyl halides **342**. These, in turn, without isolation were allowed to react with primary aliphatic, aromatic and heterocyclic amines **343** to yield N-substituted 2-methoxycarbonylbenzenesulphenamides **344**. The latter underwent base-catalysed cyclization affording 2-substituted 1,2-benzoisothiazolin-3-ones **345** in good to excellent yields (see Table 22 and Scheme 2).

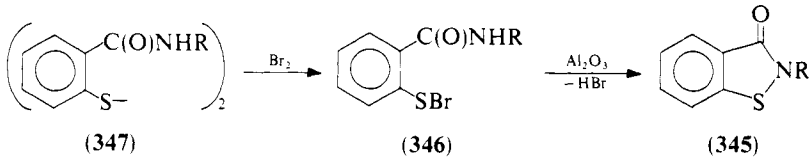
An improved method for the preparation of **345** based on a novel cyclization of N-substituted 2-carbamoylbenzenesulphenyl bromides on activated basic alumina has been reported by Kamigata and coworkers[281]. They found that sulphenyl bromides **346** prepared by bromination of the corresponding disulphides **347** could be easily converted to **345** in yields above 84% when activated basic alumina was used in the dehydrobromination step (Scheme 3). Another route to **345** based on the Pummerer-type rearrangement of 2-(methylsulphinyl)benzamides **348** taking place in the presence of thionyl chloride has been reported by Uchida and Kozuka[282], who found that benzamides **348** prepared by



SCHEME 2

TABLE 22. Preparation of 1,2-benzoisothiazolin-3-ones **345** from sulphenamides **344**[280]

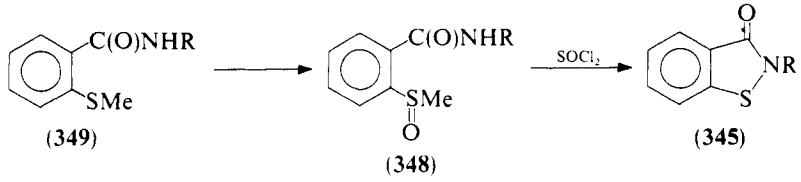
345	R	Solvent	Base	Yield (%)
a	$PhCH_2$	MeOH	MeONa	92
b	Pr	MeOH	MeONa	72
c	$CH_2CH{=}CH_2$	MeOH	KOH	56
d	$HOCH_2CH_2$	MeOH	Triton B	72
e	Ph	*i*-PrOH	*i*-PrONa	82
f	*p*-ClC_6H_4	MeOH	MeONa	92
g	*p*-$MeOC_6H_4$	EtOH	MeONa	85
h	*o*-MeC_6H_4	MeOH	MeONa	87
i		EtOH	MeONa	70



(**a**), (**e**), (**f**), (**g**) and
(**k**) R = *p*-Tol
(**l**) R = *p*-CNC_6H_4
(**m**) R = R = *c*-C_6H_{11}
(**n**) R = *t*-Bu
(**o**) R = Et

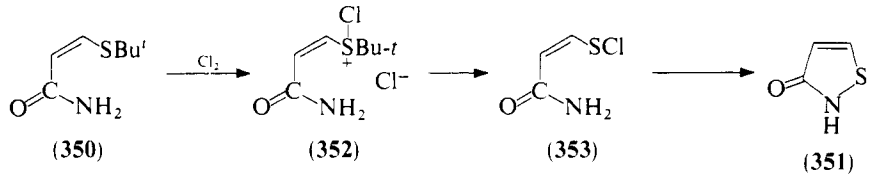
SCHEME 3

the oxidation of the corresponding sulphides **349** form sulphenimines **345** when refluxed for a short time with thionyl chloride in dry dichloromethane (equation 212). *Cis*-(3-*t*-butylthio)acrylamide **350** was converted by treatment with chlorine to 3-isothiazolone



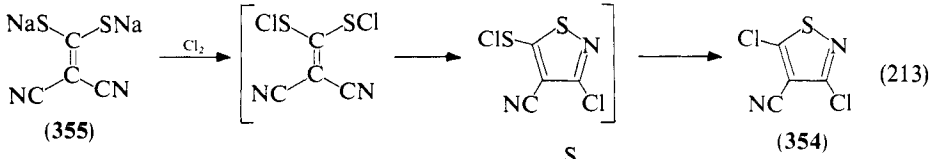
(212)

351. It was proposed[283] that this conversion may follow a pathway shown in Scheme 4. The formation of the chlorosulphonium chloride **352** in the initial step can be succeeded by fragmentation to a vinylsulphenyl chloride **353** which undergoes internal nucleophilic attack by the amide nitrogen to form the final product **351**.

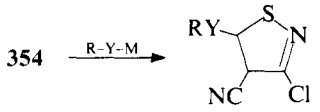


SCHEME 4

3,5-Dichloro-4-isothiazolecarbonitrile **354** has been prepared by treatment of disodium salt of malononitrile **355** with an excess of chlorine in boiling carbon tetrachloride (equation 213)[284]. Nucleophilic reagents replace, under mild conditions, the chlorine atom in the 5-position of **354** and in this way a series of 5-substituted 3-chloro-4-isothiazolecarbonitriles **356–358** were prepared from amines, alkoxides, phenolates and anionic sulphur reagents (Scheme 5)[284]. As early as 1923 the preparations of cyclic sulphenimines **359** and **360** were reported by Fries and Schurmann[285]. They found that aminolysis of *ortho*-substituted sulphenyl bromide **361** gave **359** (equation 214) while heating the primary sulphenamide **144** in acetic acid afforded **360** (equation 215)[285].



(213)

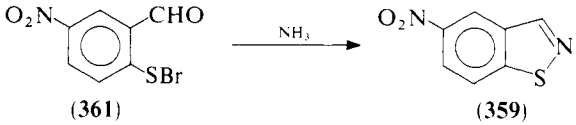


356: Y = O; M = Na; R = Me, Et, $PhCH_2$, Ph, *p*-ClC_6H_4

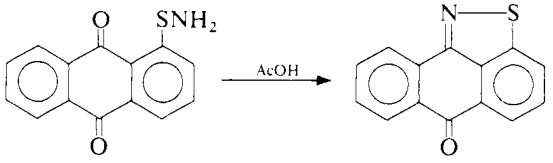
357: Y = NH, NMe; M = H; R = H, NH_2, Me, Ph

358: Y = S; M = Na; R = Me, Et, Ph, Me_2N–C(S), EtOC(S)

SCHEME 5



(361) (359) (214)



(144) (360) (215)

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The Chemistry of Sulphenic Acids and their Derivatives
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CHAPTER 7

Acidity, hydrogen bonding and complex formation

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I. SULFENIC ACIDS

A. Acidity

There is a unique aspect of simple sulfenic acids compared with any other type of common acid. This is the fact that the anhydride in equation 1, which has the thiolsulfinate form **2**, is thermodynamically much more stable than the parent acid **1**. A value of the equilibrium constant K higher than 10^6 has been estimated[1] for the reaction of equation 1 (R = Ph) in 60% aqueous dioxane (v/v) at 40 °C. Kice[2] pointed out that 'if the same stability relationship between acid and anhydride were to exist for carboxylic

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acids, acetic acid would spontaneously dehydrate to acetic anhydride!'.

$$2\,RSOH \overset{K}{\rightleftharpoons} R\overset{O}{\overset{\|}{S}}—SR + H_2O \qquad (1)$$

(**1**) 'acid' (**2**) 'anhydride'

Owing to the fact that thiosulfinate (**2**) formation[3], or further disproportionation reactions[4], prevail over the proton transfer equilibrium (equation 2), pK_{AH} values of simple sulfenic acids are not known with any certainty. However, it has been clearly shown[5,6] that **1** (R = Me, Ph) readily exchanges its proton with D_2O to give RSOD. Facile H/D exchange is also implied[7,8a] for the sulfenic acid forms believed to be in thermal equilibrium with penicillin sulfoxides.

$$RSOH \rightleftharpoons RSO^- + H^+ \qquad (2)$$

(**1**) (**3**)

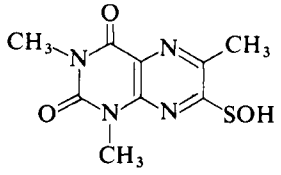
IR spectra of two sulfenic acids **1**, R = Ph and *t*-Bu, generated by flash vacuum pyrolysis show[6] that these acids can exist in both the O (**1**) and S (**4**) protonated forms at −197 to −50 °C. However, this does not seem to be the general situation (see[5], for example, R = Me), at least in solution[8b], and sulfenic acids are generally considered[2] as oxygen acids.

R—S—O—H R—S(O)H

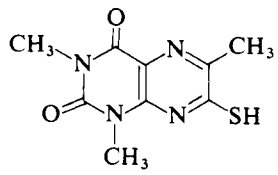
(**1**) (**4**)

It has long been known[9] that for oxygen acids containing elements of variable oxidation levels (N, S, P etc.) acid strength is determined to a great extent by the number of nonhydroxylic oxygen atoms present in the molecule. For example, sulfinic acids in water are some four pK_{AH} units weaker than their sulfonic acid analogues (Table 1). Sulfenic acids (**1**) that possess no nonhydroxylic oxygen atoms should accordingly be weaker than sulfinic acids. Aromatic sulfenic acids are believed to be *at least* as acidic as phenols, being completely converted to their anions in dilute base (pH ≃ 12).

The pK_{AH} of 1,3,6-trimethyllumazine-7-sulfenic acid, which in solution prefers[8b] the O-protonated form (**5**), has been measured[10] spectrophotometrically in water and found to be 4.48.



(**5**) $pK_{AH} = 4.48$



(**6**) $pK_{AH} = 2.29$

This relatively high acidity is certainly not 'typical' of aromatic sulfenic acids due to the strong electron-withdrawing effect of the 'aza'-activated moiety in **5**. However, if one assumes that ΔpK_{AH} [i.e. $pK_{AH}(PhSOH) - pK_{AH}(\mathbf{5})$] is the same as that existing for the

TABLE 1. Acid strengths[a] of sulfinic and sulfonic acids

Sulfinic acid	pK_{AH}	Sulfonic acid	pK_{AH}	ΔpK_{AH}
$MeSO_2H$	2.28	$MeSO_3H$	−1.9	4.2
$PhSO_2H$	1.21	$PhSO_3H$	−2.8	4.0
$4\text{-}O_2NC_6H_4SO_2H$	0.64	$4\text{-}O_2NC_6H_4SO_3H$	−3.8	4.4
$4\text{-}MeC_6H_4SO_2H$	1.24	$4\text{-}MeC_6H_4SO_3H$	−2.7	3.9

[a] Values at 25 °C in water taken from Reference 9.

corresponding thiols [i.e. $pK_{AH}(PhSH)^{11} - pK_{AH}(\mathbf{6})^{10}$], a value of pK_{AH} equal to 8.80 can be estimated for PhSOH in water. This value is probably somewhat too high as the transmission of the 'substituent' effect should be more effective in aromatic thiols[11] ($\rho = 1.81$) than in aromatic sulfenic acids [cf. $\rho = 0.67$ for ArS(O)OH as estimated from Table 1]. In addition, the observed[10] acidity difference between **5** and **6** could be partly due to intramolecular hydrogen bonding being more important for **5** than for **6**.

Values of pK_{AH} in the range 7 to 10 for simple aromatic and aliphatic sulfenic acids can probably also be obtained by considering that they are the thio analogues of hydroperoxides. Hydroperoxy compounds are by four to five pK_{AH} units stronger acids[9] than the corresponding alcohols in water and values close to 11.5 are common for simple aliphatic hydroperoxides (see Table 2), while typical aliphatic and aromatic thiols have pK_{AH} values close to 10.5 and 6.5, respectively[9], in water at 25 °C.

Sulfenic acids behave as basic species[12, 13] when treated with strong acids and are considered only slightly less basic than the corresponding sulfenate esters[12] (see Section III). Their conjugate acids, $RSOH_2^+$, are generally written[2, 13b] as oxygen-protonated species, but there is no firm evidence for that being necessarily the case, as chemical reactions again prevail over simple proton transfer equilibria.

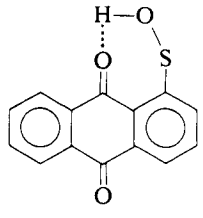
TABLE 2. Effect of additional oxygen atom on alcohol acid strength[a]

Hydroperoxy compounds	pK_{AH}	Analogous alcohol	pK_{AH}	ΔpK_{AH}
t-BuOOH	12.8	*t*-BuOH	19.2	6.4
i-PrOOH	12.1	*i*-PrOH	17.1	5.0
H-OOH	11.6	HOH	15.7	4.1
EtOOH	11.8	EtOH	15.9	4.1
MeOOH	11.5	MeOH	15.5	4.0
CF_3OOH	6.4	—	—	—

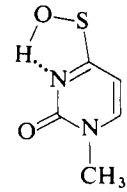
[a] Values in water taken from Reference 9.

B. Hydrogen Bonding

Intramolecular hydrogen bonding is probably the main cause of the relatively high stability of the few very special sulfenic acids proved capable of actual isolation[14], such as the anthraquinone derivative **7**, the pyrimidine derivative **8** and some similar derivatives[8, 15]. Indeed, in the absence of stabilizing factors sulfenic acids are elusive[2] species.

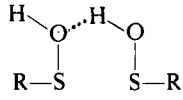


(7)



(8)

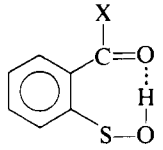
'*t*-Butylsulfenic acid' (2-methylpropane-2-sulfenic acid, *t*-BuSOH) (**9**) is also moderately stable in various solutions[16]. Its stability depends upon the solvent, and it is most stable[17] in polar solvents favoring H bonding. It is widely accepted[18-20] that a hydrogen-bonded dimer (**10**) is a prerequisite for thiolsulfinate (**2**) formation in the reaction of equation 1. Infrared evidence for the involvement of **10** in this reaction has recently been presented[6]. This is, *inter alia*, consistent with the observation that, in contrast to simple RSOH (**1**), their conjugate bases, RSO^- (**3**), are relatively stable[10, 20-22] in solution.



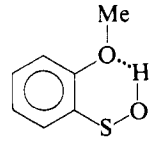
(10)

Intermolecular hydrogen bonding as in **10** should be particularly effective in lowering the potential energy or enthalpy of the reaction (equation 1). Therefore those features that inhibit[20] *inter*molecular hydrogen bonding, such as *intra*molecular hydrogen bonding as in **7**, **8** and similar derivatives[15]; steric hindrance[17, 19, 23] as in **9** and in 9-triptycenesulfenic acid[23]; reduced electron density on the sulfur atom[20] or hydrogen bonding with a polar solvent[17], will relatively reduce the propensity of **1** to display the reaction of equation 1.

The importance of intramolecular hydrogen-bonding ring size on the reactivity has also been considered[20]. Apparently a seven-membered ring as in **11** is more effective than a six-membered ring as in **12** at reducing the reactivity of **1**. However, this difference could also be due to different substituent electronegativity effects and no firm conclusions have been reached on this point.



(**11**) X = H, OMe, NEt_2



(12)

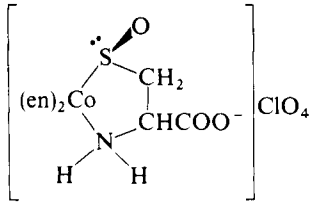
C. Complex Formation

There is a strong downfield shift of the ^{1}H-NMR signal of the *t*-Bu group of **9** on passing from nonaromatic to aromatic solvents[16]. This diamagnetic shift with aromatic solvents can be attributed[16] to π complexation between the acid (**9**) and the solvent

causing the *t*-Bu group to be deshielded. The effect of this complexation has been discussed in various publications[13a, 17–19, 21b] and is thought to be the main cause for **9** being more stable in aromatic than in nonaromatic nonpolar solvents. There is kinetic evidence of tight cation–molecule pairs between carbenium ions and benzenesulfenic acid, PhSOH. These species have been proposed[24, 25] as intermediates in the cleavage of protonated phenyl sulfoxides in concentrated perchloric acid.

Complexation of the potassium ion with the cryptand 18-crown-6 affects[26] oxygen and sulfur selectivity in the alkylation reaction of potassium anthraquinone-1 sulfenate in acetonitrile.

The first report[27] of a metal–sulfenato complex was by George and Watkins who prepared $IrCl_2(MeSO)(CO)(PR_3)_2$ by reaction of MeS(O)Cl with $IrCl(CO)(PR_3)_2$ where $PR_3 = PPh_3$ and PPh_2Me. It was subsequently discovered that controlled oxidation of thiols coordinated to cobalt(III) leads to coordinated, S-bonded sulfenic acids[28–32]. For example, oxidation of (cysteinato)-*N*,*S*-bis(ethylene diamine)cobalt(III) perchlorate, $[Co(en)_2(CyS)]ClO_4$, with H_2O_2 in a 1:1 molar ratio yielded[29] an orange solid formulated as **13**.



(**13**) en = ethylenediamine

The resultant sulfenato complexes [Co–S(O)R] are much more stable than the corresponding free sulfenic acids. In fact there is an increase[29] in ligand field strength in the series: [Co–SR], [Co–S(O)R], $[Co–S(O)_2R]$. This increase is associated with the rise in oxidation state and a corresponding decrease in the number of lone pairs on sulfur. Therefore sulfenato complexes provide a means of investigating[32] the chemistry of sulfenic acids and hopefully the potential role of protein sulfenic acids in enzyme-catalyzed oxidations.

By this oxidative route several bis(ethylenediamine)cobalt(III) complexes containing chelated, S-bonded sulfenic acid ligands have been synthesized and characterized[32, 33] by Deutsch and coworkers. The prototypes of their complexes are **14** and **15**. The visible-UV spectra of **14** and **15** are characterized by an intense charge-transfer band[34] at *ca* 360 nm which is diagnostic[32] for the S-bonded sulfenato moiety. In concentrated perchloric acid solutions the intensity of this band decreases and eventually disappears with increased acid concentration[34, 36]. S-bonded sulfenato ligands, [CoS(O)R], are protonated to form the corresponding coordinated sulfenic acids. This protonation is easier[35] than that of a coordinated thiolato ligand (Co–SR). Over relatively short time periods these are both reversible protonation reactions, and acid dissociation constants K_a for the following (protonated) complexes have been determined[32, 35] spectrophotometrically at 25 °C and

$[(en)_2Co(S(O)CH_2CH_2NH_2)]^{2+}$ (**14**)

$[(en)_2Co(S(O)CH_2COO)]^{+}$ (**15**)

the ionic strengths (μ) specified:

$[(en)_2Co(SCH_2CH_2NH_2)]^{2+}$ $K_a = 6.5 \pm 1.2$ $\mu = 8.0$

(16)

$[(en)_2Co(S(O)CH_2CH_2NH_2)]^{2+}$ $K_a = 0.69 \pm 0.09$ $\mu = 4.0$

(14)

It is believed[33,35] that the protonation site, as well as the coordination site[33] to 'hard' Lewis acids (e.g. BF_3) of **14** is the pendant oxygen atom, rather than the sulfur atom. On the other hand, palladium(II) and **14** interact[33] in dilute aqueous solutions to form a 1:1 adduct in which the 'soft' Lewis acid (as either $PdCl_4^{2-}$ or $[Pd(OH_2)_2]^{2+}$) coordinates the sulfur atom. Neither silver(I) nor mercury(II) bind detectably to S-bonded sulfenato ligands and this is presumably due[33] to a lesser affinity of Ag^+ and Hg^{2+} for sulfur coordination than that of Pd^{2+}.

Single-crystal X-ray structure analysis has been reported[32] for (2-sulfenatoethylamine *N,S*) bis(ethylenediamine) cobalt(III) thiocyanate, **14** $(SCN)_2$. Figure 1 shows that the cobalt(III) center is six-coordinate (five nitrogen atoms and the sulfur atom) in an approximately octahedral configuration. The sulfenato sulfur atom is four-coordinate (the cobalt atom, the carbon atom of the chelate ring, the oxygen atom and the lone pair of electrons) in an approximately tetrahedral configuration [cf. the cysteinato analogue **13** above].

The sulfur atom is a chiral center[30-32] and the stereochemical possibilities[32] for the cation **14** are rather complex. In fact the sulfur atom configuration may be either *R* or *S*,

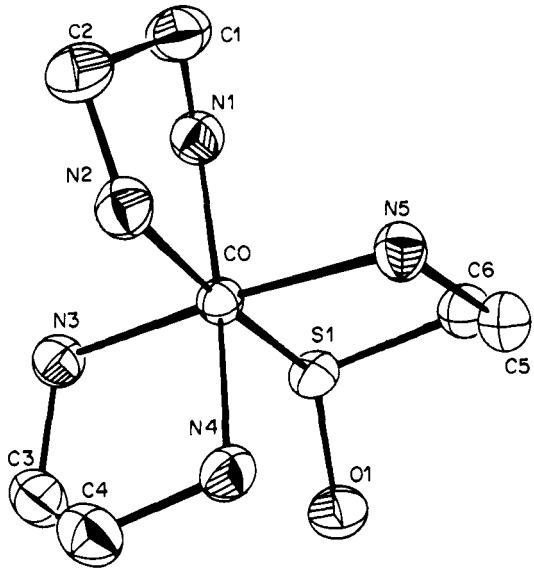


FIGURE 1. Perspective view of $\Delta\lambda'(S)\lambda\delta$-$[(en)_2Co(S(O)CH_2CH_2NH_2)]^{2+}$. The ellipsoids represent 50% probability. Hydrogen atoms have been ommited for clarity. Reprinted with permission from Adzamli *et al.*, *Inorg. Chem.*, **18**, 303. Copyright (1979) American Chemical Society

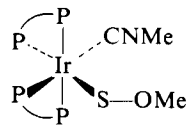
the wrapping of the chelate rings about the cobalt center may be either a Δ or Λ, the sulfenato chelate may adopt either a δ' or λ' conformation and the two (en) chelates may be $\lambda\lambda$, $\lambda\delta$ or $\delta\delta$. Combination of these possibilities leads to 12 overall enantiomeric pairs of diastereoisomers. The particular crystal for which the structure was determined[32] contained only the $\Delta\lambda'(S)\lambda\delta$ configuration (Figure 1).

Kinetic studies have been carried out on the formation of Co(III) coordinated sulfenates by H_2O_2 oxidation of the corresponding thiolato complexes[30, 37] (e.g. **16**), and of the subsequent oxidation[32] of coordinated sulfenates (e.g. **14**) to coordinated sulfinates. Both reactions were interpreted[30, 32, 37] in terms of nucleophilic substitution by coordinated sulfur on the O–O bond of H_2O_2 (an S_N2-type mechanism), the former reaction being over 10^3 times faster than the latter[30, 37]. Coordinated thiols react with H_2O_2 at about the same rate as S_2O^{2-}, while the coordinated sulfur atom of **14** displays a nucleophilicity close to that of the sulfur atom of SCN^-.

The observed acid catalysis presumably reflects the greater reactivity of $H_3O_2^+$ as an electrophilic substrate than that of H_2O_2. Methylation reactions of both **14** and **15** by methyl iodide, as well as reduction by thiols, have also been studied[33] and possible mechanisms for these reactions have been presented. All of the above-mentioned reactivity studies demonstrate that sulfenato–cobalt(III) complexes [Co–S(O)R] display[33] reactivity intermediate between that of noncoordinated sulfenate anions and that of noncoordinated sulfoxides. It has also been remarked by Deutsch[33] that 'while free sulfenic acids are notoriously unstable a cobalt(III) coordinated, S-bonded sulfenic acid enjoys stability similar to that of an organic sulfoxide. This constitutes a remarkable example of the stabilization of reactive organic ligands via coordination to a metal center'.

Interestingly, the analogous sulfenato–chromium(III) complexes are not available by the same synthetic route [i.e. the H_2O_2 oxidation of thiolato complexes of chromium(III)]. Presumably the inherent instability of the Cr–S bond causes the S-bonded sulfenato moiety to be unstable and the expected [Cr–S(O)R] intermediates are not observed[37].

An iridium complex of the not reported O-alkyl sulfenic acids, ROSH, has been prepared[38] and characterized by ^{1}H-NMR–IR spectroscopy and field desorption mass spectrometry. Structure **A** was assigned, where P–P = 1,2 bis(diphenylphosphino)ethane, showing once more that relatively stable complexes of extremely reactive organosulfur compounds can be prepared.



(A)

II. SULFENAMIDES

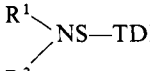
A. Basicity and Acidity

Systematic studies on the protonation equilibria, pK_{BH^+}, for simple sulfenamides have not yet been reported, possibly due to the instability[39–41] of these compounds to acids. Therefore, the quantitative behavior of simple sulfenamides as bases is still uncertain.

However, the lower basicity of *N*,*N*-dialkyl alkanesulfenamides compared to that of the corresponding hydroxylamines was observed[42] long ago. The basicity of sulfenamides has been more recently considered[43] resembling that of the related amides. This greatly

reduced basicity would be in sharp contrast with the enhanced[43,44] nucleophilicity exhibited by sulfenamides, mostly due to lone-pair interaction on the adjacent heteroatoms (the so-called 'α effect').

It has recently been reported[45,46] that sulfenamides having the general structure **17** are not protonated by 10% aqueous sulfuric acid. This would correspond[47] to $pK_{BH^+} \leqslant -2.4$ if **17** were Hammett bases. However, this order of magnitude probably cannot be taken as 'typical' for the basicity of simple sulfenamides, owing to the strong electron-withdrawing effect[45] of the TDE group in **17**.

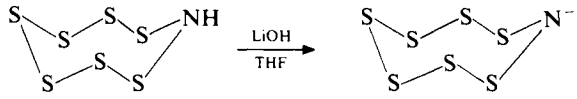


(**17**) $R^1 = R$ or Ar; $R^2 = H$, R or Ar; $TDE = -C(CF_3)Ph_2$

It is generally assumed[39,41,48,49] that protonation occurs on the nitrogen atom of sulfenamides. Although nitrogen protonation appears quite reasonable on the basis of both chemical intuition and product distribution of known acid-promoted decomposition reactions[39,48,50,52], there is no direct evidence for this being the case. However, N-protonated sulfenamide conjugate acids are considered[39-41,48-52] necessary precursors for a number of interesting sulfenamide reactions. The formation of the conjugate acid of 4'-nitrobenzenesulfenanilide (**18**), $4'NO_2C_6H_4NHSPh$, through autoprotolysis, was considered[53] kinetically significant even in the 'spontaneous' thermolysis of **18** in benzene or furan at 85 and 150 °C. In fact, the decomposition reaction of **18** was totally suppressed by the addition of traces of triethylamine in benzene and furan, and strongly catalyzed by the addition of trifluoroacetic acid in benzene without leading to changes in product pattern.

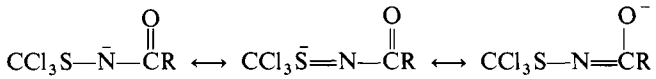
Primary and secondary sulfenamides, $RSNH_2$ and RSN(R)H, can in principle behave as acids. However, pK_{AH} values for simple sulfenamides are not available.

Sulfurimides can be deprotonated[54] by a variety of bases, among which LiOH seems particularly effective in the deprotonation of heptasulfurimide **19** in anhydrous THF, to give the corresponding anion **20** (equation 3) which can be conveniently alkylated and



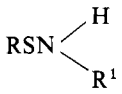
(**19**) (**20**) (3)

acylated. *N*-acyltrichloromethanesulfenamides in acetone have N–H acidities comparable to that of dichloroacetic aicd. These enhanced acidities have been attributed[55] to the fact that the negative charge on their conjugate bases is spread out over three atoms as follows:



The acid dissociation constants, pK_{AH}, of some twenty-six *N*-substituted sulfenamides of general structure **21** have been determined potentiometrically[56] in 50% aqueous ethanol (or acetone) at 24 °C. Acidity increases linearly with the electron-acceptor properties of R and R^1 owing to the stabilization of the corresponding anions. The aryl substituent in the arylsulfenyl (ArS) group has a greater effect on pK_{AH} than the substituent in the

arylsulfonyl ($ArSO_2$) group. The reported[56] ρ values are 4.72 and 1.54, respectively, showing that the dicoordinate sulfur transmits the substituent effect more readily than the tetracoordinate sulfur atom. Observed pK_{AH} values fall within a very wide range, from 2.4 up to 12.7.



R = Ar, CCl_3

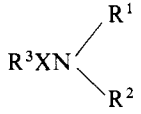
R^1 = arylsulfonyl or acyl

(**21**)

B. Hydrogen Bonding

IR spectra of ethanol or phenol mixed with a number of aliphatic amines, disulfides and sulfenamides were reported[57], in CCl_4, as a measure of the electron-donor ability of sulfenamides. The recorded spectra showed a great deal of interaction between sulfur and nitrogen (see also Reference 43). This interaction decreases the donor ability of nitrogen in H-bond forming and complex-forming energy for sulfenamides was only about 50% of that for the corresponding amines.

The electron-donor ability of heteroatoms in H bonding declined in the order :N≫ : NSN: > S > S–S. Similar measurements have been reported[58] for mixtures of ethanol, phenol or chloroacetic acid with bases of general structure **22** in CCl_4 or heptane.



X = S, Se, P, As

R = Alk, Ph

(**22**)

The electron-donor properties, as measured by H-bond (or ion-pair) complex formation, decrease in the order: $Et_2NR \gg$ **22** > RXR (X = Se, S, As). The donor properties of **22** increase on changing X from P or S to As or Se and on changing X from S or Se to P or As. In all cases the donor center of **22** is the nitrogen atom.

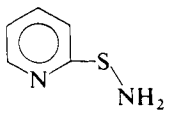
C. Complex Formation

N,N'-Thio-bisdimethylamine was reported[59] to readily yield with BF_3 a solid adduct, $(Me_2N)_2S{\cdot}2BF_3$, described as 'very stable'. In contrast, $(Me_2N)_2SO_2{\cdot}BF_3$ was found[59] to be 'very unstable' and the main cause of the observed trend of adduct stability was suggested to be the inductive effect of oxygen in increasing the N→S π bonding. This would render the otherwise unshared electrons of N less available for bonding to BF_3. The bonding preference for nitrogen to boron, rather than sulfur (or oxygen) to boron, was firmly established. On the other hand, it was subsequently reported that alkanesulfenamide complexes with diborane[60] and boron trichloride[61] are 'unstable' leading to the rupture of the N–S bond.

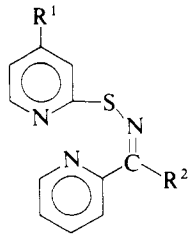
It soon became clear that this 'instability' due to activation by Lewis acids is a general property[40] of sulfenamides. In fact, coordination of an electrophilic species with the nitrogen lone pair is usually followed by displacement of the activated nitrogen fragment by nucleophilic attack on sulfur. For example, a number of decomposition reactions[52, 53, 62, 63] occur via complexation of benzenesulfenanilides with etherated BF_3.

Metallic compounds similarly activate the sulfur–nitrogen bond by accommodating the nitrogen lone pair of electrons. Hard metals, such as zinc[64], appear particularly effective in promoting this kind of activation.

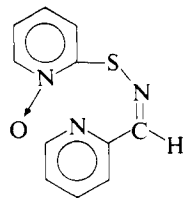
Stable complexes of divalent iron, cobalt, nickel and, in several instances, copper and zinc with 2-sulfenamidopyridine (**23**) and the Schiff bases (**24–26**) have been prepared and characterized[65].



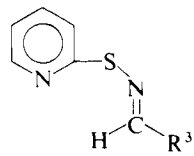
(**23**)



(**24**) $R^1 = H$, Me
$R^2 = H$, Me



(**25**)



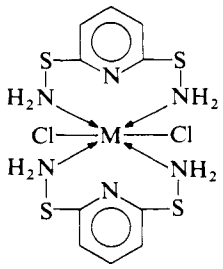
(**26**) R^3 = Me, Et

Two different types of complex[65] have been isolated from the reaction of **23** with Co(II) and Fe(II), of general formulas ML_2X_2 and ML_3X_2, where M is the metal (Co or Fe), L is **23** and X is a univalent anion. In all the present cases **23** functions as a bidentate ligand. The type of complex formed depends on the coordinating ability of X. If chloride is utilized, the former type of complex prevails, whereas if perchlorate is employed, the latter forms. Conductivity data and magnetic susceptibility values support the two-to-one structure ML_2X_2, while the second type of complex, formulated as three-to-one complexes ML_3X_2, probably do not involve simple monomeric structures.

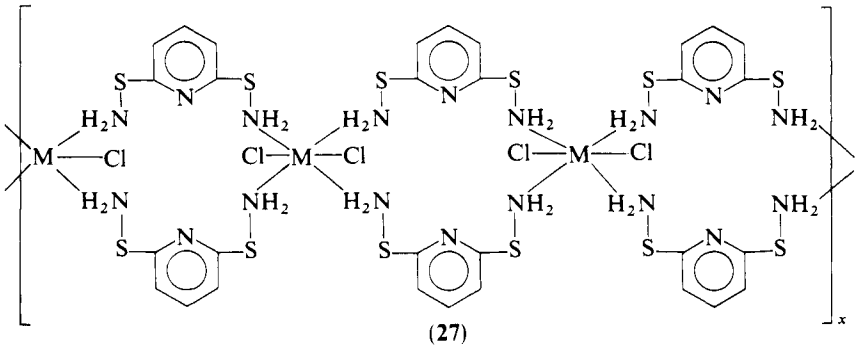
The Schiff base ligands **24** and **25** both chelate in a tridentate manner. However, in contrast with **24** where chelation occurs through the three nitrogen atoms, coordination in **25** is through one oxygen and two nitrogen atoms.

A study[65] of the visible spectra of the nickel complexes of the various ligands (**23–26**) suggests that the electron pair on the sulfur atom of the sulfenamide moiety is *not* appreciably delocalized. Complexes of 2,6-disulfenamidopyridine, L, with divalent iron, nickel and cobalt chlorides have also been prepared[66], formulated as ML_2Cl_2 [M = Ni(II), Fe(II), Co(II)] and described as high-melting (above 300 °C) noncrystalline materials, which were insoluble in water, ethanol, ether and acetone.

This evidence together with low molar conductance values and UV/IR spectra indicate that chloride ions were part of the coordination sphere. Two alternative structures have been proposed[66]: an octahedral structure **B** where the ligand acts in a bidentate manner through the two amine nitrogens, with chloride ions occupying the remaining two sites, or, more likely, a polymeric structure (**27**).



(B)

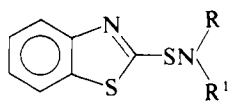


(27)

The fact that L coordinates through the two exocyclic nitrogens in preference to the endocyclic 'aza' nitrogen is unusual and apparently due to the size of the sulfur atoms and the molecular angles that they subtend. This steric effect precludes the ring nitrogen from partaking in complexation. The Schiff base of 2,6-disulfenamidopyridine with 2-pyridinaldehyde, L^1, gives with the same divalent metal chlorides the respective complexes of empirical formula ML^1Cl_2, for which probable structures have also been proposed[66].

Two different complexes were identified for simple sulfenamides in the ternary system: $ZnCl_2$/sulfenamide/acetone, and the general formulas $ZnCl_2L$ and $2ZnCl_2L$ (where L = sulfenamide) were assigned[67] by thermogravimetry as well as chemical and X-ray analyses.

Complexes of *N*-cyclohexyl-2-benzothiazolyl[68] and of *N*,*N*-dicyclohexyl-2-benzothiazolyl[69] sulfenamides (**28**) with cobalt(II) halides have been prepared and shown to have the general formula CoL_2X_2 (where L = **28** and X = Cl, Br). In these pseudotetrahedral complexes, **28** is monodentate and coordinated through the thiazole N atom. Furthermore, **28** with zinc halides[70] gives analogous complexes $[ZnL_2X_2]$ in which the ligand **28**, L, is again monodentate and coordinated through the heterocyclic N atom. $[ZnL_2X_2]$, on heating, affords $[ZnL_2]X_2$ in which **28** is now bidentate and coordinated through both N atoms.



(**28**)

R = H, R^1 = cyclohexyl
R = R^1 = cyclohexyl

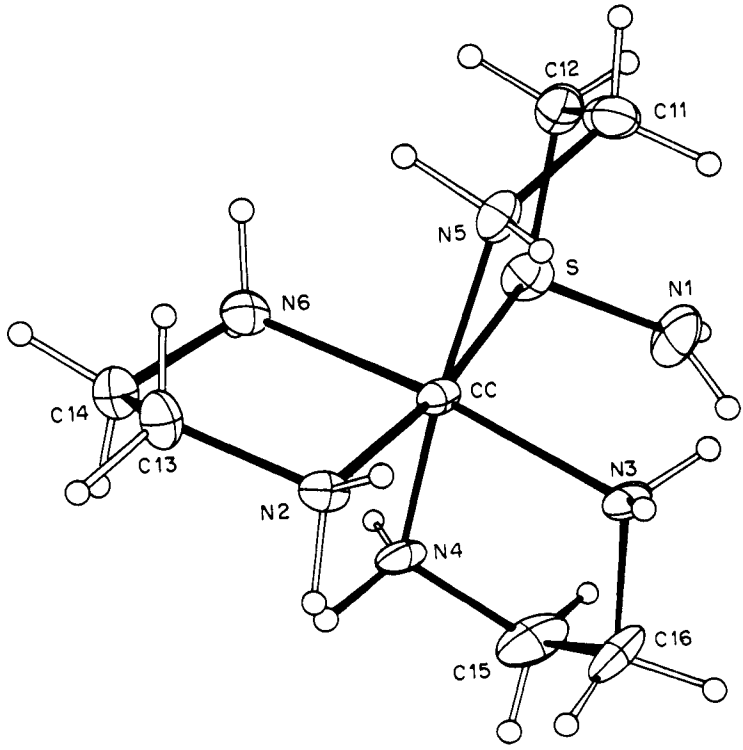


FIGURE 2. Perspective drawing of the $[(en)_2Co(S(NH_2)CH_2CH_2NH_2)]^{3+}$ cation (30% probability ellipsoids). The hydrogen atoms are drawn artificially small for clarity. Reprinted with permission from Reynolds *et al.*, *Inorg. Chem.*, **22**, 3632. Copyright (1983) American Chemical Society

2-Benzothiazolylsulfenamide (**28**; $R = R^1 = H$) with copper(II) halides ($X = Cl$, Br) gives complexes[71] of general formula $CuLX_2$, while *N*,*N*-diethyl-2-benzothiazolylsulfenamide (**28**, $R = R^1 = Et$) with the same copper(II) salts gives CuL_2X_2, where L = **28** as appropriate. The coordination modes are $[CuN_2X_2]$, i.e., **28** is coordinated through both N atoms in the former and $[CuN_2S_2]$, i.e., two molecules of **28** are coordinated through nitrogen on the exocyclic sulfur, in the latter complex.

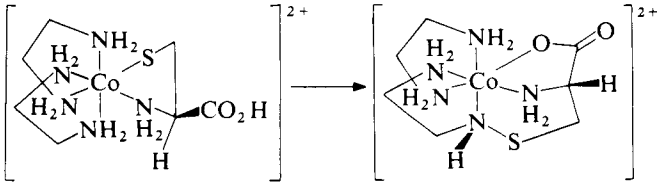
Complexation of sulfenamides with cobalt(III) is of special interest as Co(III) gives[72] S-bonded sulfenamide octahedral complexes. These complexes, of prototype **29**, are, of course, closely related to the sulfenic acid analogues described in Section I.C above. They were prepared by Deutsch and coworkers by reacting their thiolate prototype (**16**) with excess hydroxylamine-*O*-sulfonic acid, NH_3OSO_3 (or $CH_3NH_2OSO_3$), in methanol (or water). In particular, the structure of the mixed oxalate/perchlorate salt of **29** (R = H), $[(en)_2Co(S(NH_2)CH_2CH_2NH_2)](ClO_4)_2(C_2O_4)_{1/2} \cdot H_2O$, was investigated[72] by single-crystal X-ray analysis (Figure 2).

$[(en)_2Co(S(NHR)CH_2CH_2NH_2)]^{3+}$ (where R = H or Me and en = ethylenediamine)

(**29**)

When R = Me in **29** the resulting complex is less stable, undergoing very rapid Co–S bond fission in alkaline media. In this case both the more difficult preparation and higher instability of **29** (R = Me) are probably due to steric reasons[72]. The S-bonded sulfenamide ligand in **29** provides nearly the same ligand field strength as the sulfenate ligand in **14**.

On the other hand, a cobalt(III) sulfenamide complex (**31**), where the sulfenamide ligand is bonded to the metal through the N rather than the S atom, was obtained[73,74] by oxidation of (*R*)-cysteinato-bis(ethylenediamine)cobalt(III) ions (**30**) in Me_2SO/Ac_2O. In this remarkable transformation (equation 4) the cysteine entity has switched from NS to NO bonding and the freed sulfur atom has then condensed in a stereospecific manner with one of the N atoms of one (deprotonated) ethylenediamine chelate. For complex **31** a pK_{AH} of about 10 (NH of the sulfenamide) has been determined[73].



(4)

(**30**) (**31**)

III. SULFENATE ESTERS

Sulfenate esters, RSOR′, are relatively strong bases[12]. For example, titration of methyl toluene-*p*-sulfenate in chloroform with trifluoroacetic acid indicates that this ester is a much stronger base than either methyl *p*-tolyl sulfoxide or methyl toluene-*p*-sulfinate.

Similarly to what we have seen in Section II.C for sulfenamides, sulfenate esters (**32**) can be activated[75] by a Lewis acid, X, to generate the ionic species **33** (equation 5). A nucleophile, such as an alkene double bond[75,76] or a sulfur nucleophile[77], can then react with **33** to form an intermediate (e.g. an episulfonium ion[75,76]) which eventually reacts with a second nucleophilic species. This Lewis acid mediated activation of **32** has recently been used in arene–alkene cyclization[75], and in the synthesis of various glycosylated products[76,77]. Best results have been obtained for X = Me_3SiOTf, $BF_3 \cdot OEt_2$, Trityl BF_4 and $SnCl_4$.

$$\mathrm{ROSPh} \xrightarrow{X} \mathrm{R\overset{+}{O}SPh}\ X^- \qquad (5)$$

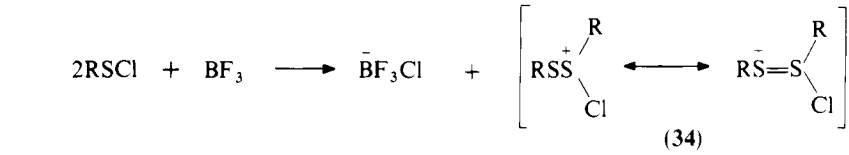
(**32**) (**33**)

The reaction of equation 5 can be viewed[77] as a hard–hard (X and **32**) acid–base interaction, which is followed by a soft–soft acid–base interaction between **33** and the nucleophile[75–77] (an alkane or a sulfur species).

IV. SULFENYL HALIDES

It is believed[78] that a protonated sulfenyl chloride, $Ar\overset{+}{S}(H)Cl$, is the species presumably generated in concentrated sulfuric acid from ArSCl, instead of the previously proposed[79,80] sulfenium ion, ArS^+. Analogously, the interaction of Lewis acids[81] (BF_3, SbF_5, BCl_3) with alkanesulfenyl chlorides in liquid SO_2 forms a dimeric monocationic species (**34**) according to equation 6, rather than the corresponding simple sulfenium ions.

H-bonded complexes of *p*-substituted arenesulfenyl chlorides, 4-XC_6H_4SCl, with phenol acting as an electron acceptor have been studied[82] by IR spectroscopy in CCl_4 and the results compared with those obtained for the corresponding arenethiols, 4-XC_6H_4SH.



(6)

(34)

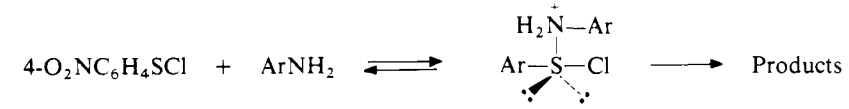
For the phenol–arenesulfenyl chloride system, two types of frequency shift, $\Delta\nu_{OH}$, are observed and attributed to two different interactions. The first interaction is the intermolecular hydrogen bond OH · · · · S; the second corresponds to the coordination of phenol with the chlorine atom. On the whole, the n-donor power of sulfur in 4-XC_6H_4SCl is higher than that of sulfur in 4-XC_6H_4SH. The electron-donor power of the Cl atom is somewhat higher than in butyl and cyclohexyl halides. An H-bonding interaction of phenol with the aromatic ring, OH · · · · π, could be observed for 4-XC_6H_4SH, but was not detectable for 4-XC_6H_4SCl.

The CT complexes with tetracyanoethylene were also studied[82] for both classes of sulfur compound. When the substituent, X, is an acceptor and weak donor, the electron-donor power of 4-XC_6H_4SCl is higher than that of the corresponding thiols 4-XC_6H_4SH. When X is a donor, the reverse situation is observed.

This inversion of donor power is apparently due to an unusually low sensitivity of the process of CTC formation of arenesulfenyl chlorides to the change of the substituent X. This is probably a consequence of the differences in the form of the frontal orbitals of the two classes of derivatives. In the HOMO of arenethiols a major contribution is made by the AO of the carbon atoms of the aromatic ring and the AO of the sulfur atom, while in the HOMO of arenesulfenyl chlorides the main contributions are made by the unshared AOs of sulfur and chlorine.

Sulfenyl halides react[83] with aromatic compounds to give aryl sulfides. In general Friedel–Crafts catalysts able to activate these halides through complexation are required in order to affect this reaction (except with activated aromatic compounds such as phenols, dialkylanilines etc.).

There is indirect evidence of a 'pentacoordinate' (lone pairs being considered ligands) complex (**35**) as intermediate in the mechanism of the reaction[84] of *p*-nitrobenzenesulfenyl chloride with substituted anilines in benzene (equation 7). This is one of the few examples[84] of the participation of sulfur d-orbitals in nucleophilic substitutions at bivalent sulfur.

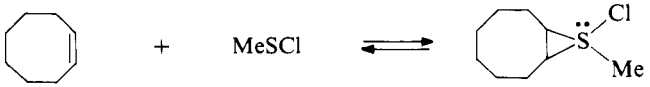


(7)

(35)

The intermediate (**35**) of equation 7 might recall those cases of addition reactions of sulfenyl halides to olefins[85] (or acetylenes[86]) in which a pentacoordinate sulfur intermediate is formed prior to, or instead of, a simple episulfonium (or episulfenium) ion. For example, ^{1}H-NMR evidence suggests[87] that adduct **36** is the important intermediate in the methanesulfenyl chloride addition to cyclooctene (equation 8). Pentacoordinate sulfur

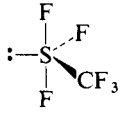
adducts have also been postulated[78,88] as intermediates in the chlorination reaction of arenesulfenyl chlorides.



(8)

(36)

A 'covalent' chlorine adduct[88], $ArSCl_3$, would be expected to have a trigonal bipyramidal structure, where two chlorine atoms would occupy the axial positions and the electron pair be situated in an equatorial position. In fact, it is known[89] that the analogous (stable) sulfur–fluorine compound [i.e. trifluoromethylsulfur trifluoride (**37**)] has trigonal bipyramidal geometry. The same geometry has been proposed[90] for **35** too.



(37)

Deutsch and coworkers[91] have found that I^+-donating reagents such as *N*-iodosuccinimide, iodine nitrate and molecular iodine react with the thiolato complex **16** to yield the remarkably stable adduct **38**. The structure of this adduct is shown in Figure 3. **38** may be viewed as a derivative of a (sulfur) coordinate sulfenyl iodide or as a stabilized derivative of the iodine ion I^+.

$$\{[(en)_2Co(SCH_2CH_2NH_2)]_2I\}^{5+}$$

(38)

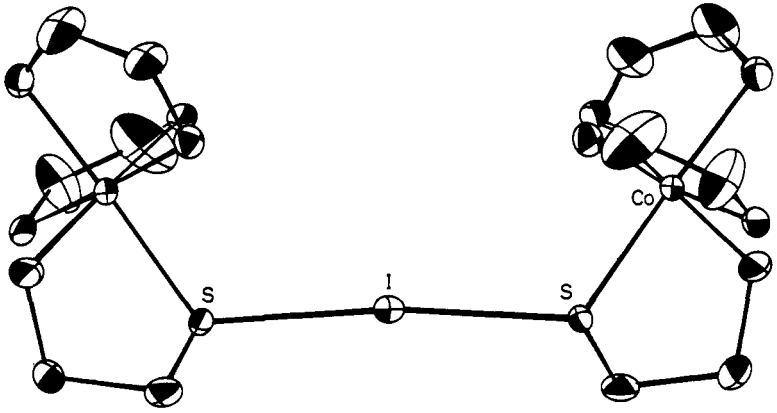


FIGURE 3. A projection of the $\{[(en)_2Co(SCH_2CH_2NH_2)]_2I\}^{5+}$ cation perpendicular to the twofold axis through the iodine atom with 20% probability ellipsoids. Selected bond lengths (Å) are S–I = 2.619 (2), Co–S = 2.244 (3) and average Co–N = 1.98 (2). The S–I–S bond angle is 173.0(1)°. Reprinted with permission from Nosco *et al.*, *J. Am. Chem. Soc.*, **102**, 7786. Copyright (1980) American Chemical Society

Single-crystal X-ray analysis[91] of the nitrate salt **38**·$(NO_3)_5 \cdot 4H_2O$ leads to the structure of Figure 3, which shows each cobalt center to be approximately octahedrally coordinated to five nitrogen atoms and a sulfur atom. The iodine atom, which lies on a twofold axis, bridges the two crystallographically related Co(III) centers by means of a nearly linear (bond angle 173°) S–I–S linkage. This complex **38** exhibits considerable stability compared with noncoordinated RSI and might offer the possibility of investigating the chemistry of these elusive species, which may be very important[91] as intermediates in many organic as well as bioorganic systems.

V. ACKNOWLEDGMENTS

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **8**

Rearrangements involving sulfenic acids and their derivatives

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

Rearrangements involving sulfenic acids and their derivatives, especially esters, have played a significant role in the development of the chemistry of these functional groups. It is therefore not surprising that all major literature surveys on sulfenic acids[1-5] or sulfoxides[6-10] also include a discussion of this subject. However, while excellent and detailed coverage exists for certain rearrangements of general mechanistic and synthetic interest, such as, for example, the penicillin sulfoxide–cephalosporin rearrangement[11-13], the treatment of all other rearrangements is usually brief and partial. An attempt has therefore been made to provide the reader with a comprehensive and systematic survey of the literature dealing with rearrangements involving sulfenic acids and their derivatives, some of which have never been reviewed before. An exception to this statement are the rearrangements of sulfenate esters to sulfoxides and the reverse rearrangements which have been extensively reviewed by the present author, as part of a chapter on rearrangements involving sulfoxides in a recent volume of this series[14]. Another exception are the rearrangements involving thiolsulfinates, also reviewed by the present author, as part of a chapter on rearrangements involving sulfinic acids and their derivatives[15]. An effort has also been made to scan the literature through 1988, as far as possible, and to cover the most significant aspects and most important advances, particularly, work of the last two decades.

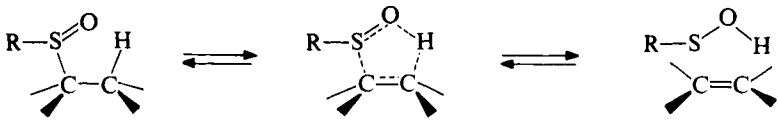
Rearrangements have been included in which sulfenic acids and their derivatives participate not only as reactants but also as products. Reactions have been classified according to mechanism, but although the main emphasis has been on mechanism and stereochemistry, special attention to synthetic applications has also been given, wherever appropriate. Obviously, due to space limitations, only selected and representative results of general importance, as judged by the concern of the reviewer, are presented below. Thus the exclusion of a particular piece of work in no way passes judgement on its scientific value.

II. REARRANGEMENTS INVOLVING SULFENIC ACIDS

A. Pericyclic Rearrangements

1. *Sulfoxide–sulfenic acid interconversions*

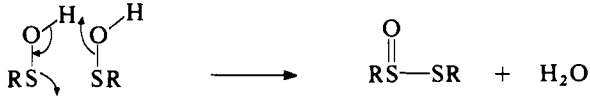
One of the best known reactions of organosulfur compounds is the thermal decomposition of sulfoxides bearing a β-hydrogen atom which provides a convenient method of making olefins[16-27]. Sulfenic acids are also produced in this reaction[17, 27], which is reversible, and which proceeds by a concerted *syn*-intramolecular mechanism, as shown in equation 1 and first suggested by Kingsbury and Cram[16]. This cycloelimination may be regarded as the sulfur analogue of the Cope elimination of amine oxides and, like the latter, involves a five-membered six-electron transition state. The stereoelectronic require-



(1)

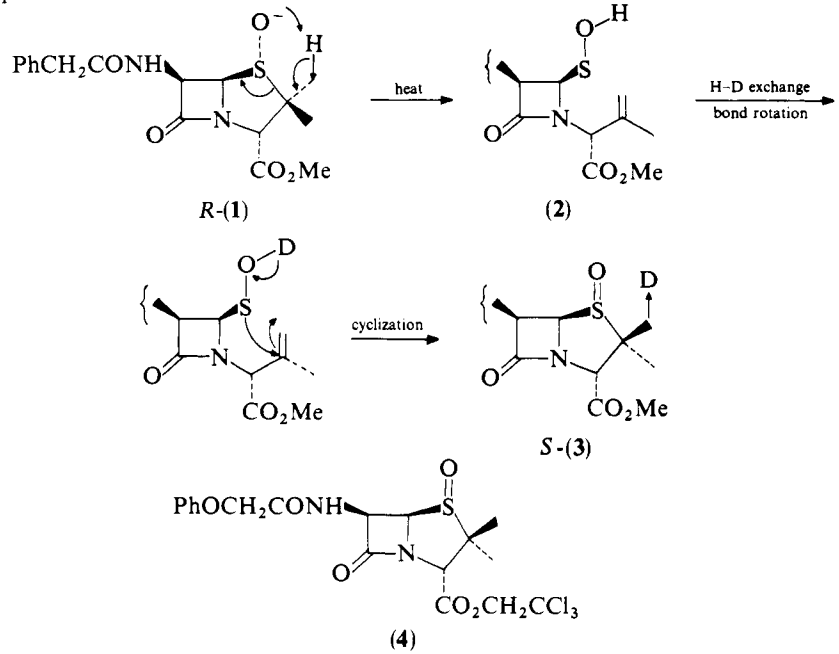
ments of this reversible six-electron sigmatropic rearrangement control the stereoselectivity[16, 21] and regioselectivity[23] of olefin formation from sulfoxides.

It is interesting to note that except for certain derivatives of anthraquinone[28], pyrimidine[29] and penicillin[30], sulfenic acids are too unstable to be isolated, and in the absence of trapping agents they readily undergo intermolecular dehydration to give thiolsulfinates (equation 2)[17, 31]. These thiolsulfinates may also undergo thermal decomposition to sulfenic acids, thiosulfoxylic acids, thiocarbonyl compounds and olefins, as discussed below, or may undergo disproportion to thiosulfonates and disulfides[31].



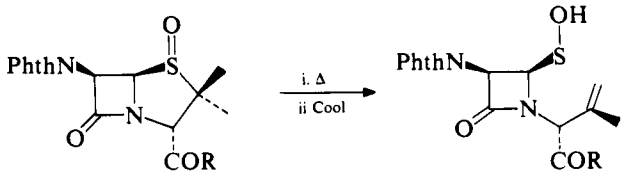
(2)

One of the best studied and most useful rearrangements involving a sulfoxide–sulfenic acid interconversion is the penicillin sulfoxide rearrangement for which some excellent reviews have been published[11–13, 32]. Archer and DeMarco[33], as well as Barton and coworkers[34], simultaneously reported a facile thermal isomerization of penicillin (*R*)-sulfoxides to the thermodynamically more stable *S*-isomers. Evidence for the fomation of a sulfenic acid intermediate in this reaction was first obtained by heating the (*R*)-sulfoxide **1** (80 °C, 3 h) in the presence of deuteriated *t*-butanol[35]. The product was the corresponding (*S*)-sulfoxide **3** in which only one atom of deuterium was incorporated into the *β*-methyl group, *cis* to the resultant sulfoxide bond (equation 3). Under identical conditions no deuterium incorporation was observed for the (*S*)-sulfoxide. Use of prolonged periods (24 h, 80 °C), however, showed that the (*S*)-sulfoxide **4** did undergo slow incorporation of deuterium specifically into the *cis*-disposed methyl group when heated in solution in the presence of deuterium oxide, thus demonstrating the reversibility of the sulfoxide–sulfenic acid equilibrium[24]. This stereospecific and reversible intramolecular cycloelimination is considered to proceed by the coplanar transition state shown in equation 1.



(3)

Further proof for the suggested penicillin sulfoxide–sulfenic acid rearrangement mechanism depicted in equation 3 was derived from the observation of a variety of intermolecular trapping reactions of the intermediate sulfenic acid with olefins[36, 37] or acetylenes[38, 26], with azo compounds[39], with arenesulfinic acids[40], with silylated amides[41], with thiols[41–44] and with trimethyl phosphite[45, 46]. Subsequently, Chou and coworkers[30] provided conclusive evidence for the intermediacy of the reactive sulfenic acid **6**, by its successful isolation from the thermal epimerization of the corresponding penicillin (*R*)-sulfoxide **5**. Sulfenic acid **6**, obtained as a crystaline solid by rapid cooling of a hot solution of sulfoxide **5**, was fully characterized and found to return to sulfoxide on standing at room temperature (equation 4)[30].



(4)

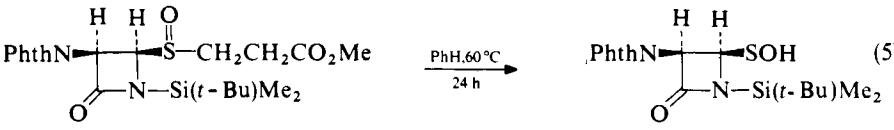
(5)

(6)

R = $OCH_2C_6H_4NO_2$-*p*

PhthN = phthalimido

In the rare examples where sulfenic acids can be isolated, their stability has often been attributed to intramolecular hydrogen bonding, steric and polar effects[3, 5, 27, 47]. To date, however, the reason for the high reactivity of these species remains elusive. Steric inhibition of thiolsulfonate formation (equation 2), the primary reaction of sulfenic acids[47], is probably responsible for the relative stability of 2-methyl-2-propanesulfenic acid (*t*-BuSOH) in solution[27, 31, 47]. The remarkable stability of a derivative of 2-oxoazetidine-4-sulfenic acid (**8**), obtained by Bachi and Gross[48] by pyrolysis of the corresponding sulfoxide **7** (equation 5), has also been attributed to steric inhibition of reaction of **8**.



(5)

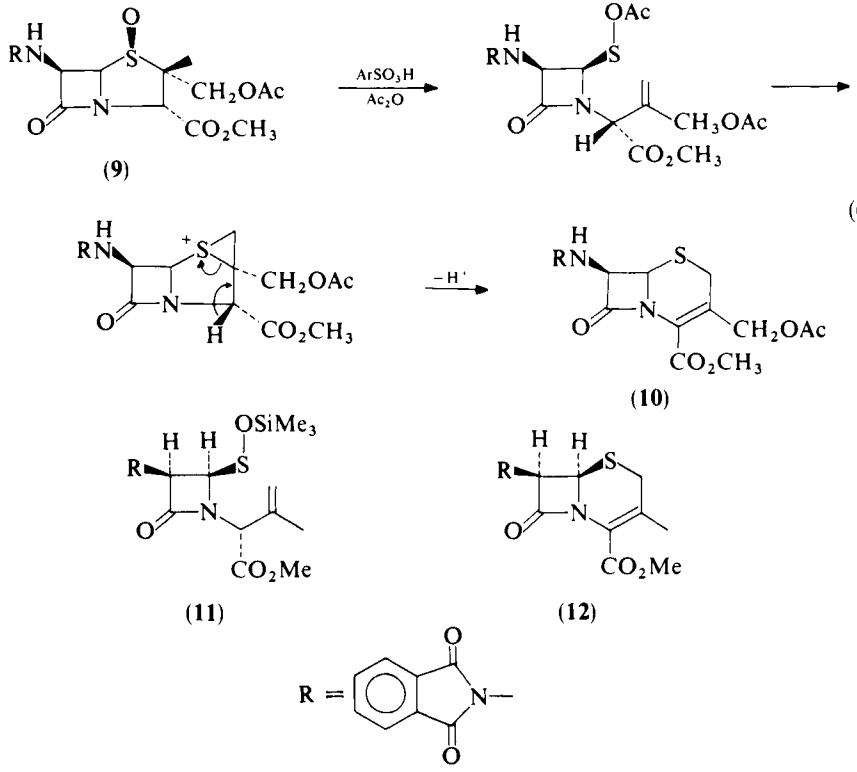
(7)

(8) 79%

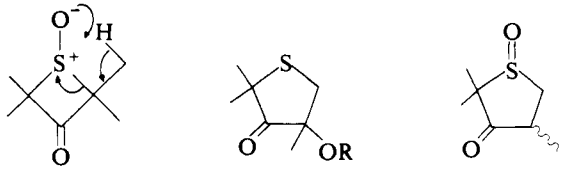
Besides the recyclization of penicillin sulfenic acid to penicillin sulfoxide mentioned above (equation 3), another recyclization proceeding with ring expansion and involving a thiiranium ion intermediate is also possible, normally under acid catalysis. This process is illustrated in equation 6, which represents the final stage of one of the most famous chemical transformations of penicillin, the conversion of penicillin to cephalosporin[49, 11–13].

More recently, Noyori and coworkers[50] reported that when penicillin sulfenic acid trimethylsilyl ester **11** (readily available from the corresponding penicillin sulfoxide) is exposed to 1.5 equivalents of trimethylsilyl triflate (TMSOTf) in dichloromethane at room temperature, the disacetoxycephalosporin **12** is obtained under elimination of a trimethylsilanol moiety.

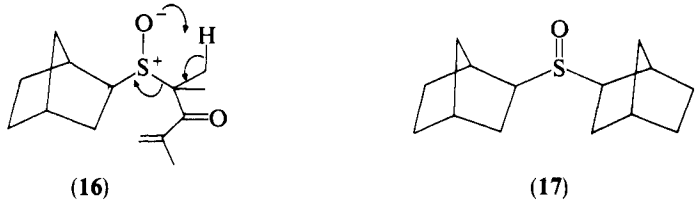
A reaction related to the ring expansion of penicillin sulfoxide is the rearrangement of the four-membered sulfoxide **13** to the ring expanded products **14a** (25%) and **15** (67%)



on heating in refluxing benzene for one and a half hours[51]. In acetic anhydride, compound **13** gives the acetate **14b** as the only significant product and, in norbornene dinorbornyl sulfoxide, **17** is formed. Presumably, the initial product **16** undergoes a cycloelimination

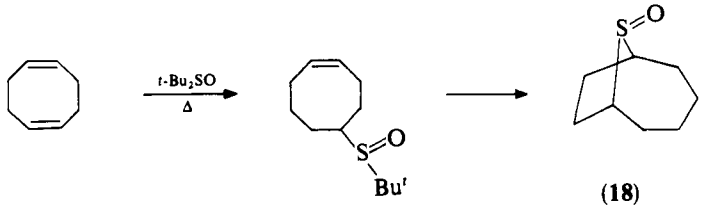


(13) (14) (a) R = H (b) R = Ac (15)



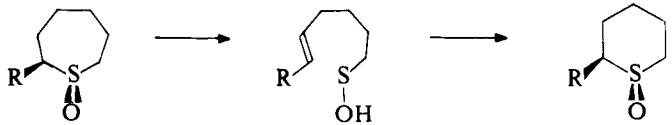
(16) (17)

as shown, giving norbornenesulfenic acid, which then adds to a second molecule of norbornene. This double elimination-addition is similar to that invoked in order to explain the formation of the bicyclic sulfoxide **18** from the reaction of di-*t*-butyl sulfoxide with 1,5-cyclooctadiene (equation 7)[52].



(18) (7)

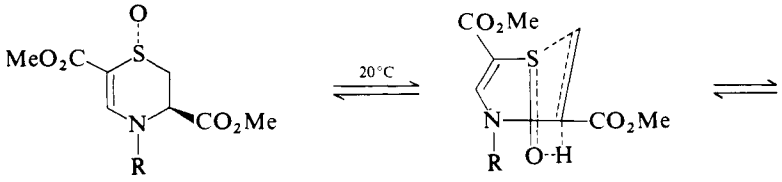
A number of similar thermal rearrangements, involving reversible intramolecular cycloelimination of sulfenic acids from cyclic sulfoxides, have also been reported[53–57]. A detailed study of this rearrangement, which in certain cases can also be accompanied by ring contraction, has been performed by Jones and coworkers[53]. These authors found that at 140 °C in xylene, conditions under which acyclic sulfoxides readily decompose[27], thian 1-oxide (**21a**) was inert after 6 days, whereas thiepan 1-oxide (**19**) decomposed with a half life of *ca* 28 h to give *cis*-2-methyl-thian 1-oxide (**21b**). The sharp contrast in reactivity between thian and thiepan 1-oxides has been explained by steric control of the transition state, with the former unable to achieve the required coplanarity of the relevant five-atom transition state[53].



(19) R = H **(20)** **(21)** (**a**) R = H (**b**) R = Me

Contrary to the lack of thermal reactivity of thian 1-oxide (**21a**)[53], a remarkably facile racemization of the thiazin sulfoxides **22a** and **22b** has been observed by Stoodley and coworkers[55, 56]. The isomerizations which involve the corresponding sulfenic acids **24a, b** were considered to proceed via the transitions states **23a, b,** and the difference in reactivity between cyclic sulfoxides **21** and **22** has been attributed to the enhanced acidity of the migrating hydrogen atom in the latter. Interestingly, the same authors[57] have also shown that the behavior of sulfenic acids is temperature-dependent. Thus, at 20 °C, sulfenic acid **24b** interconverts with the thiazine sulfoxide **22b**, but at 111 °C it equilibrates with both the thiazine sulfoxide **22b** and the thiazoline sulfoxide **25**. The authors[57] suggested that at the higher temperature the higher-energy transition state involving the conjugate *syn*-addition is also accessible and the outcome of the reaction is determined by the thermodynamic stabilities of the products **22** and **25** (equation 8).

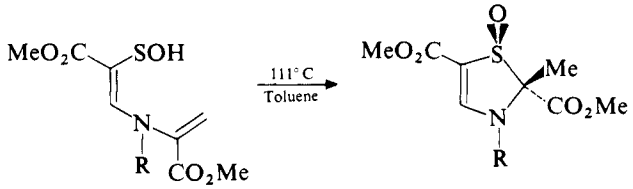
Jones and coworkers have also demonstrated the utility of the intramolecular addition of sulfenic acids to olefins[58–62] and acetylenes[63] as a stereospecific method for the synthesis of various four-, five- and six-membered cyclic sulfoxides. A nice example is the stereospecific preparation of *cis*-2-methylthiolan 1-oxide (**28**) upon heating 5-*t*-butylsulfinyl-1-pentene (**26**) at 160 °C, the *cis*-geometry being the result of an intramolecular *cis*-addition of the intermediate **27** (equation 9). This stereochemistry has also been exploited synthetically in order to construct specifically the 6-thia-5β-cholestane-6α-oxide



(22) (a) R = H
(b) R = CH_2OEt

(23 a,b)

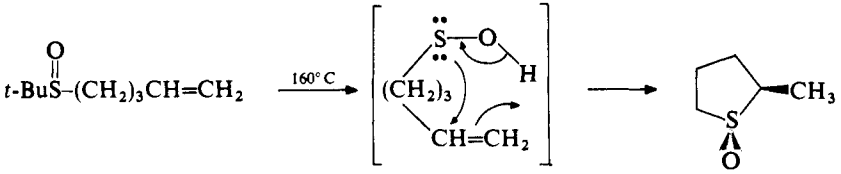
(8)



(24a, b)

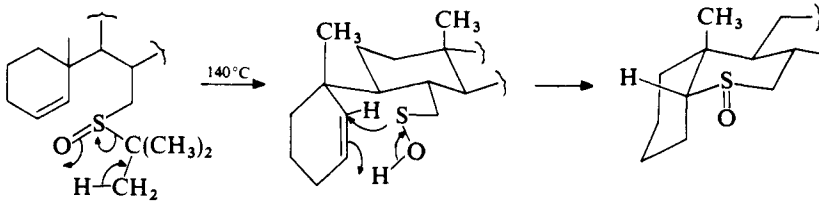
(25)

(30) by thermolysis of the precursor **29** (equation 10), as well as some prostaglandin analogues such as thietanoprostanoids[61]. Similarly, alkyne-ω-sulfenic acids **32**, generated by thermolysis of ω-(*t*-butyl-sulfinyl) alkynes (**31**) at 140 °C, cyclized regiospecifically to 2-methylenethiacycloalkane 1-oxides **33** (equation 11) in good yields[63].



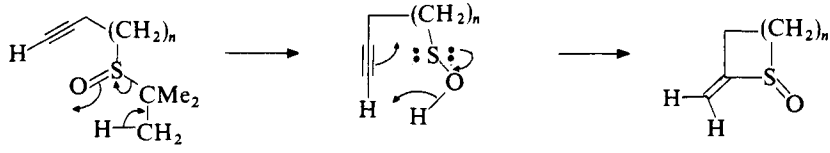
(9)

(26) (27) (28)



(10)

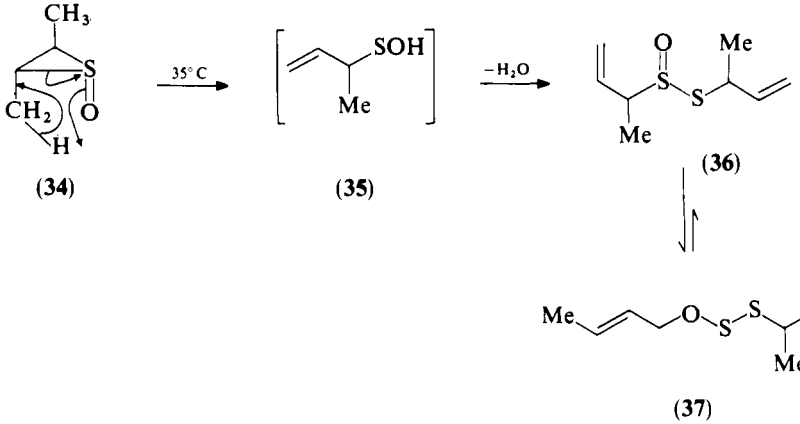
(29) (30)



(11)

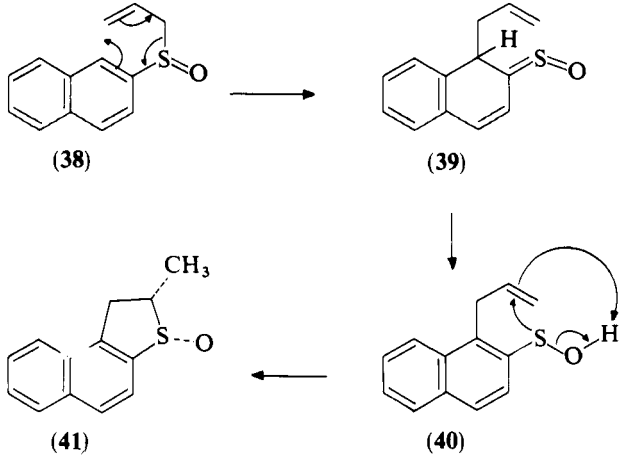
(31) (32) (33)

In certain cases unsaturated sulfenic acids prefer to react, by alternative mechanisms rather than by intramolecular addition. An interesting example is the thermal behavior of *cis*- and *trans*-2-butene episulfoxides, studied by Baldwin and coworkers[64]. While the *cis*-isomer is stable at 35 °C, the *trans*-isomer (**34**) decomposed smoothly in methylene chloride at this temperature with separation of water. The β,γ-unsaturated sulfenic acid in this case undergoes dehydration, followed by [2,3]-sigmatropic rearrangement of the resulting thiolsulfinate, to the sulfoxylate **37** (equation 12).



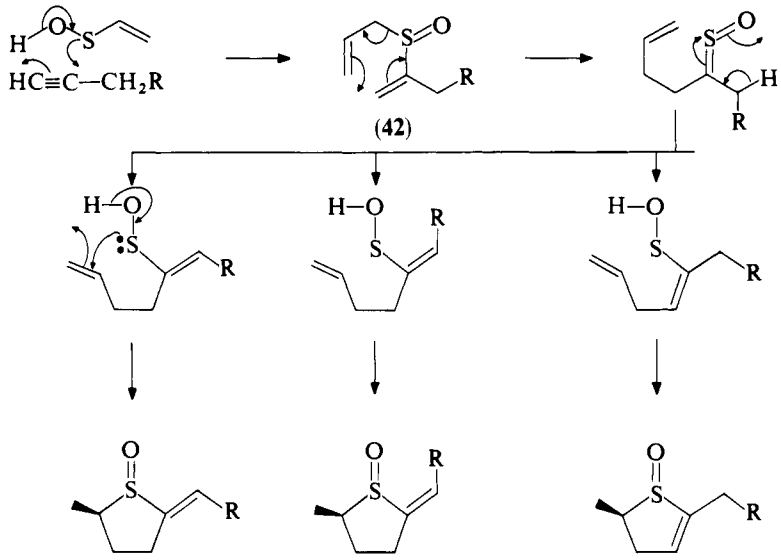
(34) (35) (36) (37) (12)

Thermal interconversion of sulfoxides and sulfenic acids is not limited to the cycloelimination discussed above. Similar to the well-known thio-Claisen rearrangement of allyl aryl sulfides[65] and sulfonium salts[65], the thio-Claisen rearrangement of allyl aryl sulfoxides has also been reported[67]. For example, heating of allyl 2-naphthyl sulfoxide (**38**) at 120 °C for 2 h in dimethylformamide resulted in quantitative isomerization to the dihydronaphthothiophen derivative **41**. A possible mechanism for the formation of the product involves initial [3,3]-sigmatropic rearrangement of sulfoxide **38** to sulfine **39**, followed by a [1,4]-sigmatropic rearrangement[68, 69] to the sulfenic acid intermediate **40** and intramolecular *cis*-addition of the latter (equation 13).



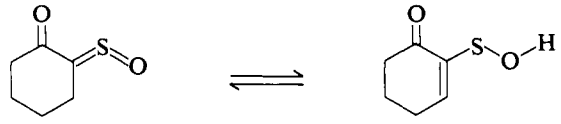
(38) (39) (40) (41) (13)

Subsequently, Jones and coworkers[69] observed a thio-Claisen rearrangement of allyl vinyl sulfoxides. These authors reported that thermolysis of 1-allylsulfinyl-2-cyanoethane initiated five consecutive pericyclic reactions which led to the formation of thiolan 1-oxide derivatives (equation 14). The unstable allyl sulfenic acid thus generated undergoes regiospecific addition to alkynes and affords the required allyl vinyl sulfoxides **42**. However, under the reaction conditions (126 °C), the latter is unstable but undergoes a double rearrangement to sulfine and sulfenic acid, followed by intramolecular cycloaddition as described for the preceding sulfoxide thio-Claisen rearrangement. This reaction has been applied for the preparation of some novel thiophenoprostanoids[62].



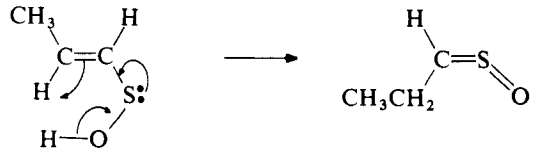
(14)

More recently, Still and coworkers[70] have observed another sulfine–sulfenic acid rearrangement in their studies of the reactivity of the novel subclass of α-oxosulfines, as illustrated in equation 15. The reverse process, namely rearrangement of sulfenic acids to sulfines, has also been observed[68], as shown in equation 16, for the formation of the lachrymatory factor of the onion, sulfine **46**.



(43) (44)

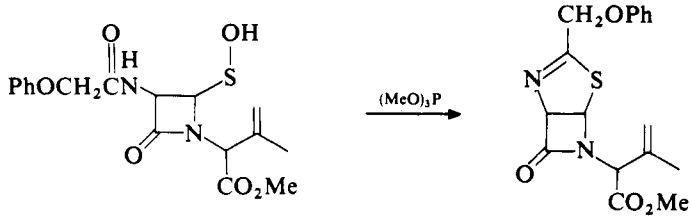
(15)



(45) (46)

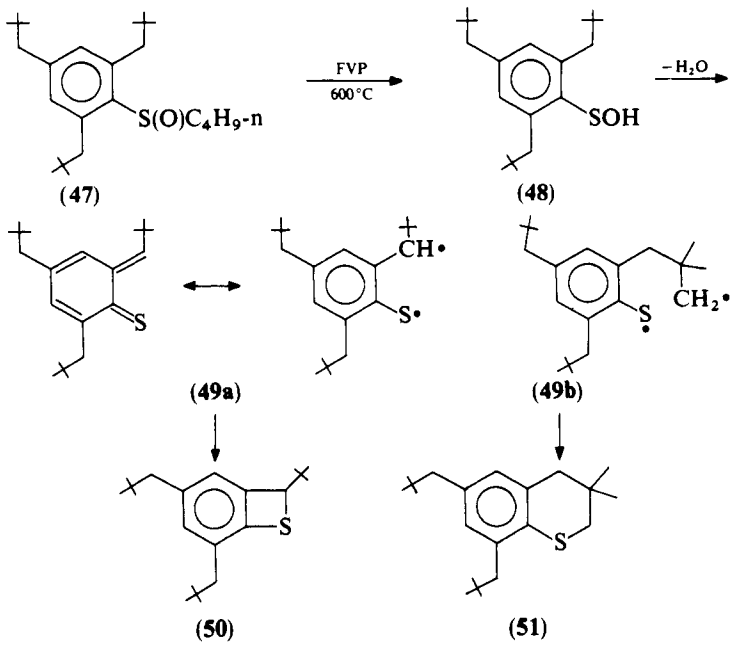
(16)

Besides the two types of recyclization of penicillin sulfenic acids mentioned above (equations 3 and 6), these acids may also undergo cyclization to thiazoline derivatives (equation 17)[45] and other thia-heterocyclic systems[71, 72].



(17)

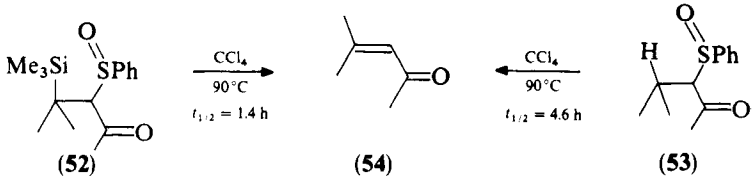
An unusual rearrangement of a sulfenic acid was recently observed by Davis and coworkers[73]. These authors reported that 2,4,6-trineopentylbenzenesulfenic acid (**48**), prepared by flash vacuum pyrolysis (FVP) of the corresponding *n*-butyl sulfoxide (**47**), undergoes a novel rearrangement to give benzo[*b*]thiete **50** and benzo[*b*]thiapyran **51**. A mechanism involving a 1,4-dehydration of the sulfenic acid to afford an intermediate *o*-thioquinone methide **49a** (equation 18) has been proposed.



(18)

The synthetic utility of sulfoxide pyrolysis for the introduction of unsaturation has been widely recognized[8]. It should also be noted that the sulfoxide cycloelimination has its counterpart in organoselenium chemistry. Thus, aryl or alkyl selenoxides undergo *syn*-fragmentation under particularly mild conditions, usually at room temperature or below[74–76]. Finally, the possibility of an analogous cycloelimination of β-silylethyl sulfoxides has been investigated by Fleming and coworkers[77, 78]. Thus, the cycloelimin

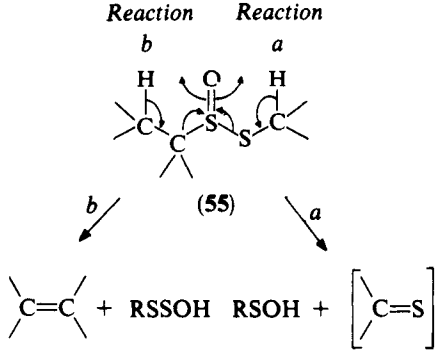
ation **52**→**54** of trimethylsilyl benzenesulfenate from a β-silyl sulfoxide was faster than the corresponding cycloelimination **53**→**54** of benzenesulfenic acid itself. The former type of equation can also be used to form acetylenes.



(52) **(54)** **(53)**

2. Thiolsulfinate–sulfenic acid interconversions

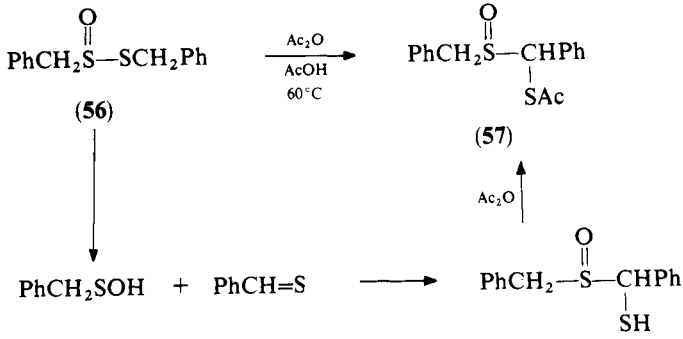
Similar to sulfoxides, thiolsulfinates can also undergo thermal cycloelimination[3, 5, 8, 79]. However, this reaction, which has been thoroughly studied by Block and coworkers[31, 80–84], can occur by two alternative pathways. The first cycloelimination, which is the more favored one, requires the presence of an α-hydrogen next to the sulfenyl sulfur atom and involves cleavage of the weaker S–S bond (**55**, reaction a, equation 19). This reaction generates a sulfenic acid and a thiocarbonyl compound, which usually undergoes polymerization. The second cycloelimination (reaction b), which requires a β-hydrogen at the sulfinyl sulfur atom, produces a thiosulfoxylic acid and an alkene. Alkyl thiosulfinates that can undergo either one of these cycloeliminations are much less thermally stable than those that cannot[31]. Both types of acid can be trapped with suitable alkynes[31, 84]. It is assumed that the inhibitory action of thiolsulfinates on autoxidation parallels the formation of sulfenic or thiosulfoxylic acids, both of which are efficient free-radical scavengers[5, 79]. In the absence of trapping agents, these reactions get readily complicated.



(19)

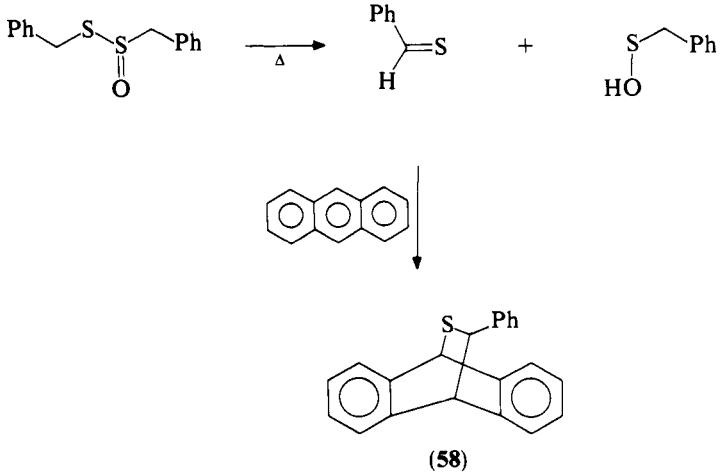
An example of the reaction shown in equation 19a, in which the initial cycloelimination is followed by recombination of the sulfenic acid and thiocarbonyl compound, is shown in equation 20, which provides a mechanism for the transformation of the thiolsulfinate **56** to the α-thioacetoxy sulfoxide **57**[85].

More recently, Baldwin and Lopez[86] have used this reaction for the generation and trapping of the highly unstable thioaldehydes. Thus, heating of **56** in toluene at 100 °C for 1 hour in the presence of an excess of anthracene resulted in the formation of the adduct **58** (equation 21). The latter undergoes a retro-Diels–Alder reaction and serves as a convenient source of the highly reactive thiobenzaldehyde, as illustrated in equation 22.

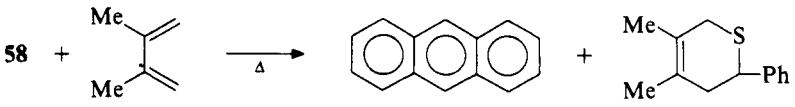


(20)

This reaction has the advantage over thiosulfinate thermolysis that no sulfenic acid is prouced, so it could have synthetic application where a thioaldehyde is required free from other reactive species.

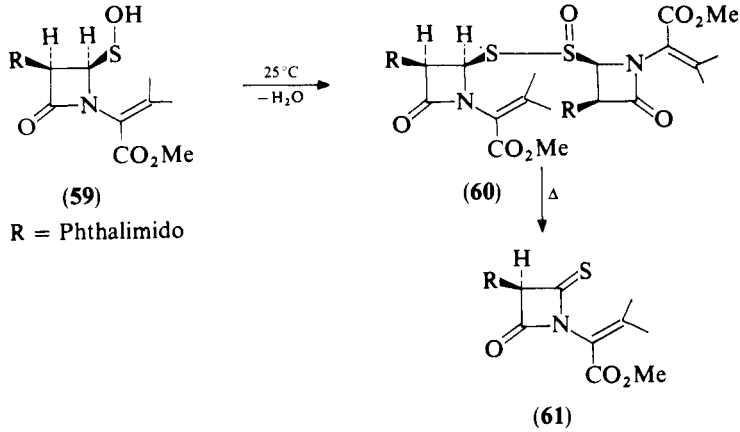


(21)



(22)

Another example of thermal thiolsulfinate sulfenic acid interconversion can be found in work related to penicillin sulfoxides. Two different groups[87, 88] have independently reported that pyrolysis of thiolsulfinate **60** in an inert solvent produced the novel thioxo-β-lactam **61**. This monocyclic thione lactam does not polymerize and can be crystallized from methanol. Thiolsulfinate **60** in turn was obtained when the corresponding penicillin sulfenic acid **59** was allowed to stand at room temperature for several hours (equation 23)[88].



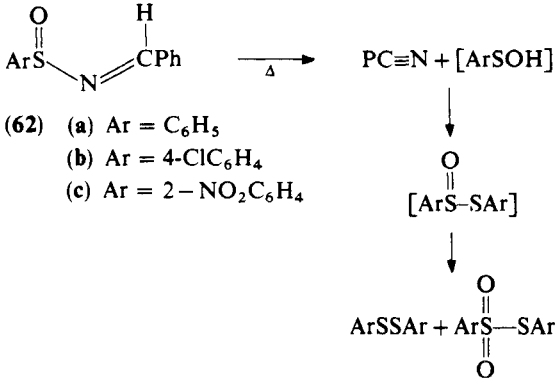
(59)
R = Phthalimido

(60)

(61)

(23)

Interestingly, Davis and coworkers[89, 90] have shown that *N*-alkylidenesulfinamides **62** prepared from aldehydes may also undergo a Cope-type elimination to yield arylsulfenic acids (equation 24)[89]. Thus, when heated in benzene for 15–36 hours, **62a, b** decompose to give disulfide, thiolsulfonate and nitrile as major products. The isolation of these products is consistent with the formation of an arenesulfenic acid, which gives the corresponding thiolsulfinate and water. Arylthiolsulfinates, as mentioned earlier, are unstable and disproportionate to give disulfide and thiolsulfonate. The same authors[90] have found that trimethylsilyl 2-nitrobenzenesulfenate, prepared by heating *N*-benzylidene-2-nitrobenzenesulfinamide (**62c**) with trimethylsilyl chloride, is a convenient, high-yield source of 2-nitrobenzenesulfenic acid and 2-nitrobenzenesulfenate ion when treated with alcohol and alkoxides, respectively.



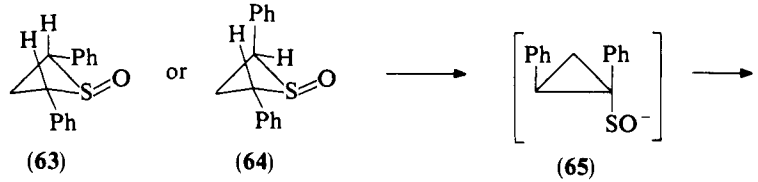
(**62**) (**a**) Ar = C_6H_5
(**b**) Ar = 4-ClC_6H_4
(**c**) Ar = 2-$NO_2C_6H_4$

(24)

B. Ionic Rearrangements

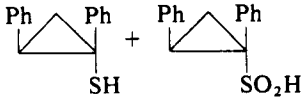
A base-catalyzed rearrangement of a cyclic sulfoxide to sulfinate anion, accompanied by ring contraction, was first observed by Dodson and coworkers[91]. These authors reported that reaction of either *cis*- or *trans*-2,4-diphenylthietane-1-oxide (**63** or **64**) with

potassium *t*-butoxide in dimethylformamide yielded a mixture of *cis*-1,2-diphenylcyclopropanethiol and *cis*-1,2-diphenylcyclopropanesulfinic acid by disproportionation of the sulfenate anion intermediate (equation 25). Subsequently, Jones and coworkers[92] performed a detailed stereochemical study of this reaction and concluded that ring contraction of the lithio anions of 3-alkyl- and 2,3-dialkylthietan 1-oxides occurred stereospecifically with retention of configuration at sulfur and the migrating residue, and inversion at the migrating terminus. For example, treatment of *cis*- and *trans*-3-hexylthietan 1-oxides **68** and **70**, separately with lithium cyclohexylisopropylamide in tetrahydrofuran at −20 °C for 15 min followed by addition of methyl iodide, gave respectively *cis*- and *trans*-2-hexyl-1-(methylsulfinyl)cyclopropane **69** and **71**. In another base-catalyzed isomerization of a cyclic sulfoxide to a sulfenate anion, 2,5-dihydrothiophen 1-oxide was found to undergo ring opening to (*Z*)-1-(methylsulfinyl)-buta-1,3-diene upon treatment with lithium diisopropylamide at −78 °C followed by rapid quenching with a slight excess of methyl iodide (equation 26)[93].

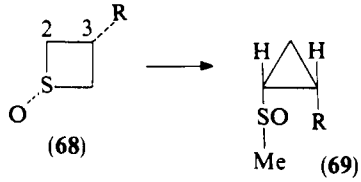


(63) (64) (65)

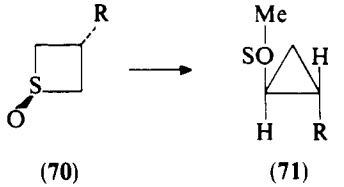
(25)



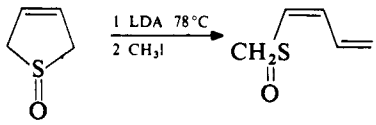
(66) (67)



(68) (69)

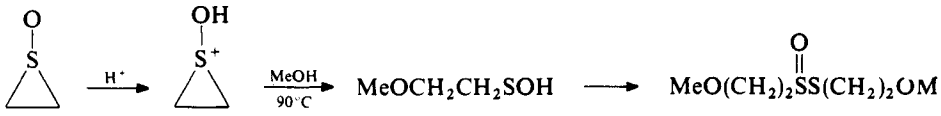


(70) (71)

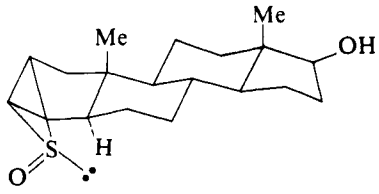


(26)

Rearrangement of sulfoxides to sulfenic acids may also occur under acidic conditions. For example, the acid-catalyzed ring opening of episulfoxide in methanol shown in equation 27 gives 2-methoxyethanesulfenic acid, which in the absence of trapping agents undergoes self-condensation to the corresponding thiolsulfinate[94]. Using this reaction, Kishi and coworkers[95] have converted 17β-hydroxy-2α,3α-epithio-5α-androstane *anti-S*-oxide (**72**) into a diastereoisomeric mixture of the corresponding di-β-methoxy-3α-yl thiolsulfinates with methanol containing a drop of sulfuric acid, by reaction at C-2, involving inversion of configuration.



(27)



(72)

III. REARRANGEMENTS INVOLVING ESTERS OF SULFENIC ACIDS

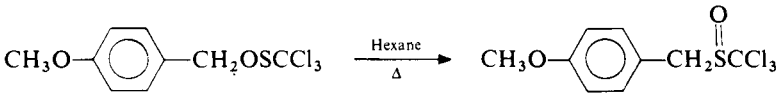
A. Rearrangements of Sulfenates to Sulfoxides

Rearrangements of esters of sulfenic acids to sulfoxides, and the reverse process, are among the best studied and most useful rearrangements of organosulfur compounds in general, and sulfenic acid derivatives in particular. The extent of interest in these rearrangements is reflected by more than two hundred papers published on this subject in the past. However, since most of this literature was recently reviewed by the present author in considerable detail[14], the following discussion will only present a summary of the main features of these reactions.

1. Rearrangements of alkyl and aryl sulfenates

In recent years, considerable interest has been focused on the thermal sulfenate–sulfoxide interconversion. However, most of the work performed has centered around the rearrangement of allyl and propargyl sulfenates which proceeds by an unusually facile [2,3]-sigmatropic shift. When this mechanism is not available, the sulfenate–sulfoxide isomerization becomes much more difficult and has only been observed in certain selected systems. This phenomenon, which is in contrast with the relatively facile sulfinate–sulfone rearrangement[96], may be attributed to the low acidity and general instability of sulfenic acids[5], as well as to the comparably reduced gain in energy in the analogous sulfenate-to-sulfoxide rearrangement[97]. It therefore follows that if the sulfenate ester is derived from a particularly acidic sulfenic acid and can generate a stable carbenium ion, then isomerization to the sulfoxide by an ionization mechanism should become possible.

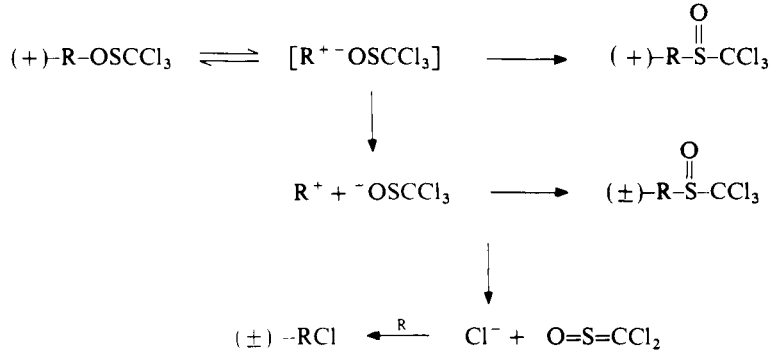
Braverman and Sredni[98a] have reported that *p*-methoxybenzyl trichloromethanesulfenate (**73**) undergoes a facile thermal rearrangement to the corresponding sulfoxide (**74**) on heating in highly nonpolar solvents (equation 28).



(**73**) (**74**) (28)

$[k = 3.4 \times 10^{-4}\ s^{-1}$ (77°C), $\Delta H^{\neq} = 28$ kcal mol^{-1}, $\Delta S^{\neq} = 5$eu]

Benzhydryl trichloromethanesulfenate rearranged to the corresponding sulfoxide after 10 min of reflux of a hexane solution, while the benzyl ester remained practically unchanged even after heating for 24 h at 120 °C in benzene. Isomerization of optically active (−)-α-phenylethyl trichloromethanesulfenate on heating in hexane yielded (−)-α-phenylethyl trichloromethyl sulfoxide. The rate of disappearance of **73** is dramatically enhanced by an increase in the ionizing power of the solvent. For example, substitution of the hexane by chloroform, under similar conditions, leads to the formation of a mixture composed of *p*-methoxybenzyl chloride and the sulfine $Cl_2C{=}S{=}O$ (70% each) and the sulfoxide **74** (30%), while the use of more polar solvents such as methylene chloride or acetonitrile leads to the almost exclusive formation of the first products. Reaction of the optically active α-phenylethyl ester in acetonitrile gave racemic chloride. To explain all these observations, the authors[98a] have suggested the mechanisms shown in equation 29.



(29)

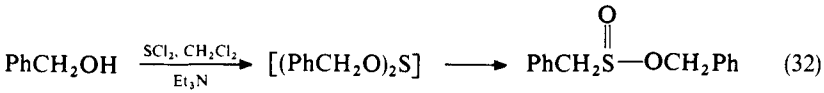
The rearrangement of benzyl *p*-toluenesulfenate (**75**) to the corresponding sulfoxide (**76**, equation 30) has been reported by Mislow and coworkers[99, 100] but is much slower than the isomerization of **73** discussed above. Although a radical-pair mechanism has also been considered for this rearrangement[99, 101], it was rejected in favor of a concerted intramolecular mechanism (equation 31) on the basis of the negative entropy of activation and the partial (35%) retention of configuration at carbon observed in the rearrangement of (−)-(*R*)-benzyl-α-d *p*-toluenesulfenate to (+)-benzyl-α-d- *p*-tolyl sulfoxide[100]. Interestingly, the somewhat analogous benzyl sulfoxylate (**77**) has been reported to readily undergo rearrangement in low yield to benzyl α-toluenesulfinate (**78**) during preparation (equation 32)[102].

Besides the thermal rearrangements of benzylic sulfenates mentioned above, the thermolysis of some alkyl and even aryl sulfenates has also been studied[103–105]. The *t*-butyl esters of arenesulfenic acids were reported to yield isobutene and sulfur dioxide on

$$\underset{\textbf{(75)}}{PhCH_2OS\text{-}Tol\text{-}p} \xrightarrow[PhH]{k_3} \underset{\textbf{(76)}}{PhCH_2\overset{\overset{O}{\|}}{S}\text{-}Tol\text{-}p} \qquad (30)$$

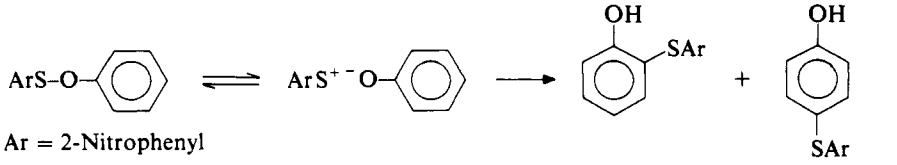
$[k = 8.7 \times 10^{-5}\ s^{-1}\ (120°C),\ \Delta H^{\neq} = 29.7\ kcal\ mol^{1},\ \Delta S^{\neq} = -2eu]$

(31)



(32)

pyrolysis under nitrogen at 120–135 °C, together with a tarry residue which could not be purified. No evidence could be obtained for a radical mechanism and the fragmentation was suggested to occur via a cyclic transition state[103]. Subsequently, Hogg and coworkers[104, 105] have carried out a detailed mechanistic study of the pyrolysis of this and other sulfenates. These authors have found that aryl 2-nitrobenzenesulfenates rearrange on heating to give 2- and 4-hydroxyphenyl 2-nitrophenyl sulfide. These aryl and the corresponding methyl and *t*-butyl sulfenates will also sulfenylate other active aromatic compounds such as anisole. Like the rearrangement, substitution occurs *ortho/para* to the more electron-releasing substituent. These reactions were suggested to involve heterolysis of the sulfur–oxygen bond, as illustrated in equation 33[104].



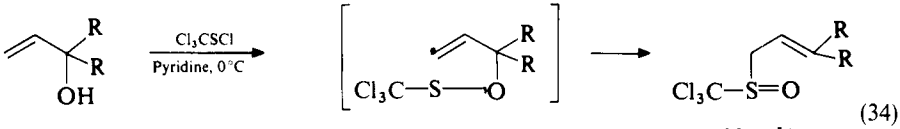
Ar = 2-Nitrophenyl (33)

2. The reversible [2,3]-sigmatropic rearrangement of allylic sulfenates to sulfoxides

Since its discovery two decades ago, the reversible interconversion of allylic sulfenates to sulfoxides has become one of the best known [2,3]-sigmatropic rearrangements. Certainly this is not only because of the considerable mechanistic and stereochemical interest involved, but also because of its remarkable synthetic utility as a key reaction in the stereospecific total synthesis of a variety of natural products such as steroids, prostaglandins, leukotrienes, etc.

a. Mechanism. As a continuation to the studies by Darwish and Braverman[106, 107] on the [2,3]-sigmatropic rearrangement of allylic sulfinates to sulfones, Braverman and Stabinsky[107–111] investigated the predictable analogous rearrangement of allylic sulfenates to sulfoxides, namely the reverse rearrangement of that attempted by Cope and

coworkers[112]. These authors[108–111] initiated their studies by preparation of the claimed allyl trichloromethanesulfenate using the method of Sosnovsky[113]. This method involves the reaction between trichloromethanesulfenyl chloride and allyl alcohol in ether at 0 °C, in the presence of pyridine (equation 34).



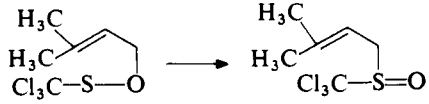
(79) (a) R = H (b) R = Me (80 a, b) (34)

However, IR and NMR spectral data indicated beyond doubt that the product isolated by these authors was allyl trichloromethyl sulfoxide (**80a**) and not allyl trichloromethanesulfenate (**79a**) as claimed[113]. This observation indicates that the initially formed ester undergoes spontaneous rearrangement to sulfoxide. Similarly, the attempted preparation of α,α-dimethylallyl trichloromethanesulfenate (**79b**) afforded γ,γ-dimethylallyl trichloromethyl sulfoxide (**80b**) thus proving the occurrence of a simultaneous 1,3-allylic shift.

The enhanced rate of rearrangement of **79a**, which proceeds spontaneously at low temperature, as compared to allyl 2,6-dimethylbenzenesulfinate, which has a half-life of 23 days at 90 °C in THF, may be assigned to the greater nucleophilicity of the sulfur atom in the sulfenate ester. This observation, in connection with the evidence previously described for the rearrangement mechanism of allylic sulfinates[106, 107], may be used as supporting evidence for a concerted [2,3]-sigmatropic mechanism for the sulfenate–sulfoxide rearrangement.

In contrast to the allylic sulfenates mentioned so far, cinnamyl trichloromethanesulfenate (**81**), prepared by the usual method, can be isolated and is relatively stable. Furthermore, its rearrangement to cinnamyl trichloromethylsulfoxide (i.e. without allylic isomerization, equation 35) proceeds at a relatively slow rate (in CCl_4 at 80.0°C, $k = 3.90 \times 10^{-5}\,s^{-1}$). Similar behavior has been detected for the γ,γ-dimethylallyl ester **83** which undergoes thermal isomerization to sulfoxide **84** (equation 36)[109, 110].

(81) (82) (35)

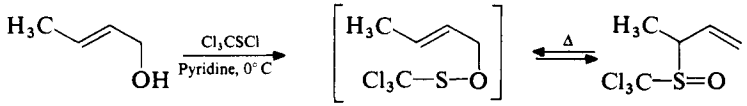


(83) (84) (36)

The authors have suggested[107] that the failure of the last two sulfenates to undergo allylic rearrangement has its source in theromodynamic rather than kinetic factors. Thus, the expected isomerization of cinnamyl sulfenate to α-phenylallyl sulfoxide would have resulted in loss of conjugation energy as well as increased steric interactions between the phenyl group and the relatively large trichloromethyl group. The allylic rearrangement

could thus be prevented by an increase in the free energy of the sulfoxide exceeding the gain in free energy obtained by the sulfenate–sulfoxide rearrangement. On the other hand, the rearrangement to sulfoxide without allylic shift is practially unaffected by these conjugative and steric effects, and may proceed by an ion-pair mechanism, similar to the rearrangement of the *p*-anisyl sulfenate **73** discussed above.

Between the two extremes of spontaneous rearrangement and total failure to rearrange, Braverman and Stabinsky[109–111] have observed intermediate behavior. The reaction of crotyl alcohol with Cl_3CSCl afforded an equilibrium mixture of both crotyl trichloromethane sulfenate (**85**) and α-methylallyl trichloromethyl sulfoxide (**86**, equation 37).

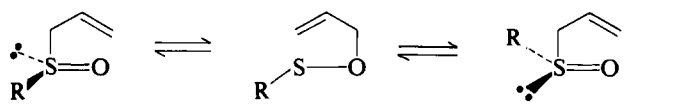


(85) (86) (37)

NMR measurements indicate that the equilibrium constant varies with the polarity of the solvent and temperature. The more polar the solvent, the greater the fraction of sulfoxide at equilibrium which is consistent with the greater dipole moment of the sulfoxide as compared with the sulfenate. Increasing temperature results in a reverse effect, due to the steric hindrance in the sulfoxide which becomes more marked at higher temperature. These results are the first published evidence for the reversibility of the sulfenate–sulfoxide rearrangement and illustrate the occurrence of the rearrangement unsuccessfully attempted by Cope[112]. A relevant study has been reported by Fava[114, 115] in connection with the rearrangement of allylic thiocyanates to isothiocyanates which has been suggested to proceed by a similar intramolecular mechanism.

In summary, the evidence presented above demonstrates three main mechanistic features of the rearrangement of allylic sulfenates to sulfoxides: (1) spontaneous and wholly concerted [2,3]-sigmatropic shift of allyl or α-substituted allyl esters (**79a,b**) at one extreme; (2) complete stability of the γ-aryl and γ,γ-dialkyl substituted allyl sulfenate as well as rearrangement *without* [2,3]-sigmatropic shift at the other extreme (equations 35 and 36); and (3) intermediate behavior of γ-alkylallyl sulfenates which rearrange by a facile reversible [2,3]-sigmatropic shift as illustrated in equation 37.

The observations of the interconversion of allylic sulfenates and sulfoxides made by Braverman and Stabinsky[107–111] are confirmed by the work of Mislow[116–119] and Zefirov[120] and their coworkers. In order to account for the unusually facile thermal racemization of optically active allyl *p*-tolyl sulfoxide [**87**-(*R*)=*p*-Tol] whose rate of racemization is orders of magnitude faster than that of allyl aryl or diaryl sulfoxides, Mislow and coworkers[116] suggested a cyclic intramolecular mechanism in which the chiral sulfoxide is in mobile equilibrium with the corresponding chiral sulfenate (equation 38).



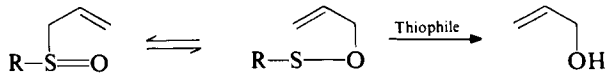
S-(**87**) (**88**) *R*-(**87**) (38)

In order to test the proposed mechanism, these authors[116] attempted the preparation of allyl *p*-toluenesulfenate (**88**) by reaction of *p*-toluenesulfenyl chloride with lithium allyl alcoholate, but obtained instead the rearranged product **87**, directly. The authors

concluded that the rearrangement proceeded by a concerted 1,3-allylic shift, since reaction of *p*-toluenesulfenyl chloride with lithium crotyl alcoholate and lithium α-methylallyl alcoholate afforded α-methylallyl and crotyl *p*-tolyl sulfoxides, respectively. This report[116] preceded that by Braverman and Stabinsky[108], but only contained information with regard to the spontaneous rearrangement of sulfenates to sulfoxides, without mentioning the possible existence of a *stable* sulfenate such as **81** or **83**, or a *detectable* equilibrium between sulfenates and sulfoxides such as shown in equation 37.

b. Stereochemistry and synthetic applications. As previously mentioned, the remarkable popularity which the reversible [2,3]-sigmatropic rearrangement of allylic sulfenates to sulfoxides has enjoyed is primarily a consequence of its high stereoselectivity. To cite Isobe[121], 'the synthetic utility of allylic alcohol-forming [2,3]-sigmatropic rearrangement of allylic aryl sulfoxides has recently been demonstrated by us and others as a key reaction for stereospecific total syntheses of natural products'. Because of the intensive activity on this subject, two excellent reviews have been published by Hoffmann[122, 123], who has also made significant contributions to the analysis and elucidation of the stereochemistry of this rearrangement. In addition, shorter presentations of the subject have appeared in general reviews on stereochemistry of organosulfur compounds[32, 124–127] or sigmatropic rearrangements[128].

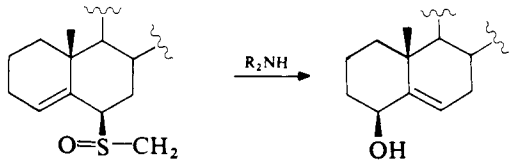
It is important to point out that although the allylic sulfoxide–sulfenate rearrangement is reversible, and although the sulfenate ester is usually in low equilibrium concentration with the isomeric sulfoxide, desulfurization of the sulfenate by thiophilic interception using various nucleophiles removes it from equilibrium and provides a useful route to allylic alcohols (equation 39).



(39)

Although the interception of allylic sulfenates in the manner described by equation 39 was first observed by Abbott and Stirling[129], the general value of this transformation and its remarkable synthetic potential has been recognized by Evans and coworkers[130], who have also introduced the previously used[45] trimethyl phosphite as a preferable trapping agent. An early review of the synthetic utility of the reversible allylic sulfoxide–sulfenate rearrangement has also been published by Evans and Andrews[131].

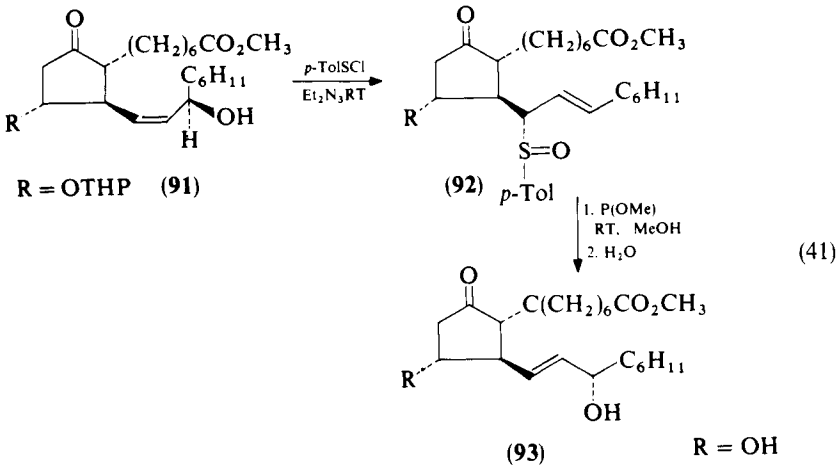
(i) 1→3 chirality transfer. The characteristic 1→3 chirality transfer accompanying the reversible allylic sulfenate–sulfoxide rearrangement could be predicted by the previously observed quantitative 1→3 chirality transfer in the analogous [2,3]-sigmatropic rearrangement of allylic sulfinates to sulfones (equation 40)[106, 107], as required by the suprafacial course of rearrangement and observed with other [2,3]-sigmatropic shifts as well[132–134]. This prediction has been completely borne out by experiment in a variety of stereospecific transformations of allylic sulfoxides derived from natural products to corresponding alcohols, by thiophilic trapping and cleavage of intermediate sulfenates[135–138]. This is nicely illustrated by the exclusive suprafacial rearrangement of the allyl group in the steroidal sulfoxide **89** shown in equation 40[135].



(89) (90)

(40)

One of the first and most remarkable uses of the reversible allylic sulfenate–sulfoxide interconversion was made by Untch, Stork, and their coworkers[140] in the total synthesis of prostaglandin. These authors have shown that the inversion of configuration of both the chiral and geometric centers in compound **91** could be accomplished via the corresponding sulfenate ester which rearranges to sulfoxide **92**. Treatment of the latter with trimethyl phosphite provides the prostaglandin of natural configuration **93**. The two-step sequence **91**→**92**→**93** proceeds with complete stereospecificity and in yields exceeding 85% (equation 41). The *E* preference in the **91**→**92** transformation results from the relative thermodynamic stabilities of the transition states, and is further explained below. More recently, a number of other applications of the stereospecific sulfenate–sulfoxide rearrangement in the synthesis of prostaglandins[141–144], their analogues[145–146], and other natural products[147–152] have also been published.

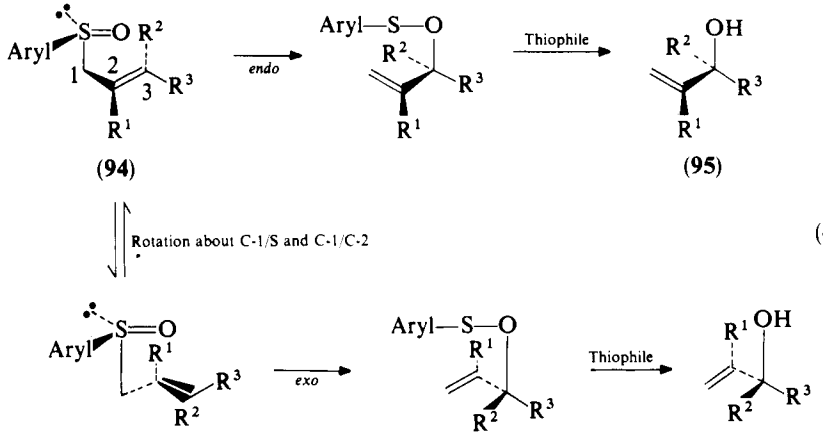


R = OTHP (**91**) (**92**) (**93**) R = OH (41)

(*ii*) *Transfer of chirality to and from a chiral sulfur.* In addition to the 1→3 transfer of chirality discussed in the preceding subsection, the reversible [2,3]-sigmatropic rearrangement of allylic sulfenates to sulfoxides also presents the opportunity for the transfer of chirality from carbon to sulfur, and *vice versa*. Both phenomena have been described. For example, Mislow and coworkers[118] reported that rearrangement of (*S*)-α-methylallyl-*p*-toluenesulfenate to (*S*)-(−)-*trans*-γ-methylallyl *p*-tolyl sulfoxide proceeds with at least 37% ee. The relatively low stereoselectivity observed in this case of transfer of chirality from carbon to sulfur has been explained by loss of configurational purity through leakage via competitive and readily interconvertible transition states, which differ only in comformation, as well as due to the reversibility of the sulfenate–sulfoxide rearrangement.

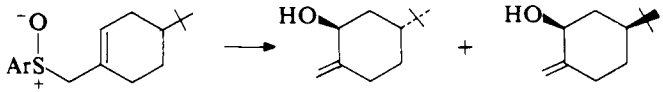
The transfer of chirality from sulfur to carbon has been thoroughly investigated and described in a series of papers by Hoffmann and coworkers[122, 123, 153–158] as a method for the asymmetric synthesis of allylic alcohols. As pointed out by Hoffmann[123], the rearrangement of an allyl sulfoxide of a given configuration such as **94** can proceed through two diastereomeric transition states designated '*exo*' and '*endo*' and afford enantiomeric forms of allyl alcohol **95** (equation 42). The extent of S→C chirality transfer will be determined by the difference in energy between these two transition states.

In a typical example, rearrangement of the (*R*)-(*E*)-sulfoxide **94** ($R^1 = R^2 = H$, $R^3 = C_5H_{11}$) gave (*R*)-(−)-1-octene-3-ol of only 29% optical purity, while rearrangement of (*R*)-(*Z*)-**94** ($R^1 = R^3 = H$, $R^2 = C_5H_{11}$) gave (*S*)-(+)-1-octene-3-ol with greater than 80%



optical purity. These results indicate that the predominant transition state conformation in both cases is *endo*, and that the energy difference between *exo* and *endo* conformations for the (*E*)-sulfoxide is small (~ 0.5 kcal mol^{-1}), but considerably larger (~ 1.5 kcal mol^{-1}) for the (*Z*)-isomer[153], due to unfavorable steric interactions between the aryl group and the R^2 substituent in the *exo* conformation.

Rearrangement of sulfoxides **96a,b** exhibited the interplay of several conformational factors. Both diastereomers afford predominant *axial* (*trans*) alcohol, but with opposite absolute configuration. The (*R,R*)-diastereomer strongly prefers the *exo*-transition state, whereas the (*R,S*)-isomer prefers the *endo* conformation. Hoffmann interprets these results in terms of an approximately 3-fold preference for the *exo*-trnasition state but a sixfold preference for formation of an axial bond, these effects reinforcing each other in one isomer but opposing each other in the second.

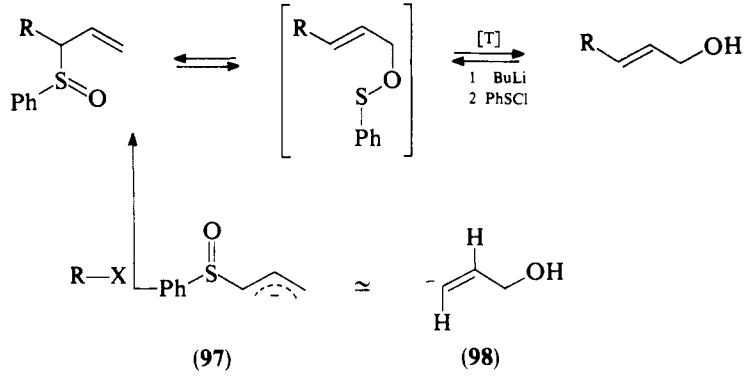


(96a) (*R,R*) ⟶ 95%(1*S*, 5*R*) + 5%(1*R*, 5*R*)

(96b) (*R,S*) ⟶ 65%(1*R*, 5*S*) + 35%(1*S*, 5*S*)

(*iii*) *Configuration of the double bond.* One of the first synthetic applications of the allylic sulfoxide–sulfenate interconversion has been a general stereoselective synthesis of allylic alcohols of defined double-bond geometry. Evans and coworkers[130, 131, 159] have first demonstrated the synthetic utility of the completely reversible allylic sulfoxide–sulfenate rearrangement as a potential new allylic alcohol synthesis, as illustrated in equation 43. This functional group transposition operation also demonstrates the utility of the relatively stable allylic sulfoxide anion **97** as a synthetic equivalent for the hypothetical vinyl anion **98**. In addition to its mildness and its efficiency, this allylic alcohol synthesis also leads, with a high degree of selectivity (>95%) via the transoid transition state **99**, to products of the *E* configuration. The high degree of stereoselectivity observed is easily rationalized by examination of the envelope conformation for the five-membered cyclic transition state (equation 44) which indicates that an R substituent at the α-carbon in the sulfoxide should prefer the equatorial position, leading to the production of *E*-alkenes.

This stereoselectivity, which is independent of stereochemistry at sulfur[122, 123], has subsequently been confirmed by other investigators for the synthesis of a variety of mono-[160–163] and disubstituted[164–180] allylic alcohols. The synthetic utility of the analogous reversible allylic selenoxide rearrangement has been recently reviewed[76].



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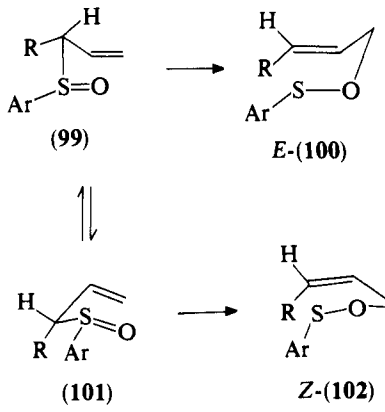
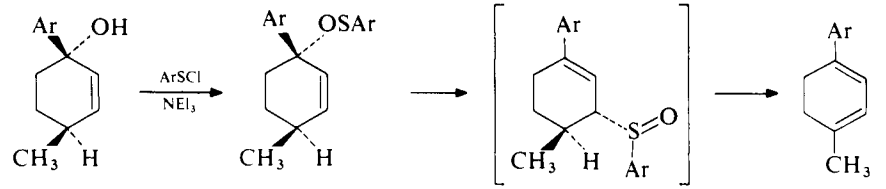
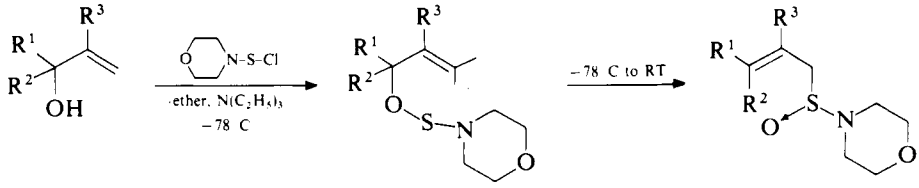


(44)

c. General synthetic utility. In addition to the synthetic applications related to the stereoselective synthesis of various systems, especially natural products described in the previous subsection, a variety of general synthetic uses of the reversible [2,3]-sigmatropic rearrangement of allylic sulfoxides has been reported[181–200]. Several investigators[181–189] have employed the allylic sulfenate-to-sulfoxide equilibrium in combination with the *syn* elimination of the latter as a method for the synthesis of conjugated dienes (equation 45)[181, 182]. Other synthetic applications include conjugated enones[190–195], various heterocyclic systems[196–199] and allylic sulfinamides (equation 46)[200].

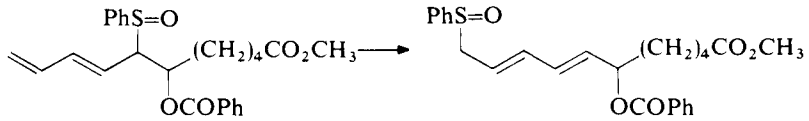


Ar = 2,5-$Cl_2C_6H_3$ Ar′ = 2,4-$(NO_2)_3C_6H_2$ (45)



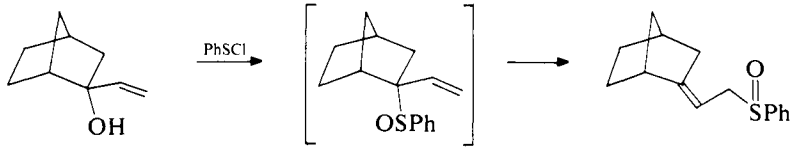
(46)

d. Consecutive sulfoxide-sulfenate rearrangements. The occurrence of double [2,3]-sigmatropic shifts involving both allylic sulfoxide–sulfenate–sulfoxide[201–205] and sulfenate–sulfoxide–sulfenate[206, 207] rearrangements has been reported. For example, during their work on the synthesis of leukotrienes, Corey and Hoover[204] have noted the unusual facility of the double [2,3]-sigmatropic rearrangement of sulfoxide **103** to **104** and explained the ratio of **104**/**103** in excess of 20 by the stabilization achieved from the internalization of the diene unit (equation 47). An example of the other version of the double [2,3]-sigmatropic rearrangement, involving the sequence sulfenate→sulfoxide→ sulfenate, is an effective 'one-pot' epimerization of bicyclic tertiary allylic alcohols, such as the epimerization of the *endo* alcohol **105** to its *exo* epimer **106** (equation 48)[207]. An *exo* to *endo* ratio of 8 to 1 was obtained in this case.

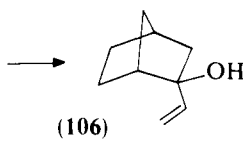


(47)

(103) (104)



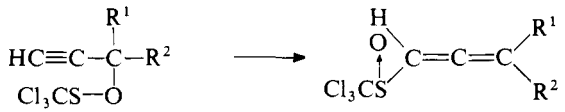
(105) (48)



(106)

3. [2,3]-Sigmatropic rearrangements of propargylic sulfenates to allenic sulfoxides

The [2,3]-sigmatropic rearrangement of propargylic sulfenates to allenic sulfoxides, like the analogous rearrangement of propargylic sulfinates[107, 208, 209], has been discovered by the present author. Thus Braverman and Stabinsky[210] first reported that propargyl, α-phenylpropargyl and α,α-dimethylpropargyl trichloromethanesulfenates (**107a–c**) are transformed spontaneously at low temperatures to allenyl, γ-phenylallenyl and γ,γ-dimethylallenyl trichloromethyl sulfoxides (**108a–c**), respectively (equation 49). This observation is suggestive of a concerted mechanism for this [2,3]-sigmatropic rearrangement as well. The great enhancement in rate of rearrangement of propargyl sulfenates as compared with the corresponding sulfinates[209] is reasonably ascribed to the greater nucleophilicity of the sulfur atom in the first compounds. In support of the postulated concerted mechanism, it was subsequently shown by Smith and Stirling[211] that treatment of (*R*)-(+)-α-methylpropargyl alcohol with *p*-toluenesulfenyl chloride in pyridine at −75 °C gave (*S*)-(−)-γ-methylallenyl *p*-tolylsulfoxide, as predicted for a suprafacial [2,3]-sigmatropic shift[211].

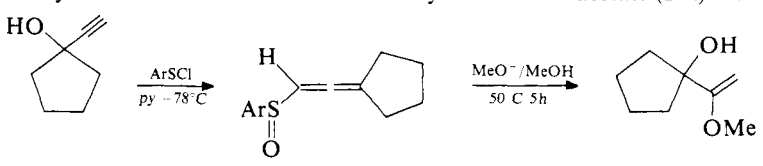


(**107**) (**a**)$R^1 = R^2 = H$ (**108a–c**)

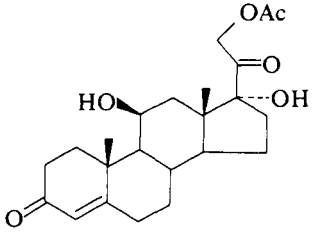
(**b**)$R^1 = H$, $R^2 = Ph$

(**c**)$R^1 = R^2 = Me$ (49)

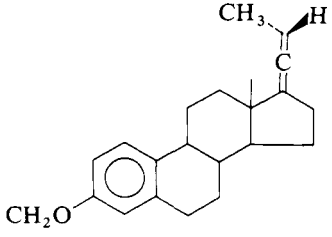
In one of its earliest applications, Horner and Binder[212] prepared a variety of allenyl aryl sulfoxides by the rearrangement of propargylic arenesulfenates, and reported some useful transformations of the former, as illustrated in equation 50. The conversion of the allenyl sulfoxide **110** to the enol ether **111** involves α,β-addition of the solvent and sulfoxide–sulfenate rearrangement of the allylic sulfoxide thus generated. The sequence shown in equation 50 was subsequently used for an efficient and stereoselective introduction of the dihydroxyacetone side-chain at the C-17 position of 17-keto steroids, and a new synthesis of corticosteroids such as hydrocortisone acetate (**112**)[213].



(**109**) (**110**) 90% (**111**) (50)

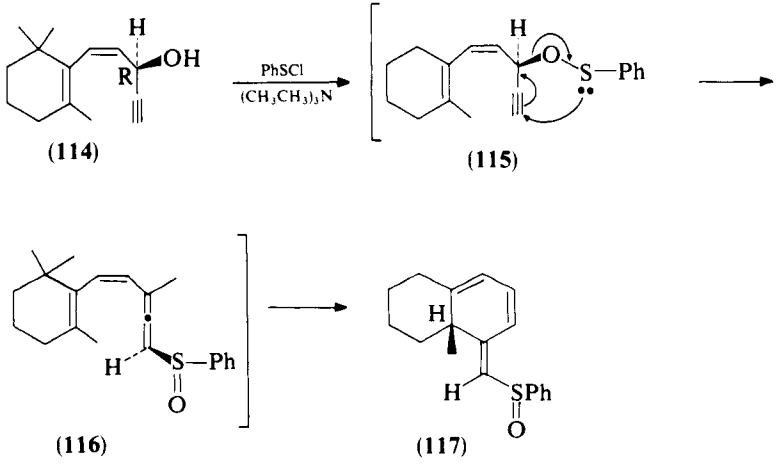


(**112**)



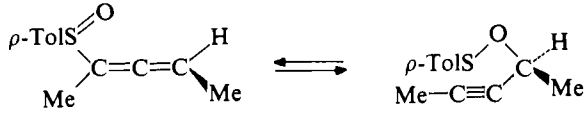
(**113**)

The synthetic utility of the [2,3]-sigmatropic rearrangement of propargylic sulfenates has been further demonstrated in a variety of preparations and interesting reactions of allenyl sulfoxides[214-233] including the preparation of steroidal allenes (e.g. **113**)[214, 215], polysubstituted butadienes[211, 216, 217] and conjugated vinylallenes[218-225] which are useful intermediates in organic synthesis in general[234] and natural products such as Vitamin A and D, in particular[225]. To cite Okamura[223], 'in our experience, the pericyclic transformations (e.g. the sulfenate ester–sulfoxide rearrangement) of chiral propargyl alcohols to chiral allenes represent the most reliable approach for achieving complete enantioselectivity in the preparation of allenes'. A typical example, taken from the extensive studies by Okamura and coworkers[218-225], illustrating an apparently unprecedented stereospecific tandem center→axis→center chirality transfer process, is shown in equation 51. Thus, reaction of optically active *cis*-propargyl alcohol **114** (84% ee) with benzenesulfenyl chloride afforded sulfoxide **117** which was shown to have retained its stereochemical integrity (84% ee) during its formation, via [2,3]-sigmatropic rearrangement of ester **115** to sulfoxide **116** and electrocyclization of the latter to the final product.



(114) (115) (116) (117) (51)

Unlike the rearrangement of allylic sulfoxides to sulfenates, the rearrangement of allenic sulfoxides to propargylic sulfenates has received relatively little attention so far. Stirling and coworkers[235, 236] have shown that (−)-α,γ-dimethylallenyl *p*-tolyl sulfoxide (**118**), which has been assigned an $(S)_S(R)_{allene}$ absolute configuration, undergoes mutarotation on standing at room temperature. Since the optical rotations of the two sulfones obtained by oxidation of **118** before and after mutarotation are practically the same, it has been concluded that chirality of the allene is unaffected and that epimerization must occur at chiral sulfur only. Thus, mutarotation is believed to involve the stereospecific suprafacial equilibration of sulfoxide **118** and sulfenate **119**, as shown in equation 52.

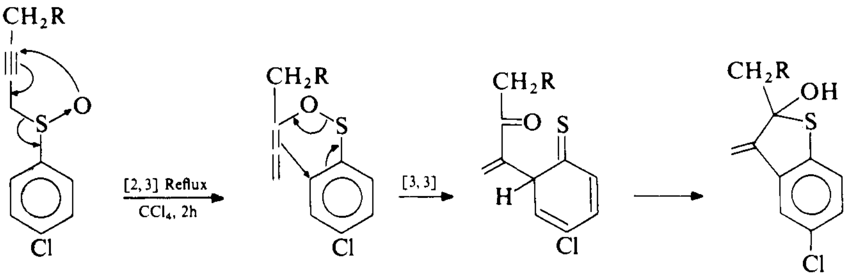


(118) $[\alpha]_D = 120°$ (119) (52)

B. Rearrangements of Sulfoxides to Sulfenates

1. Thermal rearrangements

Analogous with the rearrangement of allylic sulfoxides is the [2,3]-sigmatropic rearrangement of propargylic sulfoxides to allenic sulfenates. This process, which has been relatively little studied so far, appears to be the first step in the facile and quantitative rearrangement of sulfoxide **120** to the hemithioacetal **123** (equation 53)[237], and is the basis of a convenient synthesis of condensed thiophens[238].



(**120**) (**121**) (**122**) (**123**)

(53)

A somewhat unusual thermal rearrangement of α-alkoxy and α-dialkylaminomethyl aryl sulfoxides has also been reported[239, 240]. For example, in the reaction of sulfoxide **124** with secondary amines **125a–c**, the *p*-toluenesulfenamides **126a–c** were obtained quantitatively, instead of the expected α-aminomethyl *p*-tolyl sulfoxides **128** (equation 54). Based on the stoichiometry of the reaction, the following reaction scheme has been suggested by the authors[239]. Subsequently, another group[240] reported that methoxymethyl phenyl sulfoxide (**129**) rearranged completely to methoxymethyl benzenesulfenate **130** in two days at 36 °C, and suggested an intramolecular S→O 1,2-shift mechanism (equatuon 55).

$$p\text{-Tol—S(=O)—CH}_2\text{Br} + 4\text{RR'NH} \xrightarrow[1\text{-}2\,\text{h}]{70\,^\circ\text{C}} p\text{-TolSNRR'} + \text{RR'NCH}_2\text{NRR'}$$

(**124**) (**125**) (**126a–c**) (**127a–c**)

$$+ \ \text{RR'NH·HBr} + \text{H}_2\text{O}$$

(**a**) R, R′ = morpholino
(**b**) R, R′ = piperidino
(**c**) R = R′ = Et

(54)

$$\text{Ar—S(=O)—CH}_2\text{X} \xrightarrow{2\text{RRNH}} \text{Ar—S(=O)—CH}_2\text{NRR'} + \text{RR'NH·HX}$$

X = Cl, Br (**128**)

$$\mathrm{ArS(O)-CH_2NRR' \rightleftharpoons ArS-O-CH_2NRR'}$$

$$\mathrm{ArS-O-CH_2NRR' \xrightarrow{RR'NH} ArSNRR' + RR'NCH_2OH}$$

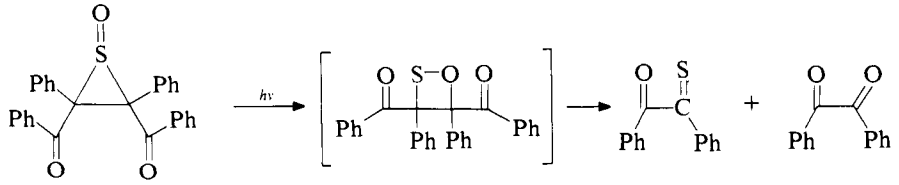
$$\mathrm{RR'NCH_2OH \xrightarrow{RR'NH} RR'NCH_2NRR' + H_2O}$$

$$\mathrm{PhS(O)CH_2OCH_3 \longrightarrow PhS-OCH_2OCH_3} \qquad (55)$$

(129) (130)

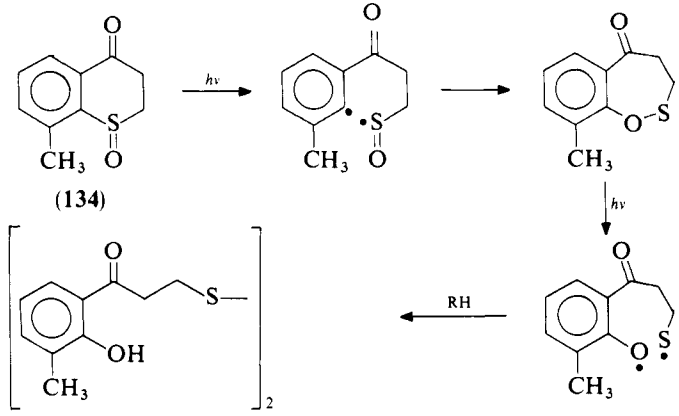
2. Photochemical rearrangements

Some interesting photochemical reactions observed for the sulfoxide group involve the conversion of a cyclic sulfoxide to a ring-expanded sulfenate, which usually undergoes further transformation under the reaction conditions[241-247]. For example, ultraviolet irradiation of dibenzoylstilbene episulfoxide (**131**) in benzene afforded monothiobenzil (**133**) and benzil, presumably by initial rearrangement to a β-sultene intermediate (**132**) which undergoes fragmentation to the observed products (equation 56)[241].



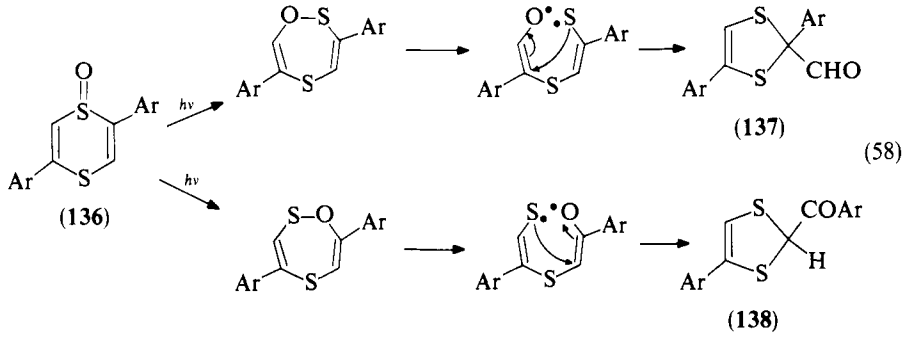
(131) (132) (133) (56)

The photochemical behavior of a number of substituted derivatives of thiochroman-4-one 1-oxides has been examined by Still and coworkers[244-246]. These authors also report that rearrangement to cyclic sulfenates, with subsequent reaction by homolysis of the S–O bond, appears to be a particularly favorable process. For example, irradiation of a



(134) (135) (57)

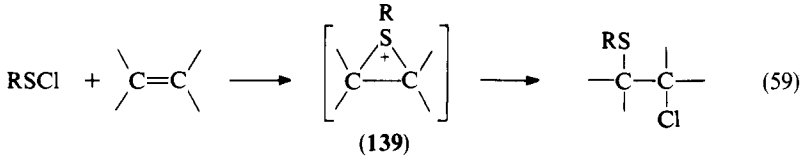
solution of **134** in benzene for 24 h afforded a single crystalline product which was assigned the disulfide structure **135** (equation 57). More recently, Kobayashi and Mutai[247] have also suggested a sulfoxide–sulfenate rearrangement for the photochemical conversion of 2,4-diphenyl-1,4-dithiin 1-oxide (**136**) to the 1,3-dithiole derivatives **137** and **138** (equation 58).



(58)

IV. REARRANGEMENTS INVOLVING SULFENYL HALIDES

In contrast to other acid halides, sulfenyl halides add smoothly to carbon–carbon and carbon–nitrogen multiple bonds. Although the addition of sulfenyl halides to simple olefins has long been known[248], the fundamental work on this reaction was made by Kharasch and his coworkers[249–254]. Since the electrophilic addition of sulfenyl halides appears to be one of the most efficient ways to transform alkenes into synthetically useful products, it has been extensively studied and reviewed[253–263]. The classical mechanistic description of this process suggests rate-determining formation of an episulfonium or thiiranium ion (**139**, equation 59) which undergoes a nucleophilic ring opening by halide ion in the second step[249–254]. Support in favor of the proposed intermediacy of thiiranium ions during sulfenyl chloride addition was derived from almost exclusive *trans*-stereospecific addition observed[264, 250, 251] over a wide temperature range[265].



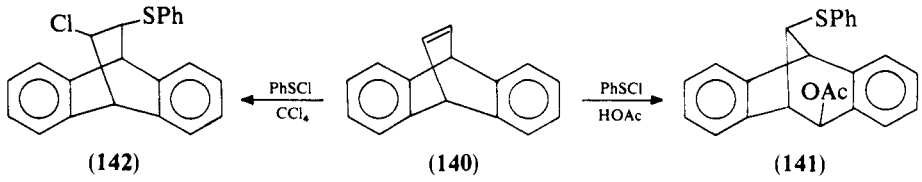
(59)

In certain cases and under certain conditions, the addition of sulfenyl halides to multiple bonds may also be accompanied by rearrangement. These rearrangements may be classified into two groups. The first type includes skeletal rearrangements of the intermediate thiiranium ion, whereas the second type results from intramolecular addition of the sulfenyl halide group to an unsaturated site, present in the molecule. These two processes are described below.

A. Skeletal Rearrangements

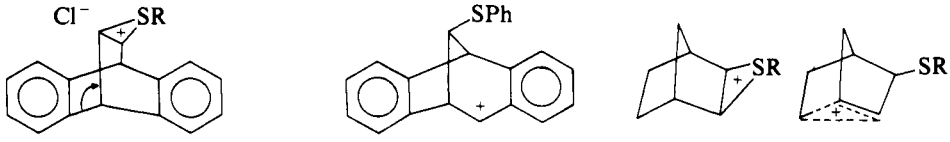
One of the first skeletal rearrangements involving the addition of a sulfenyl halide to an unsaturated bicyclic system has been reported by Cristol and coworkers[266–268]. These

authors observed that reaction of dibenzobicyclo[22.2]octatriene (**140**) with benzenesulfenyl chloride in acetic acid as solvent gives mainly rearranged acetate **141**, but gives the unrearranged *trans*-adduct **142** in carbon tetrachloride or ethyl acetate as solvent[266, 268] (equation 60). The authors[268] consider that collapse of the intermediate thiiranium ion pair **143** is rapid in aprotic media, but that solvation by acetic acid reduces the nucleophilicity of the chloride ion, allowing **143** to rearrange to the benzylic cation **144** which then collapses to **141**.



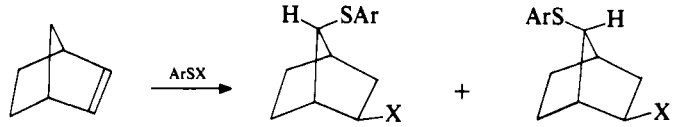
(142) **(140)** **(141)**

(60)



(143) **(144)** **(145a)** **(145b)**

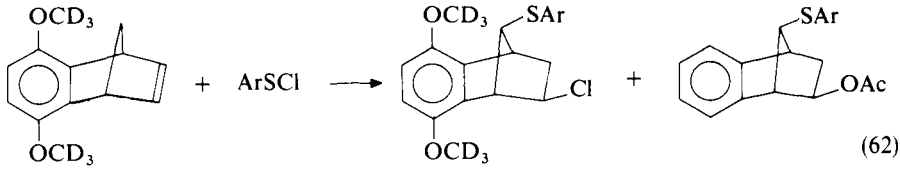
Earlier studies by Cristol[266, 269] and by Kwart[270, 271] failed to detect substantial skeletal rearrangement with either norbornene or norbornadiene, and was interpreted to result from the special stability of the episulfonium ion **145a** which does not readily rearrange to the nonclassical ion **145b**. More recently, however, and through the detailed and elegant studies by Zefirov and coworkers, it has been shown that this may be modified by the addition of strong electrolytes such as $LiClO_4$ in acetic acid. This method, also referred to as 'doping-addition', has led to some spectacular results. Thus, the addition of arylsulfenyl chloride to norbornene in the presence of $LiClO_4$ results in the formation of the rearranged *syn*- and *anti*-acetates **146** and **147**, as the main products (equation 61)[272, 273].



(146) **(147)**

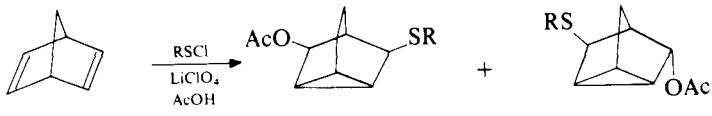
(61)

The addition of 2,4-dinitrobenzenesulfenyl chloride to dimethoxybenzonorbornene **148** in acetic acid results in the predominant formation of the rearranged chloride **149** (equation 62), but in the presence of $LiClO_4$ the formation of the rearranged acetate **150** is predominant[274]. This may indicate a shift from an ion-pair to a more dissociated type of ionization, facilitating the concurrent attack by solvent.



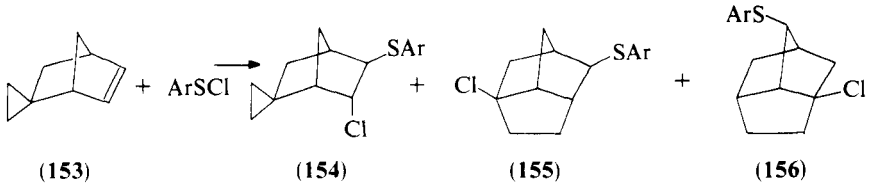
(148) (149) (150) (62)

In the case of norbornadiene, the addition of sulfenyl chloride in the presence of $LiClO_4$ proceeds with homoallylic participation of the second double bond and gives a mixture of the two nortricyclenic acetates **151** and **152** (equation 63)[275]. More recently, it has been shown by Adam and coworkers that high yields of rearranged products can also be achieved in the absence of added salts, when electron-deficient arenesulfenyl chlorides are reacted with electron-rich benzonorbornadiene derivatives[276].

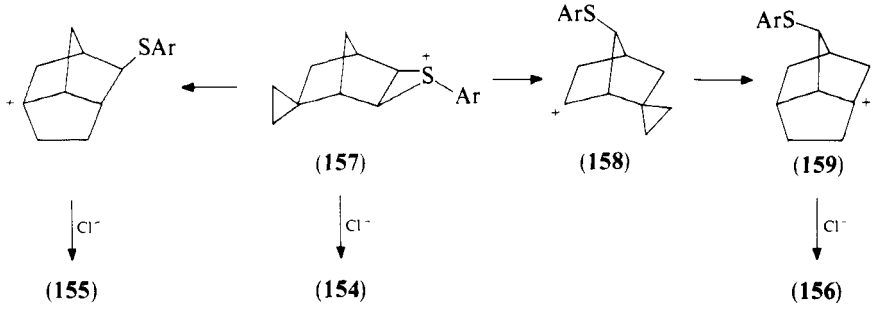


(151) (152) (63)

The same authors[277] have examined the behavior of cyclopropyl substituted norbornenes in the reaction with *p*-toluenesulfenyl chlorides. The reaction of **153** gives a mixture of three products, **154**, **155** and **156**, in a 2:5:3 ratio (equation 64). The last two products are brendane derivatives, which are generated by rearrangement and/or ring expansion of thiiranium ion intermediate **157**, as shown below.

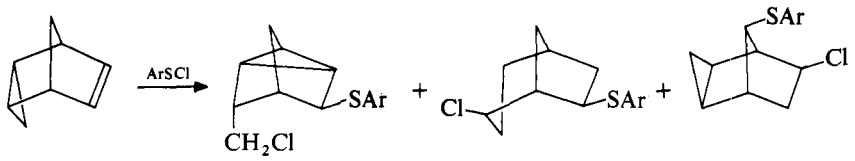


(153) (154) (155) (156) (64)

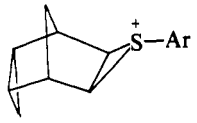


(155) (157) (158) (159) (154) (156)

Similarly, the reaction of *endo*-fused cyclopropylnorbornene **160** with the same reagent gives a mixture of chlorosulfides **161–163**, formed by skeletal rearrangement of thiiranium ion intermediate **164**.

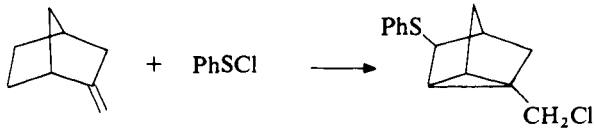


(160) **(161)** **(162)** **(163)**



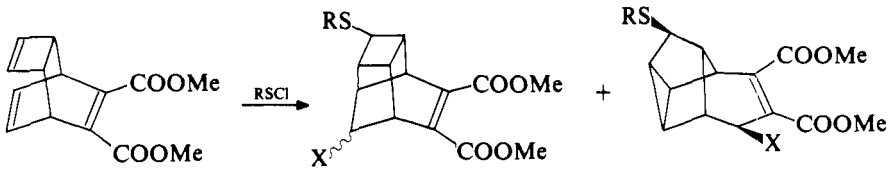
(164)

Addition of benzenesulfenyl chloride to 5-methylene-2-norbornene leads to the rearranged nortricyclyl phenyl sulfide shown in equation 65[278]. This reaction has been employed in the synthesis of several interesting natural products, components of East Indian sandalwood oil[279].

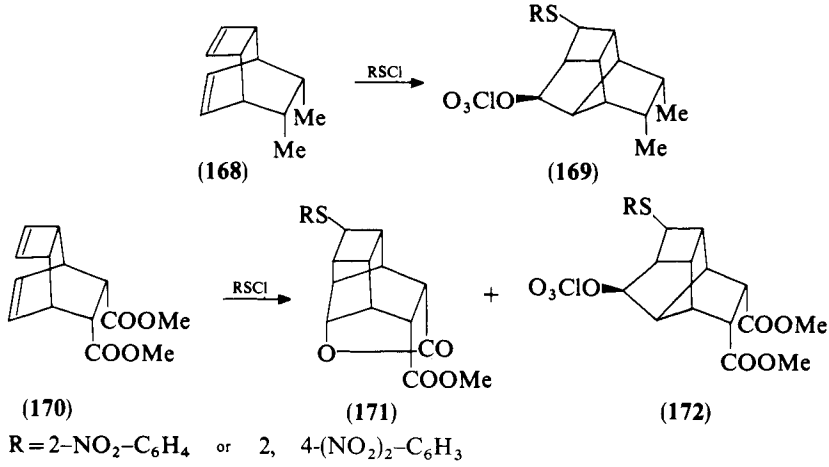


(65)

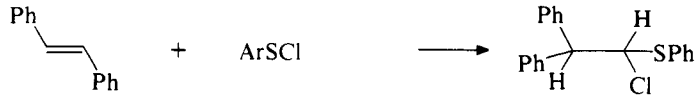
The reactions of tricyclic olefins **165**, **168** and **170** with sulfenyl chlorides in the presence of lithium perchlorate have been studied by Zefirov and coworkers[280–283], and are of particular interest due to their extensive skeletal rearrangements. For example, substrate **165** affords a mixture of the polycyclic sulfides **166** and **167**. The ratio of these products depends on the nature of the sulfenyl chloride, solvent polarity and concentration of the added salt. On the other hand, hydrocarbon **168** reacts with sulfenyl chlorides in diethyl ether with a different type of skeletal rearrangement, and affords the covalent perchlorate **169**, as the only product in very high yields. This is a rather rare case of perchlorate isolation. Perchlorate formation has also been detected in the rearrangement of hydrocarbon **170**, though lactone **171** is the major product in this case, as expected.



(165) **(166)** **(167)**



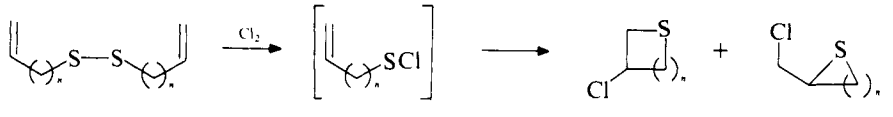
Finally, the occurrence of some 1,2-aryl migration during the addition of sulfenyl halides has also been observed[284, 285], as shown in the following equation.



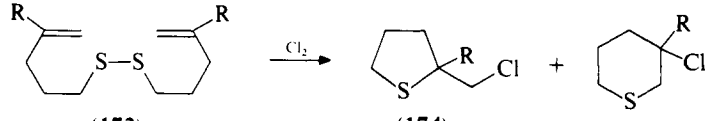
B. Intramolecular Cyclizations

Intramolecular cyclization is one of the most popular strategies for the synthesis of heterocyclic systems, often involving carbon–carbon multiple bonds. A wide variety of intramolecular cyclizations of alkenes, alkynes and other unsaturated functionalities, involving or promoted by sulfenylating agents, has been used for the synthesis of heterocyclic compounds[1, 4, 262]. The utility of this powerful tool is further enhanced by the presence of an alkyl- or arylthio group, which allows further modifications to be carried out, such as the introduction of a double bond by its oxidative elimination. The simplest reaction of this type is the intramolecular addition of sulfenyl chloride to an unsaturated site, resulting in the formation of a thia-heterocyclic product. The unsaturated site may in turn involve carbon–carbon or carbon–nitrogen multiple bonds. The sulfenyl halide functionality is usually generated *in situ* by various methods, including halogenation of a disulfide and addition of sulfur dichloride or some other bis-sulfenyl chloride to a dienic system.

The general scheme for the first method involving a variety of olefinic or acetylenic disulfides[286–290] is presented in equation 66, and a specific example is shown in equation 67. Thus, reaction of disulfide **173** with chlorine produces a mixture of thiolane **174** and thiene **175** (equation 67)[287]. These two products, which represent the *exo*- and *endo*-cyclization of the corresponding sulfenyl chloride, respectively, can however interconvert, with the kinetic product **174** being transformed into the thermodynamic product **175** on standing at room temperature. A similar phenomenon has also been reported for the chlorination of the disulfide **176** which affords a mixture of bicyclic products **177** and **178** in the ratio 7:3 (equation 68). However, on standing this mixture is transformed into pure **177**.

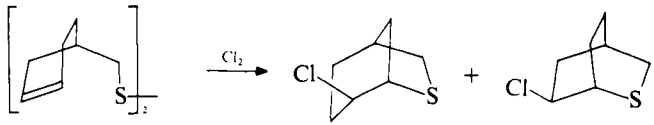


(66)



(173) (174) (175)

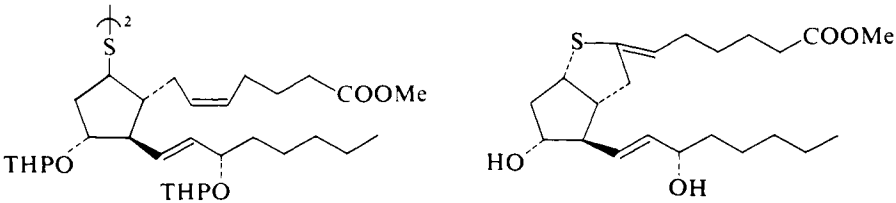
(67)



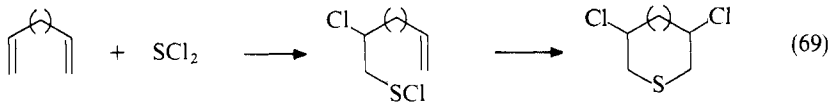
(176) (177) (178)

(68)

This sulfenyl cyclization has been used as the key step in the synthesis of thiaprostacyclin **180** by bromination of the disulfide **179**, followed by dehydrobromination and deprotection of the hydroxy groups[288]. Subsequently, the halogenation of appropriate thiols has also been used[291, 292] for the synthesis of **180**.

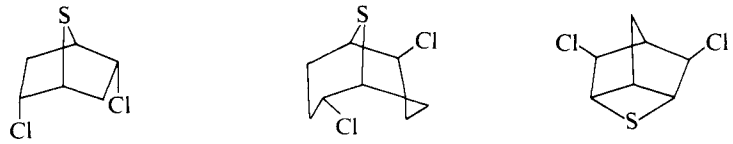


(179) (180)

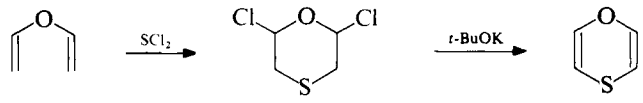


(69)

As mentioned above, an alternative method for the *in situ* generation of the unsaturated sulfenyl halides is to react a conjugated or nonconjugated diene with sulfur dichloride[293–296] as shown in equation 69. A variety of cyclic and bicyclic systems can be obtained by this reaction using acyclic and cyclic dienes, respectively. For example, thiaheterocycles **181**, **182** and **183** have been obtained by reaction of sulfur dichloride with 1,4-cyclohexadiene, 1,5-cyclooctadiene and norbornadiene, respectively; an application of the same reaction for the synthesis of 1,4-oxathiin is shown in equation 70.

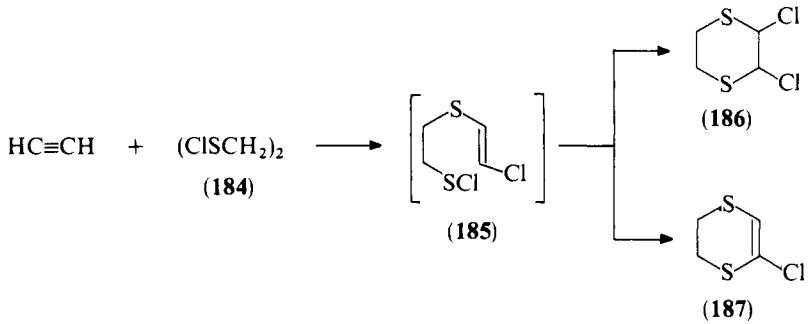


(181) (182) (183)



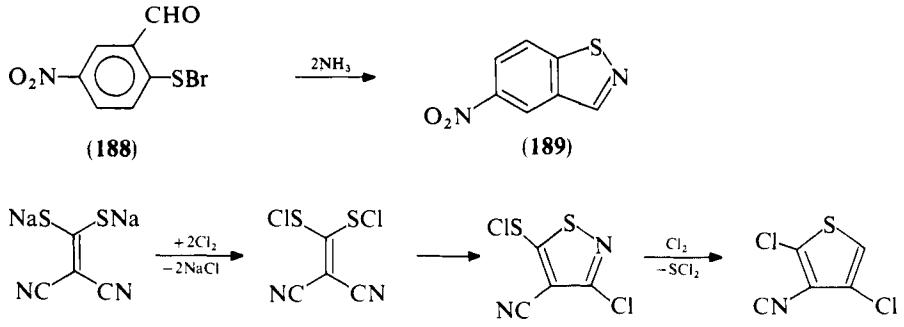
(70)

Similar to the reaction of sulfur dichloride described above, the bis-sulfenyl chloride **184** reacts with acetylene with repeated addition; the intermediately formed adduct **185** reacts intramolecularly with the sulfenyl chloride residue still remaining to give a mixture of *trans*-1,2-dichloro-1,4-dithiane (**186**) and 2-chloro-5,6-dihydro-1,4-dithiin (**187**)[297].



(184) (185) (186) (187)

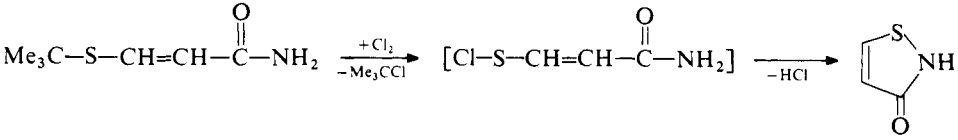
The intramolecular addition of sulfenyl halides to C–N multiple bonds has also been documented[298–300]. For example, the conversion of sulfenyl bromide **188** to 5-nitro-1,2-benzisothiazol (**189**) by treatment with ammonia may be regarded as involving intramolecular addition of the sulfenyl bromide to the imine intermediate, followed by dehydrobromination. Similar reactions involving intramolecular addition of an *in situ* generated sulfenyl chloride to a cyano group have also been reported[299, 300], as illustrated in equation 71.



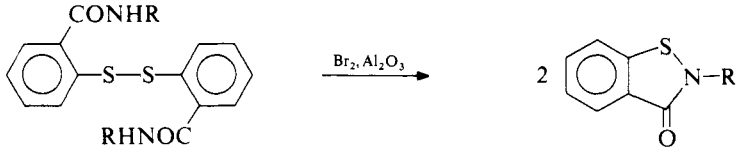
(188) (189)

(71)

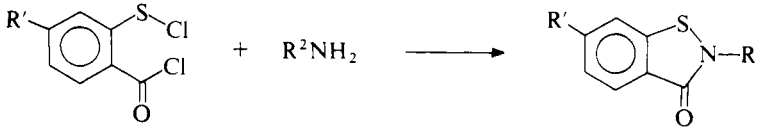
Another type of sulfenylating cyclization is the one proceeding by intramolecular nucleophilic attack on sulfur, rather than by addition of the sulfenyl halide group. An early example of such a reaction is that reported by Leonard and Wilson[301] and shown in equation 72. Some other examples also resulting in the formation of 3-oxo-1,2-isothiazole derivatives are presented in equations 73 and 74[302-305].



(72)



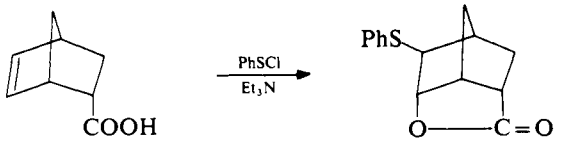
(73)



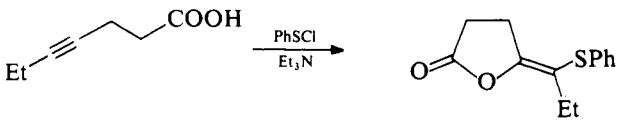
(74)

Besides the intramolecular cyclizations described above which involve direct reaction of a sulfenyl halide functionality, there are also a wide variety of intramolecular cyclizations which are promoted by sulfenyl halides. In this process, which applies to unsaturated carboxylic acids, alcohols, amines and amides, the sulfenyl halide provides electrophilic activation of the carbon–carbon double bond by formation of the corresponding episulfonium ion intermediate. Since this reaction has recently been reviewed by Capozzi and coworkers[262], only representative examples are presented below.

The lactonization of unsaturated carboxylic acids promoted by electrophilic attack by a sulfenyl chloride at the carbon–carbon multiple bond generally requires the presence of a tertiary amine base[306-310] and is illustrated by equations 75 and 76. It is interesting to note that in the absence of base the reaction shown in equation 76 does not take place, but rather simple addition of the benzenesulfenyl chloride to the triple bond occurs[310]. Furthermore, the reaction shown in equation 75 is regiospecific, whereas the PhSCl addition proceeds with practically no regiocontrol.

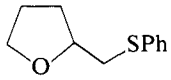


(75)

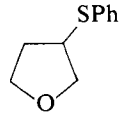


(76)

Cyclic ethers with four- to seven-membered rings have also been synthesized by the use of sulfenyl halide promoted intramolecular cyclization of alkenols[311]. Generally, *exo*-cyclization is favored, unless thermodynamic factors oppose this trend. Thus, cyclization of 4-penten-1-ol affords cyclic ether **190**, whereas cyclization of 3-buten-1-ol results in the formation of cyclic ether **191**, upon reaction with benzenesulfenyl chloride, in the presence of triethylamine. The *endo*-cyclization observed in the latter case avoids formation of a four-membered ring, which has much greater strain than the five-membered analog actually produced[311].

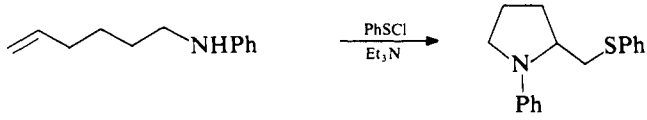


(190)

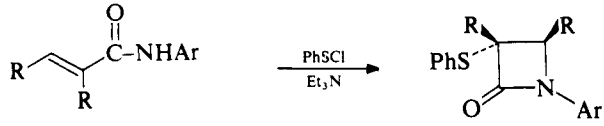


(191)

Sulfenocyclization has also been used for the syntheses of various aza-heterocycles, including arylthio-substituted pyrrolidines, piperidines and β-lactams[312-314]. Similar to the cyclization of alkenols, *exo*-cyclization is also preferred in this case, except for thermodynamically disfavored cases, as exemplified by equation 77 and 78.



(77)

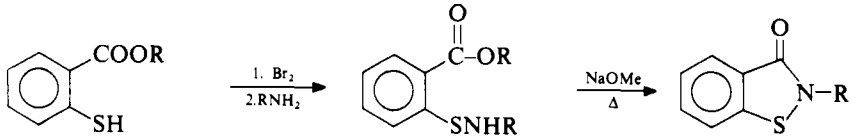


(78)

V. REARRANGEMENTS INVOLVING SULFENAMIDES

A. Intramolecular Cyclizations

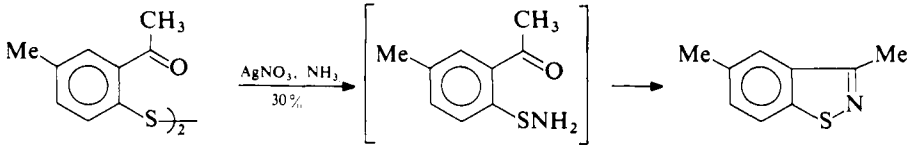
The preparation of 1,2-benzisothiazole derivatives, described in the preceding section (equations 73 and 74), can also be achieved by an alternative intramolecular cyclization, involving the condensation of arylsulfenamides possessing an *ortho*-carbonyl function[315-317]. Thus, the sequential conversion of 2-mercaptobenzoic acid by esterification, halogenation to the sulfenyl chloride, conversion to the sulfenamide and cyclization with a strong base gives 1,2-benzisothiazolin-3-one in good yield (equation 79)[315].



(79)

The cyclization step is believed to involve substitution at the carbonyl group of the ester by the conjugate base of the sulfenamide. Alternatively, the sulfenimine synthesis[316] can

be utilized as an intramolecular condensation to give 3,5-dimethyl-1,2-bezisothiazole in a one-step synthesis (equation 80).



(80)

B. Sigmatropic Rearrangements

Analogous to the well-known [2,3]-sigmatropic rearrangement of allylic sulfoxides to sulfenates, discussed in Section III, is the [2,3]-sigmatropic rearrangement of allylic sulfilimines to sulfenamides, first discovered by Challenger and Greenwood[318]. Thus, reaction of chloramine *T* with diallyl sulfide gives, within seconds at room temperature in aqueous medium, a crystalline sulfilimine product (**192**). The latter is not stable, but is converted into an oil after several days at room temperature, or rapidly at 100°C, identified as *N*-allyl-*N*-tosyl-allylsulfenamide (**193**, equation 81)[319].

(**192**) (**193**) (81)

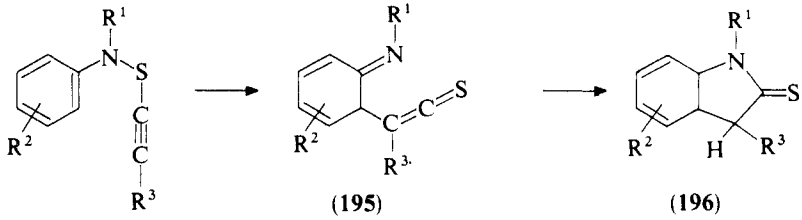
Further studies by the same and other authors[320-323] indicated that this reaction is quite general and conforms with the requirements of a concerted process. Thus, when cinnamyl phenyl sulfide and chloramine *T* interact, the sulfilimine cannot be isolated, but immediately isomerizes to *N*-α-phenylallyl-*N*-tosylbenzenesulfenamide (equation 82). The isomerization of the sulfilimine is therefore accompanied by allylic shift, even in this extreme case[321]. As previously noted, cinnamyl sulfenates have failed to undergo such a shift and, in the case of allylic sulfenates, the sulfoxides are thermodynamically more stable products.

(82)

Although tnere was little evidence that a nitrene intermediate was formed from chloramine *T* in the above reactions, it was subsequently shown that addition of *N*-nitrenes to allyl aryl sulfides gives *N*-(heretocyclic) sulfenamides by [2,3]-sigmatropic rearrangement of the initially formed sulfilimines[324, 325]. Recently, the application of the [2,3]-sigmatropic rearrangement of allylic sulfilimines to a stereocontrolled synthesis of unsaturated vicinal diamines has also been reported[326].

Besides the [2,3]-sigmatropic rearrangements mentioned so far, a [1,3]- and a [3,3]-sigmatropic rearrangement involving sulfenamides have also been published[327, 328]. For example, *N*-aryl-1-alkyne-sulfenamides **194** undergo a thermal [3,3]-sigmatropic rearrangement to indoline-2-thiones (**196**)[328]. The sulfenamides are obtained by reaction of

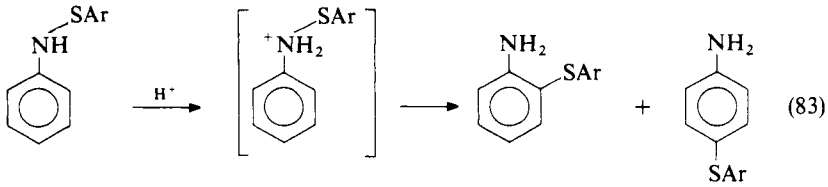
bromomagnesium benzeneamides with 1-alkynyl thiocyanates and are believed to rearrange first to intermediate thioketenes **195**, followed by cyclization to the observed products.



(194) (195) (196)

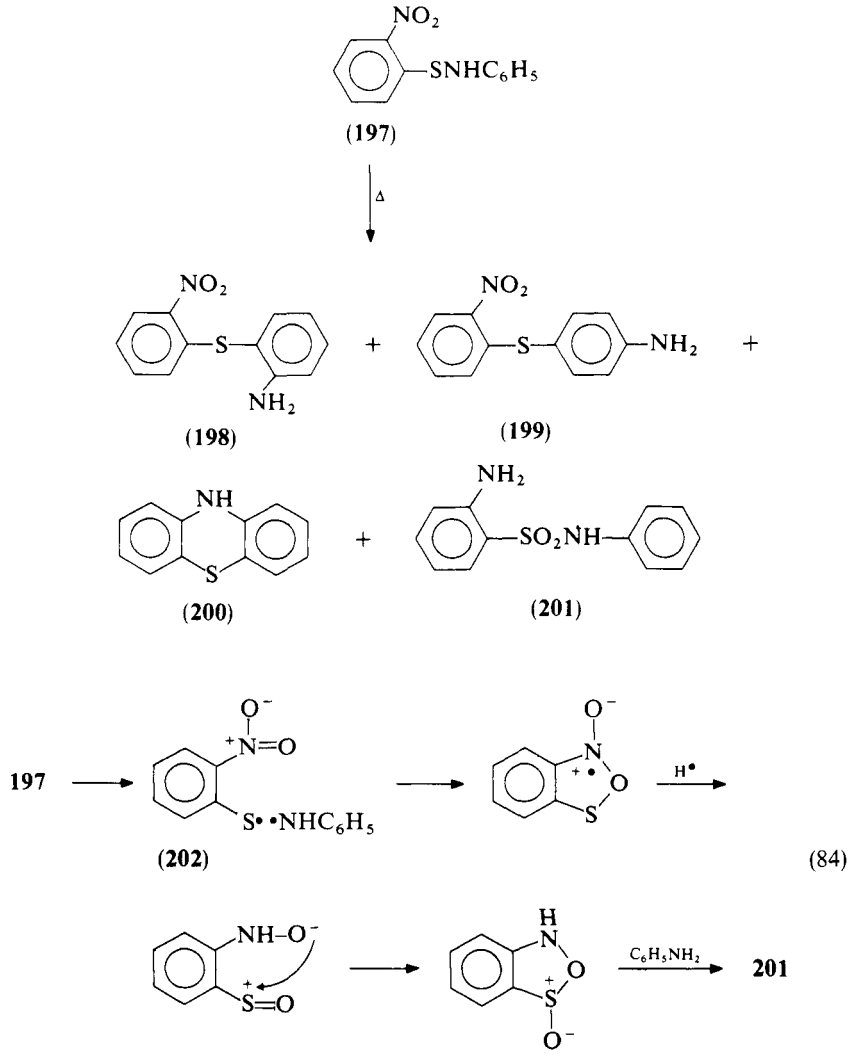
C. Thermal Rearrangements

Apparently, the best known rearrangement of sulfenamides is the thermal rearrangement of arenesulfenanilides to aminophenyl aryl sulfides[329-337], first reported by Zincke and Eismayer[329]. Later, the rearrangement of various sulfenanilides was studied by Moore and Johnson[330], and more recently by Davis[331-335] as well as other workers[336, 337]. This rearrangement which is analogous to the famous benzidine rearrangement is also acid catalyzed, suggesting the involvement of the conjugate acid of the sulfenamide in the transition state for rearrangement (equation 83). The rearrangement is particularly assisted by electron-donating groups on sulfur and, like the benzidine rearrangement, is believed to take place by an intramolecular mechanism. Support for this mechanism was provided by the failure of trapping experiments and the high *ortho/para* ratio observed[335]. However, in certain cases, the reaction may be, at least in part, intermolecular[337]. A caged ion (ArS^+NH_2Ph) was also considered[335], but it was ruled out since 2-phenylbenzenesulfenanilide failed to form dibenzothiophene under the reaction conditions, as expected.

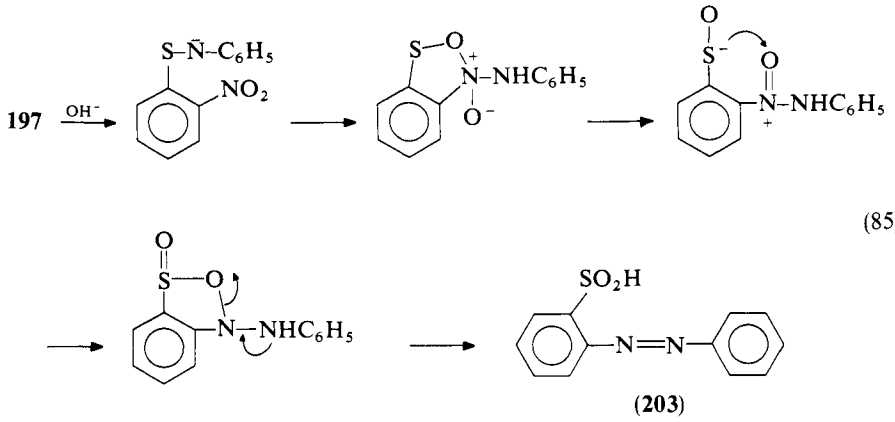


(83)

Of special interest is the thermal rearrangement of 2-nitrobenzenesulfenanilides, which may be accompanied by transfer of oxygens from the nitro group to sulfur and formation of byproducts resulting from reduction of the nitro group and oxidation of sulfur. This type of behavior, which is also observed in the thermal rearrangement of 2-nitrobenzenesulfenates[105], is well known and quite general for *ortho*-substituted aromatics[338]. Thus, on heating of 2-nitrobenzenesulfenanilide (**197**) in aniline at 195°C for 15 hours, four products were obtained: the 2- and 4-aminodiphenyl sulfides **198** and **199**, phenothiazine (**200**) and the major product 2-aminobenzenesulfonanilide (**201**)[332]. This reaction was found to give crossover products when carried out in amine solvents other than those in the sulfenamide substrate. While formation of the phenothiazine (**200**) has been shown to result from a thermal Smiles rearrangement of **198**[339], the major product **201** is believed to be formed by an intramolecular oxidation–reduction of the 2-nitrobenzenesulfenyl radical **202**, generated by homolytic cleavage of the S–N bond (equation 84)[333].



A related rearrangement of 2-nitrobenzenesulfenanilide under base-catalyzed conditions has also been reported. Heating of this compound (**197**) in ethanol with sodium hydroxide resulted in rearrangement to 2-azobenzenesulfinic acid (**203**)[340]. Brown[341] has shown that when the rearrangement of **127** is conducted using[18] O-labeled sodium hydroxide solution, essentially zero incorporation of label into the sulfinate anion was observed. These results rule out any mechanism involving oxygenation of sulfur by attack of hydroxide, as previously suggested[340], and clearly show that both oxygens of the NO_2 group are transferred to sulfur. Based on these results and the failure of 4-nitrobenzene sulfenanilide to rearrange, the mechanism shown in equation 85 has been suggested[341] to account for the formation of **203**.



(85)

(203)

VI. MISCELLANEOUS REARRANGEMENTS

Two more derivatives of sulfenic acids, namely the thiosulfinates and thiocyanates, should also be considered with regard to rearrangement. Thiolsulfinates[5] are isomers of the nonexistent sulfenic anhydrides, RSOSR, and were actually considered as such in the older literature. This is similar to the case of sulfinic anhydrides which also exist as the isomeric and thermodynamically more stable sulfinyl sulfones, with but only a few exceptions[5, 15]. In the case of thiolsulfinates, RS-S(O)R, there are no exceptions known and, in addition, this is a rare example where the 'anhydride' is more stable than the corresponding acid. Thiolsulfinates are not only derivatives of sulfenic acids but also of sulfinic acids as well. As such, their rearrangements were fully reviewed by the present author[15]. Therefore, their rearrangements will not be further discussed here, except for those already mentioned in Section II above.

The isomerization of thiocyanates to isothiocyanates is probably the best studied reaction of this functional group. The rearrangement of alkyl thiocyanates is believed to proceed by an ion-pair mechanism, whereas the rearrangement of allylic thiocyanates has been shown to involve a [3,3]-sigmatropic rearrangement. Both rearrangements have been extensively reviewed by Fava[115] who has also been the main contributor to this field. More recently, the isomerization of organophosphorous thiocyanates to isothiocyanates (equation 86) has also received intensive attention, but since the subject has been thoroughly and very recently reviewed by one of its major contributors[342], the reader is referred to that review.

$$R_2P-S-C\equiv N \rightarrow R_2P-N=C=S \tag{86}$$

VII. ACKNOWLEDGMENTS

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER 9

Chemistry of sulphenic acids and esters

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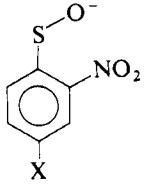
The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

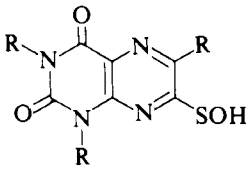
Sulphenic acids, RSOH, are derived from the unknown inorganic acid, H_2SO_2, and hence from the highly reactive and unstable sulphur monoxide, SO. They are a highly reactive species particularly with respect to self-condensation to give thiolsulphinates, RSO. SR, and in the absence of special stabilizing factors such as intramolecular hydrogen bonding or steric hindrance, discussed elsewhere in this volume, they are known under normal conditions only as transient intermediates.

Sulphenate esters, $R^1S–OR^2$, which are isomeric with sulphoxides, are much less reactive than the parent acids and are readily isolable. In general the liquid esters can be distilled at reasonable temperatures but can be sensitive to moisture and air. Like the sulphenyl halides, the stability tends to be increased by the presence of electron-withdrawing groups in the sulphenic acid.

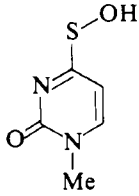
In alkaline solution sulphenic acids rapidly disproportionate to give a mixture of thiolate and sulphinate ions but certain sulphenate anions, notably those derived from 4-substituted-2-nitrobenzenesulphenic acids[1] (**1**) and the lumazine-7-sulphenic acids[2] (**2**), have unusual stability and can be studied in solution. The latter acids (**2**) and 1-methyluracil-4-sulphenic acid[3] (**3**) form relatively stable silver salts.



(**1**)

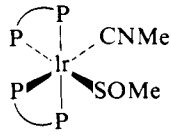


(**2**) R = Me, H



(**3**)

The so-called alkyl *O*-sulphenic acids, ROSH, and their salts, ROS^-M^+, have not as yet been reported and in the absence of special stabilizing factors must be considered to be very reactive. The transition metal sulphenate, $[Ir(\eta^1\text{-SOMe})\,(MeNC)\,(dppe)_2]^{2+}$, has however been prepared from the η^2-S_2OMe analogue by reaction with methyl isocyanate[4].

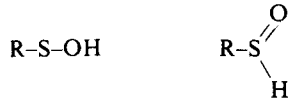


P–P = 1,2-bis(diphenylphosphino)

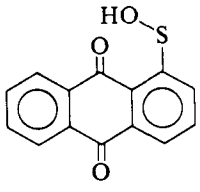
The importance of sulphenic acids as transient intermediates in organic and bio-organic sulphur chemistry is widely recognized[5]. The two most important reactions of the thiol group in living systems are arguably oxidation to disulphides and to higher sulphur acids. These reactions have long been considered to involve sulphenic acid intermediates and recently evidence has been advanced to support these assumptions. As will also be seen, much of the chemistry of the penicillin sulphoxides hinges on ring-opening to give sulphenic acids and their subsequent reactions. In recent years there has been considerable interest in the allylic sulphoxide/sulphenate ester rearrangement which has been widely exploited in synthetic studies and which will be covered elsewhere in this volume.

II. TAUTOMERISM

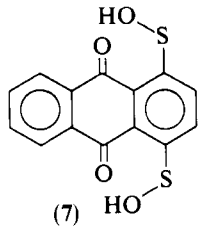
In principle two tautomeric structures, **4** and **5**, can be considered for sulphenic acids. IR studies[6] in solution on anthraquinone-1-sulphenic acid (**6**) and anthraquinone-1,4-disulphenic acid (**7**) favoured the *O*-protonated form (**4**) and this conclusion was supported[7] by similar studies on 9-triptycene sulphenic acid (**8**) and on the solid 2-oxoazetidine-4-sulphenic acids[8] (**9**). Unfortunately the complex nature of these acids and the high degree of polar functionality led to a degree of uncertainty in the location of the protons. In contrast absorptions at 3400 cm^{-1} and 2600 cm^{-1} in the solution IR of 2-methylpropane-2-sulphenic acid were attributed[9] to the *O*-protonated and *S*-protonated tautomers, (**4**) and (**5**), respectively. 1,3, 6-Trimethyllumazine-7-sulphenic acid (**2**; R = Me) in the solid state shows[10] bands at 2500 cm^{-1} (S–H) and 1050 cm^{-1} (S=O) and presumably exists in the *S*-protonated form (**5**), although in solution a comparison of the UV spectrum with that of the methyl-blocked derivatives of the tautomeric forms leads to the conclusion that the *O*-protonated form (**4**) predominates.



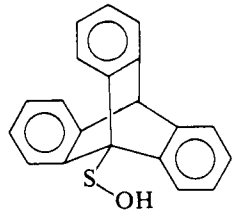
(**4**) (**5**)



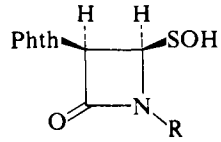
(**6**)



(**7**)

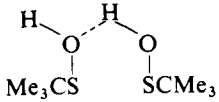


(**8**)



(**9**) R = CH_2=CMeCH(CO_2Me), Me_2C=C(CO_2Me);
Phth = phthalimido

Ab initio calculations[11] with configurational interaction on HSOH and H_2SO concluded that both structures could exist as stable species although the former was the more stable. Studies[12] on the IR spectra of benzenesulphenic acid and 2-methylpropane-2-sulphenic acid, prepared by the flash vacuum pyrolysis of the appropriate *t*-butyl sulphoxides, showed that the spectra varied with temperature. At −196 °C broad OH absorptions were found at 3300 cm^{-1} and weaker absorptions at 2600 cm^{-1} (SH) and 1000 cm^{-1} (S=O) for benzenesulphenic acid, and at 3250 cm^{-1}, 2630 cm^{-1} (SH) and 1060 cm^{-1} (S=O) with 2-methylpropane-2-sulphenic acid. The absorption at 3250 cm^{-1} in the case of the more hindered acid was attributed to the hydrogen-bonded dimer (**10**).



(**10**)

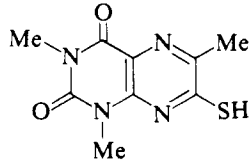
These assignments were supported by deuteration studies. The spectra remain unchanged on warming to −70°C to −50°C when the –SH absorptions slowly disappeared and the S=O absorptions broadened and moved to 1080 cm^{-1} and 1068 cm^{-1}, respectively. Cooling failed to restore these absorptions. As dehydration to the thiolsulphinates occurs at −40°C to −20°C and as the S=O absorptions in the corresponding thiolsulphinates occur at 1080 cm^{-1} and 1068 cm^{-1}, respectively, the change in the spectrum with increasing temperature was attributed to self-condensation to give the thiolsulphinate. It was therefore concluded that simple sulphenic acids can exist in both tautomeric forms **4** and **5** at low temperatures. Microwave studies[13] on the simplest alkanesulphenic acid, methanesulphenic acid, and various isotopic modifications, which were obtained by flash vacuum pyrolysis of the appropriately substituted methyl *t*-butyl sulphoxide at 240–400°C and 0.1–0.2 Torr, showed that the methanesulphenic acid in the pyrolysis products contained only dicoordinated sulphur and hence that under these conditions only the *O*-protonated tautomer (**4**) was present. It was also shown that methanesulphenic acid exchanges with deuterium oxide in the wave guide giving methanesulphenic acid-*hydroxy*-d_1 (equation 1). The half-life of methanesulphenic acid in the gas phase at 0.1 Torr and 25°C was calculated[13] to be approximately 1 min.

$$CH_3SOH + D_2O \rightleftharpoons CH_3SOD + HOD \quad (1)$$

III. ACIDITY

Owing to the reactivity of sulphenic acids and their salts, quantitative data on the acidity of sulphenic acids is not generally available. The pK_a of 1,3,6-trimethyllumazine-7-sulphenic acid (**2**; R = Me) is reported[2] to be 4.84 whereas that of the corresponding thiol

(**11**) is found to be 2.5. If the latter is considered[2] to be a vinylogous acid, the former is a vinylogous peracid, and peracids usually have an acidity 2–3 orders of magnitude lower than the corresponding acids in agreement with this assignment. Anthraquinone-1,4-disulphenic acid (**7**), which is stabilized by intramolecular hydrogen bonding, has been estimated to have a first ionization constant between 10^{-6} and 10^{-12}. Aromatic sulphenic acids such as 4-substituted-2-nitrobenzenesulphenic acids[14] and benzenesulphenic acid[15] are completely converted to their anions in dilute base ($[OH^-] \leq 0.01$ M) and consequently aromatic sulphenic acids must presumably be at least as acidic as phenols.



(**11**)

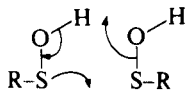
IV. SELF-CONDENSATION REACTIONS

A. Thiolsulphinate Formation

Probably the most frequently observed reaction of sulphenic acids is the extremely facile self-condensation to give thiolsulphinates. Originally these compounds were considered to be sulphenic anhydrides (**12**) but subsequent work[16] showed that they contained a sulphinyl group and had the thiolsulphinate structure (**13**). Sulphenic acids are unique among acids in that the anhydride (thiolsulphinate) is preferred thermodynamically over the acid at equilibrium; even the stable anthraquinone-1-sulphenic acid (**6**) does not melt on heating but decomposes to the thiolsulphinate[6] (equation 2). Thiolsulphinate formation clearly demonstrates the nucleophilic/electrophilic character of sulphenic acids (**14**) and has been postulated to proceed through the hydrogen-bonded dimer (**15**) for which IR evidence has been advanced[12]. The formation of intermolecular hydrogen bonds leads to a structure (**15**) which is considered to be similar to the transition state for thiolsulphinate formation and thus the free energy of activation for thiolsulphinate formation is considerably reduced[17]. It is significant that in cases where intramolecular hydrogen bonding competes with intermolecular hydrogen bonding, the stability of the sulphenic acid is considerably enhanced, e.g. anthraquinone-1-sulphenic acid[6] (**6**), anthraquinone-1,4-disulphenic acid[6] (**7**), 1-methyluracil-4-sulphenic acid[3] (**3**) and the lumazine-7-sulphenic acids (**2**). This effect has been clearly demonstrated[17] by generating a series of 2-substituted-benzenesulphenic acids in the presence of methyl propiolate as a trapping agent. The acids which could not form intramolecular hydrogen bonds were not stable enough to be intercepted to any considerable extent by the trapping agent and hence reacted to give thiolsulphinate and its decomposition products, disulphide and thiolsulphonate, by equations 3 and 4. In contrast, acids capable of forming strong intramolecular hydrogen bonds reacted extensively with the trapping agent forming the *trans*-vinyl sulphoxide by the reaction in equation 5.

(**12**) (**13**)

$$2RSOH \rightleftharpoons RS(=O)SR + H_2O \qquad (2)$$



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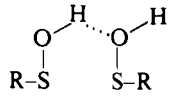


(15)

$$2ArSOH = ArSOSAr + H_2O \qquad (3)$$

$$2ArSOSAr = ArSSAr + ArSO_2SAr \qquad (4)$$

$Ar = 2XC_6H_4$; X = H, OMe

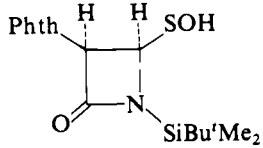
$$ArSOH + HC \equiv CCO_2Me \longrightarrow ArS(=O)C(H)=C(H)CO_2Me \qquad (5)$$

$Ar = 2-XC_6H_4$; X = CHO, CO_2Me, CH_2OMe

The stability of sulphenic acids is further enhanced by substituents with electron-withdrawing effects, which will also contribute to the stability in the case of the 2-carbomethoxy and 2-formyl compounds listed above, and by steric hindrance. 2-Methylpropane-2-sulphenic acid (*t*-butylsulphenic acid), which is stabilized by the bulky *t*-butyl group, may be generated by thermolysis of di-*t*-butyl sulphoxide in various solvents, particularly polar solvents, when the acid is stabilized by hydrogen bonding with the solvent. Such solutions slowly decompose on standing to give the thiolsulphinate[18]. In contrast the neat acid reacts rapidly at $-20°C$[12] (equations 6 and 7). The silylated oxoazetidene-4-sulphenic acid (**16**) can be trapped with methyl acrylate in the usual manner but was recovered unchanged after heating under reflux for 24 h in benzene[19]. The high stability to thiolsulphinate formation was attributed to steric hindrance occasioned by the bulky *t*-butyldimethylsilyl group.

$$Me_3CS(=O)CMe_3 \xrightarrow{\Delta} Me_3CSOH + CH_2{=}CMe_2 \qquad (6)$$

$$2Me_3CSOH \longrightarrow Me_3CS(=O)SCMe_3 + H_2O \qquad (7)$$



(16)

Thiolsulphinates are also obtained[16, 20] from sulphenate ions on exposure to water (equation 8). Kinetic studies[21] suggest that this reaction involves nucleophilic attack of one sulphenate ion on another in a reaction subject to general acid catalysis by the solvent. The intermediate (**17**) can then undergo loss of hydroxide ion to give thiolsulphinate or base-catalysed reversion to products (equation 9). Unusually 1,3,6-trimethyllumazine-7-sulphenate (**2**; R = Me) is stable[2] in alkaline solution, although in acid solution the disulphide and sulphinic acid were readily obtained.

$$2PhSO^-Li^+ + H_2O = PhS(=O)SPh + 2LiOH \quad (8)$$

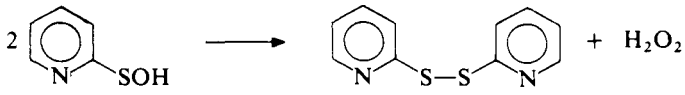
$$ArSO^- + ArSO^- + H_2O \rightleftharpoons \underset{\textbf{(17)}}{ArS(=O)(\overset{\ominus}{O})(Ar)SOH} + OH^- \rightleftharpoons ArS(=O)SAr + 2OH^- \quad (9)$$

Ar = 2-NO_2–4-$CF_3C_6H_3$

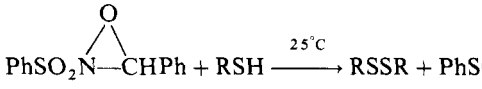
Sulphenate esters are, in general, readily hydrolysed to sulphenic acids or sulphenate ions depending on the conditions, and consequently form thiolsulphinates or their hydrolysis products, as the final products of hydrolysis.

B. Involving Liberation of Hydrogen Peroxide

2-Pyridinesulphenic acid (**18**), obtained by flash vacuum pyrolysis of the *n*-butyl sulphoxide, is a yellow solid which can be trapped by methyl propiolate[22]. On allowing the neat acid (**18**) to warm to room temperature, 2,2′-dipyridyl disulphide was isolated as the only organic product. The reaction mixture was also shown to contain 25–39% of active oxygen based on equation 10. Similar results were obtained with pentafluorobenzenesulphenic acid but 4-nitrobenzenesulphenic acid gave only disulphide, thiolsulphonate and sulphinic acid, products derived from the decomposition of the thiolsulphinate, the more usual product. Oxidation of 2-mercaptopyridine with one equivalent of 2-(benzenesulphonyl)-3-phenyloxaziridine at room temperature immediately gave the disulphide and hydrogen peroxide (40–75%) identified by NMR (equation 11). No hydrogen peroxide could be detected when the oxidation was carried out at −50°C to −20°C and the solution remained yellow, presumably due to the formation of unreacted acid (**18**). Similar oxidation of pentafluorobenzenethiol and of 4-nitrobenzenethiol with 2-(benzenesulphonyl)-3-phenyloxaziridine was much slower and did not consume all the oxidant. The disulphide formed in these latter oxidations is considered to arise from a nucleophilic displacement on the sulphenic acid by the thiol as in equation 12. Although the reason why acid **18** and pentafluorobenzenesulphenic acid condense to form hydrogen peroxide and disulphide rather than thiolsulphinate and water is not as yet clear, it is however relevant that certain sulphenyl chlorides and particularly sulphenyl bromides decompose on standing to give disulphide and halogen (equation 13). The demonstrated oxidation of 2-mercaptopyridine to the sulphenic acid (**18**), and later supporting evidence[23] for the more general nature of this reaction, is highly significant as the catalytic activity of thiol groups in certain enzymes is considered to involve initial oxidation to sulphenic acid groups.



(18) (10)



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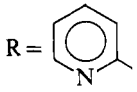


$$ArSH + ArSOH \longrightarrow ArSSAr + H_2O \quad (12)$$

$Ar = C_6F_5$, $4\text{-}NO_2C_6H_4$

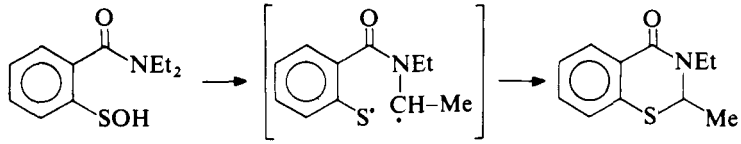
$$RSX \longrightarrow RSSR + X_2 \quad (13)$$

V. DECOMPOSITION REACTIONS

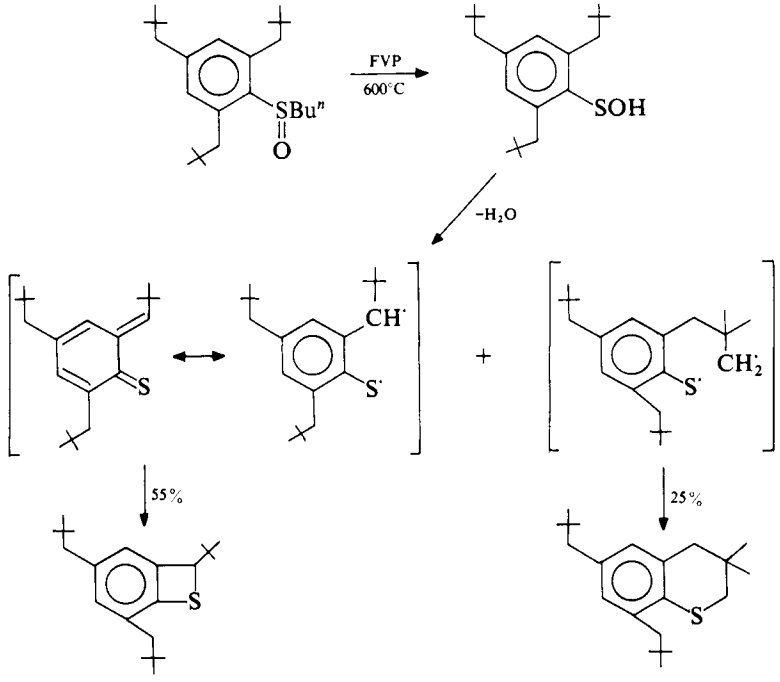
The rapid self-condensation of sulphenic acids to give thiolsulphinates usually renders other decomposition pathways uncompetitive. Unique structural features or exceptional physical conditions can however promote other modes of reaction.

A. Involving Elimination of Water

2-(*N*,*N*-diethylcarboxamido)benzenesulphenic acid (**19**), prepared[17] by flash vacuum pyrolysis (FVP), can be trapped with methyl propiolate. Unlike other 2-substituted-benzenesulphenic acids, allowing the acid (**19**) to warm to room temperature gave *N*-ethyl-2-methyl-1,3-benzothiazin-4-one (**20**) in 89% isolated yield (equation 14). Dehydration of **19** to give **20** was suggested to involve homolysis of the S–OH bond followed by hydrogen abstraction by the hydroxyl radical giving the diradical intermediate. A mechanism involving concerted loss of water was not however excluded. Attempts to prepare 2,4,6-trineopentylbenzenesulphenic acid, in which the sulphenic acid group resides in a hydrophobic pocket and which should therefore be stable to thiolsulphinate formation, gave[24] 2-*t*-butyl-4,6-dineopentylbenzo[*b*]thiete (**21**) and 3,3-dimethyl-4,6-dineopentyldihydrobenzo[*b*]thiapyran (**22**) together with a small amount of bis (2,4,6-trineopentylphenyl)disulphide. **21** and **22** were also considered to arise by homolytic cleavage of the S–OH bond as before (Scheme 1). Similar attempts to prepare 2,4,6-tri-*t*-butylbenzenesulphenic acid on the other hand gave[25] a variety of products arising from the homolytic fission of the aryl–SOH bond and it was concluded that this acid is actually destabilized by the adjacent *t*-butyl groups. In contrast, 2,4,6-tri-*i*-propylbenzenesulphenic acid readily gave the thiolsulphinate even in the presence of methyl propiolate as a trapping agent[25].



(19) (20) (14)



SCHEME 1

Methanesulphenic acid, generated by flash vacuum pyrolysis, was shown[12] to decompose at 750 °C and 0.1 to 0.2 Torr to give thioformaldehyde (equation 15). Thiolsulphinate formation occurs at lower temperatures (see Section II). Thioformaldehyde is also detected in the pyrolysis of dimethyl sulphoxide at 600–800 °C and presumably arises from the dehydration of methanesulphenic acid formed in the pyrolysis.

$$CH_3SOH \xrightarrow[0.1-0.2\ \text{Torr}]{750^\circ C} HCHS + H_2O \tag{15}$$

B. Involving Elimination of Hydrogen Chloride

Derivatives of trichloromethanesulphenic acid (**23**) tend to behave abnormally on hydrolysis. On treatment with water the sulphenyl chloride gives[26] the lachrymatory liquid, dichlorosulphine, which is postulated to be formed by loss of hydrogen chloride from the sulphenic acid (**23**) (equation 16). Complete hydrolysis gives sulphur, carbon dioxide and hydrogen chloride (equation 17).

$$Cl_3CSCl \xrightarrow[-HCl]{H_2O} \underset{(23)}{[Cl_3CS\text{–}OH]} \longrightarrow Cl_2C{=}S{=}O + HCl \tag{16}$$

$$Cl_3CSCl + 2H_2O \longrightarrow 4HCl + CO_2 + S \tag{17}$$

C. Other Reactions

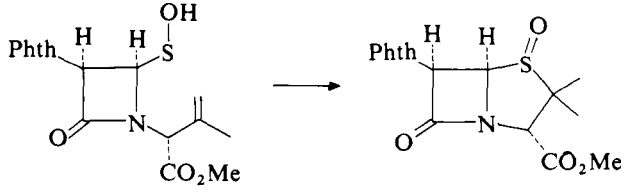
1. Sulphenic acids

The lachrymatory factor of the onion, identified[27] as the sulphine (**24**), is considered to be derived from a sulphenic acid precursor by an intramolecular proton shift (equation 18).

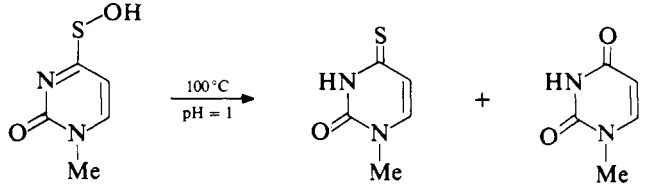
(18)

(**24**)

The β,γ-unsaturated 2-oxoazetidine-4-sulphenic acid (**9**, R = CH_2=$CMeCHCO_2Me$), which is stable in the solid state, reverts readily in solution to the penicillin sulphoxide by the reverse of the electrocyclic process via which it is obtained[19] (equation 19). The α,β-unsaturated isomer [**9**, R = Me_2C=$C(CO_2Me)$], on the other hand, gives the thiol-sulphinate. 1-Methyluracil-4-sulphenic acid (**3**), which is stabilized by hydrogen bonding, decomposes[3] on heating in acid solution (pH = 1) at 100°C to give a 1:2 mixture of 1-methyl-4-thiouracil (**25**) and 1-methyluracil (**26**) in quantitative yield (equation 20). Although the mechanism of this unusual reaction was not investigated, it was established that the thione (**25**) was not converted into **26** under these conditions.



(19)



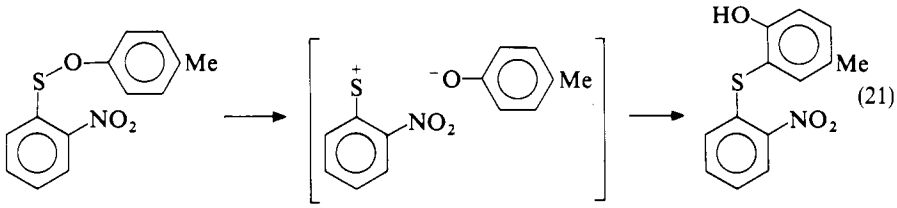
(20)

(**3**) (**25**) (**26**)

2. Sulphenate esters

p-Tolyl 2-nitrobenzenesulphenate decomposes[28] on storage and on heating under reflux in carbon tetrachloride in the dark to give 2-hydroxy-5-methylphenyl 2-nitrophenyl sulphide together with a little bis(2-nitrophenyl) disulphide. The reaction (equation 21) is considered to involve heterolysis of the S–O bond followed by an electrophilic substitution of the sulphenium ion into the phenoxide ion. In accord with this proposal, phenyl 2-nitrobenzenesulphenate similarly gives[28] a mixture of 2-hydroxy- and 4-hydroxy-phenyl 2-nitrophenyl sulphide, and on heating in anisole yields a mixture of 2-

methoxy- and 4-methoxy-phenyl 2-nitrophenyl sulphides. *t*-Butyl 2-nitrobenzenesulphenate in anisole similarly gives[29] the mixture of methoxyphenyl sulphides together with *t*-butanol and products derived from it and from the hydrated sulphenium ion.



(21)

VI. SUBSTITUTION AND RELATED REACTIONS

The substitution reactions of sulphenic acids and esters are complicated by their dual electrophilic/nucleophilic nature and hence by the possibility of reversal of the type of reactivity during the same reaction sequence. Consequently this section is organized on the basis of the reagent rather than on the mechanism of the reaction involved.

A. With Carbon Compounds

1. Carbon nucleophiles

Alkyl arenesulphenates react[30] with compounds containing active methylene groups in the presence of sodium ethoxide to give sulphides (equation 22). Methyl esters tend to give lower yields.

$$\begin{matrix} MeCO \\ MeCO \end{matrix}\!\!>\!CH_2 + ArSOEt \xrightarrow[70-80\%]{EtONa} \begin{matrix} MeCO \\ MeCO \end{matrix}\!\!>\!CHSAr \qquad (22)$$

Ar = 2,4-$(NO_2)_2C_6H_3$, 2-$NO_2C_6H_4$, 1-anthraquinonyl

Sulphides are also obtained[31] with Grignard reagents (equation 23).

$$PhSOMe + PhMgBr \xrightarrow{48\%} PhSPh \qquad (23)$$

2. Alkylations

Sulphenate ions are ambident nucleophiles and may be alkylated at sulphur to give the sulphoxide or at oxygen to give the sulphenate ester. Alkylation of 4-trifluoromethyl-2-nitrobenzenesulphenate ion[32], obtained from the alkaline hydrolysis of the corresponding disulphide, with methyl iodide in 30% (v/v) aqueous dioxan gave exclusively the methyl sulphoxide, whereas the much faster reaction with methyl fluorosulphonate gave predominantly the methyl sulphenate (39:1). Dimethyl sulphate was intermediate in behaviour but still gave the ester as the major product (2:1) (equation 24). These results were rationalised[32] on the basis of the HSAB principle in terms of a 'tight' S_N2-type transition state for reaction of methyl iodide with the softer nucleophilic centre (sulphur)

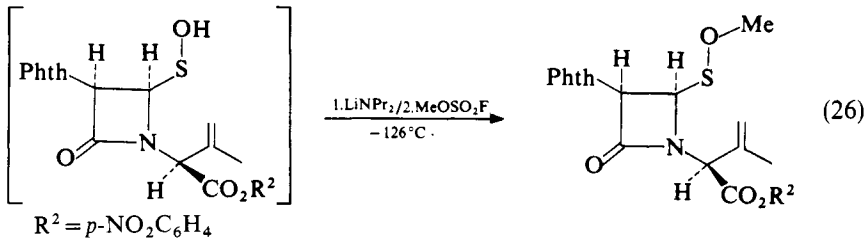
and a looser transition state with considerable S_N1 character for reaction of methyl fluorosulphonate with the harder oxygen atom.

$$\underset{\text{ArSMe}}{\overset{\overset{O}{\|}}{}} \xleftarrow{\text{MeI}} \text{ArSO}^- \underset{\text{OH}^-}{\overset{\text{MeOSO}_2\text{F}}{\rightleftharpoons}} \text{ArSOMe} \qquad (24)$$

$$\text{Ar} = 4\text{-}CF_3\text{-}2NO_2C_6H_3$$

The alkylation of the benzenesulphenate ion with benzyl chloride to give[20] benzyl phenyl sulphoxide, and of an oxoazetidine sulphenate ion with methyl fluorosulphonate, which gave[33] exclusively *O*-methylation, are in accord with these observations (equations 25 and 26). The ratio of sulphenate to sulphoxide obtained on alkylation has also been shown[34] to depend upon the reaction conditions, the ratio being increased in more polar solvents and by the addition of crown ethers, which increase the reactivity of the sulphenate anion by increasing the solvation of the counter ion. Alkylation of the 2-nitrobenzenesulphenate ion, which is less stable[33] than the 4-trifluoromethyl analogue, with methyl iodide in 25% (v/v) aqueous dioxan gave[34] a mixture of sulphenate and sulphoxide in the ratio (sulphenate/sulphoxide) 0.53, which was increased to 1.03 in the faster reaction resulting from the addition of 15-crown-5. These alkylations are suggested[34] to be kinetically controlled with the more reactive reagents, which favour reaction at oxygen, but in less reactive systems the reaction is essentially thermodynamically controlled and occurs at sulphur giving the sulphoxide.

$$\text{PhSO}^-\text{Li}^+ + \text{PhCH}_2\text{Cl} \rightarrow \underset{\text{PhSCH}_2\text{Ph}}{\overset{\overset{O}{\|}}{}} + \text{LiCl} \qquad (25)$$

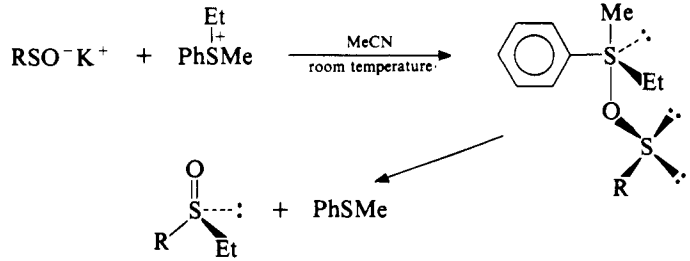


$$\text{R}^2 = p\text{-}NO_2C_6H_4 \qquad (26)$$

In contrast alkylation of sulphenate ions with sulphonium salts follows a different pattern. Potassium anthraquinone-1-sulphenate reacts with *i*-propylmethylarylsulphonium perchlorate to give a mixture of methyl and *i*-propyl sulphenates and sulphoxides, suggesting[35a] that this alkylation does not follow an S_N2 mechanism. Furthermore *S*-alkylation is favoured by more polar solvents and by addition of crown ethers (equation 27). When optically active (*S*)-(+)-ethylmethylphenylsulphonium *d*-camphorsulphonate in acetonitrile was used, optically active (*S*)-(−)-methyl- and ethyl-anthraquinon-1-yl sulphoxides were formed[35a] in 10.5% and 44% yield, respectively. These results were explained by assuming the formation of an *O*-sulphurane intermediate in which only the pro-*S* pair of the two lone pairs on the sulphenyl sulphur atom comes close to the ethyl group in the radial plane. The asymmetric induction in the methyl sulphoxide was much smaller than in the ethyl analogue (Scheme 2).

(27)

R = 1-anthraquinonyl



R = 1-anthraquinonyl

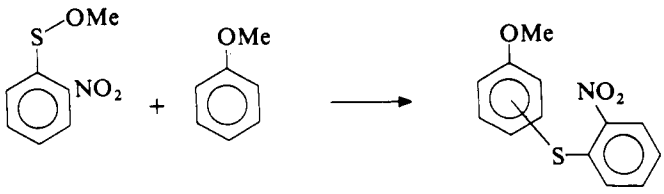
SCHEME 2

Alkylation of alkyl benzenesulphenates with 1 equivalent of methyl triflate in nitromethane gives[35a] the alkoxysulphonium salts (equation 28).

$$PhSOCH_2CMe_3 + CF_3SO_3Me \xrightarrow{34.0^\circ C} Ph\text{-}\overset{Me}{\underset{|}{S}}{}^{+} - OCH_2CMe_3 \qquad (28)$$

3. *Aromatic substitution*

Methyl 2-nitrobenzenesulphenate reacts[28] with anisole under reflux to give a 35:60 mixture of 2-methoxy- and 4-methoxy-phenyl 2-nitrophenyl sulphide (equation 29). Similar reactions occur in toluene and *p*-xylene, and with aryl 2-nitrobenzenesulphenates (see Section V. C. 2). Arene annelation reactions involving sulphenate esters are discussed in Section VII. B.

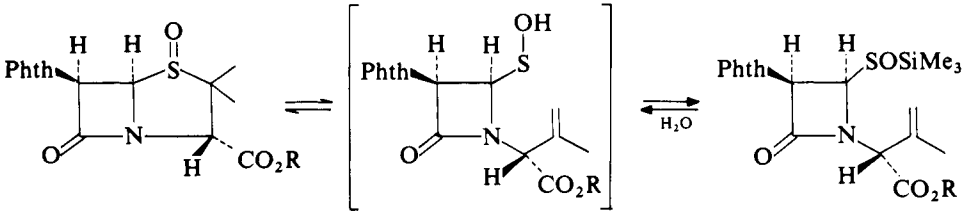


(29)

B. With Silicon Compounds

1. Formation of trimethylsilyl esters

The conversion of sulphenic acids into the trimethylsilyl esters has been developed[36] as a method for the protection of this reactive function and as a means of providing a convenient stable source of the acid or its anion. Generation of the oxoazetidine sulphenic acids (**28**) by refluxing the penicillin sulphoxide esters (**27**) in benzene in the presence of 100% excess of trimethylsilyl chloride–hexamethyldisilazane (2:1) gave the trimethylsilyl ester (**29**) in nearly quantitative yield (equation 30). The sulphenic acid (**28**) can be regenerated by stirring **29** in chloroform under moist air. The protecting function is stable to bases such as triethylamine.

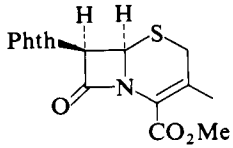


(**27**) (**28**) (**29**)

(R = Me,H,$CH_2C_6H_4NO_2$-*p*) (R = Me,$SiMe_3$,$CH_2C_6H_4NO_2$-*p*)

(30)

Treatment of the ester (**29**; R = Me) with methanesulphonic acid in benzene/dimethylacetamide or with trimethylsilyl triflate[37] gives the cephem derivative (**30**) in good yield.



(**30**)

2-Nitrobenzenesulphenic acid, generated by the thermolysis of the corresponding *N*-alkylidenearenesulphinamide, 2-$NO_2C_6H_4SON{=}CR_2$, similarly gives[38] the trimethylsilyl ester. The sulphenic acid, or its anion, is obtained by treatment with ethanol or sodium ethoxide, respectively (equation 31).

$$ArSOH + Me_3SiCl + Me_3SiNHSiMe_3 \longrightarrow ArSOSiMe_3 \xrightarrow{EtOH} ArSOH \quad (31)$$

$$ArSOSiMe_3 \xrightarrow{EtO^-} ArSO^-$$

2. Exchange reactions

Arenesulphenate esters react with aminotrimethylsilanes[39], trimethylchlorosilane[40], trimethylsilyl cyanide[40] and trimethylsilyl thioethers[41] to give substitution products and

methoxytrimethylsilane. *N*-Alkylaminotrimethylsilanes give a mixture of sulphenamides and *N*-trimethylsilylbenzenesulphenamides due to competitive cleavage of the N–Si and N–H bonds[39].

$$PhSOMe + Me_3SiNR_2 \longrightarrow PhSNR_2 + Me_3SiOMe \quad (32)$$

$$PhSOMe + Me_3SiNSO \longrightarrow PhSNSO + Me_3SiOMe \quad (33)$$

$$2\text{-}NO_2C_6H_4SOMe + Me_3SiCl \longrightarrow 2\text{-}NO_2C_6H_4SCl + Me_3SiOMe \quad (34)$$

$$PhSOMe + Me_3SiCN \longrightarrow PhSCN + Me_3SiOMe \quad (35)$$

$$PhSOMe + Me_3SiSR \longrightarrow PhSSR + Me_3SiOMe \quad (36)$$

$$PhSOMe + Me_3SiNHR \longrightarrow PhSNHR + PhSNRSiMe_3 + MeSiOMe + MeOH \quad (37)$$

Significantly arenesulphenyl chlorides do not react with methoxytrimethylsilane[40].

C. With Nitrogen Compounds

Sulphenate esters react with primary and secondary amines to give[39] sulphenamides. Although the reaction is understandably slower and less exothermic than with the corresponding sulphenyl halides, disubstitution occurs with primary amines and an excess of sulphenate ester.

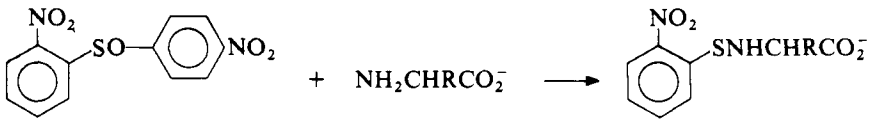
$$PhSOMe + HNPr_2 \xrightarrow{85\%} PhS\text{-}NPr_2 + MeOH \quad (38)$$

$$2PhSOMe + H_2NMe \longrightarrow (PhS)_2NMe + 2MeOH \quad (39)$$

The reactions between *p*-nitrophenyl triphenylmethanesulphenate and a wide variety of amines in 45% aqueous dioxan were found[42] to be first order in each reactant and the kinetics were consistent with a nucleophilic substitution at dicoordinated sulphur. The high values of the Brønsted coefficients, $\alpha = 1.5$ for anilines, 0.84 for pyridines, 0.75 for secondary heterocyclic amines and 0.58 for aliphatic primary amines, suggest a high degree of bond formation in the transition state for the rate-limiting step.

$$Ph_3CSOC_6H_4NO_2\text{-}p + \text{amine} \longrightarrow Ph_3C\text{Samine} + {}^-OC_6H_4NO_2\text{-}p \quad (40)$$

The 2-nitrobenzenethio group has been widely used for *N*-protection during peptide synthesis. Generally the sulphenyl halide is used as the source of the protecting group but 4-nitrophenyl 2-nitrobenzenesulphenate is a useful alternative[43].



(41)

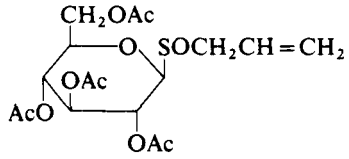
D. With Phosphorus Compounds

Although phosphorus III compounds are often considered to be thiophilic reagents, benzyl methanesulphenate and methyl 2-methylpropane-2-sulphenate react with tributyl-

phosphine in toluene at −20°C to give[44] exclusively tributylphosphine oxide and the corresponding sulphide. The reaction is proposed to proceed via a phosphorane intermediate which dissociates to a tributylalkoxyphosphonium salt and hence to the sulphide (equation 42). Both intermediates were synthesized. In agreement[45] the allyl β-glycosyl sulphenate (**31**) was found to be deoxygenated with triphenylphosphine.

$$PhCH_2OSMe + Bu_3P \longrightarrow PhCH_2OPBu_3 \quad (42)$$

$$PhCH_2S + Bu_3PO \longleftarrow PhCH_2O\overset{+}{P}Bu_3 + MeS^-$$

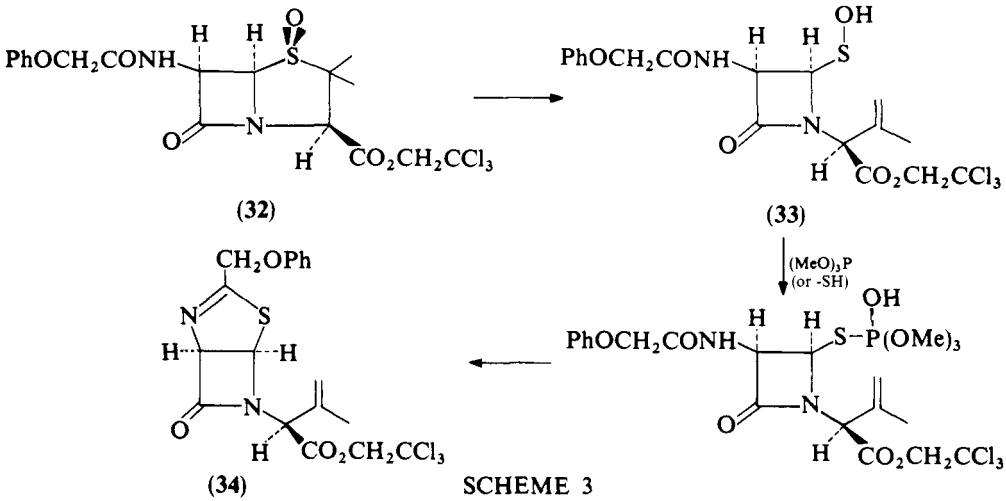


(**31**)

Trisubstituted phosphites react with alkyl benzenesulphenates to give[46] the pentaalkoxyphosphorane and the diaryl disulphide, presumably via the mixed oxythiophosphorane which reacts with another molecule of sulphenate.

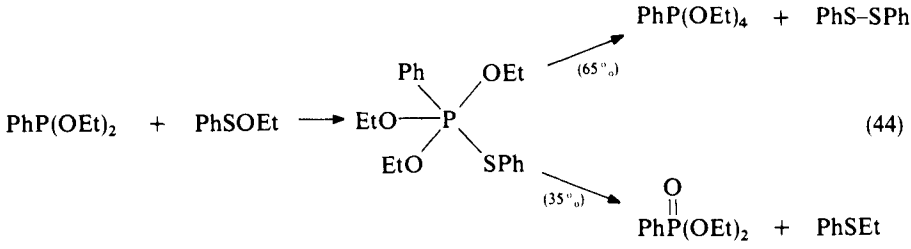
$$PhSOEt + (EtO)_3P \rightarrow [(EtO)_4PSPh] \xrightarrow{PhSOEt} (EtO)_5P + PhSSPh \quad (43)$$

A similar reaction is presumably involved in the reaction of 2,2,2-trichloroethyl phenoxyacetamidopenicillanate sulphoxide (**32**) with trimethyl phosphite in which the phosphite is considered to be involved in the reductive trapping of the intermediate sulphenic acid (**33**) to give a thiol or thiol-type intermediate which condenses with the amido side-chain to give[47] the product (**34**) (Scheme 3).



SCHEME 3

Diethoxy phenylphosphonite reacts with ethyl benzenesulphenate to give[48] tetraethoxyphenylphosphorane and diphenyl disulphide, together with diethyl phenylphosphonate and ethyl phenyl sulphide. The two pairs of products are suggested to arise from reaction of the intermediate phosphorane (**35**) with another molecule of sulphenate, and by P–S bond fission followed by an Arbusov reaction, respectively (equation 44).



(44)

(35)

E. Hydrolysis and Related Reactions

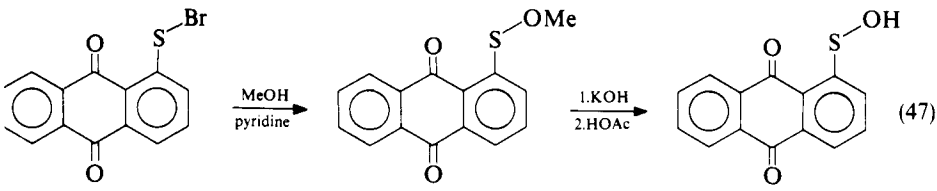
Hydrolysis of sulphenic acid derivatives initially gives the sulphenic acid or its anion and can therefore be considered to be a substitution reaction. However, the high nucleophilic reactivity of this initial product towards dicoordinated sulphur atoms which have a readily displaceable group can lead to a rapid reaction with starting material and the formation of thiolsulphinate, which can alternatively be formed by self-condensation from the sulphenic acid or its anion (see Section IV.A).

$$RSX + H_2O \xrightarrow{k_1} RSOH + HX \tag{45}$$

$$RSOH + RS\text{–}X \xrightarrow{k_2} RS(O)SR + HX \tag{46}$$

$$RSOH + RSOH \longrightarrow RS(O)SR + H_2O \tag{46A}$$

The high rate of reaction 46 is indicated[49] by kinetic studies on the compounds PhSX (X = Cl, Br, $\overset{+}{S}Bu_2$) which show that k_2 is 4×10^4 to 4×10^5 times greater than k_1. Even the relatively unreactive anthraquinonesulphenic acids could not be isolated[50] from the hydrolysis of the sulphenyl bromide which had to be converted to the less electrophilic methyl ester prior to hydrolysis to give the acid (equation 47).



(47)

Similarly, the relatively stable 4-trifluoromethyl-2-nitrobenzenesulphenate ion could not be detected[21] by ^{19}F NMR in the alkaline hydrolysis of the sulphenyl chloride although it was observed as a transient intermediate using the ethyl sulphenate. The products from the hydrolysis of sulphenate esters, and from other reactions which generate sulphenic acids or anions, therefore arise, in general, from the subsequent reactions of the thiolsulphinate.

Anhydrous solutions of methyl toluene-*p*-sulphenate in solvents such as dioxan, chloroform, benzene and nitrobenzene containing sulphuric or trifluoromethanesulphonic acid are stable[51]. When the solvent is moist a rapid reaction occurs giving the methyl sulphinate, disulphide and methanol.

$$3ArSOMe + H_2O \xrightarrow{H^+} ArS(=O)OMe + ArSSAr + 2MeOH \qquad (48)$$

If more water is present a different rapid reaction occurs and in dioxan containing $>1\%$ of water, thiolsulphonate, disulphide, methanol and a trace of thiolsulphinate are formed. Addition of water to the completed reaction 48 does not give thiolsulphonate.

$$4ArSOMe + 2H_2O \xrightarrow{H^+} ArSO_2SAr + ArSSAr + 4MeOH \qquad (49)$$

In the absence of water, methyl toluene-*p*-sulphenate reacts with thiolsulphinates by a fast acid catalysed reaction to give the methyl sulphinate derived from the thiolsulphinate and the mixed disulphide[51]. Methyl methanesulphenate gives a similar reaction with methyl methanethiolsulphinate[52].

$$ArSOMe + Ar'S(=O)SAr' \xrightarrow{H^+} Ar'S(=O)OMe + Ar'SSAr \qquad (50)$$

In contrast the presence of water leads to a similarly fast acid-catalysed reaction to give thiolsulphonate, disulphide and methanol[51].

$$ArSOMe + ArS(=O)SAr \xrightarrow{H^+} ArSO_2SAr + ArSSAr + MeOH \qquad (51)$$

Furthermore sulphinic acids react rapidly with sulphenate esters, even in the absence of a catalysing acid, to give thiolsulphonate.

$$ArSO_2H + ArSOMe \longrightarrow ArSO_2SAr + MeOH \qquad (52)$$

The slow step in the acid-catalysed hydrolysis of sulphenate esters is proposed[51] to be the nucleophilic reaction of water with the protonated ester. Another nucleophilic substitution by thiolsulphinate on the protonated ester gives a sulphonium ion (**36**), which reacts with methanol to give the methyl sulphinate or with water to give the sulphinic acid and hence the thiolsulphonate.

$$ArSOMe + H^+ \rightleftharpoons ArS^+(H)OMe \qquad (53)$$

$$H_2O + ArS\overset{H}{\overset{|}{O}}{}^+Me \xrightarrow{\text{slow}} ArSOH + MeOH + H^+ \quad (54)$$

$$2ArSOH \longrightarrow Ar\overset{O}{\overset{\|}{S}}SAr + H_2O \quad (55)$$

$$Ar\overset{O}{\overset{\|}{S}}SAr + ArS\overset{H}{\overset{|}{O}}{}^+Me \longrightarrow Ar\overset{ArS=O}{\overset{|}{S}}{}^+ - SAr + MeOH \quad (56)$$

(36)

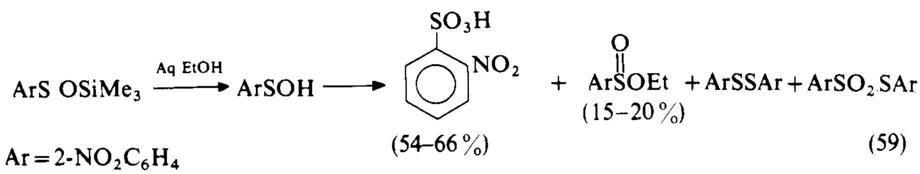
$$Ar\overset{O}{\overset{\|}{S}}-\underset{SAr}{\underset{|}{\overset{+}{S}}}Ar + MeOH \longrightarrow Ar\overset{O}{\overset{\|}{S}}OMe + ArSSAr + H^+ \quad (57A)$$

$$Ar\overset{O}{\overset{\|}{S}}-\underset{SAr}{\underset{|}{\overset{+}{S}}}Ar + H_2O \longrightarrow Ar\overset{O}{\overset{\|}{S}}OH + ArSSAr + H^+ \quad (57B)$$

$$ArSO_2H + ArS\overset{H}{\overset{|}{O}}{}^+Me \longrightarrow ArSO_2SAr + MeOH + H^+ \quad (58)$$

A similar series of reactions involving the conjugate acid of the sulphenic acid, $ArSOH_2^+$, has been proposed[49] for acid-catalysed hydrolyses in which the sulphenic acid, rather than a derivative, participates in the later stages of the reaction.

2-Nitrobenzenesulphenic acid, prepared from the trimethylsilyl ester by treatment with aqueous ethanol and hydrogen chloride, reacted[38] on standing to give orthanilic acid, ethyl 2-nitrobenzenesulphinate and minor amounts of disulphide and thiolsulphonate (equation 59). Similar results were also obtained in the absence of hydrogen chloride.



(59)

Oxidation of sulphenyl sulphur by the *o*-nitro group is frequently observed[1, 53] in solvolyses of 2-nitrobenzenesulphenyl derivatives and there is evidence that the oxygens can be transferred intramolecularly[54]. The unexpected formation of the ethyl sulphinate was attributed[38] to ethanolysis of the thiolsulphinate, but it could also have arisen from a reaction sequence[51] similar to reactions 56 and 57, which would be expected to be much faster.

The base-catalysed hydrolysis of ethyl 2-nitrobenzenesulphenate gives[55, 14] disulphide and sulphinate ion, but if the reaction remains homogeneous the disulphide is also

hydrolysed. The overall stoichiometry is:

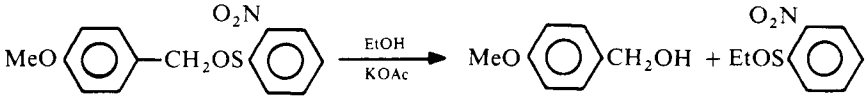
$$3ArSOEt + 4OH^- = ArSSAr + ArSO_2^- + 3EtO^- + 2H_2O \quad (60)$$

$$2ArSOEt + 4OH^- = ArS^- + ArSO_2^- + 2EtO^- + 2H_2O \quad (61)$$

The hydrolysis is kinetically of the second order, first order in ester and hydroxide ion, and is considered[56] to involve an 'S_N2 type' displacement at sulphur in the rate-limiting step. The ester does not appear to be involved in a major later reaction in this case.

$$HO^- + ArSOEt \xrightarrow{slow} HOSAr + EtO^- \xrightarrow{fast} ArSO^- + EtOH \quad (62)$$

Ethyl 4-substituted-2-nitrobenzenesulphenates give a 'J-shaped' Hammett plot analogous to those obtained for the bimolecular reactions of benzyl bromides with nucleophiles in accord with the proposed mechanism. The importance of steric effects in the alkyl group of the ester on the rate was demonstrated by a correlation with the Taft alkyl steric parameter, E_S', in a one-parameter equation with $\delta = 0.6$, and the identity[55] within experimental error of the rates of hydrolysis of *p*-tolyl and *p*-chlorophenyl 2-nitrobenzenesulphenates. The reaction of benzhydryl and *p*-anisyl 2-nitrobenzenesulphenates with ethanol in the presence of base has also been shown[57] to involve S–O bond fission and to proceed by an 'S_N2-type' mechanism.



(63)

In the base-catalysed hydrolysis of a series of ethyl 4-substituted-2-nitrobenzenesulphenates the concentration of sulphenate ion increased[21] to a maximum. At this maximum 80% of the original ester was present as sulphenate ion in the case of the 4-trifluoromethyl derivative and 17.5% in the case of the 4-hydrogen derivative which gives the more nucleophilic sulphenate ion. The rate of disappearance of sulphenate ion was found to be second order in this ion, consistent with the mechanism for the formation of thiolsulphinate discussed in Section IV.A.

$$ArSO^- + ArSO^- + H_2O \longrightarrow ArS(=O)SAr + 2OH^- \quad (64)$$

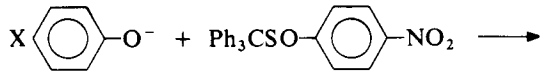
Thiolsulphinates may react with hydroxide ion at either the sulphenyl or sulphinyl sulphur atoms (equation 65). Kinetic evidence from other reactions involving phenyl benzenethiolsulphinate is consistent[15] with these reactions being competitive. The resulting thiolate ion reacts rapidly with the 'softer' sulphenyl sulphur atom of the thiolsulphinate to give disulphide.

$$PhS(=O)SPh + OH \rightleftharpoons \begin{matrix} PhSO^- + PhSOH \\ PhSO_2H + PhS^- \end{matrix} \quad (65)$$

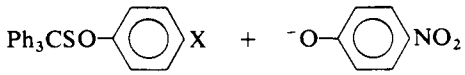
$$ArS^- + ArS(=O)SAr \longrightarrow ArSSAr + ArSO^- \quad (66)$$

The kinetics of the reactions of a series of 4-substituted-phenyl triphenylmethanesulphenates with hydroxide ion or 4-substituted-phenoxide ions were also found[58] to be first

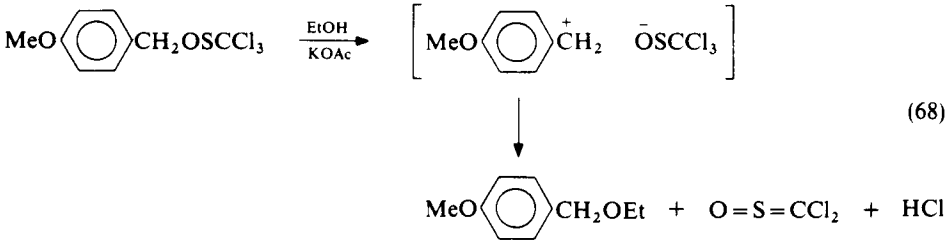
order in each reactant up to a high percentage reaction. Excellent Brønsted plots were obtained with $\beta = 0.25$ for the nucleophiles and -0.97 for the leaving groups indicating that bond breaking is far more advanced than bond formation and hence that the kinetically observed reaction is a one-step (S_N2) process involving S–O bond fission in a very loose transition state which may be necessitated by steric hindrance from the very bulky triphenylmethyl group.



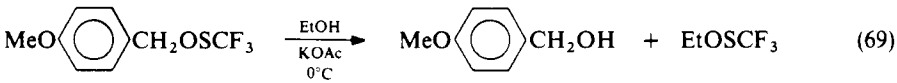
(67)



In contrast to these reactions of triphenylmethane- and 2-nitrobenzenesulphenate esters, benzhydryl, furfuryl and *p*-anisyl trichloromethanesulphenates react[57] rapidly with ethanol in the presence of base by a first-order reaction to give dichlorosulphene and the ethyl ether. In this case the high acid strength of trichloromethanesulphenic acid makes its anion a good leaving group resulting in C–O bond fission and carbonium ion formation. When these esters are heated in hexane, recombination of the ions occurs to give the sulphoxide. Esters giving less stable carbonium ions, e.g. benzyl, give S–O bond fission and do not rearrange on heating in hexane to give the sulphoxide. The corresponding trifluoromethanesulphenates do not react similarly but instead[59] undergo S–O bond fission similar to the 2-nitrobenzenesulphenates. This was tentatively attributed to the greater strength of the C–F bond compared with the C–Cl bond and the possibility of concerted C–Cl and C–O bond fission occurring in reaction 68.



(68)



(69)

Although these reactions of alkyl 2-nitrobenzenesulphenates[55, 57] and aryl triphenylmethanesulphenates[58] are considered to involve linear S_N2-type transition states and although intramolecular rearrangements which would involve a non-linear transition state were not observed[60] with γ-hydroxyalkyl 2-nitrobenzenesulphenates, frontside nucleophilic attack at sulphur has been frequently proposed. Formation of the thiolsulphinate directly from the hydrogen-bonded dimeric acid (see Section IV.A) obviously

involves frontside displacement in which the incoming and outgoing groups could occupy the axial and radial positions[17].

F. With Sulphur Compounds

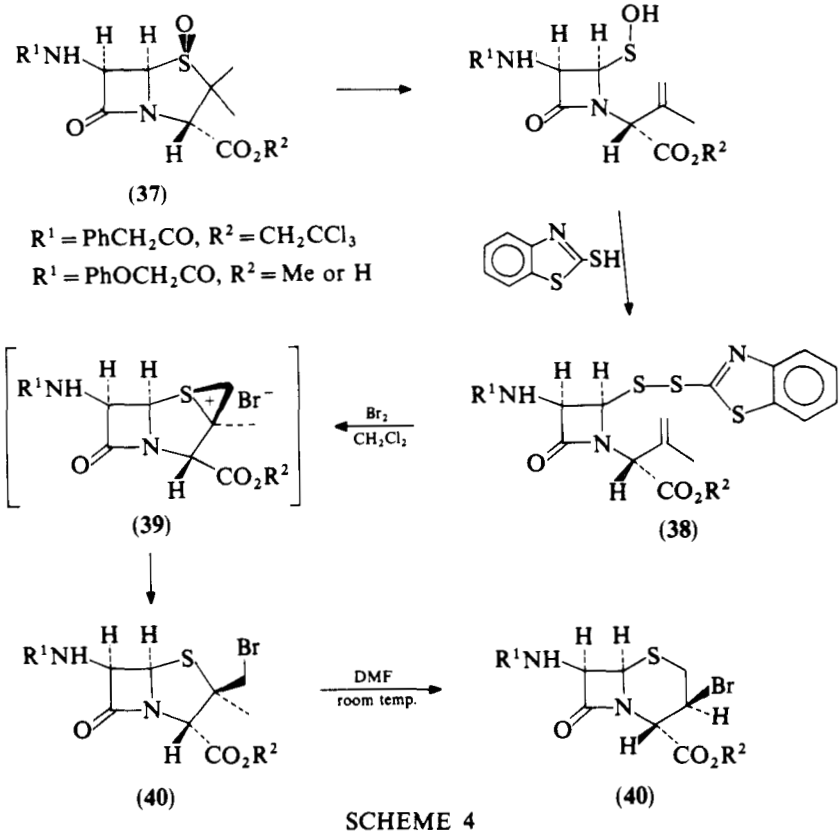
1. *Thiols*

Thiols react readily with sulphenic acids and with sulphenate esters to give disulphides.

$$R^1SH + R^2SOH \longrightarrow R^1SSR^2 + H_2O \quad (70)$$

$$R^1SH + R^2SOR^3 \longrightarrow R^1SSR^2 + R^3OH \quad (71)$$

Reaction with thiols has been used for trapping oxoazetidinesulphenic acids[61, 62] and the resulting unsymmetrical disulphides have been used in the derivatisation[62] of the β-methyl group. Refluxing the penicillin sulphoxides (**37**) with 2-mercaptobenzothiazole in toluene for 4 h gave[62] the mixed disulphides (**38**) in high yield. These were readily halogenated to give the 2-halogenomethyl penams (**40**). Cyclization is suggested to involve formation of the sulphenyl chloride or bromide and ring closure via the



(37)

$R^1 = PhCH_2CO$, $R^2 = CH_2CCl_3$

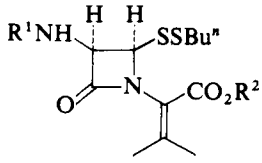
$R^1 = PhOCH_2CO$, $R^2 = Me$ or H

(39) (38) (40) (40)

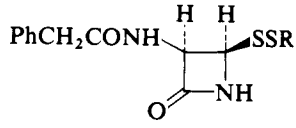
SCHEME 4

episulphonium ion intermediate (**39**); see Scheme 4. Heterocyclic mono- and dithiols are the preferred reagents[63].

In contrast, trapping penicillin sulphoxide (**37**, $R^1 = PhCH_2O$, $R^2 = CH_2CCl_3$) with butanethiol gave the corresponding conjugated α,β-unsaturated disulphide (**41**) which, on 1,3-dipolar addition of diazomethane across the conjugated ester chromophore followed by mild reduction, gave[61] the β-lactam fragment (**42**).



(**41**)



(**42**)

R = Bu^n, Bu^i

2. Sulphenyl halides

Sulphenic acids and their anions react rapidly with sulphenyl halides to give thiolsulphinates, which then react further (see Section VI.E). Arenesulphenate esters are normally prepared by reaction of the sulphenyl chloride with an alcohol in the presence of base or with the alkoxide ion. Reaction of arenesulphenate esters with arenesulphenyl chlorides is not normally observed[64].

$$PhSCl + NaOMe \xrightarrow[80\%]{\text{ether}} PhSOMe + NaCl \qquad (72)$$

The preparation of alkanesulphenate esters by this method gives[52] only moderate yields of the ester, although this may be increased by using an excess of alkoxide.

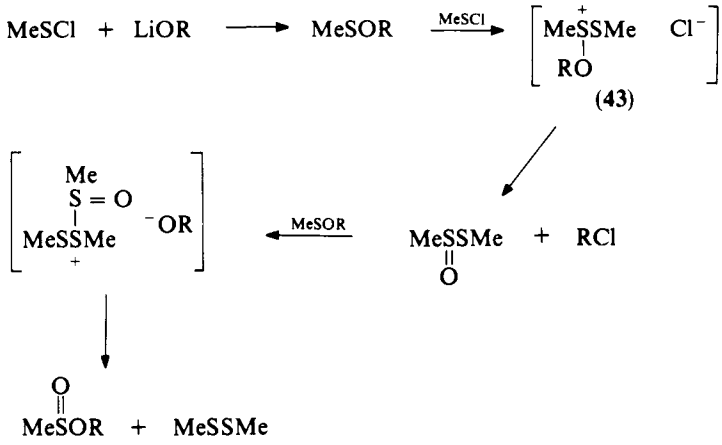
$$MeSCl + LiOC_5H_{11} \xrightarrow[35\%]{\text{DME}} MeSOC_5H_{11} + LiCl \qquad (73)$$

With the alkoxides of primary and secondary alcohols the sulphenate ester was not isolated when an excess (> 1.5 equiv.) of sulphenyl chloride was used; instead the above reactants gave pentyl methanesulphinate, dimethyl disulphide and pentyl chloride. Similar products were obtained directly from the ester and sulphenyl chloride.

$$3MeSCl + 2LiOC_5H_{11} \xrightarrow{\text{DME}} MeS\overset{\overset{O}{\|}}{O}C_5H_{11} + MeSSMe + C_5H_{11}Cl + 2LiCl \qquad (74)$$

$$MeSCl + 2MeSOC_5H_{11} \xrightarrow{\text{DME}} MeS\overset{\overset{O}{\|}}{O}C_5H_{11} + MeSSMe + C_5H_{11}Cl \qquad (75)$$

These products can be explained[52] by an initial reaction of alkoxide ion with sulphenyl halide (Scheme 5) to give the sulphenate ester, which then reacts as a nucleophile with the sulphenyl halide to give the charged intermediate (**43**). This collapses to give pentyl chloride and thiolsulphinate which in turn reacts with the sulphenate ester, now reacting as an electrophile, to give disulphide and the sulphinate ester (compare Section VI.E, reactions 55 and 56A).



SCHEME 5

Similarly the 2-chloroalkyl methanesulphenates, formed from methanesulphenyl chloride and 1,2-epoxyalkanes, react with methanesulphenyl chloride to give[65] 1,2-dichloroalkanes, dimethyl disulphide and methanesulphinyl chloride which is formed by reaction of the thiolsulphinate with excess methanesulphenyl chloride.

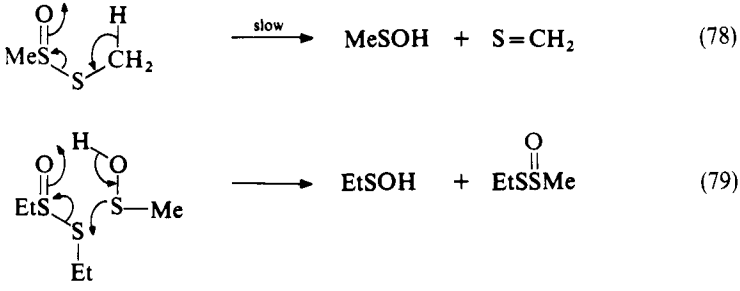
$$MeSOCH_2CH_2Cl + 2MeSCl \rightarrow ClCH_2CH_2Cl + MeSSMe + MeS(=O)Cl \qquad (76)$$

3. *Thiolsulphinates*

Sulphenic acids are reported to be involved in the rapid equilibration of thiolsulphinates which have α-hydrogens[66]

$$MeS(=O)SMe + EtSSEt \longrightarrow MeSSEt + EtS(=O)SMe \qquad (77)$$

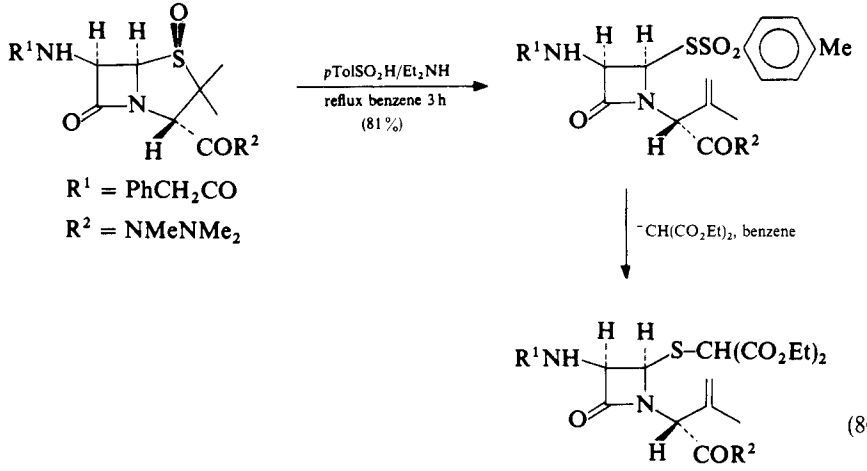
The sulphenic acid, formed by the thermolysis of the thiolsulphinate, reacts as an *S*-nucleophile with another molecule of thiolsulphinate forming another molecule of sulphenic acid. As expected, the reaction is inhibited by the addition of methyl acrylate which traps the intermediate sulphenic acid and is subject to dramatic acid-catalysis (equations 78 and 79). Reaction is retarded by base.



The electrophilic reactions of sulphenate esters with thiolsulphinates are discussed in Sections VI.E. and VI.F.2.

4. Sulphinic acids

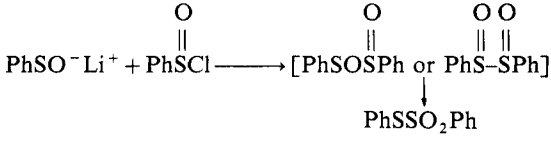
Sulphenic acids and esters react with sulphinic acids to form thiolsulphonates (Section VI.E). This reaction has also been used for trapping oxoazetidinesulphenic acids and the resulting thiolsulphonate reacted[67] with nucleophiles, thus extending the range of substituents that can be introduced to the penicillin sulphur atom after opening the thiazolidine ring (equation 80).



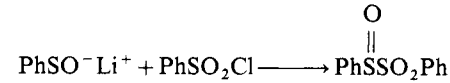
(80)

5. Sulphinyl and sulphonyl chlorides

Sulphinyl chlorides and sulphonyl chlorides react[16] with sulphenate anions to give thiolsulphonates and sulphinyl sulphones, respectively (equations 81 and 82). These reactions involve a nucleophilic reaction by the sulphenate anion. In the former reaction this gives a product which is unstable with respect to thiolsulphonate[68] and rapidly isomerizes to it.



(81)

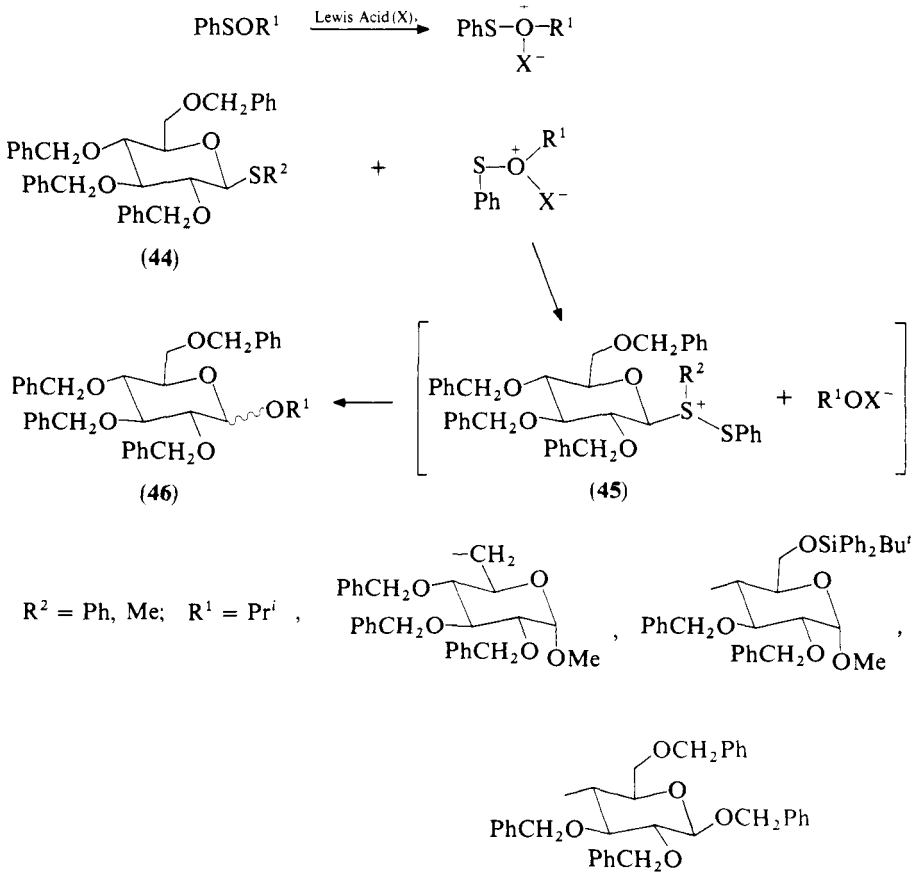


(82)

6. Thioglycosides

Sulphenate esters are activated to nucleophilic attack by the addition of Lewis acids and, in the presence of catalytic amounts of trimethylsilyl triflate (TMSOTf), they react[69] under mild conditions (1 h, −35 °C) with thioglycosides to give glycosylated products (**46**)

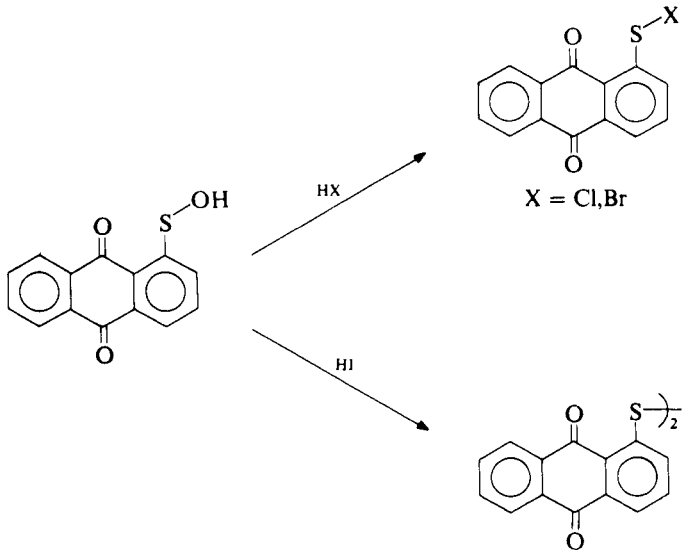
in high yields. Sulphenate esters derived from glucopyranosides serve as satisfactory glycosyl acceptors to give disaccharides. Using 1-deoxy-1-thio-β-D-glucopyranoside (**44**) as the glycosyl donor it was found that the stereoselectivity was solvent-dependent being α-selective in ether and β-selective in acetonitrile. β-Selectivity is enhanced with less sterically hindered substrates and, at low temperatures, α-selectivity was higher with more hindered substrates and was essentially temperature-invariant. The activated sulphenate ester is postulated to react with the thioglycoside to form a cationic intermediate (**45**), which in turn reacts with the nucleophilic residue from the ester to give product **46** (Scheme 6).



SCHEME 6

G. With Halogen Compounds

The stable anthraquinone-1-sulphenic acid reacts with hydrogen chloride or hydrogen bromide to give the corresponding sulphenyl chloride or bromide, but with hydrogen iodide reduction occurs to give the disulphide[50] (equation 83). Alkyl sulphenate esters react similarly with concentrated hydrochloric acid to give initially the alcohol and

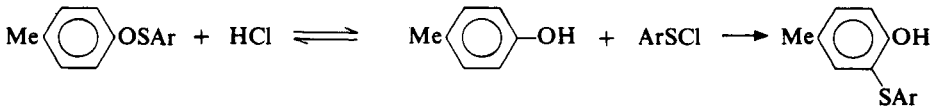


(83)

sulphenyl chloride, thus reversing a usual method of preparation[50, 28] (equation 84). Aryl esters also reversibly give[28] the phenol and sulphenyl chloride on treatment with hydrogen chloride in benzene (equation 85) but in this case an irreversible electrophilic substitution leads to the formation of hydroxyphenyl sulphides (see Section VI.A.3).

$$RSOMe + HCl \rightleftharpoons RSCl + MeOH \qquad (84)$$

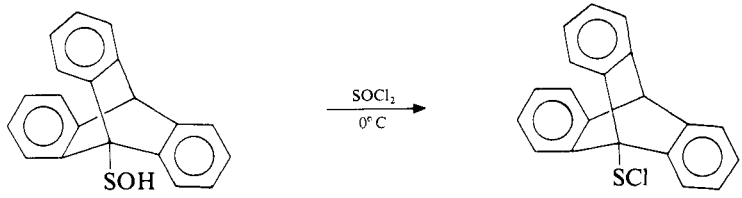
$R = 2\text{-}NO_2C_6H_4$, 1-chloro-2-naphthyl



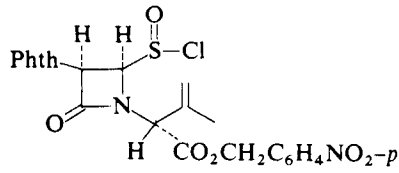
$Ar = 2\text{-}NO_2C_6H_4$

(85)

The stable 9-triptycenesulphenic has been reported[7] to react with thionyl chloride at 0 °C to give a chlorine-containing compound, presumably the sulphenyl chloride (equation 86). Sulphuryl chloride chlorinates and oxidizes the oxoazetidinesulphenic acid (**28**, $R = CH_2C_6H_4NO_2\text{-}p$) to give[8] the sulphinyl chloride (**47**) in almost quantitative yield.

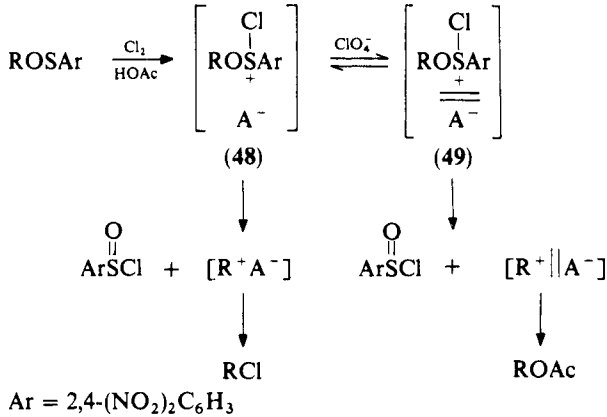


(86)



(47)

Chlorinolysis of alkyl[70] and cycloalkyl[71] 2,4-dinitrobenzenesulphenates in acetic acid using a 2–3 molar excess of chlorine has the overall effect of oxidizing the sulphur moiety to give the sulphinyl chloride and the sulphonyl chloride. The main interest in this reaction arises from its suitability for studying carbonium ion-pairing behaviour and hydride ion shifts. Reaction (see Scheme 7) involves the initial formation of an intimate sulphoxonium ion pair (**48**) which may decompose to the sulphinyl chloride and a carbonium ion pair before, or after, solvent reorganisation to a solvent-separated sulphoxonium ion pair (**49**). The carbonium ion pairs are therefore formed in an inherited solvent environment. Excess chlorine oxidises the sulphinyl chloride to sulphonyl chloride, particularly during aqueous work-up.



SCHEME 7

VII. ADDITION REACTIONS

Addition to alkenes, such as ethyl acrylate, and alkynes such as methyl propiolate, has been extensively used for trapping sulphenic acids, particularly those formed by the thermolysis of sulphoxides and thiolsulphinates, and has been mentioned *inter alia* in previous sections of this Chapter.

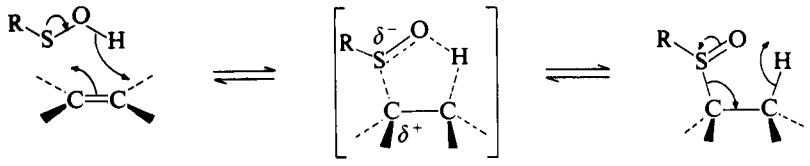
A. Concerted Additions of Sulphenic Acids to Alkenes

Contrary to some early reports sulphenic acids add readily to unactivated alkenes, as well as to alkenes conjugated with an activating group, to give sulphoxides. 2-Methylpropane-2-sulphenic acid, obtained by the thermolysis of di-*t*-butyl sulphoxide at

140 °C, adds rapidly to pentene-1 to give[72] predominantly the Markownikoff adduct in good yield (equation 87). The reaction has been extended[72] to a wide variety of alkenes and substituted alkenes, although much lower yields were obtained with cycloalkenes (cyclopentene, 28%; cyclohexene, 8%; cyclo-octene, 12%).

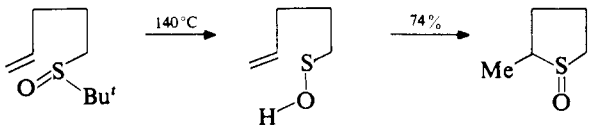
$$t\text{-BuSOH} + CH_2{=}CH(CH_2)_2Me \xrightarrow[4\ min]{140\ ^\circ C} \underset{(83\%)}{CH_3\overset{t\text{-BuS}=O}{\overset{|}{C}}H(CH_2)_2Me} \qquad (87)$$

Addition is a cyclic concerted process which is the reverse of the elimination of sulphenic acids from sulphoxides and should therefore proceed through the same transition state (**50**), which is considered[73] to resemble the sulphoxide more than the sulphenic acid (equation 88). It is therefore reasonable that the partial C–S bond in the transition state is polarized giving the carbon cationic character in accord with the observed regiospecific Markownikoff addition. Intramolecular additions occur[72] in good yield giving the sulphur heterocycles expected on the basis of *cis*-addition through a transition state resembling **50**. Pent-5-enesulphenic acid, obtained by the thermolysis of 5-*t*-butylsulphinylpentene-1, gives *cis*-2-methylthiolan 1-oxide uncontaminated with the *trans*-isomer or thian 1-oxide, neither of which would be expected on the basis of the above mechanism (equation 89). *cis*-2-Methylthian 1-oxide (88%) was similarly obtained, but the preparation of *cis*-2-methylthiepan 1-oxide was complicated by a stereospecific ring contraction under the reaction conditions to give *cis*-2-ethylthian 1-oxide.



(88)

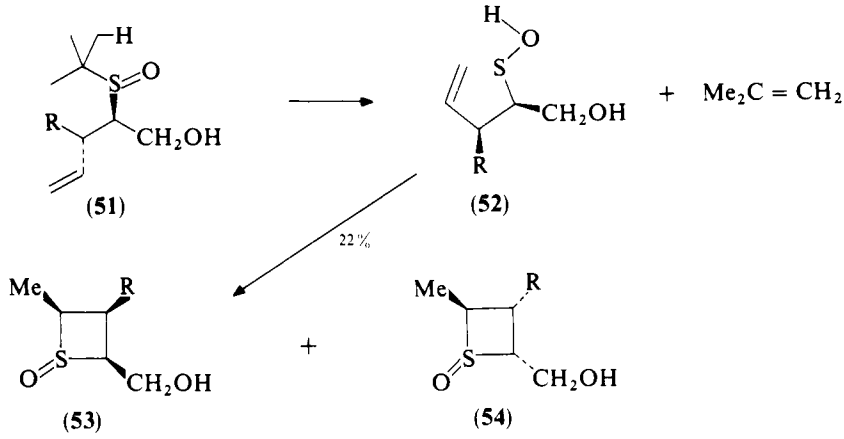
(50)



(89)

The stereospecific cyclisation of substituted but-3-enesulphenic acids to give thietan 1-oxides of known stereochemistry was exploited[74] in the synthesis of prostaglandin analogues containing thietan rings in place of the isosteric cyclopentane rings. Thermolysis of the *erythro* isomers (**51**) in boiling xylene for 15 min gave[75] the sulphenic acid (**52**) which added intramolecularly to both diastereotopic faces of the alkene to give a mixture of *rel*-(1*R*,2*R*,3*S*,4*R*)-3-hexyl-2-hydroxymethyl-4-methylthietan 1-oxide (**53**) and the (1*R*,2*S*,3*R*,4*R*)-isomer (**54**) in a 1:3 ratio, which was attributed to greater steric compression in the transition state leading to **53** (Scheme 8). The *threo* diastereomers similarly gave a 3:1 mixture of the (1*R*, 2*R*, 3*R*, 4*R*) and (1*R*, 2*S*, 3*S*, 4*R*) isomers in 44% yield. In the latter case steric repulsion between the hexyl group and the nascent methyl was considered paramount.

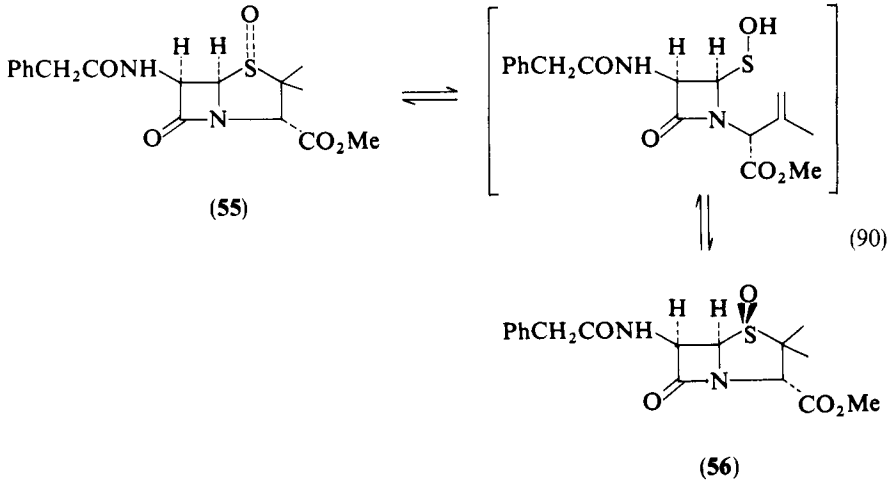
Epimerisation of the penicillin (*R*)-sulphoxide (**55**) to the (*S*)-sulphoxide (**56**) in refluxing benzene is considered[47] to involve ring-opening to give the sulphenic acid by the thermal



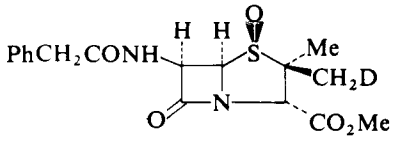
SCHEME 8

six-electron sigmatropic rearrangement indicated in equation 90 followed by ring-closure by the reverse process[76]. If the reaction is carried out in benzene containing an excess of deuterium oxide, an average of one deuterium atom is incorporated stereospecifically into the β-methyl group, which is *cis* to the sulphoxide bond[77] (compound **57**). The greater thermodynamical stability of **56** is attributed[77] to intramolecular hydrogen bonding with the NH group in the amido side-chain. In the absence of such a group the (*R*)-sulphoxide is the more stable on steric grounds. Heating the phthalimido analogue of **55** under reflux in benzene containing an excess of deuterium oxide consequently leads to incorporation of deuterium in the α-methyl group which is *cis* to the sulphoxide bond in this case (compound **58**). Epimerization by pyramidal inversion or by homolytic scission-recombination was rejected[77, 78] on the basis of energy considerations.

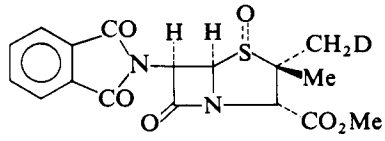
Evidence for the intermediacy of a sulphenic acid in these ring-openings was obtained[79] by trapping experiments (equation 91).



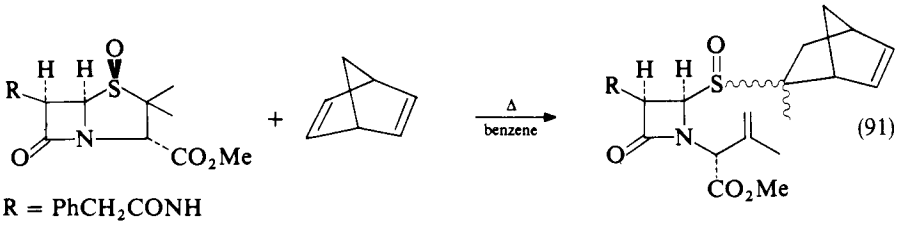
(90)



(57)



(58)



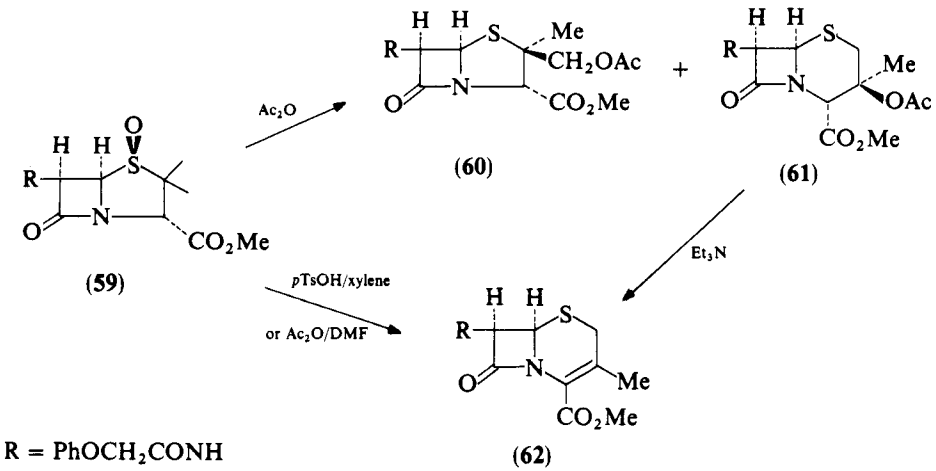
(91)

R = $PhCH_2CONH$

B. Stepwise Additions of Sulphenic Acids to Alkenes

Interest in the stepwise addition of sulphenic acids to alkenes in acidic media was stimulated by the attractive possibility of converting penicillin, obtained by fermentation, into a cephalosporin which could then be modified via enzymatic removal of the side-chain. Conversion of a thiazolidine ring into a dihydrothiazine ring involves an oxidation and consequently attention was concentrated on penicillin sulphoxide.

The sulphoxide of methyl phenoxyacetamidopenicillanate (**59**) did not give[80] a normal Pummerer reaction on refluxing with acetic anhydride but instead gave a 2: 1 mixture of two isomers **60** and **61** in 60% yield. The latter on treatment with base gave **62**, which could also be obtained in low yield by refluxing **59** in xylene containing toluene-*p*-sulphonic acid or as the only isolable product (60%) on treatment of **59** with 5% acetic anhydride in DMF[77,47] (Scheme 9).

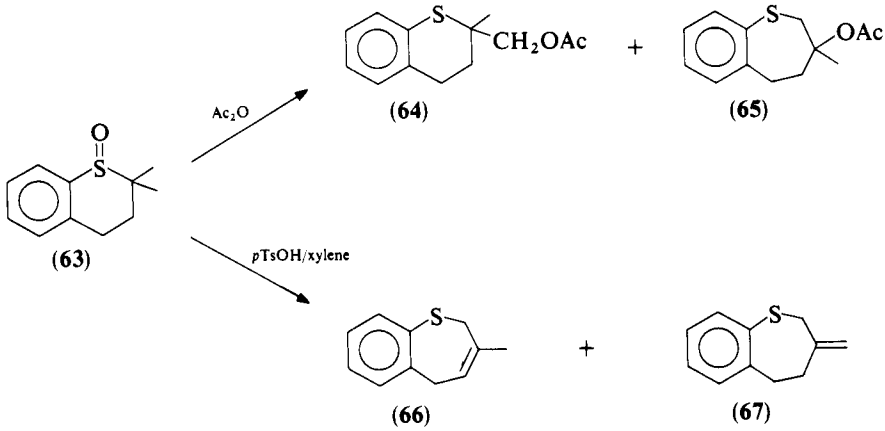


(59) (60) (61) (62)

R = $PhOCH_2CONH$

SCHEME 9

Similar reactions were observed with model compounds, 2,2-dimethylthiochroman sulphoxide (**63**) gave[81] a 10:1 mixture of the acetoxy derivatives **64** and **65** on heating under reflux with acetic anhydride, whereas in xylene containing toluene-*p*-sulphonic acid the unsaturated benzothiepins (**66**) and (**67**) were obtained (Scheme 10).

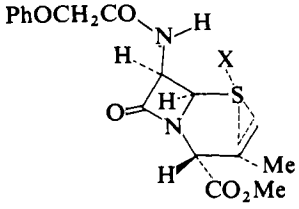


SCHEME 10

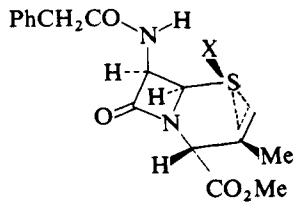
These reactions of **59** and **63** are suggested[82] to proceed by an initial thermal ring opening to give a sulphenic acid, the trapping of which by various reagents has been described in other sections of this Chapter. This sulphenic acid is then considered to form a mixed anhydride with the acidic reagent, thus converting the sulphur atom into a powerful electrophile and the remainder of the mixed anhydride into a leaving group with considerable steric requirements, which have important consequences for the reaction stereochemistry. Ring closure then involves electrophilic addition to the double bond through an episulphonium ion intermediate which yields the main products.

In the reaction of the penicillin sulphoxide (**59**) with acetic anhydride, the mixed anhydride will be a sulphenyl acetate and the acetate will tend to leave from the α-face of the molecule due to its possible interaction with the β-amido side-chain, and the double bond will consequently tend to approach from the β-face, the three reacting centres being collinear. The preferred transition state leading to formation of the episulphonium ion intermediate is therefore (**68**) rather than **69**)[82]. The collapse of the episulphonium ion pair (**70**) arising from **68** will therefore give (see equation 92) the β-acetoxymethylpenicillin ester (**71**) and the β-acetoxymethylcepham ester (**72**) (**60** and **61**, Scheme 9). When the acidic reagent is toluene-*p*-sulphonic acid the resulting anion is a much stronger leaving group and a weaker nucleophile, consequently elimination is favoured to give the observed 3-cephem product (**62**). Sulphuric acid is proposed to react similarly but with an additional pathway yielding the β-hydroxy analogue of **72**, possibly involving internal collapse of the bisulphate ester, liberating sulphur trioxide and forming the alcohol.

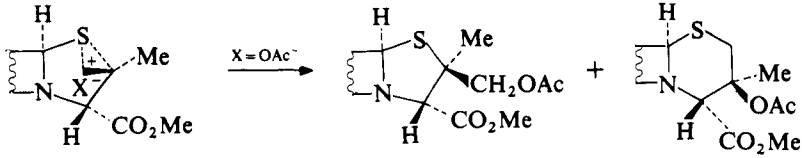
Other non-β-lactam minor products obtained in the reaction of **59** with acetic anhydride, and in similar reactions, have been suggested[80, 82] to be derived from the sulphenic acid intermediate. The isothiazolone **73** has been proposed to arise from nucleophilic displacement on sulphenyl sulphur by the lactam nitrogen, and the dihydro-1,3-thiazin-4-one **74** by a base catalysed ring expansion involving a carbanion stabilised by the ester group.



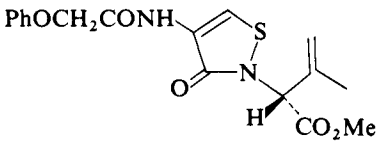
X = OAc (68)



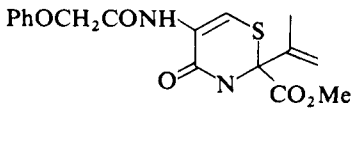
X = OAc (69)



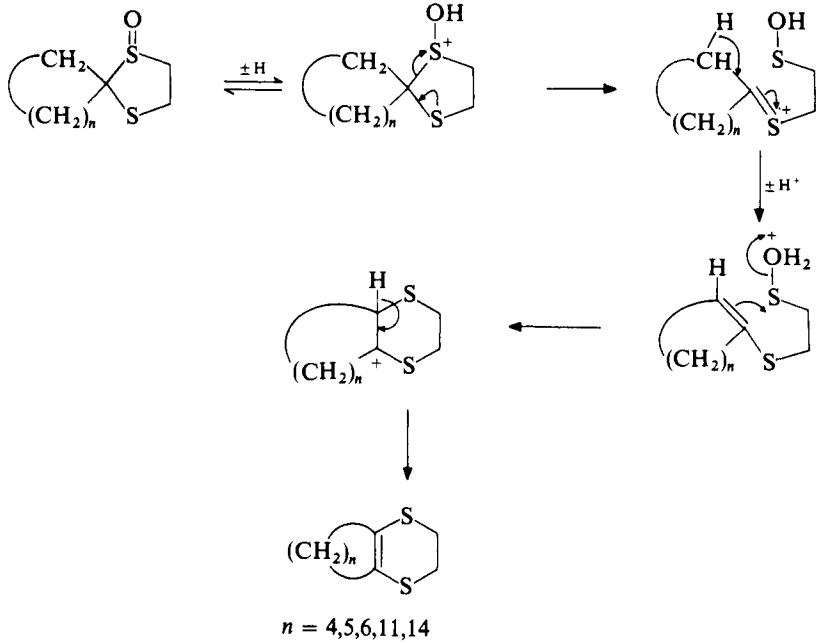
(70) (71) (72) (92)



(73)



(74)



n = 4,5,6,11,14

SCHEME 11

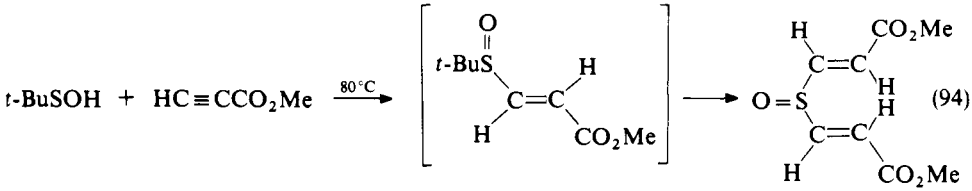
Replacement of the *s*-amido side-chain in **59** with a phthalimido side-chain is considered[82] to increase the steric interaction of the side-chain with the double bond approaching from the β-face and thus make the two transition states **68** and **69** more competitive. In this case both the β- and α-acetoxymethylpenicillins are obtained together with the 3-cephem ester formed by a facile *trans*-elimination of acetic acid from the 3-α-acetoxycepham.

Addition of a sulphenic acid to an alkene is postulated[83] as the ring-closing step in a method for constructing carbocyclic fused dihydro-1,4-thiins from spiro-1,3-dithiolan 1-oxides by azeotropic distillation in benzene containing catalytic amounts (10%) of toluene-*p*-sulphonic acid (Scheme 11). Yields were essentially quantitative.

C. Additions of Sulphenic Acids to Alkynes

Sulphenic acids add to alkynes by a concerted cyclic mechanism similar to that described for the similar stereospecific *syn*-additions to alkenes (Section VII.A). It is not necessary, contrary to earlier reports, for the alkyne to be conjugated with an activating group. 2-Methylpropane-2-sulphenic acid, prepared by the thermolysis of di-*t*-butyl sulphoxide, adds to octyne-1 to give[84] predominantly the Markownikoff adduct (equation 93). A mixture of dioctenyl sulphoxides (10%) was also obtained. These are considered to arise from thermolysis of the above *t*-butyl octenyl sulphoxides to give the octenylsulphenic acids, which then also add to the octyne. Essentially complete thermolysis of the expected product was observed[18] in the addition of 2-methylpropane-2-sulphenic acid to methyl propiolate at 80 °C which gave dimethyl sulphinyl-*trans*, *trans*-diacrylate (equation 94). Normal 1:1 addition was obtained at room temperature.

$$t\text{-BuSOH} + HC{\equiv}C(CH_2)_5Me \xrightarrow[2.5\ h]{80\ ^\circ C} \underset{(61\%)}{H_2C{=}C(t\text{-BuS}{=}O)(CH_2)_5Me} + \underset{(4\%)}{HC(t\text{-BuS}{=}O){=}CH(CH_2)_5Me} \qquad (93)$$

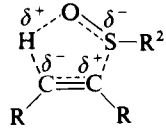


(94)

Benzene-, methane- and ethoxycarbonylmethanesulphenic acids, obtained by thermolysis of the appropriate 1-cyano-2-(aryl- or alkylsulphenyl)ethanes, $RS(O)CH_2CH_2CN$, do not contain β-hydrogens which can participate in further sulphoxide eliminations, and their additions give alkenyl sulphoxides in excellent yields (equation 95). Benzenesulphenic acid showed[85] the greatest regiospecificity.

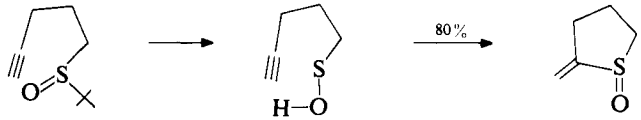
$$PhSOH + HC{\equiv}C(CH_2)_5Me \longrightarrow \underset{(94\%)}{H_2C{=}C(PhS{=}O)(CH_2)_5Me} \qquad (95)$$

NMR studies indicate[85, 86] stereospecific *cis*-addition expected for a pericyclic mechanism and the regiospecificity indicates that the partial S–C bond in the transition state

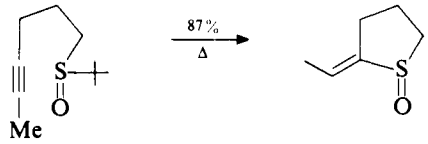


(75)

(75) gives rise to some carbonium ion character. This is in accord with the higher stereospecificity of addition for benzene- compared with methanesulphenic acid. Intramolecular additions occur[84] readily in high yield. 2-Methylenethiolan 1-oxide (80%), 2-methylenethian 1-oxide (88%) and 2-methylenethiepan 1-oxide (53%) were obtained by thermolysis of the appropriate ω-(*t*-butylsulphinyl)alk-1-ynes in boiling xylene for 2.5 h (equation 96). The corresponding thietan 1-oxide could not be obtained. The transition states leading to the exocyclic alkenyl sulphoxides are strain-free, whereas those leading to highly strained endocyclic *trans*-alkenyl sulphoxides are clearly unfavourable. In the case of terminal alkynes, these factors are reinforced by electronic factors favouring Markownikoff addition. The operation of these factors can be seen in the preparation of (*E*)-2-ethylidenethiolan 1-oxide (equation 97).



(96)

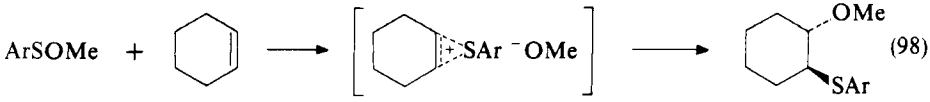


(97)

α,β-Unsaturated sulphoxides are useful synthetic intermediates owing to their reactivity as dienophiles and Michael acceptors; their ready availability by this stereospecific route is therefore of synthetic significance.

D. Addition and Arene Annelation Reactions of Sulphenate Esters

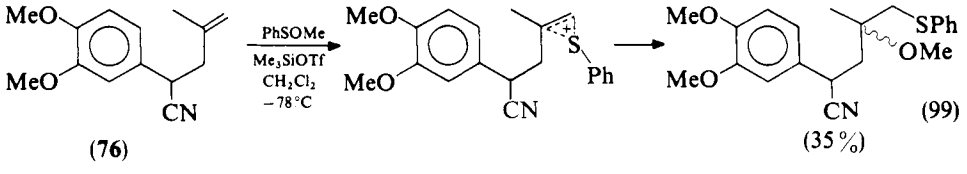
Although sulphenyl halides react readily with alkenes at room temperature, the much lower electrophilic reactivity of sulphenate esters renders their uncatalysed reactions with alkenes less useful. Methyl 2-nitro- and 2,4-dinitrobenzenesulphenates however add[28] to alkenes on prolonged heating in methanol to give the *trans*-adducts (equation 98).

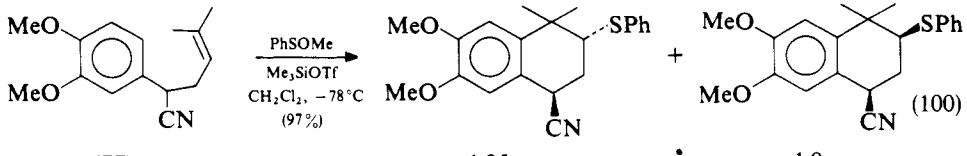


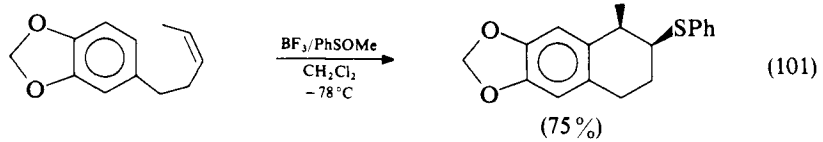
(98)

The electrophilic reactivity can however be increased by addition of suitable acids. Methyl benzenesulphenate in combination with the Lewis acids, trimethylsilyl triflate (1 equiv.) or boron trifluoride etherate (2 equiv.) is an effective combination for promoting electrophilic addition to alkenes and, more importantly, cationic arene–alkene cyclisation

in a wide range of substrates including both activated and non-activated aromatic nuclei[86]. Reaction proceeds via an episulphonium ion intermediate and anti-Markownikoff addition. The episulphonium ion undergoes scission with net inversion of configuration as observed[87] in similar reactions. The highly electrophilic BF_3/PhSOMe combination is capable[86] of effecting annelation in mono-, di- or trisubstituted alkenes, but the more selective Me_3SiOTf/PhSOMe combination is the preferred reagent for trisubstituted alkenes. 1-Cyano-3-methyl-1-(3,4-dimethoxyphenyl)butene-3 (**76**) gave only addition with Me_3SiOTf/PhSOMe (equation 99) but the trisubstituted alkene (**77**) gave the annelated isomers in a 1.25:1.0 ratio (equation 100). (*E*)-1-(3,4-methylenedioxyphenyl)pentene-3 gave[86] the *trans* substituted tetralin derivative as the only isolated product on treatment with BF_3/PhSOMe, whereas the *Z*-isomer gave only the *cis*-product consistent with formation of an episulphonium ion intermediate (equation 101). Pentene-4 and hexene-4 derivatives gave only six-membered ring products.

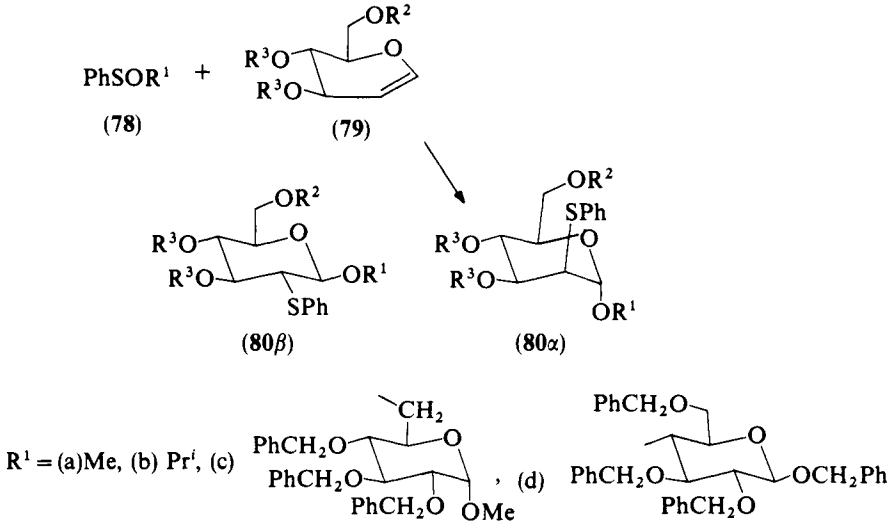






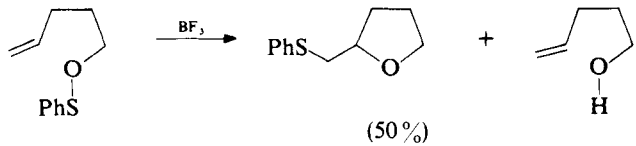
Annelation with incorporation of latent functionalization has considerable synthetic utility. Other similar reactions involving episulphonium ion intermediates[87, 88] are of lesser value as they require the use of sensitive silver salts or generate the inconvenient nucleophilic by-product, dimethyl sulphide.

The addition reaction has been utilized[89] for a synthesis of 2-deoxyglycosides under mild conditions in which the sulphenate ester is used as a glycosyl acceptor. Various 3,4,6-tri-*O*-substituted-D-glucals (**79**) were reacted with benzenesulphenate esters (**78**) in the presence of trimethylsilyl triflate in dichloromethane to give a mixture of the α- and β-anomers of 2-deoxy-2-phenylthioglycosides (**80**) in high yield (Scheme 12). Even acid labile trityl and silyl ethers survived the reaction conditions. Addition was almost exclusively 1,2-*trans* and the stereochemical outcome appears to be governed mainly by the steric interaction between the incoming phenylsulphenyl group and the benzyloxy group giving rise to 1,2-diequatorial addition as the major reaction path. The phenylthio group is readily removed under reductive conditions. The reaction was also applied to the synthesis of disaccharides, using the substituted glucopyranoside 6-, and 4-benzenesulphenates **78c** and **78d**.



SCHEME 12

Alkenyl benzenesulphenates have been shown[90] to cyclize on treatment with boron trifluoride etherate or silica gel to give tetrahydrofurans (equation 102). The yield is however reduced by formation of the parent alcohol and the reaction was unsuccessful with more complex alkenyl groups.



(102)

VIII. OXIDATION AND REDUCTION REACTIONS

Sulphenic acids and esters behave as compounds of intermediate oxidation state which can be oxidized in general to sulphinic acids and esters and hence to higher oxidation states, or reduced to thiols and hence disulphides. Many examples of such oxidations and reductions have been included *inter alia* in previous sections in this chapter and more specific examples are included in this section.

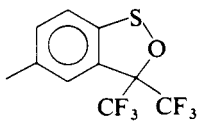
A. Oxidations

Salts of the anthraquinonesulphenic acids are oxidized in solution by air or more readily by ferricyanide ion to give sulphinates[50]. Lithium benzenesulphenate behaves similarly[16].

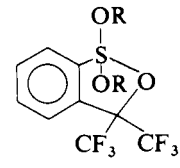
$$PhSO^-Li^+ + [O] \longrightarrow PhSO_2^-Li^+ \qquad (103)$$

1,3,6-Trimethyllumazine-7-sulphenic acid (**2**; R = Me) is oxidized by hydrogen peroxide to give[2] the sulphinic acid but potassium permanganate gives the sulphonic acid.

Pentyl methanesulphenate was readily oxidized[52] to the sulphinate ester with air or potassium permanganate. *s*- and *t*-Alkyl esters were more resistant to aerial oxidation but all these esters were oxidized[52] by selenium dioxide, potassium dichromate and acid potassium iodide. The cyclic sulphenate (**81**) reacted in minutes with water and moist air, or much more slowly with *t*-butyl perbenzoate, to give[91] the sulphinate. A sulphurane intermediate formed by sulphur insertion into the peroxide bond was suggested for oxidation with the latter reagent. The sulphurane (**82**) was obtained[91] on oxidation with bromine and 2 equiv. of the potassium salt of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol.



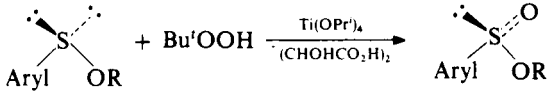
(**81**)



R = $Ph(CF_3)_2C$

(**82**)

Oxidation of methyl toluene-*p*-sulphenate with (+)-monoperoxycamphoric acid in chloroform at −25 °C gave[92] the optically active sulphinate ester having the (*R*)-configuration in accord with the Montanari rule. Enantiomeric excesses of up to 36% were obtained[93] by asymmetric oxidation of sulphenates with a modification of the Sharpless reagent, *t*-butyl hydroperoxide and titanium isopropoxide in the presence of 2 mol equivalents of (+)-diethyl tartrate and 1 mol equivalent of water (equation 104). Excellent yields of the (*R*)-sulphinate esters were obtained except in the case of 2,4-dinitrobenzenesulphenates.



(104)

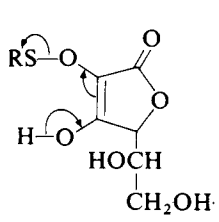
Aryl = Ph, *p*-Tolyl; R = Me, Pr^i

B. Reductions

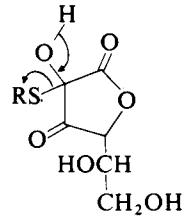
Sulphenic acids are reduced to thiols by a variety of reagents including sodium arsenite[50], sodium sulphide[50] and sodium borohydride[2]. The sulphenic acid formed by oxidation of the essential thiol group, Cys-149, of pig muscle glyceraldehyde-3-phosphate dehydrogenase with trinitroglycerine is similarly reduced back to the thiol form with arsenite at neutral pH, thiols, thiosulphate, thiourea, azide, hydrazines and L-ascorbate[5]. These reactions are suggested to involve basically an initial nucleophilic substitution on the sulphenic acid by the reducing agent followed by either a further substitution (reaction 105) or an elimination (reaction 106)[94]. L-Ascorbate can form two possible intermediates (**83** and **84**) in the initial substitution reaction both of which can form thiol as indicated. Reduction with an excess of azide is suggested to involve initial formation of the sulphenyl azide which loses nitrogen to form the nitrene, which by further reaction with azide and loss of nitrogen gives the thiol[94].

$$R^1SOH \xrightarrow{R^2SH} R^1SSR^2 \xrightarrow{R^2SH} R^1SH + R^2SSR^2 \quad (105)$$

$$R^1SOH \xrightarrow{R^2NHNH_2} R^1SNHNHR^2 \longrightarrow R^1SH + HN{=}NR^2 \quad (106)$$



(83)



(84)

$$RSOH + N_3^- \longrightarrow RSN_3 + OH^- \quad (107)$$

$$RSN_3 \longrightarrow RS\ddot{N}: + N_2 \quad (108)$$

$$RS\ddot{N}: + N_3^- \longrightarrow RS^- + 2N_2 \quad (109)$$

Deoxygenation of sulphenic acids and esters by phosphorus III compounds has been discussed in Section VI.D.

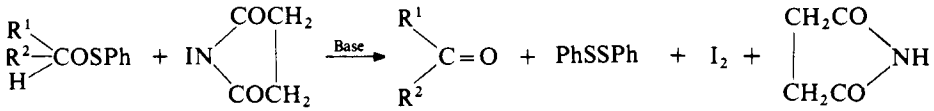
The atypical sulphenic acid, 1-methyluracil-4-sulphenic acid (**3**), was quantitatively reduced[3] to the thione, 1-methyl-4-thiouracil (**25**), by dethiothreitol.

Sulphenate esters are reduced to disulphides quantitatively by hydrazine[39] and by tripropylamine and trichlorosilane[95].

$$4PhSOMe + N_2H_4 \longrightarrow 2PhSSPh + 4MeOH + N_2 \quad (110)$$

$$PhSOMe + HSiCl_3 + Pr_3N \xrightarrow{88\%} PhSSPh + Pr_3\overset{+}{N}HCl^- + (SiCl_2O)_n \quad (111)$$

Trimethylsilyl esters react with an excess of trimethylphosphite in benzene at room temperature to give[36] the methyl sulphide. Sulphenate esters containing an α-hydrogen react with *N*-iodosuccinimide and an excess of 2,6-lutidine in an inert solvent at room temperature to give[96] a carbonyl compound in low yield together with disulphide and hydrolysis products. The reaction, which is considered to involve formation of an intermediate sulphenyl iodide, is suggested to be a possible biological model for oxidations involving alcohol dehydrogenases[96].



(112)

Polarographic reduction of methyl benzenesulphenate is considered to involve[97] reductive cleavage of the S–O bond to give methanol and mercury thiophenolate which is reduced to thiophenol in the second step.

The powerful antioxidant action of dialkyl sulphoxides and thiolsulphinates on the autoxidation of hydrocarbons has been ascribed[98] to the extremely active radical

scavenging properties of the sulphenic acids produced on thermolysis. Photolysis of 2-methylpropane-2-sulphenic acid and di-*t*-butyl peroxide in toluene or isopentane at −40 to −60 °C has been shown[99] to give the *t*-butylsulphinyl radical, *t*-BuSO·. The rate constant for reaction of sulphenic acids with peroxy radicals is estimated[98] to be at least 10^7 litre mol^{-1} s^{-1}.

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **10**

Chemistry of sulphenyl halides and sulphenamides

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

The chemistry of sulphenyl halides, sulphenamides and related compounds has been reviewed several times in a comprehensive way[1-18]. The reader should therefore refer to these articles for a detailed account of the extremely rich chemistry of these compounds. The aim of the present chapter is to present the most significant advances in the chemistry of sulphenyl halides and sulphenamides, from both the synthetic and theoretical point of view. Therefore only the most important classes of compounds and their reactions will be reviewed.

A. General Reactivity

Sulphenyl halides, as well as a large variety of compounds in which an R–S residue is linked to a group more electronegative than carbon, can be considered as derivatives of sulphenic acids 1 where the OH group is substituted by the generic group X as in the

'formal' equations 1 and 2.

$$\underset{(1)}{RS\text{–}OH} + HX \longrightarrow \underset{(2)}{RS\text{–}X} + H_2O \quad (1)$$

$HX = HCl, HBr, (HI, HF), HNR_2, HOR, HSR, HS(O)R, HS(O_2)R$

$$\underset{(1)}{RS\text{–}OH} + B + H^+ \longrightarrow RS\text{–}B^+ + H_2O \quad (2)$$

$B = R_2S, R_2S_2, NR_3$, etc.

Considering the formal analogy of S with CH_2, the sulphenic acids **1** may be regarded as a type of alcohol and sulphenyl halides as a type of alkyl halide. Finally, when X is a halogen atom, the sulphenyl halides (RSX) may be considered *pseudo*-halogens and indeed their chemistry is very similar to that of typical *pseudo*-halogens like $(SCN)_2$, CN–Hal, etc., and to that of the halogens themselves.

Besides the specific properties of the sulphenic acids[18] and of their more simple derivatives (like, for example, the sulphenic esters, RS–O–R′), that may be related to the ambidentate character of sulphenate anion **3** (equation 3), which, in turn, is responsible for the well-known rearrangement of sulphenate esters to sulphoxides (equation 4, see Reference 18 for a more detailed discussion), and besides the oxidation of the sulphenic sulphur to higher oxidation states such as S^{+4} and S^{+6}, the largest set of reactions of sulphenyl compounds may be represented in a schematic way by equation 5.

$$\underset{(1)}{RS\text{—}OH} \rightleftharpoons \left[RS\text{—}O^- \longleftrightarrow \underset{(3)}{RS{=}O^-}\right] + H^+ \rightleftharpoons RS(H){=}O \quad (3)$$

$$RS\text{—}O\text{—}R^1 \longrightarrow R\text{—}\overset{\overset{O}{\|}}{S}\text{—}R^1 \quad (4)$$

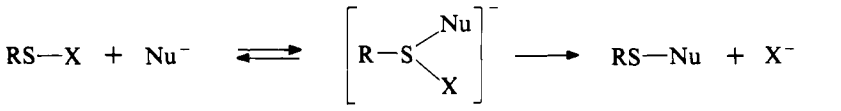
$$RS\text{—}X + X' \rightleftharpoons RS\text{—}X' + X \quad (5)$$

The reactivity of sulphenyl compounds may be also considered as a nucleophilic substitution of X by various neutral or negative nucleophiles X′ (in equation 5 charges are not indicated for simplicity).

As for every substitution reaction, three limiting mechanisms, dissociative, concerted and associative, may be considered (equations 6, 7 and 8, respectively).

$$RS\text{—}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(4)}{RS^+} + X^- \xrightarrow[+Nu^-]{k_2} RS\text{—}Nu + X^- \quad (6)$$

$$RS\text{—}X + Nu^- \longrightarrow \left[Nu^{\delta-}\text{—}\overset{\overset{R}{|}}{S}\text{—}X^{\delta-}\right] \longrightarrow RS\text{—}Nu + X^- \quad (7)$$



(8)

1. The sulphenylium cation and the unimolecular substitution mechanism

The dissociative mechanism (equation 6) requires the intermediacy of a sulphenylium cation **4**. The presence of these species as intermediates along the reaction path is at least doubtful even though ions of such a composition are routinely reported in mass-spectroscopy studies[19-24] and claims of their intervention in condensed phase reactions[25-32] have been advanced at various times.

Sulphenylium ions, as the halogen cations, may have either a closed or an open-shell structure **5a** and **6a** or **5b** and **6b**.

(5a) **(6a)** **(5b)** **(6b)**

Quantum-mechanical calculations[33-47] on HS^+, CH_3S^+ and other simple ions at various levels of sophistication indicate that the ground states have the triplet structure **5b** whereas the singlet structures **5a** correspond to excited states located at significantly higher energies. Therefore such species cannot be directly compared to well-established cations like carbocations or nitronium ions, which may be generated by neutral or charged precursors in their singlet ground states by thermal processes. On the contrary, sulphenylium ions **4** (as well as halogen cations) should be generated in the first excited state and this makes these processes rather unlikely owing to the great endothermicity of the reaction.

Besides these theoretical considerations, the suggestions derived from gas-phase studies[19-24] must be critically re-examined. First of all a distinction between aliphatic and aromatic sulphenylium ions has to be made.

Rather careful studies by mass spectroscopy, ion cyclotron resonance, etc. allowed the detection of species having masses corresponding to CSH_3^+, $C_2SH_5^+$, etc.[19-24].

The most stable structure of these ions is that of protonated (or alkylated) thioaldehydes **7** which is always the most abundant species at the lower ionization energies. Evidence for isomeric ions **8** is sometimes obtained at higher ionization energies. The behaviour of the species so generated might suggest that they have a triplet character[37].

(7) **(8)**

It appears therefore that, at least for alkane derivatives, the process of ionization is accompanied by a 1,2-hydride or a 1,2-alkide shift, thus avoiding the formation of the high-energy species RS^+, which may only be formed when excess energy is at disposal. Of course, solution reactions usually follow the lowest possible energy path and therefore alkanesulphenylium ions as intermediates are highly improbable in solution chemistry.

At least in principle, the case of arenesulphenylium ions might be different, since the presence of the adjacent π-system may stabilize the ion and may also lower the energy of the singlet state below that of the triplet.

In any case, the claims[25-32] of the formation in solution of sulphenylium ions by the action of strong Lewis or Brønsted acids have to be considered with caution.

The first claim on the formation of a sulphenylium cation in solution dates back to the early work of Kharasch[26]. He observed that 2,4-dinitrobenzenesulphenyl chloride dissolved in concentrated sulphuric acid gave rise to coloured ionic species, which were thought to have the structure of sulphenylium ions on the basis of cryoscopic measurements. However, these conclusions were criticized a few years later[31]. Cryoscopic data supplemented by conductometric studies and other related experiments were better explained by protonation of the sulphenyl chloride at sulphur[31].

However, a more recent study of benzene- and 2,4-dinitrobenzenesulphenyl chlorides in disulphuric acid would suggest that 2,4-dinitrobenzene-, but not benzenesulphenylium ion, may exist in this very strong acid[32]. Furthermore, the 2,4-dinitro derivative gave salt-like compounds by the action of strong Lewis acids[32]. This rather interesting result was not confirmed by further studies even though claims of the obtainment of strong sulphenylium ion transfer agents of general formula RS^+X^- ($X^- = AlCl_4^-$, $SbCl_6^-$, BF_4^-, etc.) by the action of Lewis acids on sulphenyl chlorides have been advanced[48].

This contrasts not only with the above discussed theoretical and gas-phase studies but also with other reports[49-51] which claim that sulphenyl chlorides react with Lewis acids in non-nucleophilic solvents to give the dimeric halonium ion **9** by the reaction reported in equation 9. In this reaction the Lewis acid acts as a sequestering agent for X^- and hence shifts the equilibrium to the right.

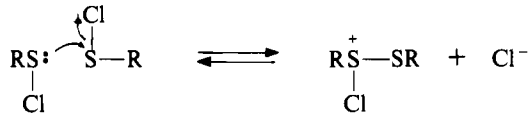
Equilibrium 9 was studied in detail by ^1H NMR for methane- and ethanesulphenyl chlorides (**10**, $R = CH_3$ and C_2H_5) and convincing evidence on the structure of **9** was offered[49-51]. The stoichiometry of equation 9 was also checked by conductometric titration of **10** with silver tetrafluoroborate or antimony pentachloride[50].

It seems very likely that this equilibrium may be the explanation for the formation of ionic species which are eventually generated from sulphenyl halides or other sulphenyl derivatives by the action of acids. Also, the acid catalysis sometimes observed in addition or substitution reactions may be explained by equation 9. Indeed, such an equilibrium may be the basis of a satisfactory description of most of the chemistry of sulphenyl halides and the intervention of sulphenylium cation should be confined to very limiting cases as far as either reaction conditions or type of substrate or both are concerned.

$$\underset{\textbf{(10)}}{2RS{-}Cl} \rightleftharpoons \underset{\textbf{(9)}}{\overset{+}{RS}{-}SR} + Cl^- \qquad (9)$$
$$\qquad\qquad\qquad\quad Cl$$

The position of equilibrium 9 depends on the nature of the R residue of **10** and more on the solvating (or complexing) ability for the ions, particularly for the anions, of the media in which the reaction occurs. The forward reaction may be simply regarded as the displacement of the chloride ion from one molecule of sulphenyl chloride by the nucleophilic attack at the sulphur atom of the other to form the halosulphonium ion **9** (Scheme 1). Accordingly, the reverse reaction may be represented as the nucleophilic attack of chloride ion at the dicoordinate sulphur of **9** with the sulphenyl chloride as leaving group.

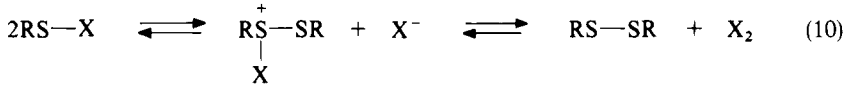
Since the sulphenyl chloride **10** has to be a much better leaving group than chloride ion, **9** is a much better electrophile than the sulphenyl chloride itself.



(**9**)

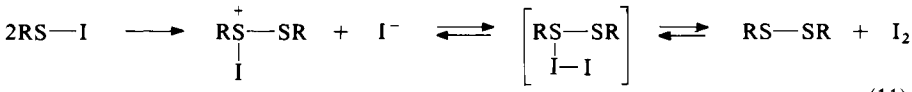
SCHEME 1

Equilibrium 9 may be extended and rewritten in a more general form as in equation 10.



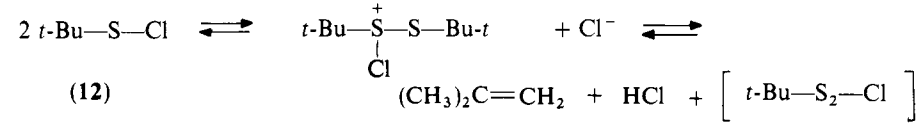
(**11**) (10)

Indeed this equation, from right to left, represents the classical reaction of formation of sulphenyl halides from disulphides and halogens. The first step is the transfer of a formally positive halogen ion to sulphur, i.e. the oxidation of disulphide. The reaction is eventually completed by the attack of the halide ion at the dicoordinate sulphur of **11** to give two molecules of sulphenyl halide. When the halogen is iodine, equilibrium 10 is shifted to the right and it represents the reduction of sulphenyl halides to disulphide which, in turn, may be considered as an attack of the iodide ion at the partially positive halogen (equation 11).



(11)

Equilibrium 10, together with equation 5, is therefore the key for understanding the behaviour of sulphenyl halides, as well as that of many other sulphenic derivatives. Obvious extensions of these reactions are those where the group linked to sulphur may also be a site of nucleophilic attack or have such intrinsic properties as to be a good cationoid leaving group. For example, *t*-butylsulphenyl chloride (**12**), although stable in diluted solution, cannot be distilled as it decomposes to hydrochloric acid, isobutene and sulphur[52] (equation 12). The thiosulphenyl chloride **13** should be an intermediate, which likely decomposes to the observed products.



(**12**) (**13**)

(12)

The formation and the stability of the thio-substituted halosulphonium ion **14** may also be discussed using an alternative point of view, i.e. the coordination of the sulphenylium ion by the sulphenyl halide as shown in **14a**.

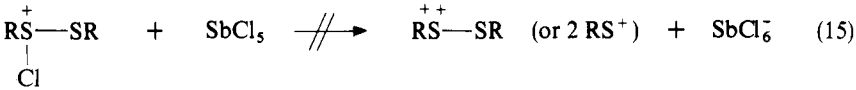
(14) (14a)

This implies that the sulphenyl sulphur has residual nucleophilic properties as also suggested by other reactions[53]. For example, chlorine adds to sulphenyl chlorides to give sulphenyl trichlorides under anhydrous conditions (equation 13) whereas in the presence of water and excess of chlorine it gives sulphonyl chlorides (equation 14).

$$RSCl + Cl_2 \rightleftharpoons RSCl_3 \quad (13)$$

$$RSCl + 2Cl_2 + 2H_2O \longrightarrow RSO_2Cl + 4HCl \quad (14)$$

The halogen atom bonded to the positive sulphur of **9** appears to have lost any nucleophilic properties as even $SbCl_5$ or silver ions are not able to remove it as an anion from sulphur to give either the disulphide dication **15** or two molecules of sulphenylium ion **4**[50] (equation 15).



(9) (15) (4)

This reaction appears to be extremely endoergonic and hence very unlikely. Furthermore, the problem of generation of the disulphide dication opens again the problem of triplet versus singlet ground state already discussed for the sulphenylium ion.

The thio-halosulphonium ion **14** is only one of the possible unconventional sulphenylium cation carrier reagents, in which this species is coupled with a neutral more or less weakly basic molecule.

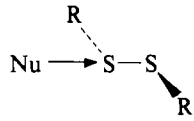
Several of these reagents have been developed in the last decades; others have been known for a long time at least as reaction intermediates. In particular, it has been shown that some bis-thiosubstituted sulphonium ions **16** can be easily prepared and eventually isolated as salts of very poorly nucleophilic anions like $SbCl_6^-$, BF_4^-[51,54–56] and are very useful reagents for the synthesis of thiiranium and thiirenium ions (see below) and in cyclofunctionalization reactions (see Section IV).

Less reactive, but much easier to handle are the thiosulphonium salts[57,58] **17**, which are now commercial reagents. Other sulphenylium ion carriers, such as **18** and **19**, are generally accepted intermediates of the acid-catalysed transformations of sulphenamides and sulphenic acid derivatives, respectively. Some compounds of type **18** have been also isolated[59].

(16) (17) (18) (19)

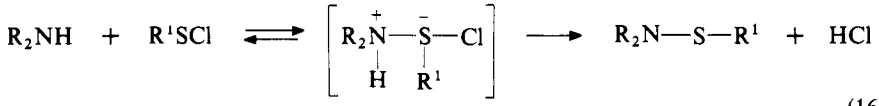
2. The concerted displacement and the associative mechanism

The mechanism and the stereochemistry of the displacement at divalent sulphur was studied almost thirty years ago on disulphides and thiosulphates[60]. It was concluded that the reaction may be represented as an S_N2-like process which has a transition state **20** with the nucleophile and the two sulphur atoms collinear.



(20)

However, the well-known ability of sulphur to give hypervalent compounds[61] like sulphuranes and similar species makes possible the hypothesis of an associative mechanism, at least under some conditions and only for some leaving groups. In particular, claims that the reaction of sulphenyl chlorides with amines occurs via a hypercoordinated intermediate have been advanced[62] (equation 16).



(16)

Similar hypotheses have been also suggested for the reaction of π-nucleophiles with sulphenyl halides. All these reactions follow a similar course and have a quite similar kinetic behaviour (see Section III).

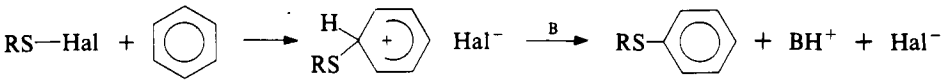
Charged nucleophiles $:Nu^-$ yield neutral sulphenic derivatives which may be more or less reactive depending on the nature of Nu^- (equation 17). Neutral n-nucleophiles yield charged products which, if carrying an acidic proton, may be stabilized by proton transfer to the solvent, to a base or to the nucleophile itself (equations 18 and 19).

$$RS\text{–}Hal + :Nu^- \rightleftharpoons RS\text{–}Nu + Hal^- \quad (17)$$

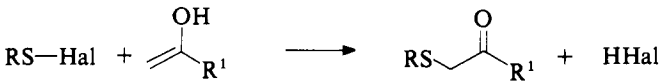
$$RS\text{–}Hal + :Nu \rightleftharpoons RS\text{–}Nu^+ + Hal^- \quad (18)$$

$$RS\text{–}Hal + :NuH \rightleftharpoons RS\text{–}\overset{+}{N}uH + Hal^- \rightleftharpoons RS\text{–}Nu + HHal \quad (19)$$

As will be discussed in Section III, some π-nucleophiles behave as the n-nucleophiles and give substitution products after proton removal. This is the case of benzene and other aromatic compounds (equation 20) and of some enols (equation 21). However, reactions with typical π-nucleophiles, like alkenes and alkynes, occur via more complex pathways.



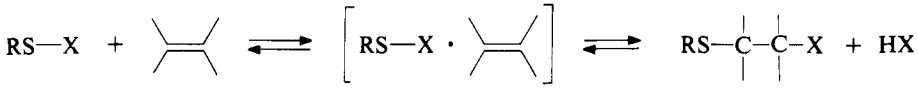
(20)



(21)

One or more intermediates, whose evolution is responsible for the formation of products, are thought to be involved, so that the reaction in a very general way may be

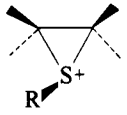
described as shown in Scheme 2. The reaction is represented as an equilibrium since, under some conditions, complete reversibility may be observed.



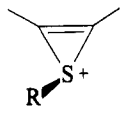
SCHEME 2

If a nucleophilic solvent is used, products derived from solvent incorporation may also be formed.

Even though the exact description of the intermediate(s) is still a matter of controversy, as will be discussed in Section III, mention must be made of the bridged sulphonium ions, the thiiranium and the thiirenium ions **21** and **22**, which are derived by the formal addition of a sulphenylium ion to double and triple carbon–carbon bonds, respectively[9, 11–15, 63].

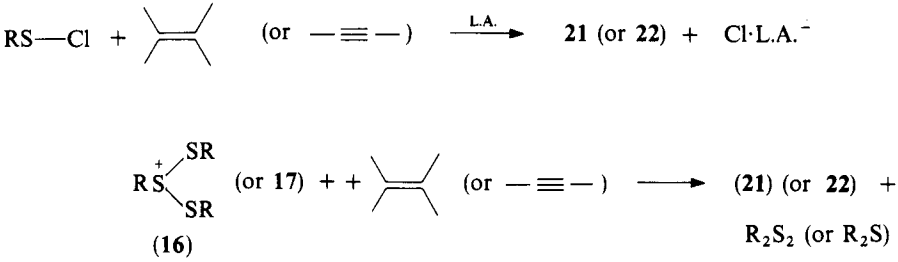


(21)

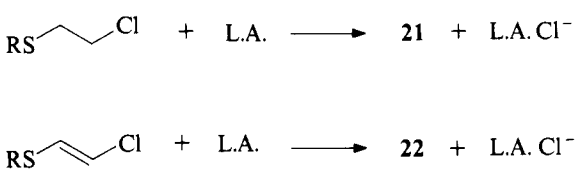


(22)

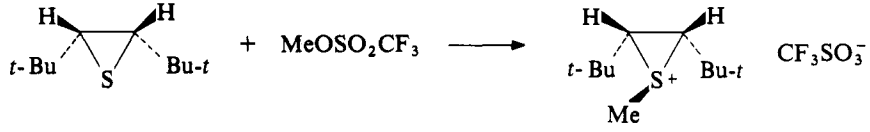
Several ions **21** and **22** have been obtained by three methods: (a) Reaction of sulphenyl chloride in the presence of a Lewis acid (L.A.) or of a sulphenyl derivative of type **16** or **17** with the appropriate alkene or alkyne in a non-nucleophilic solvent[12–15, 64–66] (Scheme 3). (b) Action of an appropriate Lewis acid on a β-thioalkyl or β-thiovinyl chloride[67, 68] (Scheme 4). (c) Alkylation or protonation of thiiranes (Scheme 5). The last method is limited to the synthesis of thiiranium ions, since thiirenes are very labile species.



SCHEME 3



SCHEME 4



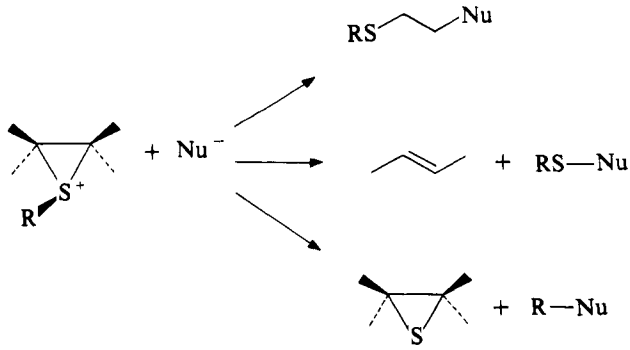
SCHEME 5

Alkylation of thiiranes has been reported[57,69] for only a few cases. Also the protonation of thiiranes, which perhaps has a wider scope, has been studied to a limited extent[70].

Several thiiranium and thiirenium salts **21** and **22** have been detected as unstable species at low temperatures by NMR spectroscopy; a few others have been isolated and fully characterized[12-15].

Spectroscopic data[13, 15] and X-ray diffractometric analyses (on the thiiranium ion)[71] show that the tricoordinated sulphur is strongly pyramidal, the angle between the ring plane and the exocyclic substituent at sulphur being about 98°, and that there is a very high inversion barrier. Theoretical computations on model compounds support the mentioned experimental results[72, 73].

Nucleophiles react with thiiranium and thiirenium ions at sulphur and at ring carbons[1-16,74] (Scheme 6). In the latter case complete inversion at the carbon is observed. A few examples of nucleophilic attack at the exocyclic S-substituent leading to thiirane derivatives have been also reported[75] (Scheme 6).



SCHEME 6

Thiiranium and thiirenium ions may also undergo skeletal rearrangement[1-16] before reacting with the nucleophile. A few cases of reactions carried out on the isolated ions have been reported; many others refer to the rearrangements observed in the addition of sulphenyl halides to π-nucleophiles (see Sections III and IV).

3. Effects of structure on reactivity

The reactivity of sulphenyl derivatives **2** of general structure RSX is a function of both the leaving group X and the nature of the group R linked to sulphur.

The effect of X, even if the spectrum of reactivity is very large, is predictable since it is roughly related to its ability as leaving group, which in turn is linked to the pK_a of its conjugate acid[76].

The effect of the nature of R on the reactivity of sulphenyl derivatives **2** is more difficult to foresee. Indeed R may vary from simple or complex hydrocarbon residues to perhalogenated alkyl groups and to aromatic residues. While for hydrocarbon residues steric factors have a dominant role, for the other classes of substituents electronic effects also have to be taken into account.

Furthermore, the atom linked to sulphur may be a functionalized carbon as, for example, in the case of acylsulphenyl halides, or may be an element different from carbon, like phosphorus or silicon. It follows that no simple general rules can be given and, indeed, the reactivity of sulphenyl derivatives may vary with the nature of R over rather wide limits. Almost all the mechanistic work in this area has been carried out with π-nucleophiles, and hence its discussion will be found in Section III. Apart from carbon-substituted sulphenyl compounds, only a few other classes will be discussed. However, a comprehensive review on special classes of reagents has been published[6].

For carbon-substituted sulphenyl derivatives, which is the more numerous and more studied class of compounds, at least four categories have to be considered: (i) alkyl and in general hydrocarbon derivatives with a limited number of heteroatoms in the hydrocarbon skeleton and aryl derivatives with no strong electron-withdrawing groups (e.g. nitro) in the *ortho* position. (ii) 2-nitrophenyl and similar derivatives which resemble alkanesulphenyl derivatives qualitatively but their reactivity differs significantly quantitatively. (iii) Acyl derivatives and other functionalized sulphenyl halides. (iv) Perhalosulphenyl halides, in particular, perfluoro and perchloromethane derivatives.

As most of the reactions have been studied with the first two classes of compounds, only limited attention will be paid to the other two. It is important to note that deduction of structure–reactivity relationships based on studies of one class of compounds cannot be transferred directly to the others.

Even though the effect of X on the reactivity of RSX (**2**) is largely characterized by its leaving-group ability, other factors, likely related to the redox potential of X, seem to play a role.

When X is either chlorine or a group centred on atoms with high oxidation potential [OR, NR_2, S (O) R, S (O_2) R, etc.] the reactivity is 'normal' and the ease of displacement roughly follows the acidity of the conjugated acid. However, sulphenyl fluorides are extremely unstable. They decompose by unknown reaction pathways and only a few perhalosulphenyl fluorides have in fact been reported[6]. Possibly fluorine, which has an extremely high oxidation potential, is incompatible with the existence of a covalent bond with such an easily oxidable atom like the bivalent sulphur. At the other extreme there are the sulphenyl bromides and particularly the iodides, which are also very unstable, likely for opposite reasons.

Sulphenyl iodides are indeed a limiting case. As shown in equation 11 they undergo facile dimerization, which as every nucleophilic reaction is hindered by bulky groups. Therefore they are, in general, prepared *in situ* by the reaction of the thiol with iodine or other iodinating agents in dilute solution, and the sulphenyl iodide is allowed to react with nucleophiles, possibly internal ones, without isolation[77,78].

Most of the work has been carried out with sulphenyl chlorides, so that only limited attention will be paid to the other sulphenyl derivatives.

II. REACTIONS OF SULPHENYL HALIDES WITH n-NUCLEOPHILES

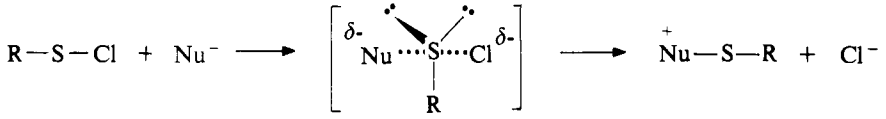
A. General Reactivity

As briefly discussed in the introduction, the reaction of n-nucleophiles with sulphenyl derivatives, typically sulphenyl chlorides, may be considered as a direct substitution reaction (equation 22). The position of the equilibrium depends on the relative basicity of

the nucleophile with respect to that of the chloride ion and consequently may be reversible or essentially irreversible.

$$RSCl + Nu \rightleftharpoons R\text{–}S\text{–}Nu^+ + Cl^- \qquad (22)$$

As also discussed in the introduction, evidence was reported that the transition state of the substitution resembles that of the S_N2 reaction at carbon, but in the present case the two unshared electron pairs mimic two of the substituents at carbon[60] (Scheme 7).



SCHEME 7

Since pentacoordination at sulphur under some conditions may be stable, the hypothesis was advanced that an unstable intermediate with a geometry similar to that of the transition state sketched above may exist along the reaction coordinate.

The substitution product, particularly when the nucleophile is neutral, may be stabilized by the removal, as a cation, of a group bonded to the nucleophilic atom.

The simplest case is when the nucleophile carries a hydrogen atom, which may be easily removed by the solvent or even by chloride ion in non-basic solvents where hydrochloric acid is undissociated and may escape from the solvent as a gas.

With major or minor ease other groups may also be removed from the positively charged sulphenyl derivative obtained in the substitution[15] shown in equation 23.

$$RSCl + NuY \rightleftharpoons RS\overset{+}{N}uY + Cl^- \longrightarrow RSNu + YCl \qquad (23)$$

The reaction is represented as a two-step process, however it may occur in one single kinetic step.

The reactions of sulphenyl derivatives with a large variety of n-nucleophiles, either neutral or anionic, have been studied mainly from the synthetic point of view and reviewed several times[6,7,15,79–82]. In this section attention will be focussed mainly on the most used nucleophiles and on those reactions which have a greater interest in organic synthesis.

B. Reactions with Nitrogen Nucleophiles

The general reaction of sulphenyl halides with amines is usually carried out using two equivalents of the nucleophile or in the presence of tertiary amines[83] and gives rise to the corresponding sulphenamides. A variety of different amines, including cyclic ones or containing other functionalities, have been used. Strong alkaline conditions favour further reactions of the sulphenamides which may give the corresponding disulphides and thioesters of sulphonic acids[84].

Kinetic studies on the model reaction between triphenylmethanesulphenyl chloride (**23**) and butylamine were performed in benzene at 25°C[85] (equation 24). Under these conditions the reaction is quantitative and irreversible. The reaction rates are accelerated by added bases, and the kinetic analysis shows the operation of general base catalysis[85]. The leaving group (X = Cl, Br, I, SCN) in **23** has a rather small effect on the rates (k_{Br}/k_{Cl} about 2). On this basis the mechanism reported in Scheme 8 was suggested[86]. According to this scheme, **24** is a sulphurane-like intermediate in which the sulphur atom is pentacovalent implying a d-orbital participation.

$$Ph_3C\text{–}SX + 2BuNH \xrightarrow{C_6H_6} Ph_3C\text{–}S\text{–}NHBu + BuNH_3Cl \quad (24)$$

(23)

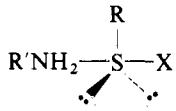
X = Cl

$$Ph_3CSX + BuNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate}$$

(23)

$$\text{intermediate} \xrightarrow{k_B[B]} \text{products}$$

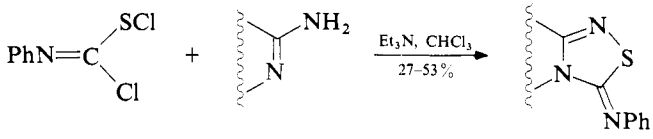
X = Cl, Br, I, SCN



(24)

SCHEME 8

The reaction of functionalized sulphenyl halides with suitable substituted amines is also used to prepare many different heterocyclic systems like, for example, 1,2,4-thiadiazoles[87] (equation 25, see also Section IV). Moreover, as reported in Section VI, several sulphenyl halides have been used as amino protecting groups in the synthesis of cephalosporins, antibiotics, peptides, etc.



(25)

C. Reactions with Alcohols

The reactions of sulphenyl halides with alcohols, allylic alcohols and the corresponding anions have been thoroughly studied[79,88]. The reactivity of allylic alcohols, which are functionalized alkenes, is discussed in Section IV.

In the reaction with simple alcohols, the sulphenic esters, formed as primary products, may rearrange to sulphoxides[89] (equation 26; see also Reference 18).

$$RSCl + R'OH \xrightarrow[-HCl]{} RS\text{–}OR' \xrightarrow{\Delta} RS(=O)R' \quad (26)$$

The hydrolysis of arenesulphenyl chlorides has been studied from a mechanistic point of view[90,91] (Scheme 9). The reaction was carried out at 25 °C in chloroform containing water in about 2×10^{-2} M concentration and was strongly catalysed by chloride ion added as tetraethylammonium chloride[90]. The substituent effect allowed one to measure a rho value of +1.04.

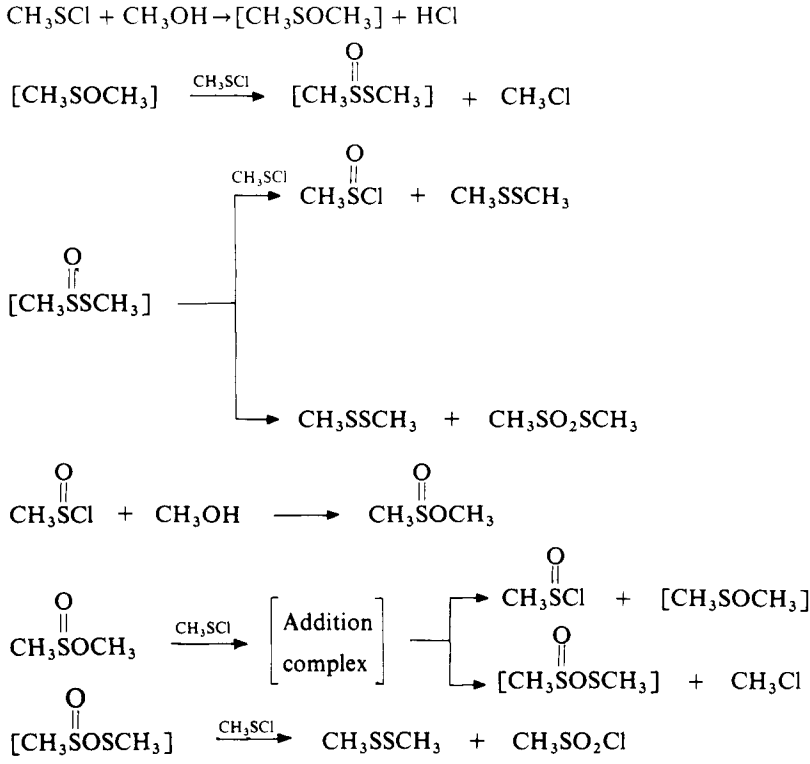
The hydrolysis of alkylsulphenyl chlorides was studied as well and showed also a positive rho value (+3.90)[91], thus suggesting a similar mechanism.

$$ArS{-}Cl + H_2O \xrightarrow[slow]{Cl^-} ArS{-}OH + HCl$$

$$ArS{-}OH + ArS{-}Cl \xrightarrow[fast]{} ArSO{-}SAr + HCl$$

SCHEME 9

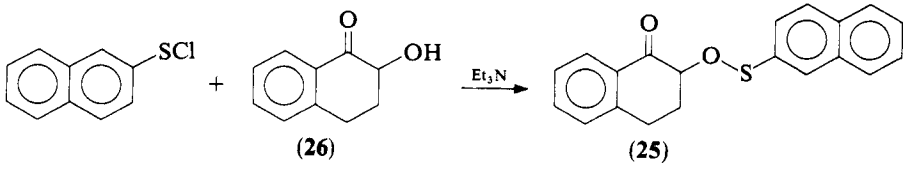
Methanesulphenyl chloride in methanol reacts in a quite complex way giving a mixture of several products[92] (Scheme 10). Indeed the methyl methanesulphenate primarily formed is unstable in the acid reaction medium.



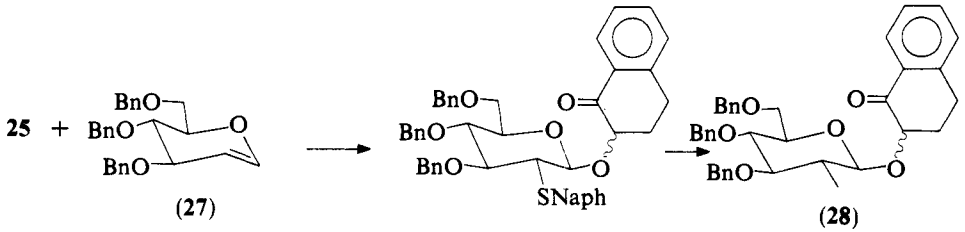
SCHEME 10

However, alkyl esters of methanesulphenic acid may be obtained in good yields by reacting the chloride with alkoxides in stoichiometric amounts[93].

Recently the sulphenate ester (Scheme 11) **25** was successfully used to build a β-linkage between the alcoholic group of **26** and the C-2 of the sugar **27**[94]. The β isomer **28**, which is a model for the aureolic acid antibiotic, was then stereospecifically obtained[94].



(26) (25)



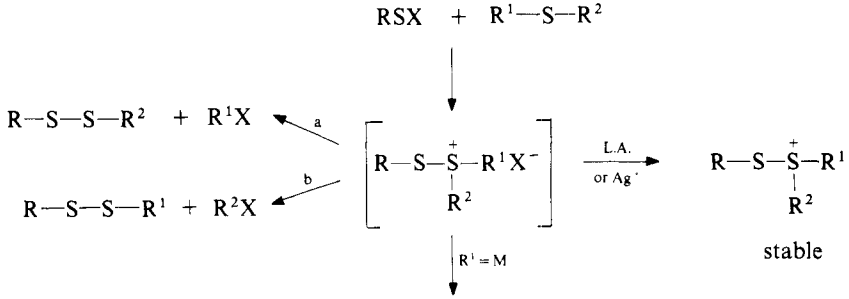
(27) (28)

Bn = $PhCH_2$

SCHEME 11

D. Reactions with Thiols, Sulphides and Disulphides

Sulphenyl halides react with thiols, sulphides and disulphides forming thiosulphonium salts as intermediates[15,95]. The reaction may follow different reaction paths, which depend on the nature and structure of the reagents (Scheme 12).



M = H, SiR_3, SnR_3

SCHEME 12

Stable thiosulphonium salts have been eventually isolated by running the reaction of sulphenyl halides with sulphides or disulphides in the presence of Lewis acids (L.A.) as BF_3 or $SbCl_5$ or of a silver salt[15]. These salts are largely used as sulphenylating agents of many nucleophiles of different nature (see Introduction).

When R^1 or R^2 in Scheme 12 is a hydrogen atom or a different element (M) like silicon or tin which makes the sulphonium sulphur–M bond quite weak, the intermediate thiosulphonium salts are so unstable that they rapidly give rise to disulphides[6,96–100] (equation 27). In fact the reactions of sulphenyl halides with thiols[6,96], thiolates[6,96] or masked thiols[97–100] are methods largely used for the synthesis of unsymmetrical disulphides.

$$R^1S\text{–}Cl + M\text{–}S\text{–}R^2 \longrightarrow R^1S\text{–}SR^2 + MCl \qquad (27)$$

An interesting application of the reaction of thiols with sulphenyl halides is the reversible protection of the thiol group[101]. Examples are reported with methoxycarbonyl sulphenyl chloride, 2-nitro- and 2,4-dinitrobenzenesulphenyl chlorides[102–104]. These groups may be easily removed under mild reductive conditions with sodium borohydride[101].

Disulphides are unstable in the presence of acids or other electrophiles so that, for example, unsymmetrical disulphides can be easily transformed into a mixture of the three possible isomeric disulphides[105,106]. However the synthesis of some unsymmetrical disulphides has been reported also by the reaction of thiosulphonium salts **17** with symmetrical disulphides and thiols under basic conditions[107]. Unsymmetrical disulphides can be also cleanly obtained in 65–80% yield from the reaction of triorganotin aryl sulphides or trimethylsilyl sulphides with sulphenyl halides[97–100] (equations 28 and 29).

In a similar way, when sulphenyl chlorides react with bis(triorganotin)sulphides, trisulphides are obtained[98] (equation 30).

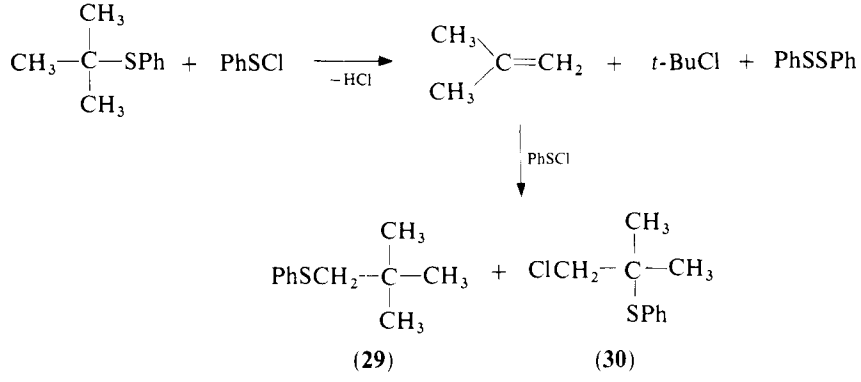
$$R_3Sn\text{–}SAr + Ar'SX \longrightarrow R_3Sn\text{–}X + ArS\text{–}SAr^1 \qquad (28)$$

X = Cl, Br
R = Ph, Bu, Pr
Ar = 4-*t*-BuC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4
Ar^1 = 2-$NO_2C_6H_4$, 2,4$(NO_2)_2C_6H_3$, 4-MeC_6H_4

$$PhSX + Me_3Si\text{–}SR \xrightarrow[75\%]{\text{neat}} PhS\text{–}SR + Me_3SiX \qquad (29)$$

$$2ArSX + R_3Sn\text{–}S\text{–}SnR_3 \longrightarrow Ar\text{–}S_3\text{–}Ar \qquad (30)$$

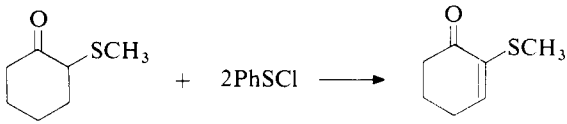
The reaction of sulphenyl halides with alkyl or aryl sulphides may be more complex than those with stannyl or silyl sulphides, since several reaction paths may be operative at the same time. After alkylthiolation at sulphur (Scheme 12) two different sulphur–carbon bonds become labile and may be broken. Thus the subsequent reaction depends on the nature of the substituents of the sulphide. An example of this behaviour is reported in Scheme 13[108]. In this case 2-methylpropene is formed and the excess of sulphenyl chloride adds to the double bond, giving the two adducts **29** and **30** in 2:3 ratio.



(29) **(30)**

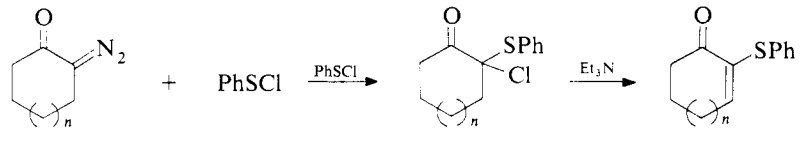
SCHEME 13

Dehydrogenation and oxidative chlorination[108] are also possible when a sulphenyl halide reacts with a sulphide. An example of the first type of reactivity is shown in equation 31.

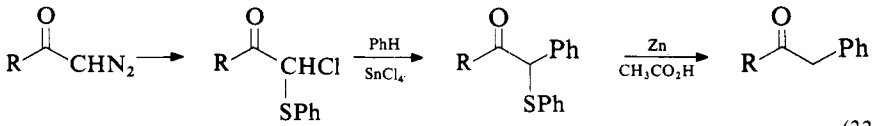


(31)

Compounds similar to **31** can be also obtained in high yield (80%) by the reaction of α-diazoketones **32** with phenylsulphenyl chloride followed by dehydrochlorination to the α-chlorosulphide **33**[109] (equation 32). This reaction has synthetic utility, since it allows the conversion of terminal diazoketones into α-phenyl-α-(phenylthio)ketones[109] (equation 33).

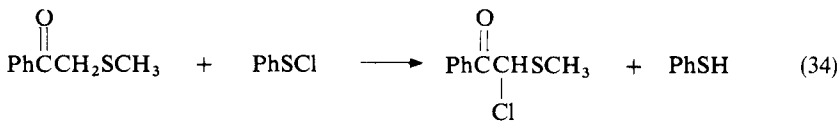


(32) (33)

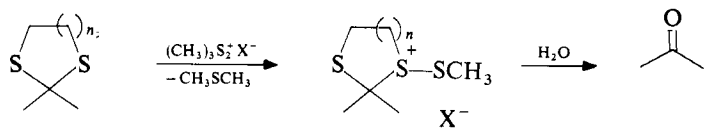


(33)

An example of oxidative chlorination is reported in equation 34[108].



The possibility of cleaving in a facile way the carbon–sulphur bond by alkylthiolation was used in organic synthesis for the hydrolysis of thioketals to the parent carbonyl compounds[110,111]. The proposed mechanism of the reaction is shown in Scheme 14.

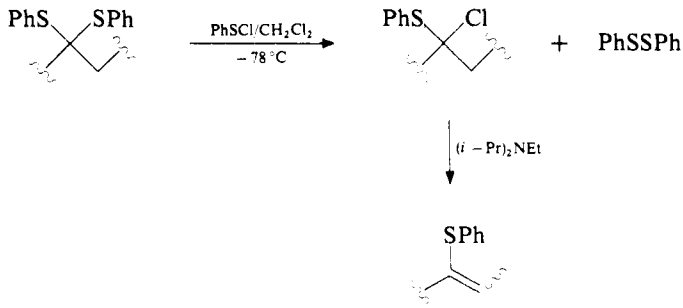


SCHEME 14

The alkylthiolation of the sulphide sulphur was also used in peptide synthesis: 2-nitrobenzenesulphenyl chloride was used for the removal of the S-*t*-butyl protection[112]

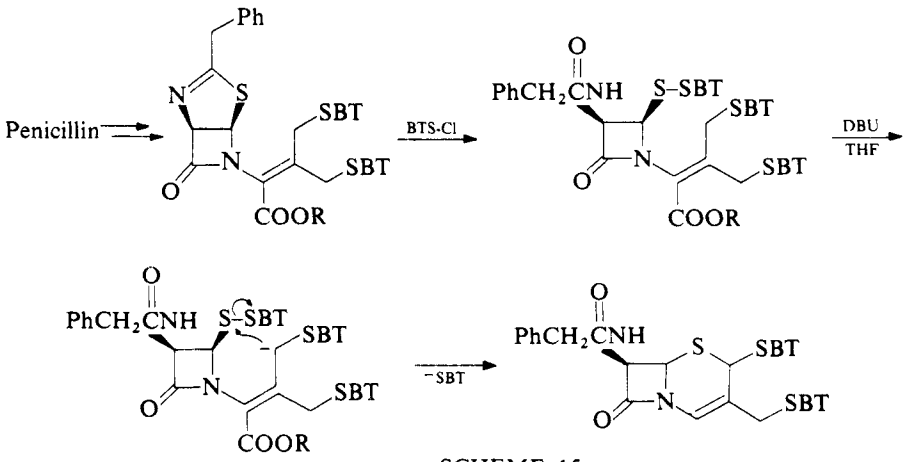
and 2-pyridinesulphenyl chloride for deprotection and for activation of the mercapto group of cysteine[112].

Under different reaction conditions, thioacetals and thioketals may also be converted by benzene sulphenyl chloride to vinyl sulphides[113] (equation 35).



(35)

Finally, it is relevant to mention that a penicillin–cephalosporin transformation was achieved by attack of 2-benzothiazolesulphenyl chloride (BTS-Cl) on the sulphur atom of the thiazoline moiety[114,115] (Scheme 15).



SCHEME 15

III. REACTIONS WITH π-NUCLEOPHILES

Sulphenyl halides and other sulphenylium cation carriers may react with π-nucleophiles to give either substitution or addition reactions as briefly mentioned in the Introduction. The former reaction may be thought of as an addition of the electrophilic part of the reagent to the π-system followed by loss of a proton or other suitable group. This reaction is typical of arenes and enols, whereas most of the olefinic and acetylenic compounds lead to addition products.

The addition reaction is, perhaps, the most studied reaction of these reagents[1–16]. It is outside the scope of the present chapter to cover comprehensively all the literature in this

field; rather we will attempt to draw a general picture of the reactions and to offer a rational scheme to help their understanding and exploitation in organic synthesis.

Attention will be focussed on the reaction of rather simple alkane- and arenesulphenyl chlorides, since these are the most used reagents. The behaviour of these reagents is also a reliable guide for the understanding of the others.

Moreover, there are minor but significant differences between the reactions of sulphenyl chlorides with alkenes and alkynes and hence the two classes of π-nucleophiles will be reviewed separately.

A. Reactions with Arenes and Enols

The reactions of sulphenyl halides with π-nucleophiles, which lead to substitution, formally resemble those with n-nucleophiles carrying a proton or other easily removable groups at the reactive centre and, indeed, there are quite a large number of reactions which may be classified as addition–elimination reactions[6].

The discussion of all these reactions are again outside the limits of the present chapter, however a brief discussion on the reactions with aromatic compounds and with enols seems worthwhile and it is reported below.

Sulphenyl halides react with benzene and, in general, with aromatic compounds to give substitution products [1, 6, 76] (equation 36).

$$RSCl + ArH \longrightarrow RS\text{–}Ar + HCl \qquad (36)$$

In most cases the reaction requires catalysis by protic or Lewis acids[26, 116]. This, however, may not be necessary with the most reactive sulphenyl halides and with activated substrates[117–119].

Polysubstitution is frequently observed[120]; in fact the RS residues, when the R group is equal to alkyl or simple aryl, are electron-releasing substituents ($\sigma_{4\text{-}SCH_3} = -0.6$)[121]. However, when the sulphenyl halide function is attached to strong electron-withdrawing residues such as trifluoromethyl or 2,4-dinitrophenyl monosubstituted products are obtained in fairly good yields[26, 117].

Even though the reaction has been known for a long time[122] very little is known about its mechanism. Efficient catalysis may be obtained not only with aluminium trichloride, but also with milder catalysts such as iron trichloride, zinc dichloride, tin tetrachloride or boron trifluoride[6]. Protic acid catalysis is also quite efficient and it has been reported that iron powder may be the catalyst of choice[120].

Finally, aromatic thiolation has been obtained by such weak sulphenylating agents as disulphides[123] and thiosulphonates[124] under appropriate acid catalysis.

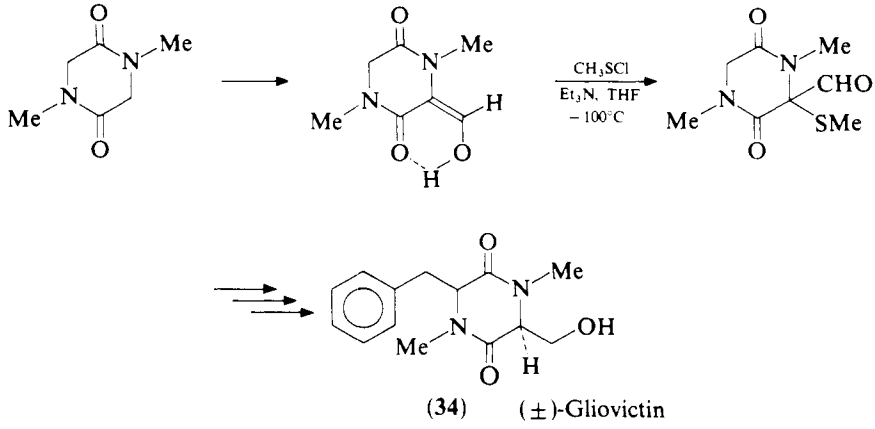
Several heteroaromatic compounds also undergo the sulphenylation reaction under mild conditions[6].

Enolizable carbonyl compounds react with sulphenyl halides as do halogens. For example, acetone reacts with excess benzenesulphenyl chloride to give complete substitution of the six hydrogens[125] (equation 37). However, methods to achieve controlled mono-sulphenylations have been described[6].

$$C_6H_5SCl + CH_3\text{—}\overset{\overset{O}{\|}}{C}\text{—}CH_3 \longrightarrow (C_6H_5S)_3C\text{—}\overset{\overset{O}{\|}}{C}\text{—}C(SC_6H_5)_3 \qquad (37)$$

Much more interest is devoted in the current literature to the monosulphenylation of stable enols, and of enol-ethers.

A critical step in the synthesis of (±)-gliovictin **34**[126] is the sulphenylation of the enol **35** as reported in Scheme 16. The reaction requires the presence of a base and was carried

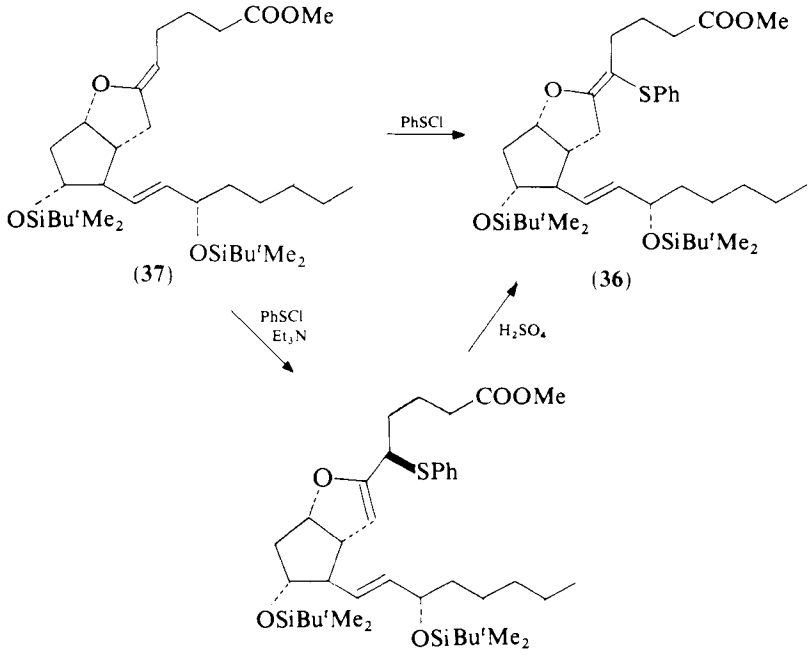


(34) (±)-Gliovictin

SCHEME 16

out with methanesulphenyl chloride in the presence of triethylamine in tetrahydrofurane at −100°C.

The use of enol ethers is, perhaps, more important as it enlarges the scope of the reaction. It has been successfully applied to the synthesis of the stable prostacycline

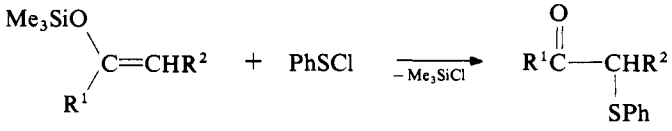


(37) (36) (38)

SCHEME 17

analogue **36**[127] (Scheme 17). The addition of phenylsulphenyl chloride to **37** gave directly **36** and the use of a tertiary base allowed one to direct the reaction towards the formation of the allyl sulphide **38**, which may then be transformed into **36** by acid catalysis.

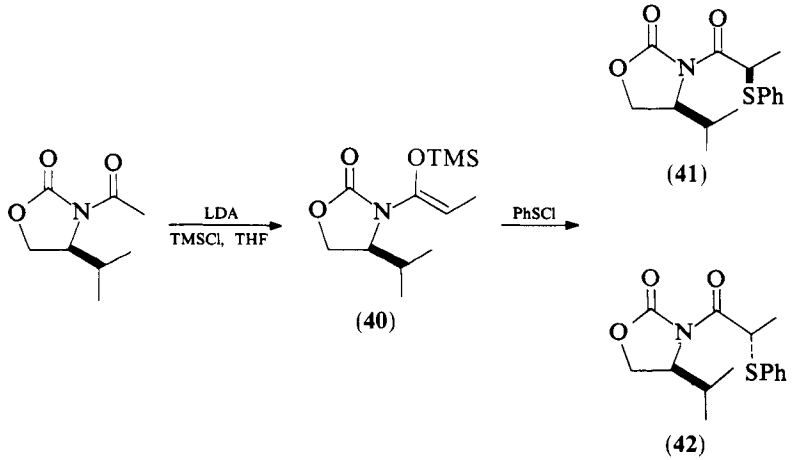
Silyl ethers, which are synthetic equivalents of enols, afford the corresponding β-ketosulphides[128-132] by reaction with sulphenyl chlorides (equation 38). The reaction is carried out in methylene chloride at low temperature and gives high yields of the β-thioketones **39**.



(38)

(39)

Sulphenylation of chiral O-silylated imide enolates occurs with high diastereoselectivity (*ca* 20:1)[133]. In particular, the reaction of the silyl enol ether **40** with phenylsulphenyl chloride in methylene chloride at −78°C yields a mixture of the two β-thioketones **41** and **42** in 83:17 ratio (equation 39). An even higher diastereoselectivity (92:8) was obtained when the reaction was carried out using the corresponding *t*-butyldimethylsilyl ether at lower temperature[133].



(40) **(41)** **(42)** (39)

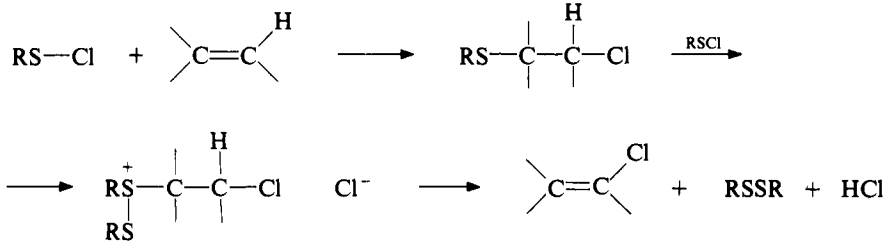
B. Reactions with Alkenes

Sulphenyl chlorides, as well as most of the sulphenyl derivatives, add to alkenes to give, in most cases, *anti* adducts with high stereoselectivity. Sometimes solvent incorporation and skeletal rearrangements[1-16] are also observed.

The reaction is better carried out with excess of olefin over the sulphenyl chloride using non-nucleophilic or weakly nucleophilic solvents like lower esters, ethers, hydrocarbons, halogenated hydrocarbons, nitrobenzene, etc. Acetic acid is also compatible with numerous sulphenyl chlorides and reacts with them only slowly. More nucleophilic solvents like alcohols or water rapidly react with most of the sulphenyl halides (see

Section II), but not with the less reactive ones like 2-nitrobenzene or 2,4-dinitrobenzene derivatives.

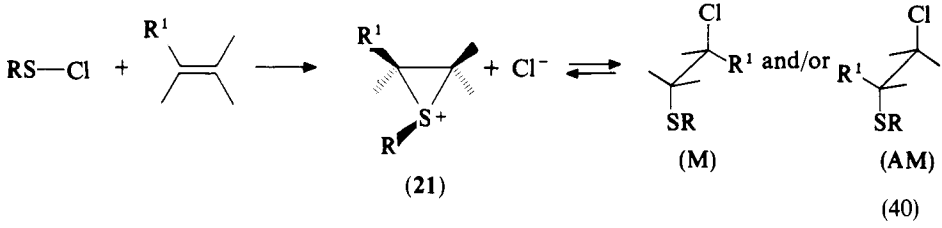
Excess of sulphenyl chloride over the alkene may sometime react further with the reaction products, since the sulphur may be basic enough to act as a nucleophilic centre as reported by several authors[133] (Scheme 18).



SCHEME 18

The addition is strictly stereospecific, at least as far as the kinetic products are concerned, with only very few exceptions[1-16, 133-135]. For example, it has been observed that the addition of 4-chlorobenzenesulphenyl chloride to *cis*- and *trans*-2-butene yields more than 99% of the *anti* adducts over a temperature range of about 200°C (from −42 to +146°C)[136]. However, 2,4-dinitrobenzenesulphenyl chloride adds non-stereospecifically to *cis*-4-methoxyphenylpropene in tetrachloethane[137] and to β-deutero *cis*- and *trans*-4-methoxystyrenes in chloroform or acetic acid[138]. Loss of stereospecificity was also observed with the 4-nitrobenzenesulphenyl chloride, although to a minor extent[138]. On the contrary, styrenes with less electron-donating substituents than 4-methoxy react with several arenesulphenyl chlorides, including 2,4-dinitro-derivatives with complete stereospecificity[138]. Loss of stereospecificity was sometimes observed in the reaction of strained cyclic alkenes[139].

This high stereoselectivity confirms the original suggestion by Kharasch and Buess[140] that the reaction (equation 40) 'usually' occurs via a bridged ion **21** (i.e. a thiiranium ion), in analogy with the proposal of Roberts and Kimball for the stereospecific halogenation[141]. This is also consistent with the very large anchimeric effect of the sulphide sulphur in the solvolysis of β-thioalkyl halides[142].



(21)

(M) (AM)

(40)

The thiiranium ions have been prepared as stable salts from both ends of equation 40 by stabilizing the intermediate ion **21** by complexation of the chloride ion with a suitable Lewis acid[12, 13, 15, 64-68].

When the two ethylenic carbons have different substituents, two regiochemical courses are possible: the 'normal', which yields the Markovnikov-like adduct (M), and the opposite, which yields the *anti*-Markovnikov one (AM). Some typical sets of results are reported in Table 1.

TABLE 1. Product distribution for the addition of sulphenyl chlorides to alkenes: effect of the substituent on the alkene[143]

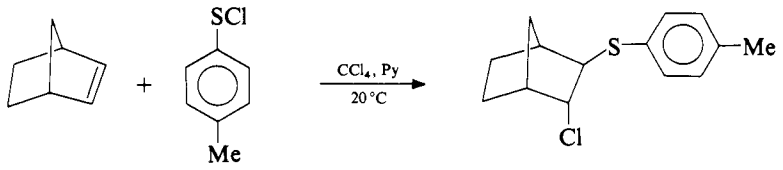
System	CH_2Cl_2	
	M	AM
$CH_3SCl + CH_3CH=CH_2$	18	82
$CH_3SCl + (CH_3)_2CHCH=CH_2$	6	94
$CH_3SCl + (CH_3)_2C=CH_2$	20	80
$C_6H_5SCl + CH_3CH=CH_2$	32	68
$C_6H_5SCl + (CH_3)_2CHC=CH_2$	13	87
$CH_3C(O)SCl + (CH_3)_2C=CH_2$	68	32
$CH_3SCl + C_6H_5CH=CH_2$	98	2

Contrary to the regiochemistry observed in the addition of mixed halides or hypohalides where the Markovnikov product is either the only one or is formed in a very high proportion[9], the addition of sulphenyl halides has a great preference for the *anti*-Markovnikov regiochemistry at least under kinetic control[134, 144]. However, the regiochemistry of the addition varies very much with the substitution pattern of the alkene, with the solvent and with the nature of the sulphenyl halide. Alkane- and simple arenesulphenyl chlorides give higher proportion of *anti*-Markovnikov adducts than 2- and 2,4-dinitrobenzenesulphenyl chlorides. Moreover, hydrogen-bonding solvents favour the Markovnikov addition (Table 2).

TABLE 2. Solvent dependence of the product ratio of the addition of 4-chlorobenzenesulphenyl chloride to *cis*-1-phenylpropene at 23–25°C[135b]

Solvent	Dielectric constant	M	AM
Benzene	2.28	50	50
$HCCl_3$	4.80	63	37
$ClCH_2CH_2Cl$	11.20	58	42
$Cl_2CHCHCl_2$	8.20	66	34
CH_3COOH	6.15	100	0

Contrary to many other electrophilic additions to alkenes, rearranged products are rather seldom observed. For example, in chlorinated solvents alkanesulphenyl chlorides yield unrearranged products with norbornene and 7,7-dimethylnorbornene[146–148] (equations 41 and 42). This was taken as evidence that the thiiranium ion built either on the *exo* or on the *endo* side of the bicyclic skeleton carries most of the positive charge on the sulphur atom. However, on changing the sulphenyl halide to the 2,4-dinitrobenzene



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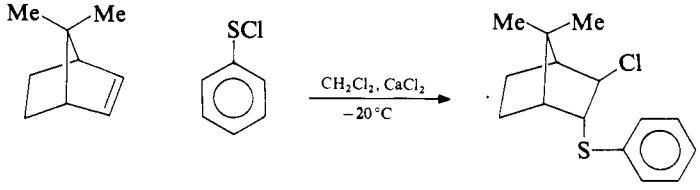
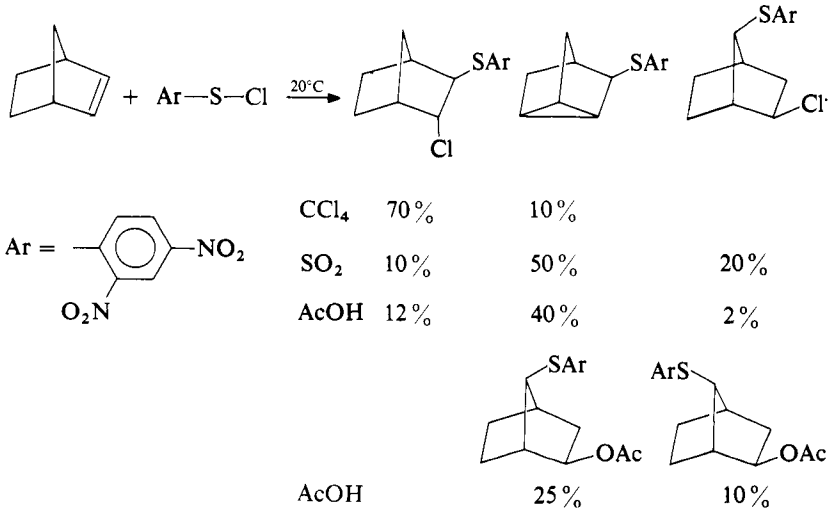


(42)

derivative or the solvent to a more electrophilic one, extensive rearrangements were observed[5, 12, 149, 150] (Scheme 19).



SCHEME 19

Under most of the reaction conditions used, the addition follows a second-order kinetic law, first in sulphenyl halide and first in alkene[9]. However, there are exceptions. The rate depends on the alkene structure in a rather complex way. As expected, it increases with the nucleophilicity of the double bond as shown, for example, by the effect of substituents in styrenes (Table 3).

Alkyl substitution at the double bond also increases the reaction rate, as expected[152] (Table 4).

However, no simple correlation with substituent parameters appears to hold, as *cis* alkenes are always more reactive than the *trans* isomers[153]. Indeed, good correlations within either isomeric series have been found[154]. The steric origin of this finding is well demonstrated when bulky substituents are involved. A typical example is offered by the 1,1- and 1,2-di-*t*-butylethylenes[155], where the 1,2-*cis* isomer is very much faster than the other two, as shown in Table 5.

The steric effect observed is another piece of evidence in favor of the reaction going via a tightly bridged species. Indeed, since tricoordinated sulphur is pyramidal[72, 73, 156] the formation of the three-membered ring intermediate in the reaction of sulphenyl halides with alkenes causes the insurgence of *cis* repulsive interactions among the substituents when *cis* arrangement cannot be avoided, like in the cases of 1,1- or *trans*-1,2-

TABLE 3. Specific rate constants for the addition of 2,4-dinitrobenzenesulphenyl chloride to a series of phenyl substituted 1-phenylpropenes in 1,1,2,2-tetrachloroethane at 25.00 °C[151]

	k_2 ($M^{-1}s^{-1}$) × 10^3	
Substituent	*cis*	*trans*
3-NO_2	3.1×10^{-3}	1.2×10^{-3}
4-Cl	7.0×10^{-2}	5.6×10^{-2}
H	0.16	0.51
4-CH_3	0.73	2.7
4-OC_6H_5	0.91	4.8
4-OCH_3	2.3	11.5
4-$OCH(CH_3)_2$	4.9	13.3

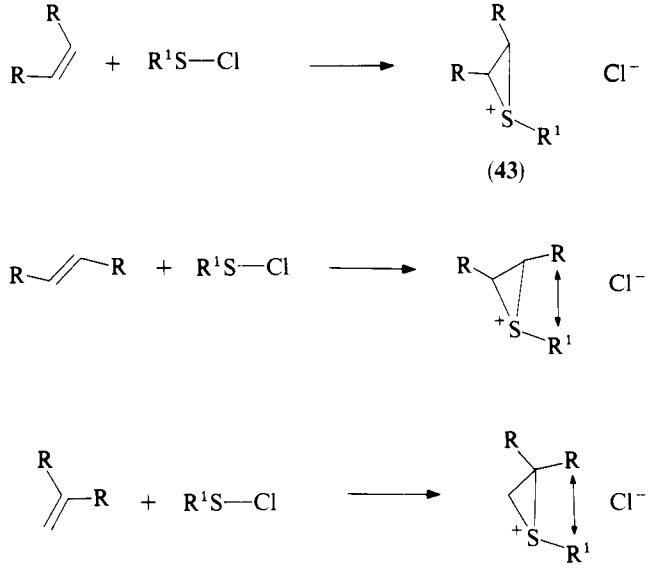
TABLE 4. Specific rate constants for the addition of 4-chlorobenzenesulphenyl chloride to a series of methyl substituted ethylenes in tetrachloroethane at 25°C[152]

Compound	No. of methyl groups	k_2 ($M^{-1}s^{-1}$) × 10^2	k_{rel}
Ethylene	0	0.65	1.0
Propene	1	2.0	3.1
cis-2-Butene	2	13.4	20.6
trans-2-Butene	2	4.34	6.7
Isobutylene	2	5.51	8.5
2-Methyl-2-butene	3	30.3	46.5
2,3-Dimethyl-2-butene	4	77.6	119

TABLE 5. Specific rate constants for the addition of 4-chlorobenzenesulphenyl chloride to a series of *t*-butyl-substituted ethylenes at 25°C in 1,1,2,2-tetrachloroethane[155]

Alkene	k_2 ($M^{-1}s^{-1}$)	k_{rel}
CH_2=CH_2	65	1
t-BuCH=CH_2	95	1.5
(*t*-Bu)$_2$C=CH_2	0.0317	4.9×10^{-4}
(*Z*)-*t*-BuCH=CHBu-*t*	846	13
(*E*)-*t*-BuCH=CHBu-*t*	0.00536	8.2×10^{-5}
(*E*-Bu)$_2$C=CHBu-*t*	0.00816	1.3×10^{-4}

disubstituted alkenes (Scheme 20). On the contrary, in the addition to *cis*-disubstituted alkenes the exocyclic substituent at sulphur may be accommodated on the side of the three-membered ring opposite that of the carbon substituents without causing a significant change of steric interaction in going from the initial to the transition state and to the intermediate (Scheme 20). In fact, under conditions where the thiiranium ions are stable (see below) only isomers of type **43** are formed[157].



SCHEME 20

The polar effects on the arenesulphenyl chlorides as measured by the Hammett relationship for *meta* and *para* substituents vary considerably as a function of the system investigated.

The reaction rates of a set of 4-substituted 2-nitrobenzenesulphenyl chlorides with cyclohexene in acetic acid correlate with σ^+ and give $\varrho = -0.715$[158]. However, in other systems even inverse effects of substituents were found[159] and in the related additions to acetylenes curved plots were observed[4, 13, 160]. A very large effect, however, is caused by the 2-nitro group[9]. It is much outside the expected one on the basis of a simple polar effect as also shown by the data reported in Table 6.

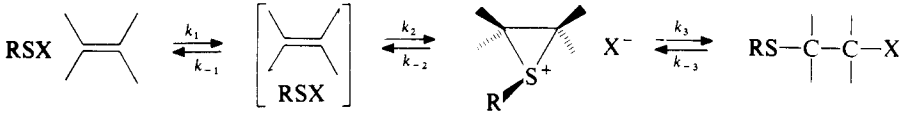
Finally, the addition rates are very sensitive to solvent polarity[161], in particular to the ability to solvate the counter anions. The magnitude of the effect compares well with that observed in the bromination of the alkenes[162].

TABLE 6. Effects of the 2-NO_2 group in the addition of arenesulphenyl chlorides to a series of alkenes[9]

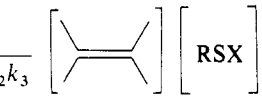
Substrate	Solvent[a]	k_2 ($M^{-1}s^{-1}$) 4-Cl	k_2 ($M^{-1}s^{-1}$) 2,4-(NO_2)	k_{Cl}/k_{NO_2}
(*Z*)-PhCH=CHCH$_3$	TCE	43	2.8×10^{-4}	15.0×10^4
	HOAc	7.1	4.5×10^{-4}	1.6×10^4
(*E*)-PhCH=CHCH$_3$	TCE	118	6.0×10^{-4}	20.0×10^4
	HOAc	30	13.0×10^{-4}	2.3×10^4
n-BuCH=CH$_2$	HOAc	33	14.0×10^{-4}	2.4×10^4
PHCH=CH$_2$	HOAc	16	9.0×10^{-4}	2.0×10^4

[a]TCE = tetrachloroethylene, HOAC = acetic acid.

The effects of structural variation of the reagents as well as those of the solvent on the overall reaction rates are, in principle and in practice, difficult to analyse since the reaction occurs via one or more intermediates as shown in equation 43 which, under the simplified conditions that the reverse reaction does not occur ($k_{-3}=0$), require the general kinetic equation 44.



(43)

$$\frac{dp}{dt} = \frac{k_1 k_2 k_3}{k_{-1}k_{-2} + k_{-1}k_3 + k_2 k_3}$$  (44)

Since the structural factors and the solvent influence, the individual rates in ways which may differ in magnitude and in sign, the experimental values cannot be discussed in simple terms unless the first step is rate-determining. This has been often assumed to be the case because of the observed second-order kinetic law. However, kinetics which follow, or appear to follow, a second-order law may be compatible with other mechanistic interpretations.

On the other hand, the rather high stability of several thiiranium ions and the development of simple synthetic methodologies opened the possibility of studying the evolution of these species by NMR. This led to a deeper insight into these reactions with the discovery of hidden reaction paths.

First of all it was shown that, beside the ring carbons, also the sulphur of thiiranium ions may be attacked by a nucleophile. This means that the addition step of sulphenyl chlorides to alkenes, which gives the bridged ion, may be reversible[74, 163–165].

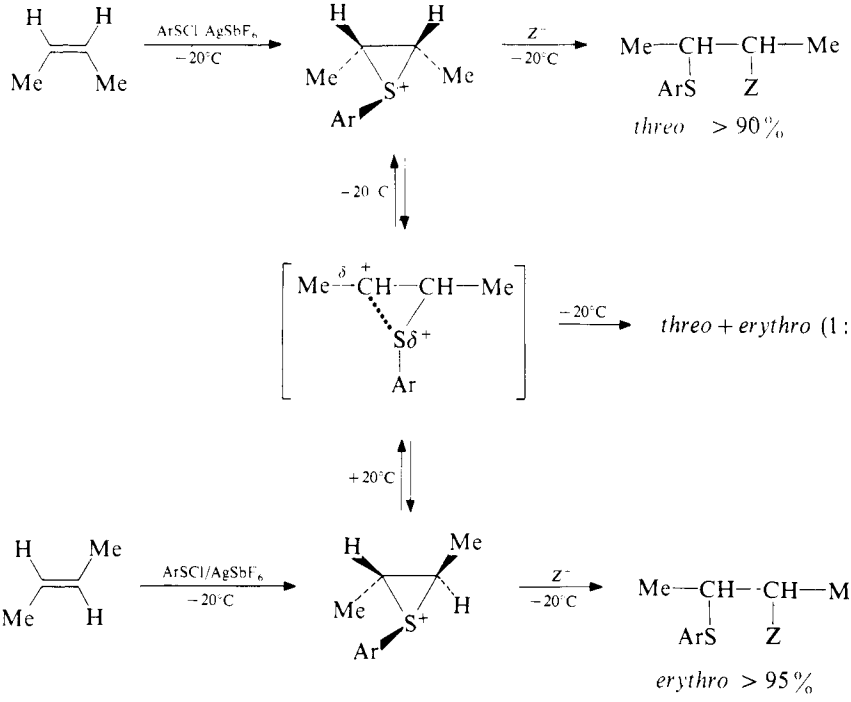
It was also observed that the ratio between the attack at carbon and at sulphur, the balance between M and AM products and the extent of solvent incorporation change very much with minor variations of the reaction conditions[166–168].

Large variations, as a function of the reaction conditions, were also observed for the isomerization of the adducts and the rearrangement of the hydrocarbon backbones.

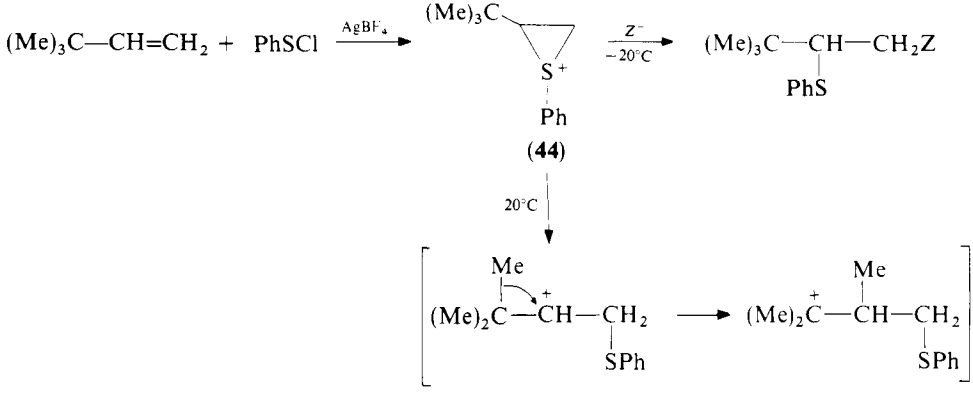
These effects are shown in the reaction of sulphenyl halides with isomerically pure 2-butenes. Sulphenyl halides add stereospecifically to *E*- and *Z*-2-butene[136]. Furthermore, as already mentioned above, the corresponding thiiranium ions may be independently synthesized and they react with chloride ion at −20°C to give the non-isomerized adduct[13, 169]. However, a mixture of *erythro* and *threo* products, whose composition is independent of the starting thiiranium ion, is formed if the thiiranium salts are kept for some time at +20°C (Scheme 21).

Furthermore, molecular rearrangement has been observed for the 2-*t*-butyl thiiranium ion **44** which undergoes 1,2-methyl shift only if the quenching of the reaction was delayed or the temperature increased up to 20°C[170] (Scheme 22).

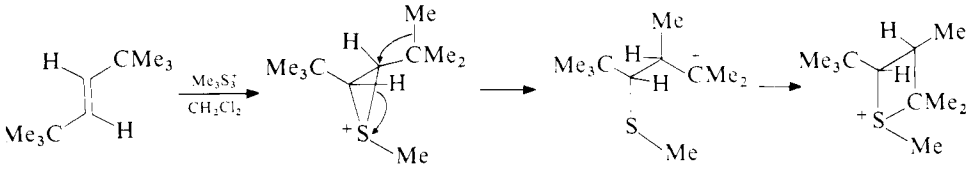
Equilibration of the bridged species with the open carbonium ion was suggested[169, 170], but such a rearrangement does not necessarily require an open ion. In fact, it was shown that the *trans*-2,3-di-*t*-butyl-1-methylthiiranium ion **45** stereospecifically rearranges to the 2,2,3-trimethyl-4-*t*-butyl-S-methylthietanium ion **46**[157]. This implies that methyl migration and carbon–sulphur bond breaking are concerted processes (Scheme 23).



SCHEME 21



SCHEME 22



(45) (46)

SCHEME 23

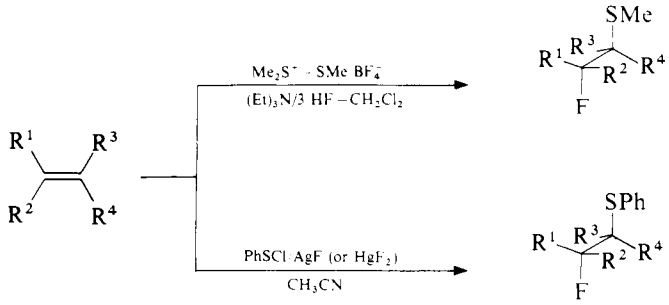
As expected, the exocyclic sulphur substituent of thiiranium ions has a large effect on the rearrangement rates. They are significantly accelerated by electron-withdrawing groups which destabilize the charge on the sulphur[5, 12, 149, 150].

Similar results have been obtained by 'doping' the reaction system. This has been done by running the addition in the presence of a large excess of lithium perchlorate[12, 171, 177] in solvents of low polarity (see also Section IV).

The low solubility of lithium chloride and the large excess of added lithium perchlorate make the chloride ion concentration very low and hence k_3 [Cl^-] (equation 44) becomes very small, allowing one to observe a variety of other reactions: skeletal rearrangement, solvent incorporation (for solvents like acetic acid, alcohols, etc.) and deprotonation. Quenching of the cationic intermediates by perchlorate ion has also been observed[174, 176, 178].

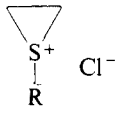
Indeed, this methodology has been found quite useful for the preparation of both simple or complex alkyl perchlorates[174, 176] (see Section IV).

A similar procedure was recently applied to the synthesis of alkyl fluorides[179, 180] (Scheme 24).



SCHEME 24

The differences in regiochemistry, stereochemistry, degree of solvent incorporation and extent of rearrangements observed by either reacting sulphenyl halides with alkenes or preformed thiiranium ions with nucleophiles, as well as the complex role of solvent, counter ion and doping effect, lead to the suggestion that, along the reaction coordinate, a number of bridged intermediates **21**, **47–49** are involved[12a] and that their polarity may be modified by the actual reaction conditions. However other authors[167], following Winstein's classical suggestion, prefer to describe the same set of 'intermediates' basically as a set of ion pairs of the same thiiranium ion[181], possibly with the only exception of the covalent sulphurane **49**[9, 182, 183]. It would indeed be even misleading to refer to 'different intermediates[181].



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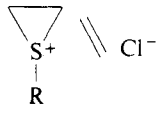

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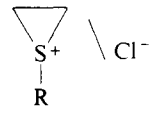

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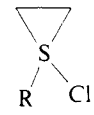
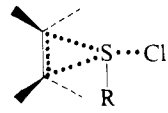


(49)

Further points which often arise, but have almost never been fully discussed, are the role played by the rate ratios among different reaction paths when more than one route is available for a specific intermediate and how the individual rates are affected by the solvent, temperature, added salts, etc.

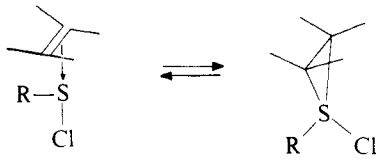
It is indeed clear that the bridged intermediate, i.e. the thiiranium ion with the counter ion more or less tightly bonded, may explore a number of reaction paths and that the actual products depend on the rate ratios and not necessarily on the intervention of specific intermediates for each specific pathway. Therefore the original scheme (equation 40) proposed by early workers in the field may still be valid. However, a large degree of flexibility must be inserted in almost every step.

The formation of the bridged intermediate may be represented as an S_N2-like displacement of the leaving group from the sulphenyl sulphur of **50**[60] as has been suggested for the reaction with n-nucleophiles. The charge at sulphur may be either positive, negative or zero depending on specific reagents and solvents, and hence the different ρ values for substituted sulphenyl halides may simply represent different positions of the transition state along the reaction coordinate of the specific system under study.



(50)

In analogy with the mechanism proposed for bromine addition to alkenes[184], the sulphenyl chloride addition may be regarded as the equilibrium formation of a π-complex **51**, a process which requires a positive ϱ value for variously substituted benzenesulphenyl chlorides, followed by the unimolecular dissociation of halide ion. The latter step requires a negative ϱ value and a very large solvent effect. If this step is rate determining, which is often the case, the overall reaction exhibits a second-order kinetic law, and the ϱ value, being the algebric sum of the two rhos, may be small and of unpredictable sign (Scheme 25).

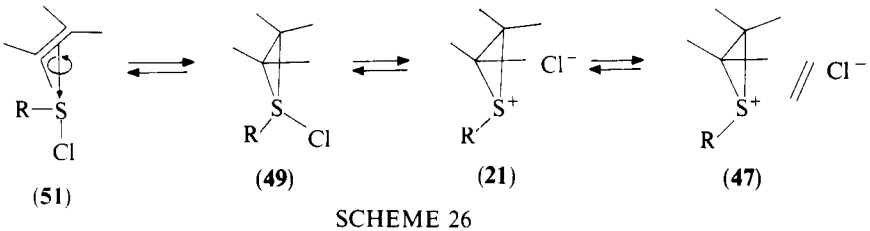


(51) (49)

SCHEME 25

The advantage of such a description is to unify the halogenation with the sulphenyl halide additions in a simple, but flexible mechanism. This has never been discussed in detail although several authors have formulated similar hypotheses.

The π-complex **51** may change to the sulphurane **49** by simple strengthening of the bonds (Scheme 26). Indeed, the formal difference between the two species is that the former should have an almost free rotation of sulphur with respect to the alkene which, of course, will be impossible in the latter.

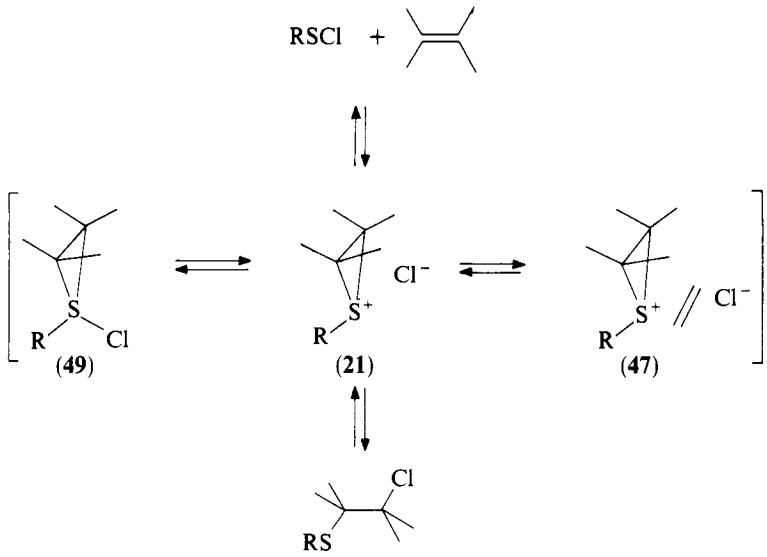


SCHEME 26

These elusive intermediates have been often invoked[9, 15, 61, 182, 183] but, so far, solid evidence of their presence along the reaction coordinate has never been offered.

For the change of the sulphurane **49** to the products, two hypotheses may be formulated: heterolysis to a thiiranium chloride tight ion pair which rapidly collapses to products, a hypothesis which is useless since so far there is no evidence for the reality of **49**, or a 'direct' rearrangement to products which, in turn, is very difficult to describe and even more challenging to test.

Under this point of view it may be assumed that the first intermediate be the thiiranium ion **21** with the counter ion more or less tightly bonded, in equilibrium with the reagents and, sometimes, with the products (Scheme 27).



SCHEME 27

It has been suggested that different tight ion pairs may exist because of different geometries[167], however their interconversion energy barrier should be in the range of the rotational energy and hence should be very low.

The bridged ion does not need to be symmetrical. Indeed the symmetrical limit is possible only in the case of identical substitution at the ring carbons. Evidence for a highly asymmetrical carbon–sulphur bond in thiiranium ions is given by the $^{12}C/^{14}C$ kinetic isotope effect measured in the addition of 2,4-dinitrobenzenesulphenyl chloride to substituted styrenes[185] (Table 7) and in the non-stereospecific addition of sulphenyl halides to 4-methoxystyrene[185] which is consistent with the intervention of a truly open ion.

TABLE 7. Carbon-14 kinetic isotope effects for the reaction of 2,4-dinitrobenzenesulphenyl chloride with 4-methyl, unsubstituted, and 4-chloro α- and β-labelled styrenes in anhydrous acetic acid at 31 °C[185]

Substituent	Isotope effect position	$^{12}k/^{14}k$
4-CH_3	$k/^{\alpha}k$	1.004
H	$k/^{\alpha}k$	1.022
4-Cl	$k/^{\alpha}k$	1.027
4-CH_3	$k/^{\beta}k$	1.037
H	$k/^{\beta}k$	1.032
4-Cl	$k/^{\beta}k$	1.035

In thiiranium ions, the substituent at sulphur will determine the amount of positive charge on this centre and consequently on the ring carbons. If the substituents at carbon are different[186], the charge distribution will no longer be symmetric and also the lengths of the sulphur–carbon bonds will be different. It is quite logical to expect a continuous variation from a symmetrical tight bridging to an asymmetrical loose bridging with significant positive charge at one of the two ring carbons and eventually to a truly open ion.

Another point of discussion is the role and nature of ion pairs. Certainly ion pairs, more or less tight, have to be present in such weakly solvating media as those usually utilized for these reactions.

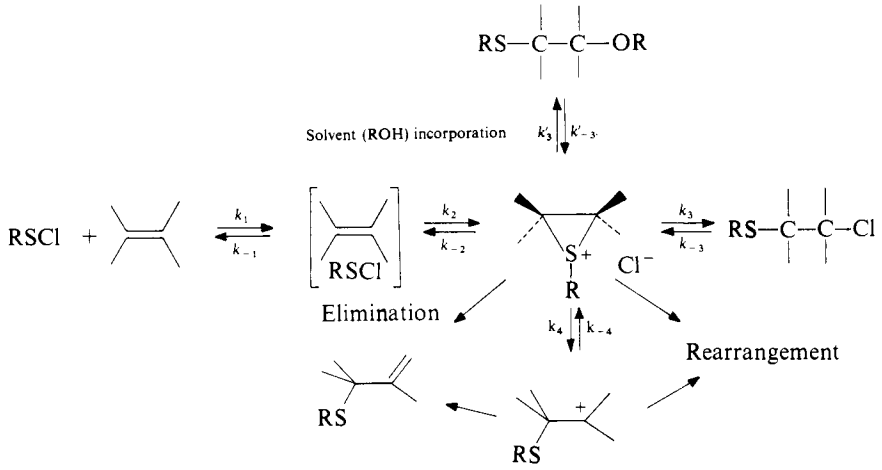
In a very general way it may be supposed that a continuum exists going from sulphurane, a really covalent species, to free solvent-separated ions.

The studies so far carried out show that the thiiranium ions have several reaction routes available (Scheme 28).

The relative rates depend on a very large number of factors. Among them the more important are the nucleophilicity of the counterion, which largely depends on the solvent, the nature of the substituent at sulphur and the intrinsic stability versus ring opening or skeletal rearrangement of the specific intermediate ion.

In weakly polar solvents the chloride ion is an extremely strong nucleophile, what makes k_3 (Scheme 28) very large and hence the bimolecular reactions dominate the product-determining step. Under these conditions the attack at sulphur is also unproductive, since the formed sulphenyl chloride adds back to the olefin.

The regiochemistry of the addition will depend on the charge density at the ring carbons and on the actual solvation of chloride ion. The former is influenced also by the charge density at sulphur which itself is modified by the exocyclic substituent. The latter is



SCHEME 28

expected to play a significant effect with such weakly polar solvents like carbon tetrachloride, chloroform or tetrachloroethylene since, as shown by the various solvent parameters[187], they have different capacities to interact with chloride ion.

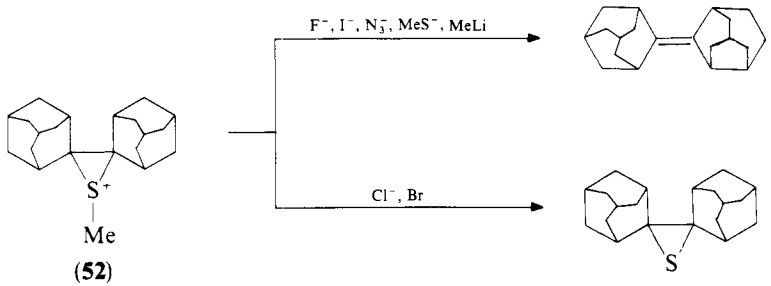
Large positive charge on one of the carbons, associated with a decreased nucleophilicity of chloride ion by solvation, favours a substitution process at carbon with more advanced bond breaking and a less advanced bond formation. This process is not influenced by steric factors but strongly affected by polar ones. Under these conditions Markovnikov products are preferentially formed. On the contrary, weakly charged carbons and unsolvated chloride ions shift the substitution process at carbon towards a transition state where bond formation is more advanced, consequently steric repulsions are maximized and *anti*-Markovnikov products are preferentially formed.

When the solvating or complexing capacity of the media is increased, the ions become more separated, the bimolecular processes are retarded and the lifetime of the bridged cation increases, i.e. k_2 becomes larger and k_3 smaller (Scheme 28).Under these conditions unimolecular processes, like ring opening or skeletal rearrangements, have a greater chance to take place. Unimolecular processes are also accelerated by substituents at sulphur which destabilize the positive charge on this centre and hence the bridged ion, as well as by the structure of the hydrocarbon backbone of the alkene.

Solvent participation depends on this complex balance of interactions, and certainly it has less chance to appear if the conditions favour the formation of tight ion pairs and rapid collapse to products than when solvent separation allows an equilibration of the nucleophilic species in the bulk of the solvent or when the nucleophilic counter ion is sequestered by lithium perchlorate or by other methods.

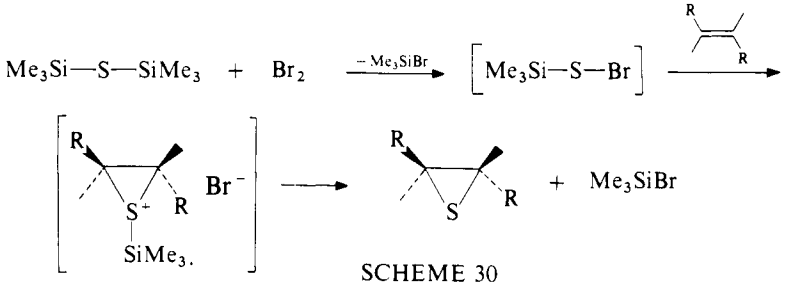
Another reaction path of thiiranium ions is the nucleophilic attack on the exocyclic substituent of sulphur. For example, this reaction has been observed in the case of 2,3-adamantyliden-1-methylthiiranium ion (**52**) where the attack of the halide ion at ring carbons is particularly hindered by the bulkiness of the substituents and the attack on sulphur is reversible[75a] (Scheme 29).

This type of reactivity has been observed also in the special case of the reaction reported in Scheme 30[188]. In this case the high electrophilicity of silicon and the ease of substitution at this atom are believed to be responsible for this behaviour.



(52)

SCHEME 29



SCHEME 30

C. Reactions with Alkynes

The addition of sulphenyl chlorides, as well as that of other sulphenyl derivatives, to carbon–carbon triple bonds has similar features to the addition reaction to double bonds, including rather similar reaction rates. Indeed the results of the two sets of data may be used together to discuss the reaction mechanism[4, 6, 11, 13, 15].

This is somewhat surprising since sulphenyl halides, being *pseudo*-halogens, should show rather different reactivity towards double and triple carbon–carbon bonds as has been found for the addition of halogens to alkenes and alkynes[189–191].

In fact, the reactivity ratios for the bromination of equally alkyl-substituted alkenes and alkynes are in the range of 10^5–10^8. Lower reactivity ratios of about 1×10^3 are found for arylalkene and arylacetylene pairs but are accompanied by a decreased stereoselectivity with respect to that typical of alkyl-substituted alkenes and alkynes[189–191].

Since protonation of alkenes and alkynes and carbonium ion attack on carbon–carbon multiple bonds show similar features and are processes which in solution should occur via open carbonium ions, the large differences observed for bromination have been related to the different stabilization of the cationic intermediates obtained by bridging of the electrophile to the two different π- systems[189].

Ab initio calculations on model bridged halonium ions show that they lay always in energy minima in the 'saturated series'[192] whereas they are energy maxima in the 'unsaturated' series[193] (Figure 1). However, the same kind of calculations show that both thiiranium[72] and thiirenium[73] ions lay in energy minima. This apparent discontinuity may be rationalized by considering that the instability of cyclic unsaturated halonium ions is related to the four-electron repulsion in the three-membered rings (Figure 2) and that such interaction is largely decreased in thiirenium ions because the pronounced pyramidality at sulphur, with consequent pushing of the unshared electron pair on

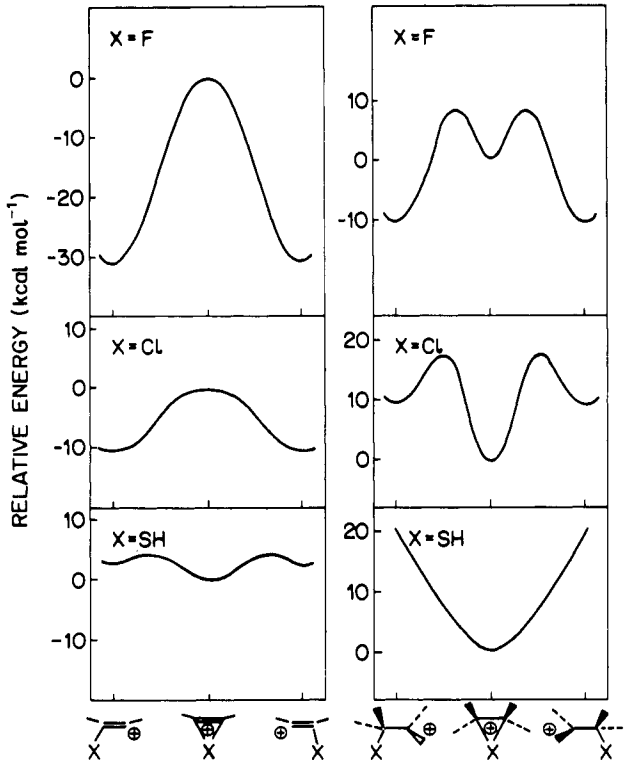


FIGURE 1. Energy profiles for the conversion of β-X-substituted vinyl cations and carbenium ions into the corresponding bridged ions as determined by *ab initio* calculations. Reprinted with permission from G. Melloni, G. Modena and U. Tonellato, *Acc. Chem. Res.*, **14**, 227 (1981). Copyright (1981) the American Chemical Society

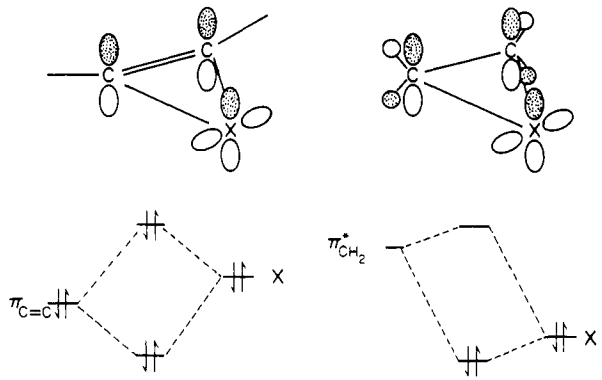
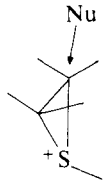


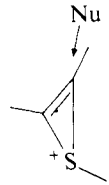
FIGURE 2. Correlation diagrams for three-membered ring saturated and unsaturated halonium ions

sulphur almost in the ring plane, positions the electron pair orthogonal to the π-electrons of the carbon–carbon double bond. More than the low electronegativity of sulphur, this geometrical feature is likely responsible for the stability of thiirenium ions and their role in the chemistry under discussion[173].

Another aspect to be considered is the process of ring opening in thiiranium and thiirenium ions. The opening of the ring in thiiranium ions amounts to a nucleophilic substitution at an sp^3 carbon with inversion of configuration, i.e. a normal S_N2-like reaction **53**. The same reaction of thiirenium ions amounts to the unusual substitution with inversion of configuration at an sp^2 carbon **54**[13, 194].



(53)



(54)

The nucleophilic substitution at the sp^2 carbon with inversion of configuration[195] is almost unknown in open-chain compounds[196] and very likely requires a high degree of bond breaking in the transition state. At the same time the more difficult attack at carbon would make the reactivity ratio between attack at sulphur and at carbon larger for thiirenium than for thiiranium ions. Though there are not enough systematic data for a signifiant comparison, this seems to be in agreement with the observations made in reactions performed on thiiranium and thiirenium ions.

According to the arguments discussed above, the reaction of sulphenyl halides with alkynes almost parallels that with alkenes[4, 11, 13, 197, 198]. As shown in Table 8 the addition is *anti*-stereospecific, the *anti*-Markovnikov regiochemistry is favoured by 'basic' solvents and the Markovnikov one in solvents with high acceptor number[4, 13, 199, 200] or in acidic media[4, 13, 200, 201].

TABLE 8. Structure and solvent effects on the regioselectivity in the addition of sulphenyl chlorides to terminal ethyl and phenyl acetylenes[13]

System	Ethyl acetate		$CHCl_3$		CH_3COOH		Ref.
	M	AM	M	AM	M	AM	
$CH_3SCl + EtC{\equiv}CH$	0	>90	0	>90			200
$4\text{-}NO_2C_6H_4SCl + EtC{\equiv}CH$	0	100			0	100	199
$2\text{-}NO_2C_6H_4SCl + EtC{\equiv}CH$	20	80	33	67	42	58	199
$CH_3SCl + PhC{\equiv}CH$	6	94			42	58	200
$4\text{-}CH_3C_6H_4SCl + PhC{\equiv}CH$	0	100	35	65	71	29	199
$4\text{-}NO_2C_6H_4SCl + PhC{\equiv}CH$	15	85	35	65	80	20	199
$2\text{-}NO_2C_6H_4SCl + PhC{\equiv}CH$	43	57	55	45	89	11	199

The regiochemistry change is more pronounced when 2-nitro-substituted arenesulphenyl halides are used. As already observed in the alkene reactions, this phenomenon likely arises because of the destabilization of the charge on sulphur in the cyclic intermediates, thiiranium and thiirenium ions.

The effects of the substitution pattern on the alkynes[190, 200] (Table 9) and of the ionizing power of the solvents[202, 203] (Table 10) on reaction rates also parallel those found for the alkenes.

TABLE 9. Effect of alkyl substitution of alkynes on the rate of addition of 4-methanesulphenyl chloride in ethyl acetate at 25°C[200]

	Alkyne		
	HC≡CH	EtC≡CH	EtC≡RCEt
10^3k ($mol^{-1}s^{-1}$)	0.035	9.6	730

TABLE 10. Solvent effect on the rate of addition of selected sulphenyl chlorides to some acetylenes at 25°C[150, 202, 203]

	10^2k ($1mol^{-1}s^{-1}$)			
System	CCl_4	Ethyl acetate	$CHCl_3$	Ref.
$CH_3SCl + BuC \equiv CH$		16.2	153.0	150
$4\text{-}CH_3C_6H_4SCl + BuC \equiv CH$		0.91	19.9	202
$4\text{-}CH_3C_6H_4SCl + EtC \equiv CH$	0.02	0.96	16.9	202
$4\text{-}CH_3C_6H_4SCl + PhC \equiv CH$		0.009	19.0	203

In most of the cases investigated the reaction follows an apparently simple second-order kinetic law, but the effect of the substituents in the reaction of substituted benzenesulphenyl chlorides with 1-butyne[4, 13, 150] (Table 11) clearly indicates that the formation of the ionic intermediate is reversible and moreover gives evidence of the peculiar effect of the nitro group when in the *ortho* position on arenesulphenyl chlorides.

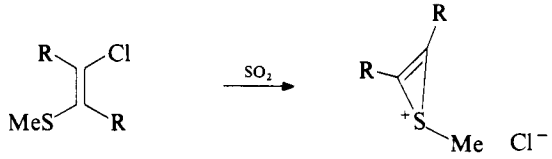
TABLE 11. Substituent effect in the addition of arenesulphenyl chlorides to 1-butyne[150, 200]

Substituent in ArSCl	Ethyl acetate $k \times 10^3$ ($M^{-1}s^{-1}$)	$CHCl_3/CH_3COOH$ 10% $k \times 10^3$ ($M^{-1}s^{-1}$)
$4\text{-}OCH_3$	5.0	128
$4\text{-}CH_3$	9.6	172
H	11.3	170
4-Cl	15.2	155
3-Cl	14.2	142
$4\text{-}NO_2$	10.9	56
$2\text{-}NO_2$	0.004[a]	—
$2,4\text{-}(NO_2)_2$	0.003[a]	—

[a] Data obtained by extrapolation from the reaction rates with 3-hexyne.

The stability and the role played by the intermediate thiirenium ions is well documented in this system. Several thiirenium salts of non-nucleophilic acids have been

prepared[13, 65]. It has been also shown that some of them may be easily obtained from β-thiovinyl chlorides by direct solvolysis in a good ionizing medium such as liquid sulphur dioxide even as chloride salts[67] (equation 45).



(45)

R = *t*-Bu, 1-Ad

Independent evidence on the role played by thiirenium ions in the chemistry of β-thiovinyl derivatives follows from the reversible 1,2-sulphur shift concomitant with the solvolysis of β-thiovinyl sulphonates[204] and in the large anchimeric effects on their reaction rates[205-208] (Table 12).

TABLE 12. Rate coefficients (at 25°C) and activation parameters for the solvolysis of selected vinyl sulphonates

	Solvelnt	$k(s^{-1})$	k_{rel}	E_a (kcal mol^{-1})	$\Delta s^{\ddagger}$ (cal mol^{-1} deg^{-1})	Ref.
Me, OSO_2TNB, Me, Me	*a*	1.1×10^{-8}	1	25.3	−12	206
Me, OSO_2TNB, MeS, Me	*a*	4.1×10^{-4}	37,000	22.3	−1	206
Ph, OSO_2TNB, Ph, Ph	*b*	1.5×10^{-5}	1,400	22.0	−11	205
Ph, OSO_2TNB, PhS, Ph	*b*	3.4×10^{-4}	31,000	23.4	+2	205

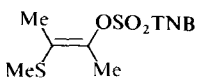
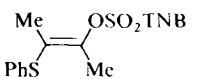
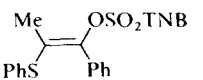
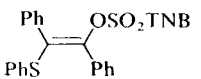
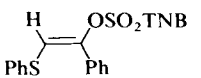
[a]Nitromethane:methanol, 9 : 1.
[b]Nitromethane.
TNB = 2,4,6-trinitrobenzene.

The stability of thiirenium ions with respect to their precursors and products depends, beside the reaction conditions, on the substitution pattern. It was observed that alkyl groups at sulphur and at the ring carbons, in particular bulky groups, stabilize the ions[13] so that, for example, the 1-methyl-2,3-di-*t*-butyl thiirenium ion is so stable as a fluoborate or a hexachloroantimonate salt that its structure could be studied by X-ray diffractometry[71].

The stability of the thiirenium ion reflects itself in the magnitude of the anchimeric effect in the β-thiovinyl sulphonate solvolysis[205, 208] shown in Table 13.

All these factors should affect the kinetic features of the addition of sulphenyl chlorides to alkynes. A limiting case is that of the addition of some sulphenyl chlorides to 2-butyne and 3-hexyne in liquid sulphur dioxide[209] which is presented in Table 14.

TABLE 13. Effect of α-thio substitution (k'_{rel}) and of β-substitution (k''_{rel}) on the unimolecular reactivity of selected vinyl sulphonates in nitromethane at 25°C, unless otherwise stated.

					
k (s^{-1})	4.1×10^{-4}	3.9×10^{-3}	4.9×10^{-3}	3.4×10^{-4}	9.4×10^{-6}
k'_{rel}	10	1	127	—	—
k''_{rel}	—	—	525	37	1

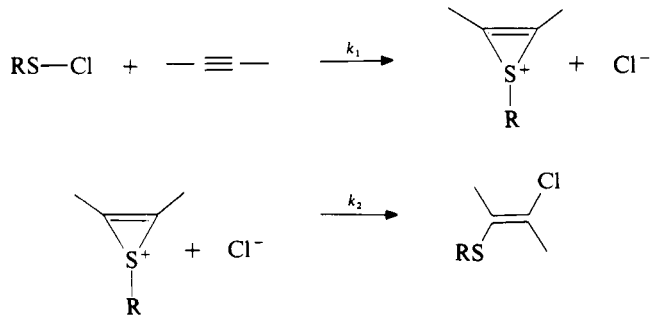
[a] In nitromethane:methanol = 9:1.
[b] References 206.
[c] Reference 207.
[d] References 205 and 208.
TNB = 2,4,6-trinitrobenzene.

TABLE 14. Rate coefficients for the formation of thiirenium ions (k_1) and *E*-2-alkylthiovinyl chlorides or *E*-2-arylthiovinyl chlorides (k_2) in liquid sulphur dioxide at $-67°C$[209]

R'SCl	$M \times 10^2$	$R^2C\,CR^2$	$M \times 10^2$	k_1 ($mol^{-1}\,s^{-1}$)	k_2 ($mol^{-1}\,s^{-1}$)
CH_3	0.6	CH_3	9.5	5.2	2.6×10^{-2}
CH_3	1.1	CH_3	9.5	5.1	—
CH_3	1.7	CH_3	9.5	5.3	—
CH_3	1.1	CH_2CH_3	6.4	8.7	2.0×10^{-2}
CH_2CH_3	0.9	CH_3	9.5	1.1	2.1×10^{-2}
Ph	0.7	CH_3	9.5	—[a]	1.4
4-$CH_3C_6H_4SCl$	0.6	CH_3	9.5	—[a]	1.1
4-ClC_6H_4SCl	0.6	CH_3	9.5	—[a]	3.2

[a]Not measurable.

In this solvent the overall reaction is split into two separate steps: fast formation of a thiirenium ion, followed by a slower nucleophilic attack of a chloride ion at the sp^2 carbon (Scheme 31).



SCHEME 31

Within the limited data available, both k_1 and k_2 basically show the same dependence on the structural variation of the substituent in the sulphenyl chloride. This feature is expected due to the electrophilic character of the attack of the sulphenyl chloride on the triple bond and because the thiirenium ion is the electrophilic reagent in the second step. However, the few data available do not allow a reliable quantitative correlation.

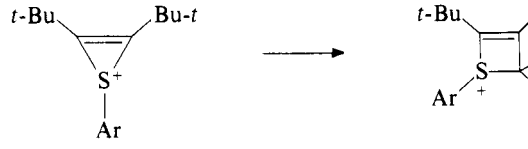
Probably because of the great solvating power of liquid sulphur dioxide, there is no evidence for the reversibility of the first step of the reaction. Also, the second step is irreversible for the substrates chosen contrary to what is found in the case of the di-*t*-butyl derivative (see equation 45).

While the hypothesis of a covalent intermediate having a sulphurane-like structure was also suggested in the addition of sulphenyl chlorides to alkynes[4], no unambiguous evidence for its existence along the reaction coordinate was obtained[13].

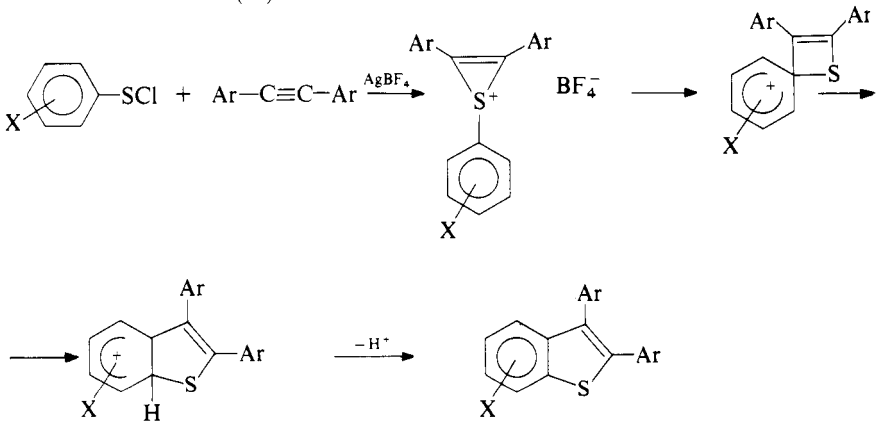
Reports on skeletal rearrangements competing with the normal sulphenyl halide additions to acetylenes are much less frequent than in the case of the analogous addition to alkenes. This is likely more due to the structure of the substrates used than to a greater difficulty of the process itself.

The 2,3-di-*t*-butyl-1-(4-chlorophenyl) thiirenium ion (**55**) does suffer a slow 1,2-methyl shift[210] (equation 46) formally analogous to the transposition observed for the *trans*-2,3-di-*t*-butylthiiranium ion **45**[157]. The transposition of **55** appears to be slower than that of **45** but it should be remembered that the *cis* isomer of **45** does not undergo rearrangement under the conditions in which the *trans* isomer does[157].

The reaction of arenesulphenyl chlorides with diarylacetylenes followed by addition of silver tetrafluoroborate leads to benzothiophenes through a complex rearrangement[208, 211, 212] as depicted in Scheme 32. However, for neither rearrangement is it known as yet whether or not they involve the formation of the open vinyl cation.



(46)



SCHEME 32

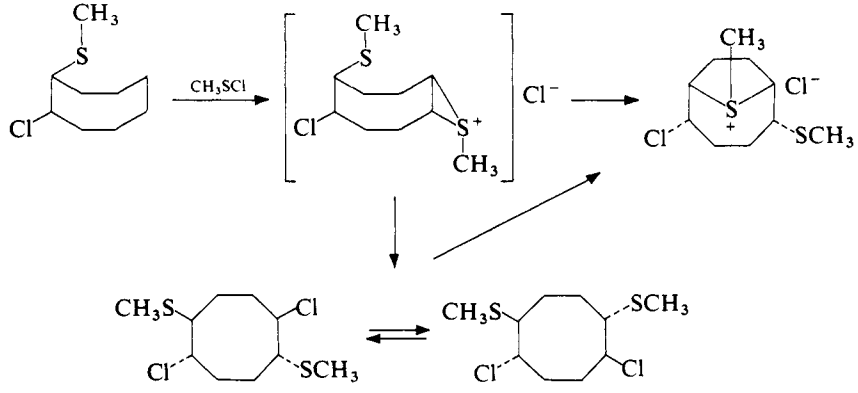
The Transposition of thiirenium ion to benzothiophene may also be viewed as a particular case of cyclofunctionalization. Other examples of these interesting reactions are discussed in Section IV.

D. Reactions with Polyunsaturated Substrates

Polyenes and polyenynes where the functionalities are fully separated behave as the simple alkenes or alkynes[6, 49].

However, cyclic polyenes may sometimes present reactions involving two or more unsaturated centres when the steric constraint of the structure forces them one near to the other or when the intermediates have particular requirements.

This is the case, for example, of the reaction of sulphenyl chlorides with *cis,cis*-1,5-cyclooctadiene. Methanesulphenyl chloride favours the formation of the bis-adduct and *trans*-annular interactions[213] as shown in Scheme 33; however, 2,4-dinitrobenzenesulphenyl chloride under rather similar conditions gives the mono adduct only[214].



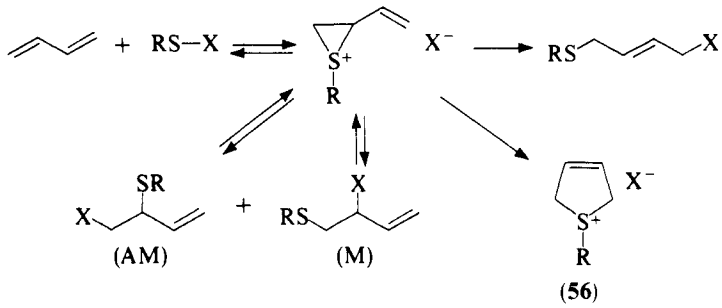
SCHEME 33

Other typical cases have been reported earlier under the general subject of skeletal rearrangements concurrent with addition to polycyclic alkenes (see Scheme 19) and others are reported in Section IV.

An extensive coverage of this field is outside the scope of this chapter; however, a brief discussion of the reactions of sulphenyl halides with conjugate dienes and with allenes is reported below.

1. *Conjugate dienes*

The addition of sulphenyl halides to conjugate dienes yields, under kinetic control, one or both of the 1,2-*anti*-adducts, of either M or AM regiochemistry, which more or less rapidly evolve to 1,4-adducts[215] (Scheme 34).

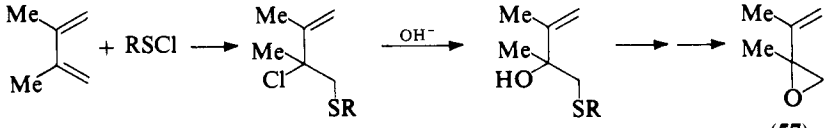


SCHEME 34

This behaviour is fully consistent with the general mechanism of the addition of sulphenyl chlorides to alkenes: initial formation of thiiranium ions which collapse to the two isomeric 1,2-adducts. The 1,2-adducts are in equilibrium with the thiiranium chloride from which, via a slower reaction, the thermodynamically more stable 1,4-adduct may be formed. In some cases evidence has been obtained on the formation of the cyclic sulphonium ion **56**[6, 9, 10].

When the two double bonds are differently substituted, a complex mixture of kinetically controlled products is formed as the reactivities of the two double bonds are affected by both electronic and steric effects[216, 217].

The selective 1,2-addition to a dienic system, as well as the 1,4-addition, correspond to the transformation of only one of the unsaturations present and may find interesting application such as, for example, in the case of the synthesis of the epoxyalkene **57**[218] (Scheme 35).

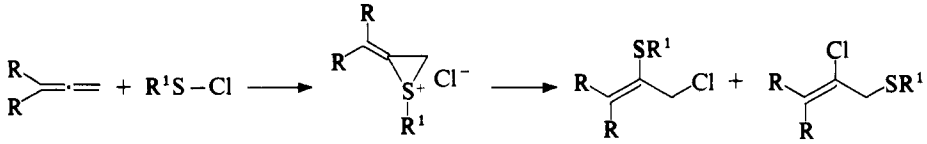


(57)

SCHEME 35

2. Allenes

The addition of sulphenyl halides to allenes may also be rationalized by assuming the intermediate formation of a thiiranium ion, followed by preferential attack at the sp^3 carbon, formally yielding an *anti*-Markovnikov-like adduct **58**[219] (Scheme 36).



(58)

major isomer minor isomer

SCHEME 36

The attack at the least substituted double bond seems to depend on steric effects whereas the ring-opening step may be controlled by the different hybridization of the two ring carbons. Under some conditions, multiple addition as well as other subsequent reactions may occur[219].

In highly substituted allenes, i.e. 1,3-disubstituted or polysubstituted derivatives, a delicate balance between steric and electronic effects directs the addition to either one of the two 'formal' double bonds, leading in several cases to an unpredictable mixture of isomers. Like in the case of simple alkenes, also in these reactions the reactivity depends significantly on the nature of the group linked to the sulphenyl sulphur[220–223].

D. Synthetic Applications

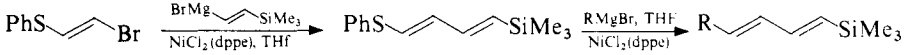
The great flexibility of the reaction of sulphenyl halides with π-nucleophiles and the possibility to select appropriate conditions for controlling the regioselectivity of the addition, associated with the intrinsic high *anti*-stereoselectivity, make this reaction very useful in synthetic organic chemistry as documented in the broad literature in the field.

Often the reaction of sulphenyl halides with multiple carbon–carbon bonds is the key step in designing a synthetic strategy. In fact the two new introduced functionalities

may activate the systems toward a number of interesting transformations[224, 225] which make the target molecule more easily accessible. These reagents have been successfully used for the synthesis of pheromones[226], prostacyclines[227], antibiotics[228] and natural products[229].

The synthetic relevance of the sulphenyl halide adducts is based largely on the stereoselectivity of the addition across the double and triple carbon–carbon bonds and the different reactivity of the halogen and of the alkylthio or arylthio groups.

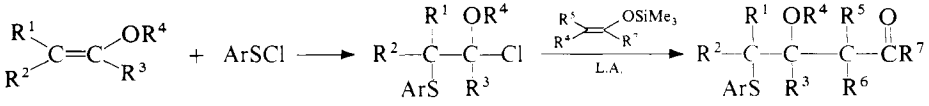
For example, the sequential cross-coupling reaction of *E*-β-phenylthio-α-bromoalkenes with Grignard reagents, which may be easily obtained by addition of benzenesulphenyl halide to alkynes, has been extensively utilized for the synthesis of a variety of mono- and polyenes, *inter alia* insect pheromones[230] (Scheme 37).



dppe = $Ph_2PCH_2CH_2PPh_2$

SCHEME 37

Other procedures for the coupling reaction have been reported[230c, 231, 232]. Dimethylzinc in the presence of titanium tetrachloride stereospecifically substitutes the chlorine atom of the adduct of sulphenyl chloride to alkenes[231] whereas the product of addition of sulphenyl chlorides to vinyl ethers, in the presence of a Lewis acid, adds to silyl enol ethers thus forming the new carbon–carbon bond[232] (Scheme 38).



SCHEME 38

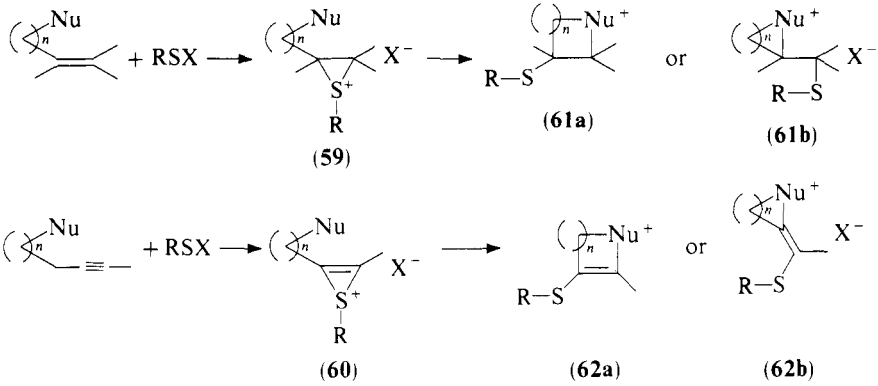
The addition of sulphenyl halides to optically active alkenes is also rather sensitive to the steric environment and leads to the formation of novel chiral centres with variable diastereoselectivity[233, 234].

The limited number of examples reported above are only a few of the many that could be mentioned, but a comprehensive coverage of even the most recent literature in this particular field would be outside the scope of this chapter.

IV. REACTIVITY OF SULPHENYL HALIDES AND OTHER SULPHENIC DERIVATIVES WITH FUNCTIONALIZED ALKENES AND ALKYNES

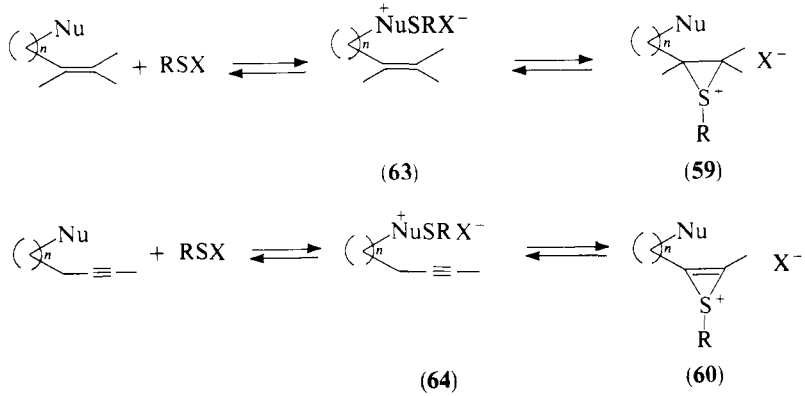
When sulphenyl halides or other sulphenic derivatives react with alkenes or alkynes containing a nucleophilic centre able to compete with the halide ion (or other external nucleophiles) for attack at the thiiranium or thiirenium intermediates **59** or **60**, cyclic products **61** or **62** are formed (Scheme 39). The regiochemistry of the internal nucleophilic attack is often controlled by the relative stability of the two heterocycles which can be formed by *endo* or *exo* ring closure.

More often the nucleophilic centre is an oxygen, a nitrogen or a sulphur atom. In some cases carbon–carbon double bonds and strained carbon–carbon single bonds behave as internal nucleophiles thus producing carbocyclic compounds.



SCHEME 39

It might be argued that the sulphenyl derivative first reacts with the nucleophilic centre to give species like **63** or **64** that may themselves transfer the RS^+ moiety to the carbon–carbon multiple bond or that may be in equilibrium with the reagents (Scheme 40). Under these circumstances, however, the final result does not change. Different is the case of the reaction of allylic alcohols with sulphenyl chlorides where the intermediate sulphenic ester rearranges to give sulphoxide derivatives.



SCHEME 40

A. Alkenes and Alkynes with Oxygen Containing Nucleophilic Centres

1. Unsaturated carboxylic acids

The reaction of sulphenyl halides with alkenes and alkynes bearing a carboxylic group gives rise to thio-substituted lactones. Lactonization is often achieved in the presence of an organic base, usually a tertiary amine.

Depending on the nature of the unsaturated carboxylic acid, mono- or polycyclic lactones can be obtained. Table 15 lists some examples of this reaction.

Inspection of the data in Table 15 shows that the lactonization is regiospecific, producing only the more stable lactone. Comparison of these data with the usual regioselectivity observed in the addition of sulphenyl halides to double or triple bonds (see Section III) indicates that the internal nucleophilic attack is sensitive to the stability of the lactone which is being formed. In other words, this may indicate a product-like transition state for the ring closure reaction.

The role of the base in the cyclization is crucial. This is especially true for the cyclization of the unsaturated acid **79** to yield the lactone **80**. In fact, the reaction of **79** with benzenesulphenyl chloride in the absence of the base gives only the two diastereomeric

TABLE 15. Synthesis of thio-substituted lactons from unsaturated acids

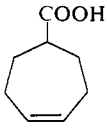
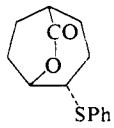
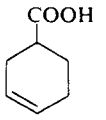
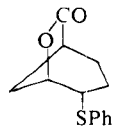
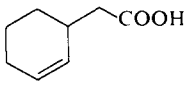
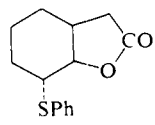
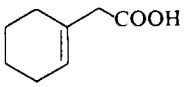
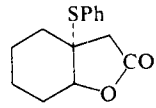
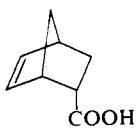
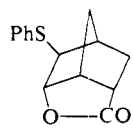
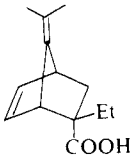
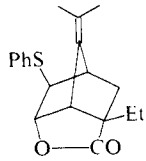
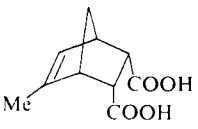
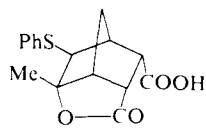
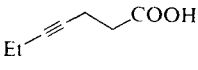
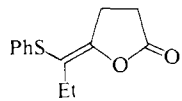
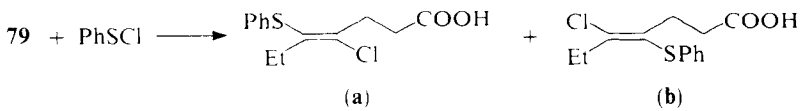
Reagent	Product	yield (%)	Base[a]	References
 **(65)**	 **(66)**	82	A	235, 236
 **(67)**	 **(68)**	95	A	235, 236
 **(69)**	 **(70)**	86	A	235, 236
 **(71)**	 **(72)**	85	A	235, 236
 **(73)**	 **(74)**	95	A	237

TABLE 15. (*continued*)

Reagent	Product	yield (%)	Base[a]	References
 (**75**)	 (**76**)	30	A	237
 (**77**)	 (**78**)	31		238
 (**79**)	 (**80**)	78 99	A B	239 239

[a] A = Et_3N; B = 3,4-dihydro-2H-pyrido[1,2-*a*]pyrimidin-2-one.

vinyl chlorides **a** and **b**, which are adducts of benzenesulphenyl chloride to the triple bond[239] (equation 47).



(47)

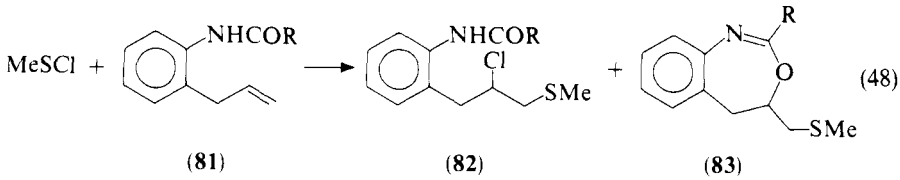
In the presence of triethylamine, the lactone **80** is the predominant product and the vinyl chlorides (**a** and **b**) are formed in 19% to 43% yield, depending on the reaction conditions. When 3,4-dihydro-2*H*-pyrido(1,2-*a*)pyrimidin-2-one is used as a base, the lactone **80** is formed exclusively in a nearly quantitative yield[239]. This reaction also shows clearly the different regiochemical control of the addition of sulphenyl halides to triple bonds with respect to the lactonization reaction.

The addition products **a** and **b** are formed from **79** without almost any regiochemical control; the two isomers are produced in a 40:60 ratio. However, the cyclization of **79** to **80** occurs regiospecifically, indicating that the thermodynamic stability of the *exo*-methylene-pentalactone with respect to the unsaturated six-membered ring isomer is responsible for the selectivity of the addition.

Recently, dimethyl(methylthio)sulphonium tetrafluoroborate has been used for lactonization of **65**, **67** and 4-pentenoic acid to the corresponding methylthio-derivatives of **66**, **68** and to 2-(methylthiomethyl)butyrrolactone[240]. In this case, the presence of a base like diisopropylethylamine is also necessary to produce lactones in high yields.

2. Unsaturated amides

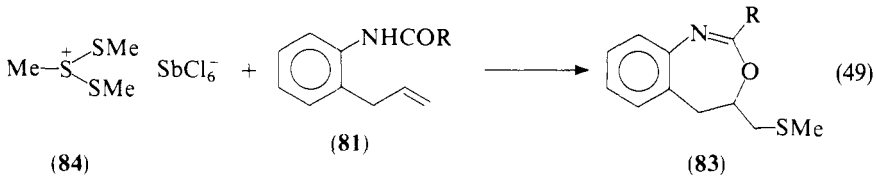
The reaction of methanesulphenyl chloride with the unsaturated amide **81** gives a mixture of **82**, which is the addition product of the sulphenyl chloride to the double bond of **81**, and the azepine **83**, which is the cyclization product[241] (equation 48).



(48)

(81) (82) (83)

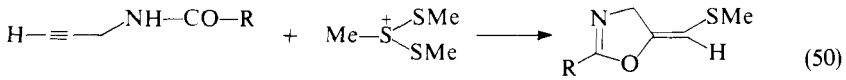
The main product of the reaction shown in equation 48 is **82**, however the exclusive formation of **83** from **81** is obtained using methyl(bismethylthio)sulphonium hexachloroantimonate **84** as methylthio transfer agent[241] (equation 49).



(49)

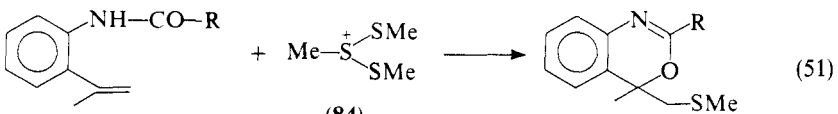
(84) (81) (83)

Other amidoalkynes and amidoalkenes of type **85** and **86** react similarly with **84** and give oxazole or benzoxazine derivatives **87**[242, 243] and **88**[244] respectively (equations 50 and 51).



(50)

(85) (84) (87)



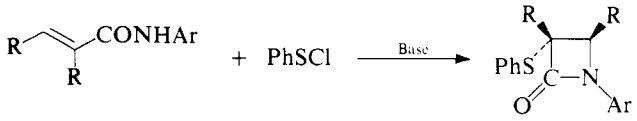
(51)

(86) (84) (88)

The oxazole derivatives **87** are formed by a Markovnikov-oriented nucleophilic attack of the amido oxygen on the intermediate thiirenium ion[242, 243]. Such an attack is rare in thiirenium ion chemistry (see Section III). The regiochemistry of this reaction may be due to the low nucleophilic character of the amido oxygen, which is only able to attack the carbon atom of the three-membered ring intermediate when some positive charge is developed at the carbon atom. In other words, the reaction must have some S_N1 character in order to proceed. The ring closure to the benzoxazine **88** follows the general rules above outlined.

Unsaturated amides of type **89** react with benzenesulphenyl chloride in the presence of a base to give *β*-lactam derivatives **90**[245-247] (equation 52). The synthesis of the *β*-lactams

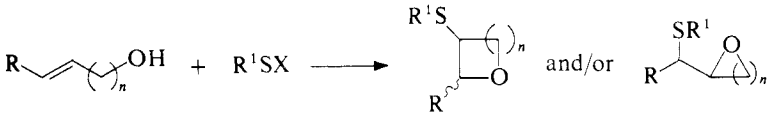
90 occurs by a two-step sequence: the addition of the sulphenyl chloride to the double bond of **89** first, and then the dehydrochlorination catalysed by the base that causes ring closure.



(89) (90) (52)

3. *Unsaturated alcohols*

The reactivity of unsaturated alcohols towards sulphenyl halides and other sulphenylium ion carriers depends on the number of carbon atoms that separates the two functionalities. When the carbon atoms are from two to five, cyclic ethers with four- to seven-membered rings can be obtained (Scheme 41).

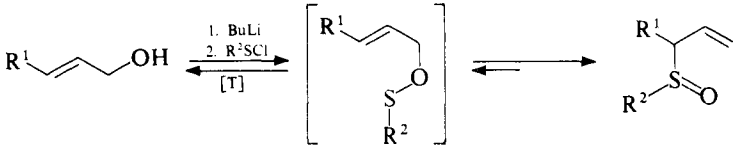


$n = 2, 3, 4, 5$

SCHEME 41

Allylic alcohols behave differently since the sulphenate esters initially formed undergo reversible rearrangement to allylic sulphoxides.

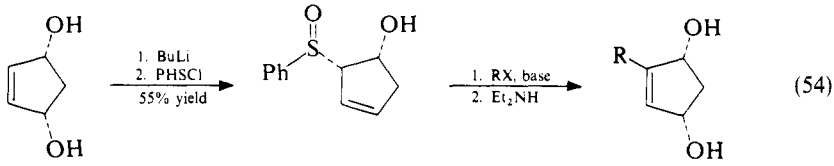
a. Allylic and propargylic alcohols. The reaction of sulphenyl chlorides with allylic alcohols occurs at the alcoholic function and leads to the corresponding sulphenate esters. However, the presence of the adjacent double bond allows the intermediate sulphenate to undergo a [2,3]-sigmatropic rearrangement to the most stable allylic sulphoxide (equation 53)[89, 248]. Another interesting feature is observed when the reaction mixture is treated with a thiophile (T): the intermediate sulphenate ester is irreversibly converted into the allylic alcohol that may have inverted stereochemistry at the carbon linked to the oxygen atom[249].



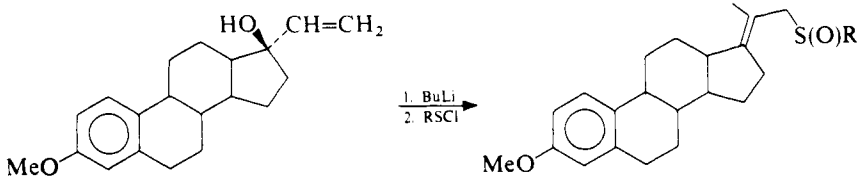
(53)

Since the mechanism and the stereochemistry of this rearrangement was recently reviewed[89, 248], we report here some examples in which the reaction of sulphenyl halides with allylic and propargylic alcohols is a key step in the synthesis of target molecules.

Interesting applications of this reaction have been reported in the synthesis of prostaglandins[250] (equation 54), as key step in the synthesis of natural products like (+/−)-*E*-nuciferol[251] and (+/−)-hirsutene[252] and in steroid modifications[253, 254] (equation 55).

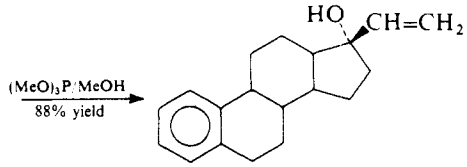


(54)



(91) only the (S) isomer

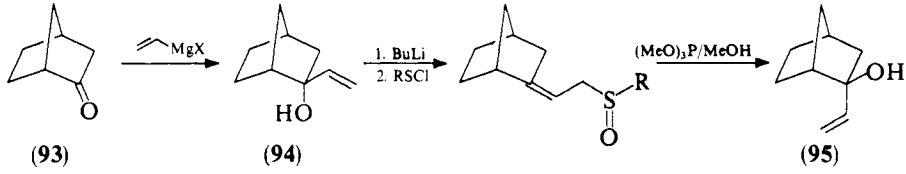
(55)



(92)

Epimerization at the C-17 of the steroid **91** is obtained by the two-step sequence using trimethyl phosphite as thiophile. The original steroid **91** is thus converted into a 73:27 mixture of **92** and **91**[251] respectively.

The possibility of inversion of chirality at the carbon bearing the alcoholic group was also applied to the allylic alcohol obtained from bicyclo[2.2.1]heptan-2-one (**93**) by the reaction with vinylmagnesium bromide[255a] (equation 56). The Grignard reaction stereospecifically affords the *endo* alcohol **94** while the benzenesulphenyl chloride-trimethyl phosphite method[249b, 256] gives the *exo* alcohol **95** with high stereospecificity.

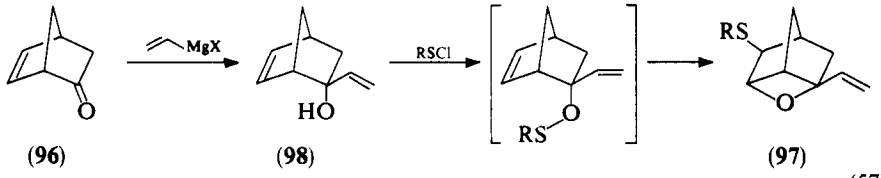


(93) (94) (95)

(56)

The same sequence of reactions carried out with norbornenone **96** resulted in the formation of the tricyclic oxetane **97**[255b] (equation 57). The presence of the endocyclic double bond allowed in this case the cyclofunctionalization of **98** (see Section IV.A.3.b).

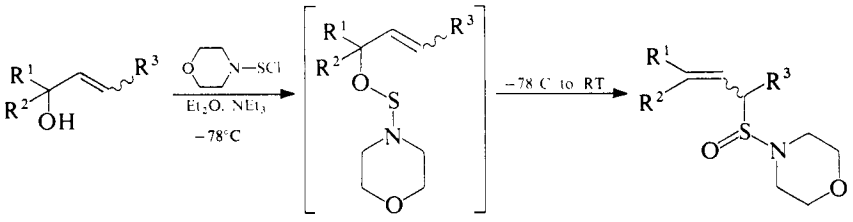
A variety of allylic alcohols were transformed into the corresponding substituted allylic sulphinamides[257] by reaction with 4-morpholinesulphenyl chloride (equation 58). The reaction is regioselective and in the case of secondary alcohols only 1'-substituted-4-(2'-alkenesulphinyl)morpholines **99** were formed. However, the intermediate sulphenate ester



(96) (98) (97)

(57)

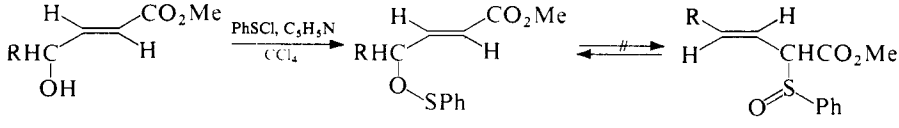
rearranges with low diastereoselectivity. In fact, starting from a pure *E*- or *Z*-allylic alcohol **100**, a mixture of the two diastereomeric sulphinamides **99** was obtained[257].



(100) (101) (99)

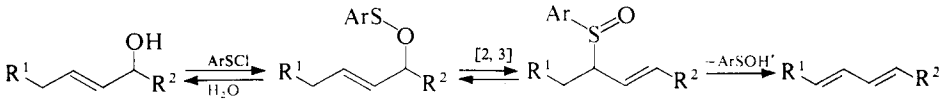
(58)

In general, electron-withdrawing substituents at the double bond of the allylic alcohols prevent the sulphur–carbon bond formation by stabilizing the sulphenate isomer[258] (equation 59).



(59)

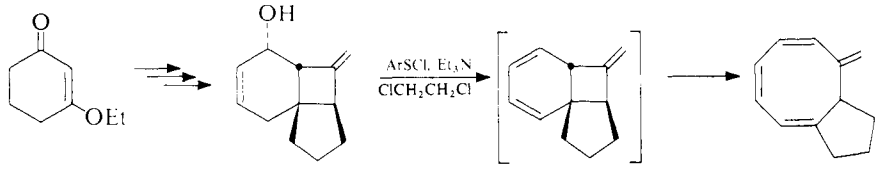
The conversion of allylic alcohols into 1,3-dienes (Scheme 41a) is another synthetic application of the reaction of sulphenyl chlorides with these unsaturated alcohols[259].



SCHEME 41a

A very large number of allylic alcohols were converted in good yield into the corresponding 1,3-diene using 2,4-dinitrobenzenesulphenyl chloride and triethylamine as a base. The reaction occurs with overall *cis* stereochemistry[259]. The only two limitations are: the presence of groups that can stabilize the sulphenate ester and the poor regioselectivity in the elimination step.

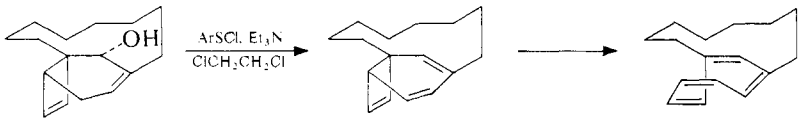
This procedure, better known as the Reich and Wollowitz dehydration reaction, has a growing interest in organic synthesis and, for example, it has been used in the synthesis of 7-methylenebicyclo[6.3.0]undeca-1,3,5-triene (**102**)[260] (equation 60). Starting from the α,β-unsaturated ketone **103** the allylic alcohol **104** was obtained in five steps. Dehydration followed by electrocyclic ring expansion gave **102** in 49% yield.



(103) (104) (102)

(60)

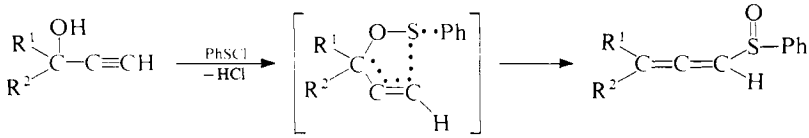
Similarly, the allylic alcohol **105** allowed one to obtain the cyclooctatetraene **106** (equation 61), the first example of a cyclooctatetraene exhibiting activation energy to bond shifting lower than that of ring inversion[261].



(105) (106) (61)

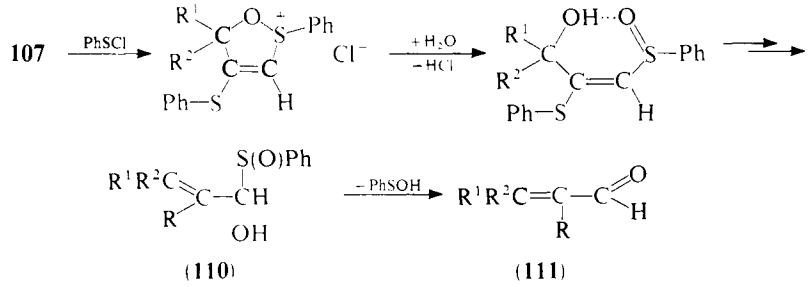
Propargylic alcohols show a reactivity towards sulphenyl chlorides very similar to that of allylic alcohols, however the different nature of the carbon–carbon multiple bond opens new synthetic approaches to the allenic system.

Allene sulphoxides **107** are readily available by reaction of alkynols **108** with sulphenyl chlorides (equation 62). This reaction occurs via intramolecular [2,3]-shift of the initially formed sulphenate ester **109**.



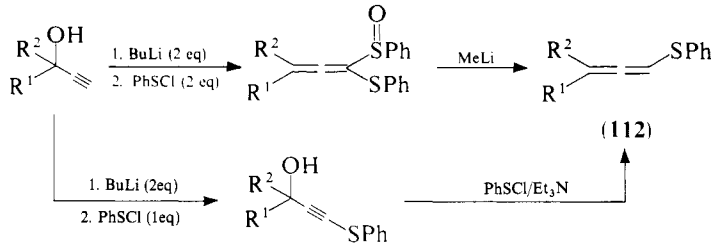
(108) (109) (107) (62)

The presence of the sulphoxidic functionality in **107** allowed several type of transformations. Addition of a second equivalent of sulphenyl chloride (or bromine) to **107** yields the allylic alcohols **110** (equation 63)[262] which in turn can be converted into the unsaturated aldehydes **111**.



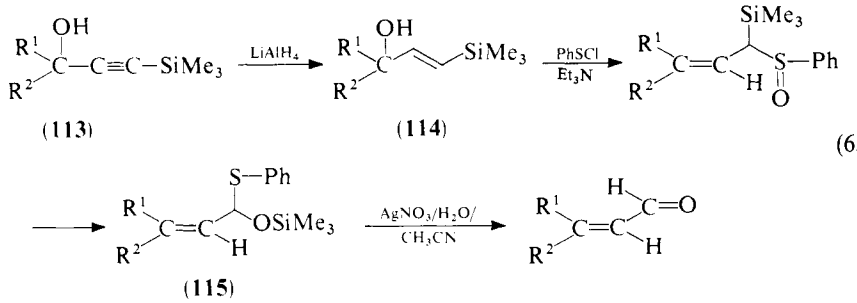
(110) (111) (63)

Masked α,β-unsaturated aldehydes **112** have also been obtained from the reaction of propargylic alcohols with sulphenyl chlorides, but using a slightly different reaction procedure[263] (equation 64).



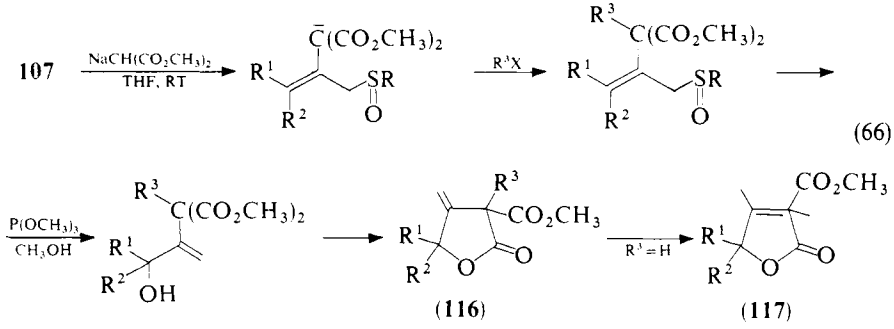
(64)

Another way to obtain α,β-unsaturated aldehydes using the benzenesulphenyl chloride method starting from silyl-protected propargylic alcohols **113** is reported in equation 65[264]. Indeed the first step of the sequence transforms **113** into the vinylsilane **114**, which is then transformed into the masked aldehyde **115**.



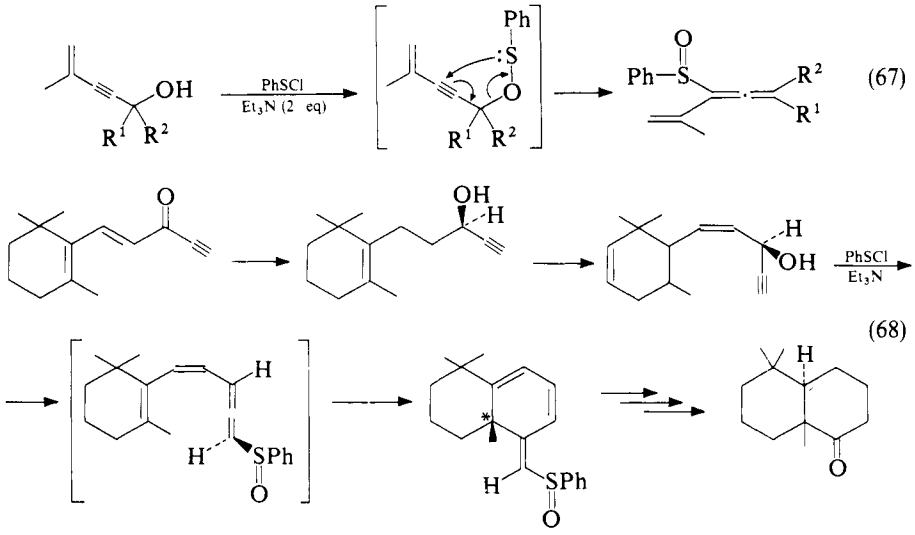
(65)

The synthetic utility of compounds of type **107** was shown in the synthesis of γ-butyrolactones **116** and **117** (equation 66)[265] or in the synthesis of prostacycline analogues[266].



(66)

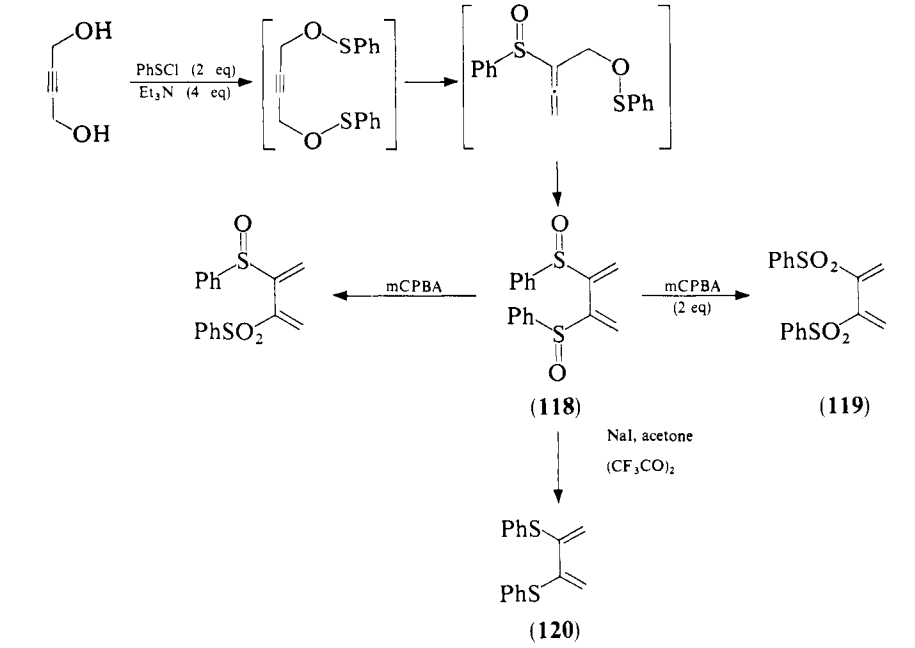
The simple entry to allene sulphoxides was applied for the preparation of vinylallenes, which were used in the synthesis of complex polyenes[248]. Two examples of this strategy are shown in equations 67[267] and 68[268].



(67)

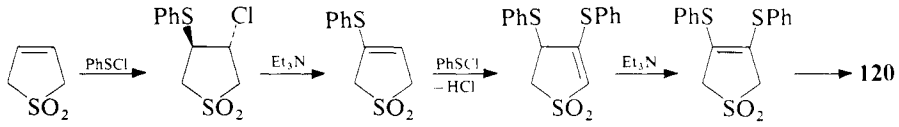
(68)

1,3-Dienes can also be prepared by the reaction of the sulphenyl chloride-triethylamine reagent with 2-butyne-1,4-diol[269, 270] (Scheme 42). This reaction allowed the synthesis of the bis-sulphoxide **118** from which the bis-sulphone **119** or the bis-sulphide **120** can be obtained by well-established procedures.



SCHEME 42

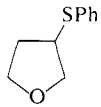
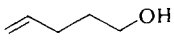
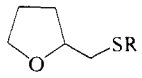
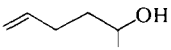
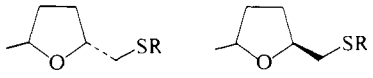
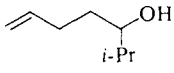
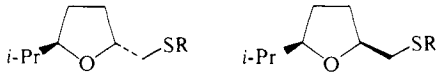
The diene **120** may also be formed in 80% yield by an alternative way[269, 271] through the reaction sequence reported in Scheme 43. The easy removal of the sulphide functionality would have made **120** a very good synthetic equivalent of butadiene in Diels–Alder reactions. Unfortunately **120** is not a good diene, as it reacts only with the most activated dienophiles[269].



SCHEME 43

b. Other unsaturated alcohols. The reaction of sulphenylating agents with alkenols different from allylic alcohols is quite general as far as the possibility to obtain the desired cyclic ether and the use of the various sulphenylating agents is concerned. Four different sulphenylating agents have been used for this purpose: benzenesulphenyl chloride-tertiary amine system (A); dimethyl(methylthio)sulphonium tetrafluoroborate diisopropylethylamine (B); methyl(bismethylthio)sulphonium hexachloroantimonate (C); *N*-(phenylthio)morpholine-trifluoromethanesulphonic acid (D). Table 16 contains most of the cyclic ethers which can be produced by this type of cyclization reaction.

TABLE 16. Synthesis of cyclic ethers from alkenols

Reagent	Product[a]	Method	Reference
(121)	 **(122)**	D	272
		A	255
 **(123)**	 **(124)**	B	240
		C	273
		D	272
 **(125)**	 **(126a)** (1:1) **(126b)**	C	273
 **(127)**	 **(128a)** (1:1) **(128b)**	C	273

(continued)

TABLE 16. (*continued*)

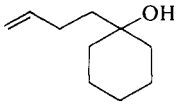
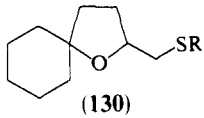
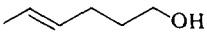
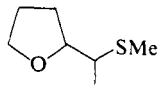
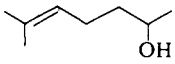
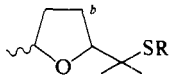
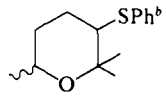
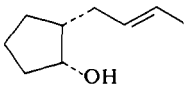
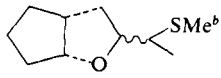
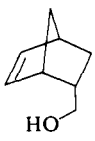
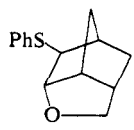
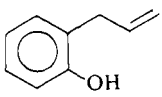
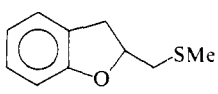
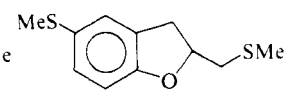
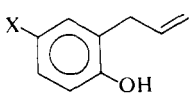
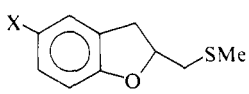
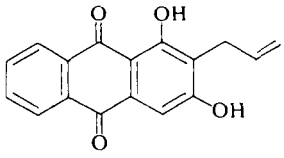
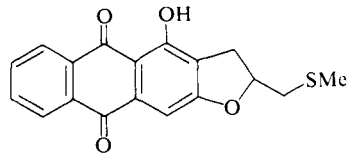
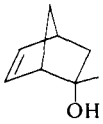
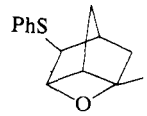
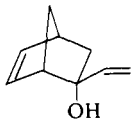
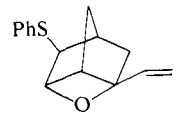
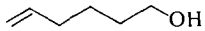
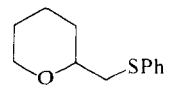
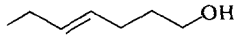
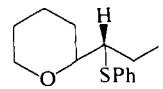
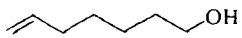
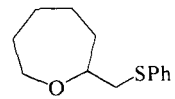
Reagent	Product[a]	Method	Reference
 (**129**)	 (**130**)	C	273
 (**131**)	 (**132**)	B	240
 (**133**)	 (**134**) (1:1)  (**135**)	A	255
 (**136**)	 (**137**)	B	240
 (**138**)	 (**139**)	A	255
 (**140**)	 (**141**)  (**142**)	C D	274 272
 (**143**)	 (**144**)	C	274

TABLE 16. (*continued*)

Reagent	Product[a]	Method	Reference
 (**145**)	 (**146**)	B	240
 (**147**)	 (**148**)	A	255
 (**94**)	 (**95**)	A	255
 (**149**)	 (**150**)	A D	255 272
 (**151**)	 (**152**)	D	272
 (**153**)	 (**154**)	D	272

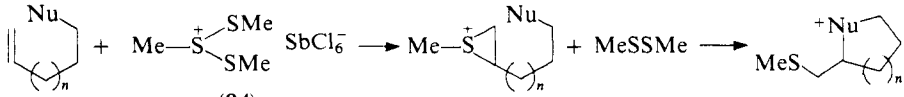
[a] Methods A and D, R = Ph; methods B and C, R = Me.
[b] Stereochemistry not indicated.
[c] For method C the ratio **141**:**142** depends on reaction conditions; method D gives **142** only.

The data in Table 16 show that in all the sulpheno-cyclizations of the alkenols that have been studied, the *exo*-cyclization[275] is favoured, with one exception: the cyclization of compound **121**. In this reaction, the *exo*-cyclization of the alcohol would have generated a four-membered ring, whose formation is likely hindered by ring strain. Generally, the more stable cyclic compound is specifically formed unless particular steric and electronic factors intervene. Therefore **133** leads to a 1:1 mixture of **134** and **135**[255]. Other data of Table 16 that are noteworthy include the lack of stereochemical control in the cyclization of **125** and **127** which produces an almost equal mixture of the cyclic ethers **126** and **128** respectively, and the reaction of **140** with the sulphonium salt **84**. Good selectivity for the formation of **141** can be achieved by strict control of the reaction conditions, while the formation of **142** alone is easily achieved using two equivalents of the sulphonium salt. This behaviour shows that the methyl(bismethylthio)sulphonium salt **84** can also be considered a potential reagent for introducing methylthio groups in activated aromatic compounds.

B. Nitrogen-containing Nucleophilic Centres in Alkenes

The reaction of the unsaturated amines **155–158** with arenesulphenyl chlorides in the presence of base gives the nitrogen-containing heterocycles **159–162** (Table 17). The general rule that the more stable heterocycle is formed is also observed in this rection.

The substituted dihydroindole **163** and the indole **164** have been prepared by reaction of the tosyl protected amines **165** and **166** with the sulphonium salt **84** (see Table 17). The reaction occurs spontaneously in dichloromethane without any catalyst.



(84) (167)

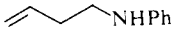
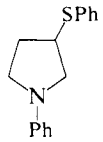
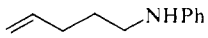
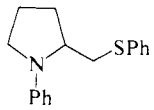
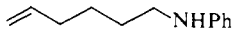
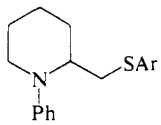
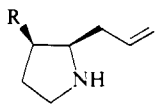
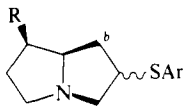
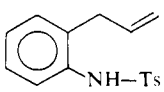
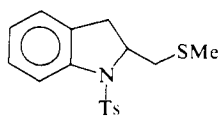
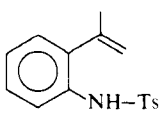
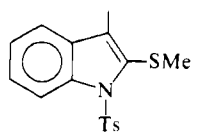
SCHEME 44

The ability of the sulphonium salt **84** to give so facile cyclization reactions is likely due to the weakness of the nucleophile associated with the sulphenylium cation in **84** (Scheme 44). As a matter of fact the internal nucleophile has to compete for attack at the three-membered ring intermediate **167** only with the weakly nucleophilic dimethyl disulphide which is released during the reaction.

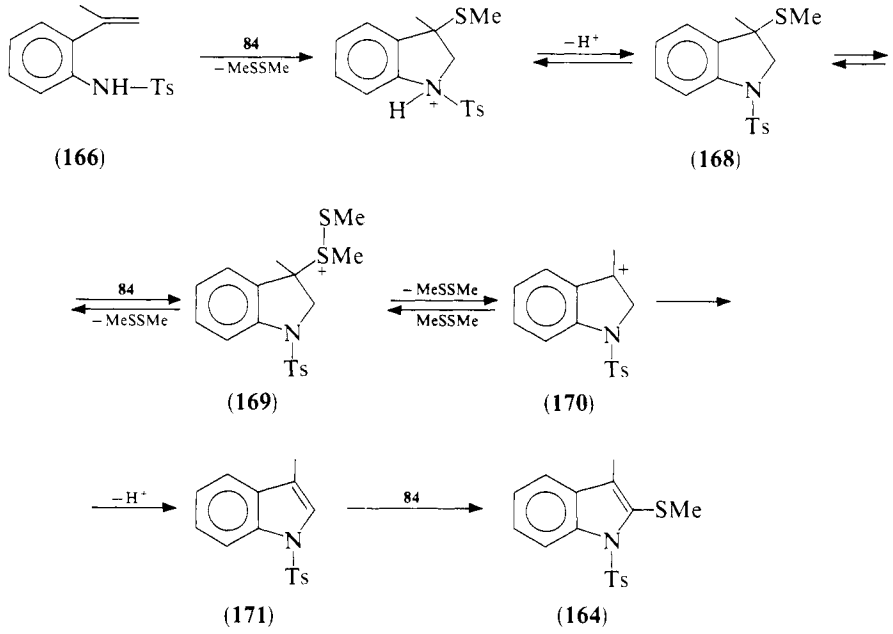
The synthesis of the indole derivative **164** is not a simple reaction fitting in the general scheme of the cyclizations promoted by sulphenic derivatives. A possible mechanism of its formation is depicted in Scheme 45.

The dihydroindole **168** is formed by methylthiolation of **166**. Compound **168** can be methylthiolated at its sulphur atom by **84**[51b] to give **169**, which may be in equilibrium with **170**. Deprotonation of **170** produces the 3-methylindole derivative **171**. This derivative reacts with sulphenylating agents to give the 2-methylthio-derivative **164**[278]. The reaction scheme requires three equivalents of **84**; however, since the medium becomes acidic with the progress of the reaction and disulphides under acidic conditions give sulphonium salts similar to **84**[51a], the reaction goes to completion with only one equivalent of **84**.

TABLE 17. Synthesis of azaheterocycles from unsaturated amines

Reagent	Product	Method[a]	Reference
 (155)	 (159)	A	276
 (156)	 (160)	A	276
 (157)	 (161)	A	276
 (158)	 (162)	A	276
 (165)	 (163)	B	277
 (166)	 (164)	B	277

[a] Method A, ArSCl; method B, sulphonium salt **84**.
[b] Mixture of diastereoisomers.

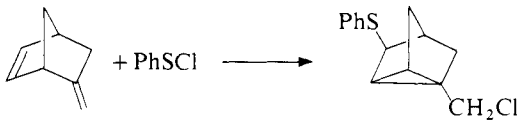


SCHEME 45

C. Carbon–Carbon Bonds as Supplementary Functionality

The reaction of sulphenyl halides with unsaturated polycyclic compounds containing at least one other double bond or a strained cyclopropyl group sometimes gives rise to molecular rearrangements with formation of new carbocyclic systems.

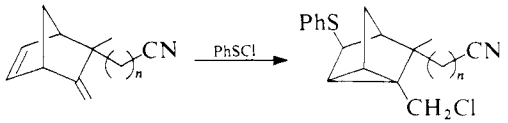
Addition of benzenesulphenyl chloride to 5-methylene-2-norbornene **172** leads to the rearranged nortricyclic phenyl sulphide **173**[279] (equation 69).



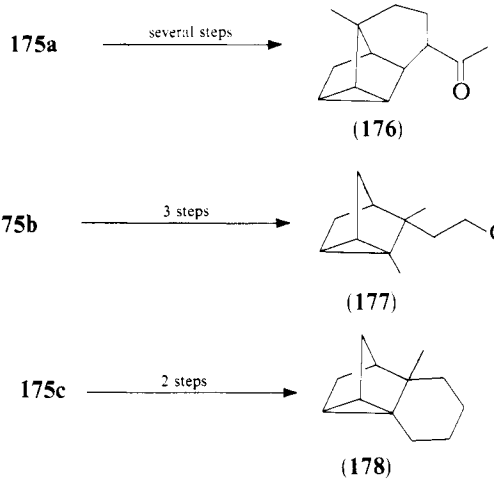
(172) (173) (69)

The same reaction with properly substituted 5-methylene-2-norbornenes **174a–c** produced the phenyl sulphides **175a–c**, which turned out to be the key intermediates for the synthesis of several interesting natural products (Scheme 46). The phenyl sulphide **175a** gave the methyl ketone **176**, which is itself a precursor of cyclosativene. The sulphides **175b** and **175c** gave the tricyclo-eka-santalol **177** and the tetracyclic hydrocarbon **178**, respectively[279, 280] (Scheme 46).

In non-ionizing solvents, norbornene reacts with sulphenyl chlorides to produce only *trans* adducts to the double bond without any rearrangement[12a, 146, 147]. In acetic acid and in the presence of dissolved lithium perchlorate, norbornene produces mainly rearranged products **179**, **180** and **181**, in which formation of new carbon–carbon bonds

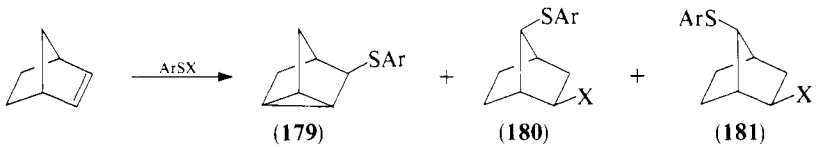


(**174a**), $n = 1$ (**175a**), $n = 1$
(**174b**), $n = 2$ (**175b**), $n = 2$
(**174c**), $n = 3$ (**175c**), $n = 3$



SCHEME 46

and the incorporation of the solvent occur[171] (Scheme 47). The mechanistic aspects of the effects of salt addition have been discussed in Section III.



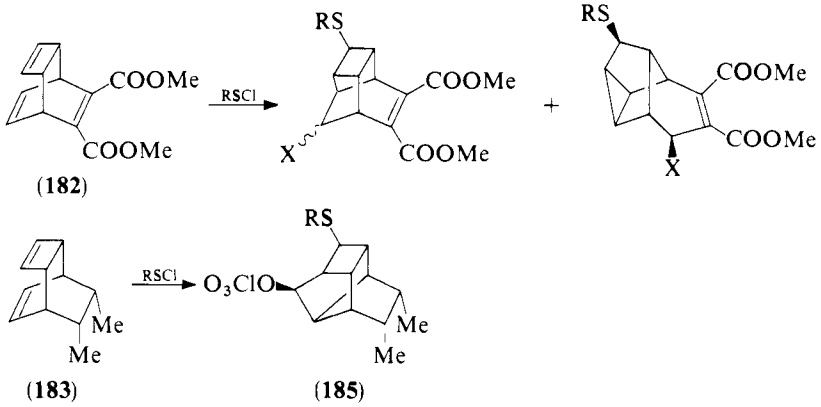
(**179**) (**180**) (**181**)

$Ar = 2,4(NO_2)_2C_6H_3$; X = Cl or CH_3COO

SCHEME 47

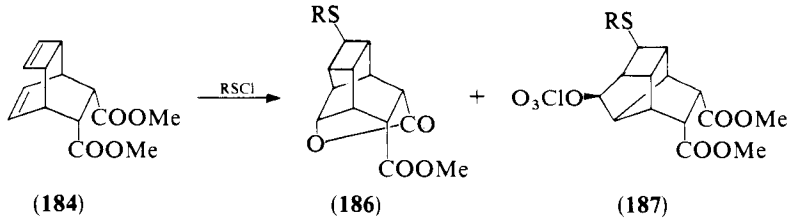
A similar behaviour is also observed in the benzonorbornadiene derivatives. In this case, the main factor which influences the pathway leading to the rearranged products is not the presence of the added salts but the electronic requirements for the stability of the intermediates. In fact, high yields of the rearranged products can be achieved in the absence of the added salts when electron-deficient arenesulphenyl chlorides are reacted with electron-rich benzonorbornadiene derivatives. Conversely, when the benzonorbornadiene has reverse electronic properties, only the addition products are obtained[281].

The behaviour of the tricyclic olefins **182–184** in the reaction with sulphenyl chlorides in the presence of lithium perchlorate[172–174, 176] is also noteworthy (Schemes 47, 48 and 49).



R = 2-$NO_2C_6H_4$ or 2,4-$(NO_2)_2C_6H_3$; X = MeCOO, O_3ClO

SCHEME 48



R = 2-$NO_2C_6H_4$ or 2,4-$(NO_2)_2C_6H_3$

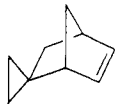
SCHEME 49

Compound **182** is converted into a mixture of two polycyclic sulphides. The ratio of the two depends on the sulphenyl chloride [2-$NO_2C_6H_4SCl$ or 2,4-$(NO_2)_2C_6H_3SCl$], the solvent (EtOEt, AcOEt or CH_2Cl_2) and the concentration of the added salt.

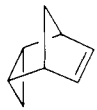
On the other hand, the hydrocarbon **183** reacts with sulphenyl chlorides in diethyl ether, to give only the covalent perchlorate **185** in very high yields. The corresponding acetate, together with other two unidentified products, is obtained in acetic acid as solvent.

The reaction of sulphenyl chlorides with **184**, which may lead to lactonization due to steric factors, produces primarily the sulphide **186**. The perchlorate **187** is also formed, in lower quantities.

The behaviour of the cyclopropyl-substituted norbornadienes **188** and **189** in the reaction with *p*-toluenesulphenyl chloride[282] is of particular interest.

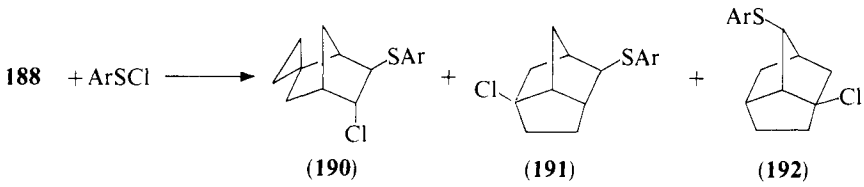


(188)



(189)

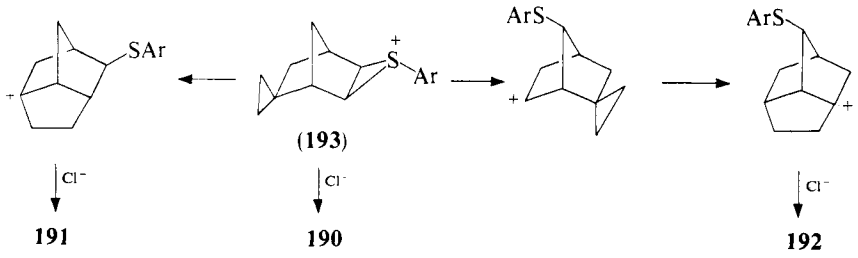
The reaction of **188** produces a mixture of three products: **190**, **191** and **192** in a 2:5:3 ratio, respectively (Scheme 50).



(190) (191) (192)

SCHEME 50

Compound **190**, the product lowest in yield, is the 'normal' adduct of the sulphenyl chloride to the double bond. The other products, **191** and **192**, are generated by rearrangement and ring expansion transformations of the intermediate thiiranium ion **193** (Scheme 51).



(193)

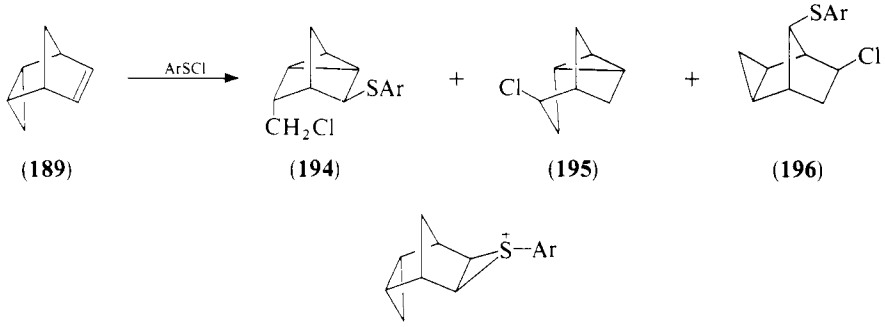
191 190 192

SCHEME 51

When the *endo*-fused cyclopropylnorbornene **189** is reacted with *p*-toluenesulphenyl chloride, a mixture of **194**, **195** and **196** is obtained. Also in this case, these compounds are products formed by skeletal rearrangement of the thiiranium ion intermediate **197** (Scheme 52).

A different way of using carbon–carbon multiple bonds for cyclization reactions promoted by the sulphenyl halide functionality is to generate *in situ* an unsaturated sulphenyl halide. Two strategies have been developed: the addition of sulphur dichloride to dienes (Scheme 53) and the reaction of chlorine or bromine with unsaturated disulphides (Scheme 54).

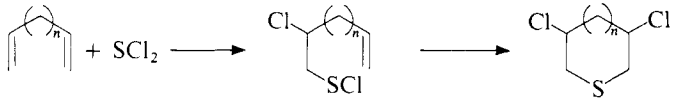
Open-chain and cyclic dienes were used for the synthesis of a variety of cyclic systems[283–286]. Some representative examples of this reaction are listed in Table 18. Dichloro-substituted cyclic sulphides are obtained by this reaction. The presence of the chlorine atoms allows further transformation of the cyclic sulphides synthesized. For example, the 1,4-oxathiin **198** has been obtained by the dehydrochlorination of **199**[283] (Scheme 55).



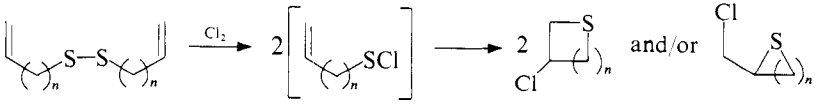
(189) (194) (195) (196)

(197)

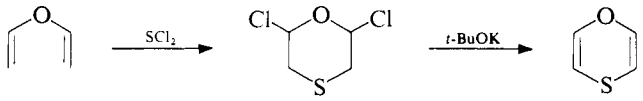
SCHEME 52



SCHEME 53



SCHEME 54



(199) (198)

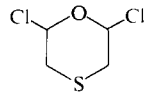
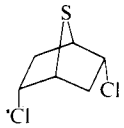
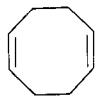
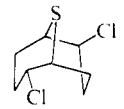
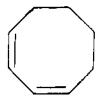
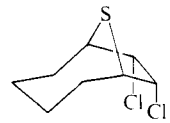
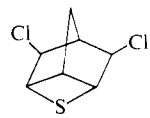
SCHEME 55

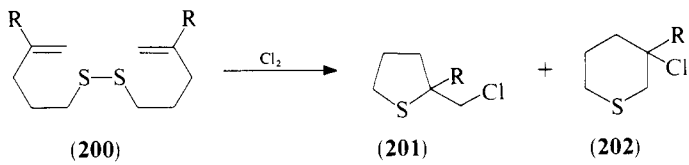
The halogenolysis of unsaturated disulphides for the generation of unsaturated sulphenyl halide intermediates in some instances produces mixtures of the two cyclic sulphides as shown in Scheme 54[287-293]. For example, the reaction of the disulphide **200** with chlorine produces mixtures of thiolane **201** and thiane **202**[288] (Scheme 56). However, it was found that they interconvert. The thiolane **201** is the main primary reaction product, while thermal equilibration indicates that the thiane **202** is the more stable isomer.

The same behaviour is shown by the disulphide **203** that produces mainly a 7:3 mixture of **204** and **205** which, when allowed to stand, is transformed into pure **204**[289] (Scheme 57).

It is noteworthy that the reaction of **206** with chlorine gives only **207**[289] (Scheme 58). No evidence for the presence of isomeric **208** has been discovered. A very rapid

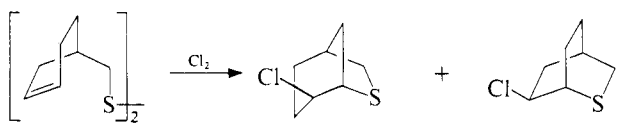
TABLE 18. Synthesis of cyclic sulphides from SCl_2 and dienes

Reagent	Product	Reference
		283
		284
		285
		285
		286



(200) (201) (202)

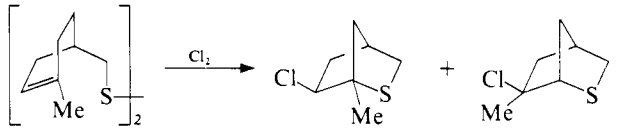
SCHEME 56



(203) (204) (205)

SCHEME 57

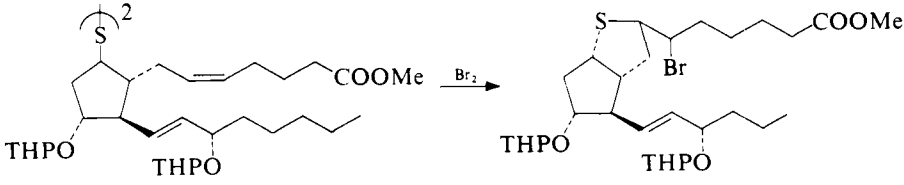
isomerization of **208** to **207** is likely to occur during the reaction. This would make the detection of the cyclic sulphide **208** impossible.



(**206**) (**207**) 100% (**208**) 0%

SCHEME 58

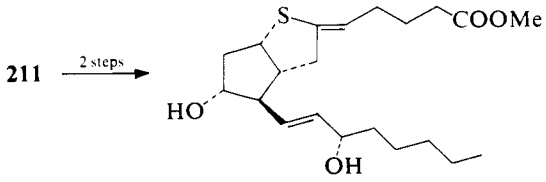
The above-described strategy has been applied to the synthesis of 9-(O)-thiaprostacyclin (**209**)[290, 291]. The key step is the cyclization of **210** to **211** (Scheme 59).



(**210**) (**211**)

SCHEME 59

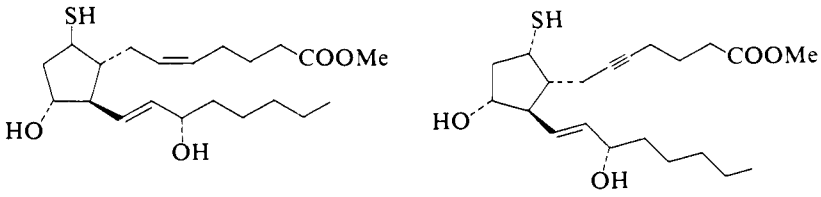
This reaction has been accomplished at 0°C by addition of bromine to **210**; when the sulphenyl bromide forms, it adds to the nearest double bond. The thiaprostacyclin **209** is obtained in two steps: first, dehydrohalogenation; then deprotection of the hydroxy groups (Scheme 60).



(**209**)

SCHEME 60

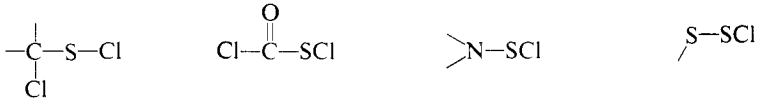
The thiaprostacyclin **209** has also been synthesized from the thiols **212**[292] or **213**[293]. Both these reactions use halogens to promote the formation of the intermediate sulphenyl halide, which gives intramolecular cyclization.



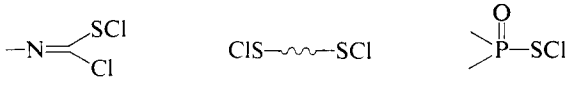
(**212**) (**213**)

V. FUNCTIONALIZED SULPHENYL HALIDES

Several classes of compounds may be included in the functionalized sulphenyl chloride category. α-Chloro- **214**, α-carbonyl- **215**, α-amino- **216**, α-thio- **217**, iminochloromethane- **218**, bis-sulphenyl- **219**, oxo- and thiophosphoranesulphenyl **220** chlorides are some of the sulphenyl chlorides which have been prepared and whose reactivities have been studied to different extents. Review articles covering the general reactivity of most of them have appeared in the past[6,8].



(214) **(215)** **(216)** **(217)**



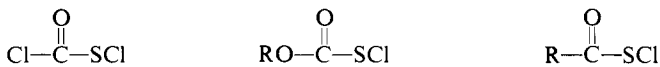
(218) **(219)** **(220)**

The reactivity of these sulphenyl halides does not differ from the reactivity of simple alkane- or arenesulphenyl halides. However, the nature of the functionality introduces a new reactive centre that may exert a strong influence on the structure of the final products.

In this section we shall focus attention mainly on this aspect of the reactivity of functionalized sulphenyl halides, however our discussion has to be necessarily limited to some of these classes. α-Carbonylsulphenyl and α-aminosulphenyl chlorides, which markedly show the above-mentioned property, will be discussed in detail.

A. α-Carbonylsulphenyl Halides

The most extensively studied α-carbonylsulphenyl halides are the chlorocarbonylsulphenyl chloride **221**, alkoxycarbonyl sulphenyl halides **222** and alkyl- or arylcarbonylsulphenyl halides **223**. The sulphenyl chloride **221** is by far the one that has given rise to the most wide synthetic applications because of its true bifunctional character.



(221) **(222)** **(223)**

1. Reactivity of chlorocarbonylsulphenyl chloride with monofunctionalized nucleophiles

Chlorocarbonylsulphenyl chloride **221** reacts with simple alkanethiols[294,295] to give chlorocarbonyldisulphides **224** (equation 70). The reaction stops at this stage even if excess of the thiol is used. On the contrary, thiophenol reacts with **221** to give diphenyl disulphide and COS that likely arises from decomposition of the thioester **225** (equation 71).

(221) **(224)** (70)

$$\mathbf{221} + 2\ PhSH \xrightarrow{-HCl} \left[PhS{-}\overset{\overset{O}{\|}}{C}{-}S{-}SPh\right] \xrightarrow{-COS} PhSSPh \qquad (71)$$

(**225**)

The phenylthio substitution at the carbonyl carbon seems to play a very important role in determining the stability of compounds of type **225**. This is shown by the fact that the diethyl derivative **225a**, prepared from **224a** and sodium ethanethiolate (equation 72), is a quite stable compound, while the phenyl ethyl derivative, prepared from **224a** following a similar route, readily decomposes to give phenyl ethyl disulphide and COS (equation 73).

$$\underset{\textbf{(224a)}}{Cl{-}\overset{\overset{O}{\|}}{C}{-}SSEt} + EtSNa \longrightarrow \underset{\textbf{(225a)}}{EtS{-}\overset{\overset{O}{\|}}{C}{-}SSEt} \qquad (72)$$

$$Cl{-}\overset{\overset{O}{\|}}{C}{-}SSEt + PhSH \xrightarrow{-HCl} \left[PhS{-}\overset{\overset{O}{\|}}{C}{-}S{-}SEt\right] \xrightarrow{-COS} PhSSEt \qquad (73)$$

Compounds of type **224** have been used in peptide synthesis as amino protecting groups of proline[296].

The reaction of chlorocarbonylsulphenyl chloride **221** with alcohols[297] and aliphatic amines[294] follows a different course. In both cases products of attack of the nucleophile at the carbonyl carbon are obtained (equations 74 and 75). However, while the alkoxy derivatives **226** are stable and can be isolated from the reaction medium, the amino analogues **227** lose elemental sulphur to give the carbamoyl chloride **228**. The sulphenyl chloride intermediate **227a** has been trapped by addition to cyclohexene (equation 76).

$$\mathbf{221} + ROH \xrightarrow{-HCl} \underset{\textbf{(226)}}{RO{-}\overset{\overset{O}{\|}}{C}{-}SCl} \qquad (74)$$

$$\mathbf{221} + 2R_2NH \xrightarrow[0°C]{-R_2NH_2Cl} \underset{\textbf{(227)}}{\left[R_2N{-}\overset{\overset{O}{\|}}{C}{-}SCl\right]} \xrightarrow{-S} \underset{\textbf{(228)}}{R_2N{-}\overset{\overset{O}{\|}}{C}{-}Cl} \qquad (75)$$

$$\underset{\textbf{(227a)}}{R_2N{-}\overset{\overset{O}{\|}}{C}{-}SCl} + \bigcirc\!\!= \longrightarrow \begin{array}{l}Cl\\ \bigcirc\\ SCONR_2\end{array} \qquad (76)$$

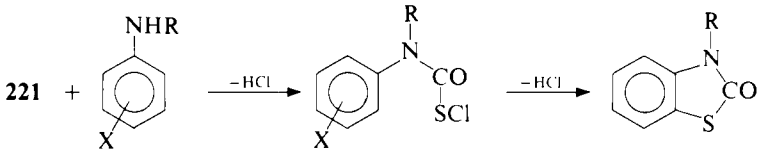
(227a); R = Me

It has been also reported that 'primary and secondary amines react smoothly with chlorocarbonylsulphenyl chloride in a molar ratio of 2:1 to give the stable carbamoylsulphenamides'[294] **229** (equation 77), but unfortunately experimental details are not given.

$$\mathbf{221} + 2RR^1NH \xrightarrow{-HCl} RR^1N{-}\overset{\overset{O}{\|}}{C}{-}SNRR^1 \quad (77)$$

(229)

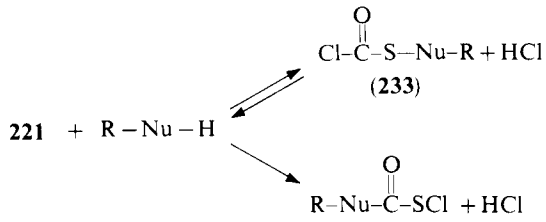
The sulphenyl chloride **221** reacts with *N*-alkylanilines **230** to give *N*-alkylbenzothiazolone derivatives **231**[294,298] through the intermediate sulphenyl chlorides **232** (equation 78).



(230) (232) (231) (78)

The reaction occurs spontaneously in the case of *N*-methylaniline, but if an electron-withdrawing group like a cyano group or a halogen is present in the aromatic residue, the intermediate **232** can be isolated. Completion of the reaction to the benzothiazolone stage is achieved by Lewis acid or concentrated sulphuric acid catalysis[298].

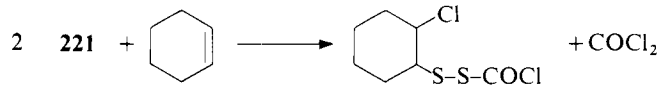
The different behaviour of chlorocarbonylsulphenyl chloride **221** towards alcohols and amines on the one hand and thiols on the other, although not explained in the original reports, can be justified on the basis of the behaviour of sulphenamides, sulphenate esters and disulphides in moderately acidic media like those generated during the reactions of **221** with amines, alcohols and thiols. It is possible that in all three reactions the hetero nucleophile attacks the sulphenic sulphur of **221** to give species of type **233** (Scheme 61) which, in the presence of hydrogen chloride, are in equilibrium with the reagents in the case of amines (Nu = NH) and alcohols (Nu = O) but not in the case of thiols (Nu = S). Under these circumstances the attack of the nucleophile at the carbonyl carbon becomes competititve and gives the observed products.



Nu = O, S, NH or NR

SCHEME 61

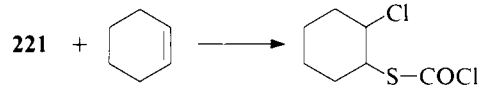
Like all the other sulphenyl chlorides, the chlorocarbonylsulphenyl chloride **221** also reacts with alkenes to give addition products. However, when excess of **221** is used, the disulphide **234** and phosgene are formed[294] (equation 79). No explanation for the formation of **234** is given.



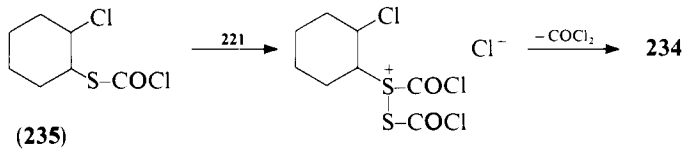
(79)

(234)

However, it may be suggested, as shown in Scheme 62, that a second molecule of **221** attacks the sulphur atom of the primarily formed chlorosulpide **235** to give the sulphonium chloride **236**. Reaction of chloride ion with the carbonyl carbon on the positive sulphur gives the disulphide **234**.



(235)

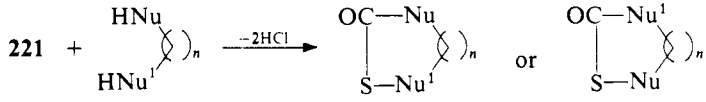


(235) (236)

SCHEME 62

2. Reactivity of chlorocarbonylsulphenyl chloride with bifunctional nucleophiles

The reaction of chlorocarbonylsulphenyl chloride with bifunctional nucleophiles has interesting applications in the synthesis of heterocyclic compounds. This involves the chelation of a –S–C (O)– unit to the two nucleophilic centres of the reagents (Scheme 63). The nucleophilic functionalities of **237** may be equal or different and therefore, in the latter case, isomeric heterocycles **238** and **239** may be formed.



(237) (238) (239)

SCHEME 63

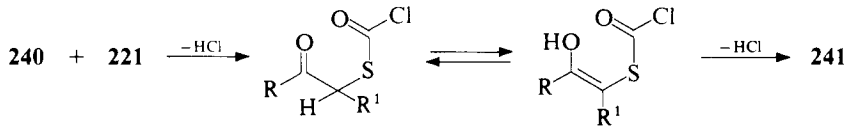
Several species of type **237** bearing carbon, oxygen, sulphur and nitrogen nucleophiles have been reacted with **221**.

a. Carbon and oxygen nucleophiles. Some examples of reactions of enolizable ketones or β-ketoesters **240** with **221** have been reported[294,299] (equation 80). The reaction gives 1,3-oxathiolene derivatives **241**.

(240) (241)

R^1 = Alk or COOEt (80)

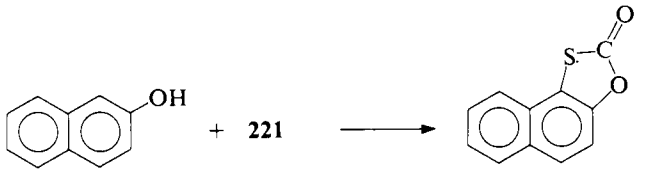
The formation of the 1,3-oxathiolene ring system likely occurs via thiolation of the carbonyl group to give **242a** and **242b**, followed by ring closure to **241** (Scheme 64).



(242a) (242b)

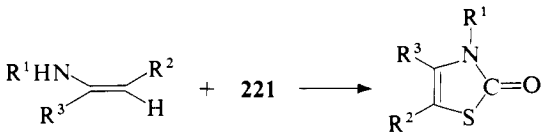
SCHEME 64

β-Naphthol behaves similarly and gives the benzofused derivative **243** (equation 81)[294].



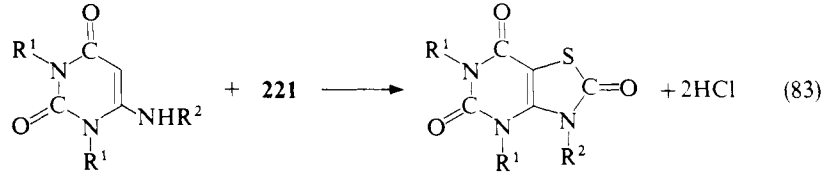
(243) (81)

b. Carbon and nitrogen nucleophiles. The reaction of variously substituted enamines **244** with chlorocarbonylsulphenyl chloride **221** gives the thiazolones **245** (equation 82)[300-302].



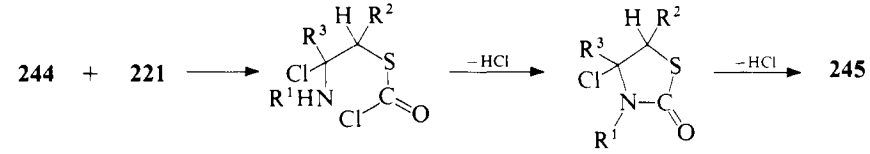
(244) (245) (82)

The reaction is quite general irrespective of the nature of the substituents present in the enamine **244**. In fact R^1, the substituent at nitrogen, can be a hydrogen atom as well as an alkyl or an aryl residue or even a secondary amino group[301]; R^3 can be alkyl or aryl; electron-withdrawing groups like carboalkoxy, *p*-nitrophenyl or cyano groups may constitute the R^2 substituent. Finally, cyclic enamines like the 6-aminouracil derivatives **246** also react with **221** to give thiazolopyrimidines **247**, which are sulphur analogues of the purine system (equation 83)[302].



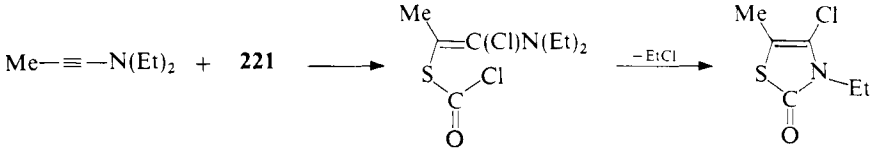
(246) (247) (83)

The first step of the cyclization of **244** to **245** is probably the Markovnikov oriented addition of the sulphenyl sulphur of **221** to the double bond of the enamine followed by ring closure and dehydrochlorination. The regiochemistry of the addition is determined by the nature of the substituents at the ethylenic carbons (Scheme 65).



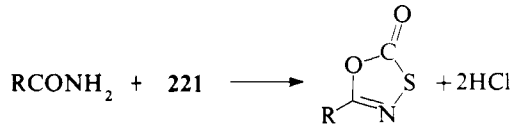
SCHEME 65

The behaviour of the ynamine **248** in the reaction with **221** is very similar to that of the enamines **244** and supports the above hypothesis[303]. In this reaction in fact, it is possible to isolate **249**, the addition product of **221** to **248**; however, it is thermally unstable and gives the thiazolinone derivative **250** (equation 84).



(248) (249) (250) (84)

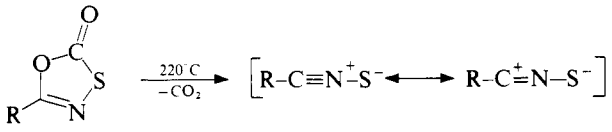
c. Nitrogen–oxygen and nitrogen–sulphur nucleophiles. Primary amides react with chlorocarbonylsulphenyl chloride **221** to give oxathiazole derivatives **251**[294,304,305] (equation 85).



(251) (85)

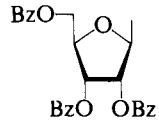
The nature of the R residue of the amide does not appear to affect the reaction and even a benzoyl protected β-D-ribosyl derivative **251a** has been synthesized; the oxathiazole **251a** may give, by thermal elimination of carbon dioxide, the corresponding nitrile

sulphide which has been trapped by suitable dipolarophiles like ethyl propiolate or ethyl cyanoformate[304] (Scheme 66).



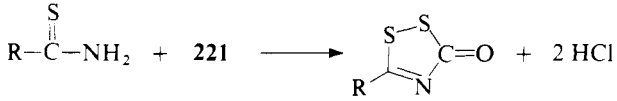
(**251a**)

251a; R =



SCHEME 66

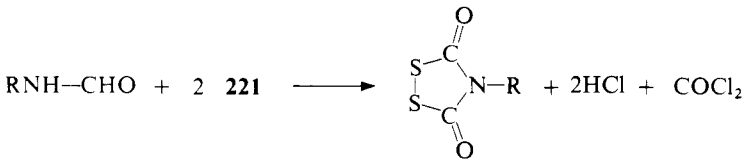
The reaction of **221** with thioamides occurs with regiochemistry opposite to that of the reaction with amides. New nitrogen–carbon and sulphur–sulphur bonds are formed giving dithiazole derivatives **252**[294, 306] (equation 86).



(86)

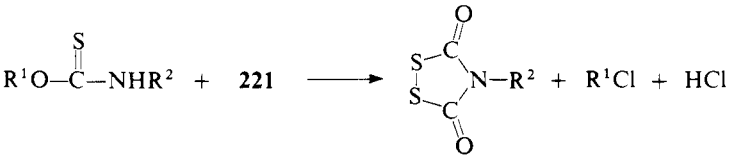
(**252**)

Monosubstituted formamides react with two moles of chlorocarbonylsulphenyl chloride to give dithiazolidine derivatives **253**[294, 307] (equation 87). Dithiazolidines **253** have also been prepared by reaction of thiocarbamates **254** with the same sulphenyl chloride (equation 88)[294, 308, 309].



(87)

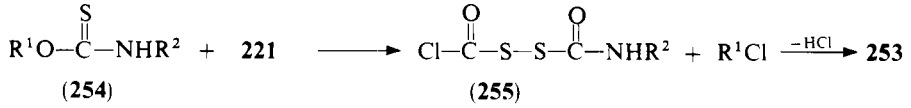
(**253**)



(88)

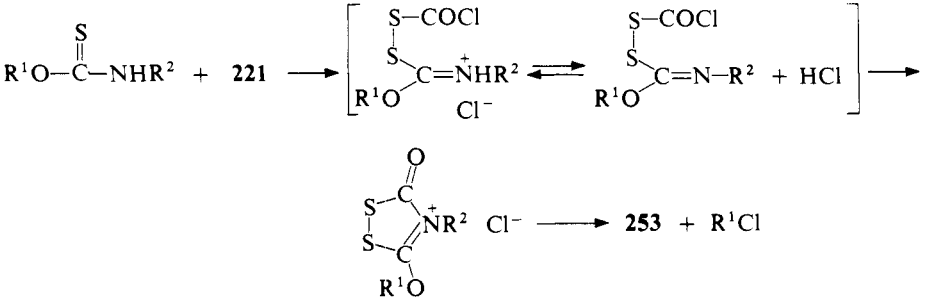
(**254**) (**253**)

The formation of **253** from thiocarbamates **254** and **221** was suggested to involve ring closure of the intermediate **255**[294] (Scheme 67). However, this hypothesis must be discharged because **255** prepared by a different route does not give ring closure to the dithiazolidine **253**.



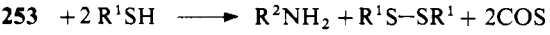
SCHEME 67

The alternative mechanism is shown in Scheme 68 and differs from the previous one in the sequence of the alkyl chloride and hydrochloric acid eliminations[310].



SCHEME 68

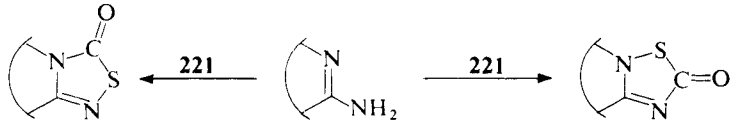
Dithiazolidines **253** behave as masked primary amino functionalities. They undergo easy reductive cleavage of the disulphide bond even with thiols[310] (Scheme 69). The dithiazolidine ring of **253** is stable in strongly acidic and mild basic conditions and these properties make **253** a good amino protecting group in peptide synthesis[310,311].



SCHEME 69

d. Two nitrogen nucleophiles. Ortho-amino nitrogen containing heterocycles of general formula **256** like 2-aminopyridines **257**, 3-aminopyridazines **258**, 2-aminopyrimidazines **259**, 2-aminothiazoles **260**, 2-aminothiazoline **261**, 2-amino-1,3,4-thiadiazoles **262**, and 5,6-dihydro-2-amino-4*H*-1,3-thiazine **263** react with chlorocarbonylsulphenyl chloride **221** to give bicyclic thiadiazole derivatives **264** or **265** depending on the nature of the substrate and on the reaction conditions[312,313] (Scheme 70).

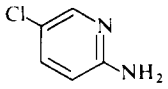
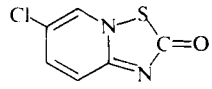
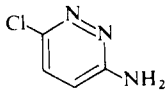
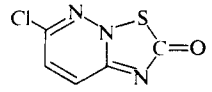
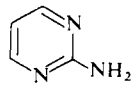
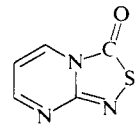
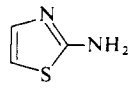
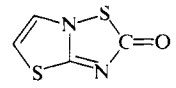
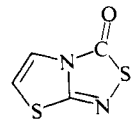
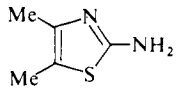
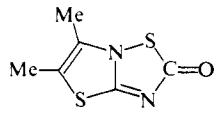
In particular 2-amino-5-chloropyridine (**266a**), 3-amino-6-chloropyridazine (**258**), 2-aminothiazole (**260a**) and its 4,5-dimethyl derivative **260b**, 1,2,4-thiadiazoles **262a–d** and the thiazine **263** gave heterocycles of type **265** when reacted with **221** in tetrahydrofuran in the presence of triethylamine[312] (Table 19). On the contrary 2-aminopyrimidine (**259a**), 2-aminothiazole (**260a**) and 2-aminothiazoline (**261**) gave compounds of type **264** when reacted with **221** in ethanol-free chloroform in the presence of the same amine[313] (Table 19).



(264) (256) (265)

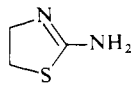
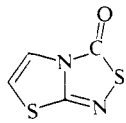
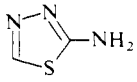
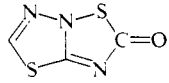
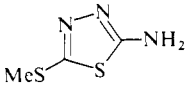
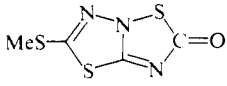
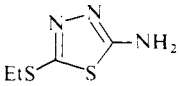
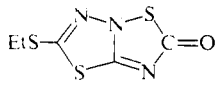
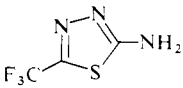
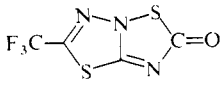
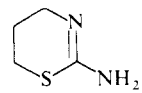
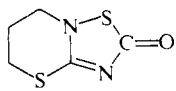
SCHEME 70

TABLE 19. Reactions of 2-amino-azaheterocycles with **221**

Substrate	Product	Yield (%)	Solvent[a]	Ref.
 **(266a)**		48	A	312
 **(258a)**		37	A	312
 **(259a)**		34	B	313
 **(260a)**		3.3	A	312
260a		41	B	313
 **(260b)**		2	A	312

(continued)

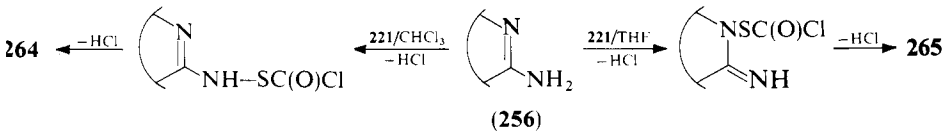
TABLE 19. (*continued*)

Substrate	Product	Yield (%)	Solvent[a]	Ref.
 **(261)**		not given	B	313
 **(262a)**		0	A	312
 **(262b)**		10	A	312
 **(262c)**		36.4	A	312
 **(262d)**		53	A	312
 **(263)**		20	A	312

[a] A. $CHCl_3$; B. THF.

The inversion of the order of the relative basicity of the endocyclic and exocyclic nitrogen atoms as a function of the solvent is not uncommon in heterocyclic chemistry. In the present case, as shown in Scheme 71, it allows one, by simple change of the solvent, to obtain compounds of type either **264** or **265** from the same precursor **256** and the same reagent.

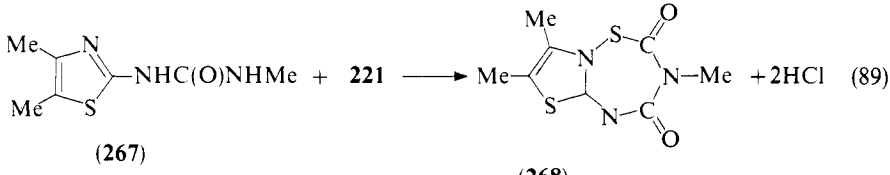
Substitution of one hydrogen atom of the amino group of heterocycles of type **256** with a *N*-methylcarbamic residue opens new reaction pathways. For instance, when the



(256)

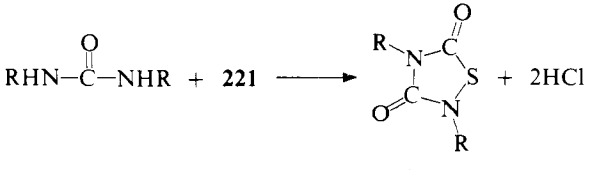
SCHEME 71

thiazole derivative **267** reacts with **221** only the thiatriazepine derivative **268** is obtained[314] (equation 89). However, similar derivatives of other heterocycles of type **256** behave differently and give mixtures of different ring closure products depending on the heterocycle, the reaction conditions and the relative nucleophilicity of the nitrogen atoms[314].

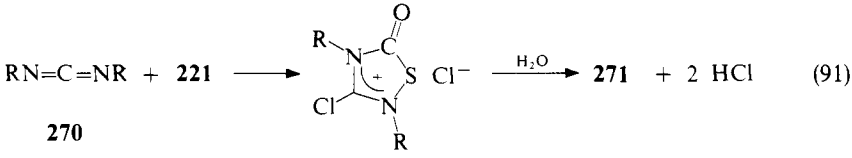


(267) (268)

N,*N*′-Disubstituted urea derivatives **269** and disubstituted carbodiimides **270** react with **221** using the two nitrogen atoms as nucleophiles to give thiadiazolidine derivatives **271**[294,315,316] (equations 90 and 91). The intermediate **272** which is formed in the reaction of the carbodiimides **270** gives the thiadiazole derivative **271** upon hydrolysis.



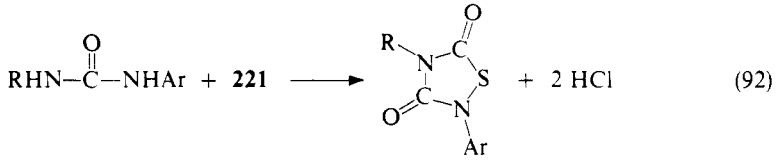
(269) (271)



270 272

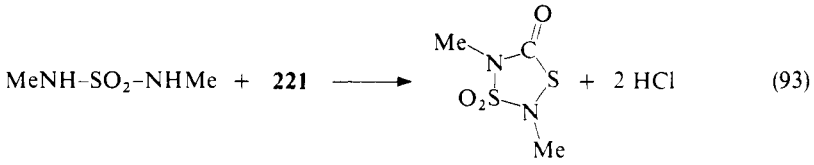
A remarkable regiospecificity has been observed for *N*-alkyl-*N*-arylurea derivatives **273** which gave the thiadiazoles **274** only[294] (equation 92).

Finally, worth of mention is the synthesis of the unusual ring system **275** obtained by reaction of chlorocarbonylsulphenyl chloride (**221**) with the sulphamide **276**[317] (equation 93) and the reaction of **221** with the cyanamide **277** that gives the thiadiazole **278**[318] (equation 94).



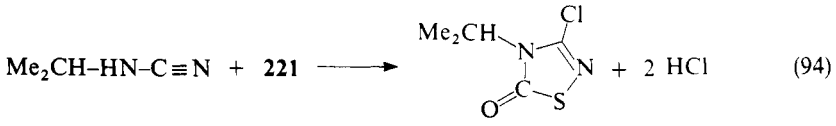
(92)

(273) (274)



(93)

(276) (275)

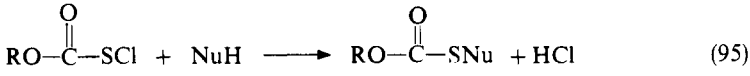


(94)

(277) (278)

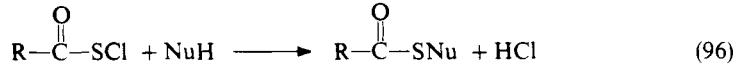
3. *Reactivity of alkoxycarbonylsulphenyl chlorides and acylsulphenyl halides*

The presence of an alkoxycarbonyl or an acyl functionality directly linked at sulphur like in sulphenyl halides **222** and **223** does not influence the general electrophilic reactivity of the sulphenyl sulphur. They react with nucleophiles like amides, thiols or dithiobenzoic acid to give substitution products[294,319–324] (equations 95 and 96) or add to the carbon–carbon double bond[325] (equation 97). Compound **279** is probably formed by a mechanism similar to that shown in Scheme 62; however, it has been shown that isopropoxycarbonylsulphenyl bromide adds to cyclohexene to give the 'normal' addition product[323].



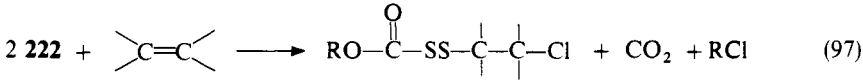
(95)

(222)



(96)

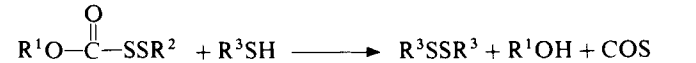
(223)



(97)

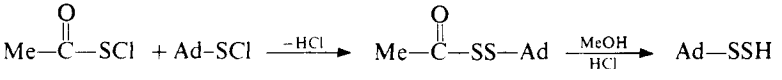
(279)

The interest for these reactions arises from the further reactivity of the product obtained, which may undergo several interesting transformations. This is the case of the synthesis of unsymmetrical disulphides which can be obtained from the reaction of **280** with thiols[324] (equation 98) or that of 1-adamantyl hydrodisulphide (**281**) which is obtained in satisfactory yield by the reaction sequence outlined in Scheme 72[319].



$$R^1O{-}\overset{\overset{O}{\|}}{C}{-}SSR^2 + R^3SH \longrightarrow R^3SSR^3 + R^1OH + COS \qquad (98)$$

(**280**)

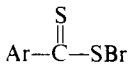


$$Me{-}\overset{\overset{O}{\|}}{C}{-}SCl + Ad{-}SCl \xrightarrow{-HCl} Me{-}\overset{\overset{O}{\|}}{C}{-}SS{-}Ad \xrightarrow[HCl]{MeOH} Ad{-}SSH$$

Ad = 1-Adamantyl (**281**)

SCHEME 72

Recently, arylthiocarbonylsulphenyl bromides **282** have been also synthesized and their reactivity found similar to that of the corresponding arylcarbonyl derivatives[326].

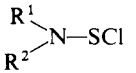


(**282**)

Ar = Ph, 4-Tol, 4-An, 4-ClC_6H_4

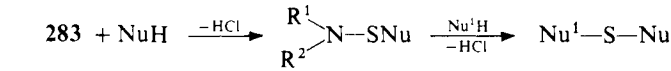
B. α-Aminosulphenyl Halides

The chemistry of aminosulphenyl chlorides **283**, because of the presence of two reactive centres, i.e. the sulphur–chlorine bond and the sulphur–nitrogen bond, has attracted the attention of many chemists.



(**283**)

Under some circumstances the sulphur atom of aminosulphenyl chlorides can be regarded as an S^{+2} synthetic equivalent, since the sulphenyl chloride functionality may react with nucleophiles to give sulphenamide derivatives, which in turn can react, under different reaction conditions, with other nucleophiles (Scheme 73).



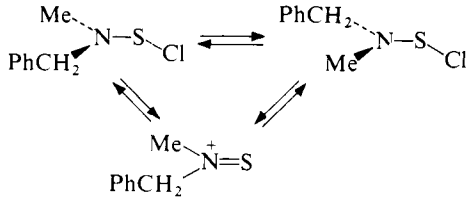
$$\mathbf{283} + NuH \xrightarrow{-HCl} \begin{matrix} R^1 \\ \diagdown \\ N{-}SNu \\ \diagup \\ R^2 \end{matrix} \xrightarrow[-HCl]{Nu^1H} Nu^1{-}S{-}Nu$$

SCHEME 73

Suitably substituted aminosulphenyl chlorides, like the sulphenamides (see Section VI), show a dynamic NMR behaviour mainly due to hindered rotation around the

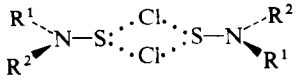
sulphur–nitrogen bond. This phenomenon has been detected for di-isopropyl-[327], diethyl-[327] and benzyl (methyl)aminosulphenyl chloride[328].

The general feature that electronegative substituents at sulphur increase the energy barrier for rotation around the sulphur–nitrogen bond was also confirmed for this class of compounds; however, it was also found that the process showed solvent[327,328] and salt effects[328]. A significant decrease of the free activation energy was found on changing the solvent from toluene to chloroform or dichloromethane. Addition of tetramethylammonium chloride or perchlorate also decreased the activation energy of the process, albeit to a lesser extent. These data were taken as evidence for the presence of a racemization process involving heterolysis of the sulphur–chlorine bond[327] in addition to the torsion around the sulphur–nitrogen bond[328] (Scheme 74).

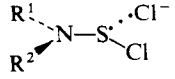


SCHEME 74

Bimolecular halogen exchange mechanisms with transition states similar to **284** or **285**, in the case of addition of external chloride ions, have been also proposed[327,328].



(284)



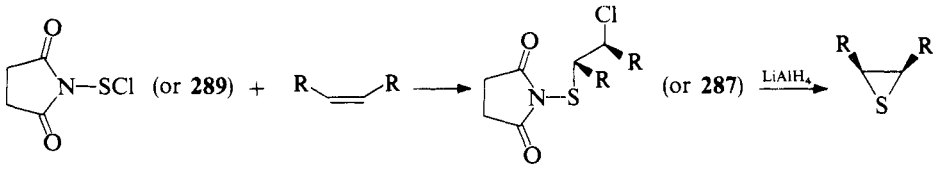
(285)

However, while the latter process cannot be ruled out since the effect of tetramethylammonium chloride was found greater than that of the tetramethylammonium perchlorate[238], the former seems not to be operative considering the insensitivity of the process to concentration changes.

1. Reaction with alkenes and alkynes

Basically, the reactivity of α-aminosulphenyl chlorides towards alkenes and alkynes does not differ from that of simple alkane- or arenesulphenyl chlorides as far as regio- and stereochemistry is concerned[329]. The synthetic potential of adducts of α-aminosulphenyl chlorides to alkenes has been utilized for a new synthesis of thiiranes[330]. It has been shown that **286** or **287**, the addition products of succinimidosulphenyl chloride (**288**) or phthalimidosulphenyl chloride (**289**) to linear or cyclic alkenes, gave thiirane derivatives by low-temperature reactions with $LiAlH_4$[330] (Scheme 75). The stereochemistry of the alkene is preserved in the thiirane since both the addition and the ring closure steps occur in the *anti*-mode.

Some features of this synthesis are its stereospecificity, i.e. that the stereochemistry of the alkene is retained in the thiirane, and its selectivity, since only 1,2-disubstituted alkenes undergo this transformation.



(288) (286)

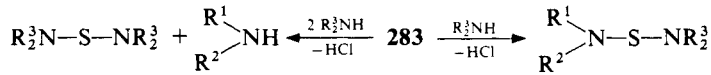
SCHEME 75

Dimethylaminosulphenyl chloride (**290**) also adds to alkynes[329] following the general rules of the addition of simple sulphenyl chlorides to carbon–carbon multiple bonds. Characteristic features of the addition products of **290** to alkenes, probably due to the presence of the dimethylamino group linked to sulphur, have been reported[329]. Reduced tendency of the adducts for isomerization processes is observed as well as thermal reversibility of the addition process during attempts to distil the adduct of **290** with 3,3-dimethylbutene (equation 99).

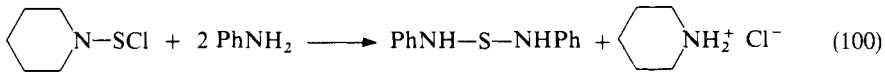
$$\underset{\textbf{(290)}}{Me_2NSCl} + H_2C{=}CHCMe_3 \xrightarrow{0\,^\circ C} Cl{-}CH_2{-}\underset{\displaystyle SNMe_2}{\underset{|}{C}}HCMe_3 \xrightarrow[55\ mm/Hg]{80\,^\circ C} \textbf{290} + H_2C{=}CHCMe \qquad (99)$$

2. Reaction with amines

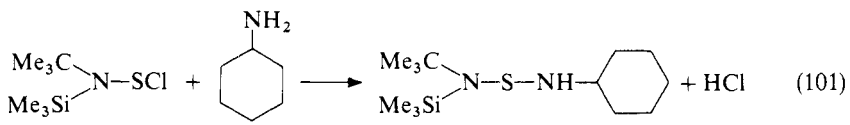
The reaction of α-aminosulphenyl chlorides (**283**) with amines may lead to mono- or di-substitution at sulphur (Scheme 76) depending on several factors like basicity and nucleophilicity of the amine, steric hindrance and reaction conditions. For example, aniline reacts with piperidine-1-sulphenyl chloride (**291**) to give the sulphides **292**[331] (equation 100), but the sterically hindered aminosulphenyl chloride **293** reacts with cyclohexylamine to give the sulphenamide **294** in which the sulphur–nitrogen bond of the sulphenyl chloride remains untouched[332] (equation 101).



SCHEME 76

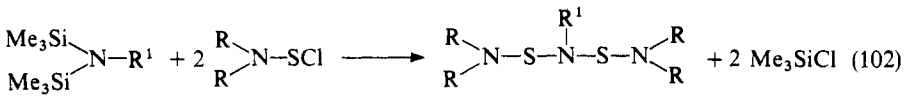


(291) (292)



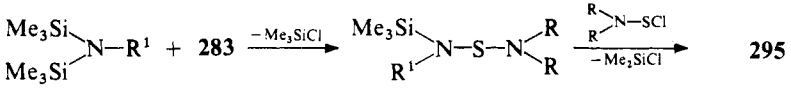
(293) (294)

Reactions similar to that reported in equation 100 occur when trimethylsilyl protected anilines or primary aliphatic amines with two equivalents of aminosulphenyl chlorides **283**[333,334]. In this case symmetric sulphenamido derivatives **295** are obtained (equation 102).



(283) (295) (102)

The sulphenamides **295** are probably formed by attack of the sulphur atom of the aminosulphenyl chloride at the nitrogen–silicon bond of the intermediate **296** (Scheme 77).



(296)

SCHEME 77

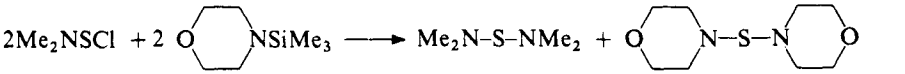
Compounds of type **296** have been prepared by reaction of piperidinesulphenyl chloride (**291**) with the sodium salt of bis (trimethylsilyl)amine or the lithium salt of *N*-(trimethylsilyl)*t*-butylamine[332] (equation 103).

(103)

$R = Me_3Si, Me_3C$

$M = Li, Na$

The synthetic value of the reaction described in equation 103 is evident if one compares other unsuccessful attempts to synthesize unsymmetric sulphenamides of type **296** by reaction of *N*,*N*-dimethylaminosulphenyl chloride and *N*-trimethylsilylmorpholine: besides chlorotrimethylsilane, only the symmetric sulphenamides **297** and **298** were obtained[333] (equation 104).

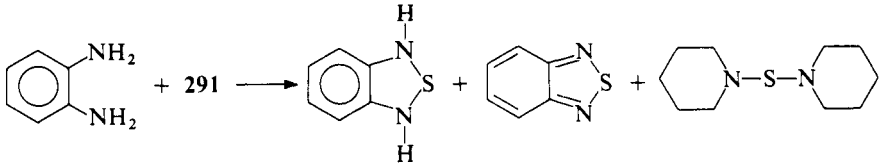


(290) (297) (298)

(104)

Finally, we should mention the reaction of piperidinesulphenyl chloride (**291**) with aromatic or aliphatic diamines which allowed the synthesis of heterocyclic compounds containing the N–S–N sequence[335]. In particular, *o*-phenylenediamine reacts with **291** to

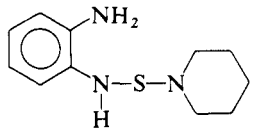
give a mixture of dihydro-2,1,3-benzothiadiazole (**299**), 2,1,3-benzothiadiazole (**300**) and the sulphenamide **301** (Scheme 78).



(**299**) (**300**) (**301**)

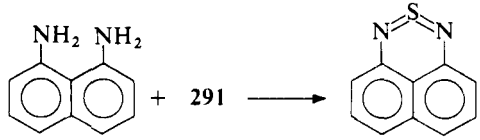
SCHEME 78

It has been suggested that the formation of **299** occurs by internal transamination of the initially formed intermediate **302** and that the occurrence of **330** is due to some oxidative process of **229.** Indeed, oxidation of **299** by 2-chloroperoxybenzoic acid gives **300**[335].

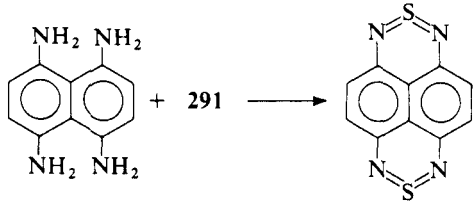


(**302**)

Other aromatic diamines like 1,8-diaminonaphthalene (**303**) and 1,4,5,8-tetra-amino-naphthalene (**304**) gave as isolable products only the 'oxidized' heterocycles **305** and **306** respectively[333] (equations 105 and 106).



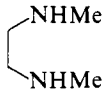
(**303**) (**305**) (105)



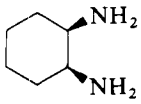
(**304**) (**306**) (106)

The reaction of aliphatic diamines with piperidinesulphenyl chloride (**291**) does not show a tendency to give oxidized products; but unfortunately the yields of the sulphur insertion products are quite low (30% maximum) and the reactions are more sluggish

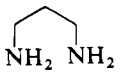
than those of the aromatic diamines with the same reagent[335]. As a matter of fact, 1,2-diaminoethane reacts with **291** to give only tars, but the corresponding *N,N'*-dimethyl derivative **307** gave the heterocycle **308**; 1,2-diaminocyclohexane (**309**) yielded the bicyclic sulphenamide **310** and 1,3-diaminopropane (**311**) the six-membered heterocycle **312**. Attempts to obtain a 1,2,7-thiadiazepine derivative by reaction of 1,4-diaminobutane with piperidinesulphenyl chloride were unsuccessful[335].



(307)

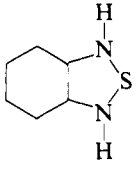


(309)

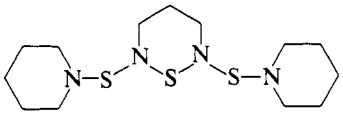


(311)

(308)



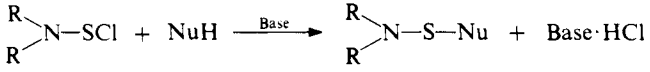
(310)



(312)

3. Reactions with sulphur, oxygen, phosphorus and carbon nucleophiles

The products of the reaction of aminosulphenyl chlorides with alcohols, thiols and thiophosphine oxides strongly depend on the reaction conditions[336,337,257a]. In the presence of added base, the reaction ends at the stage of the substitution of the chlorine atom of the sulphenyl chloride by the heteronucleophile to give species of type **313** which are still sulphenamide derivatives (Scheme 79).

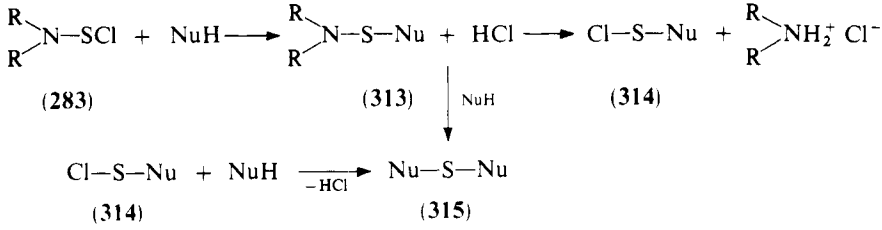


(283) (313)

Nu = EtO, 4-Tol, $R_2P(S)$, Allyl-O

SCHEME 79

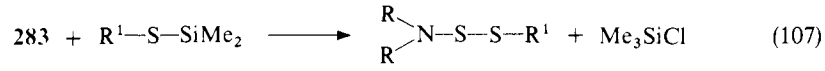
In the absence of added base, the hydrochloric acid, formed in the first step of the reaction, breaks the sulphur–nitrogen bond of **313** and gives the sulphenyl chloride **314** (see also Section VI), which further reacts with the nucleophilic species NuH to give the sulphide **315** (Scheme 80). Indeed, the protonated **313** may also react with the nucleophile to give **315** without formation of the sulphenyl chloride **314**.



(283) (313) (314) (314) (315)

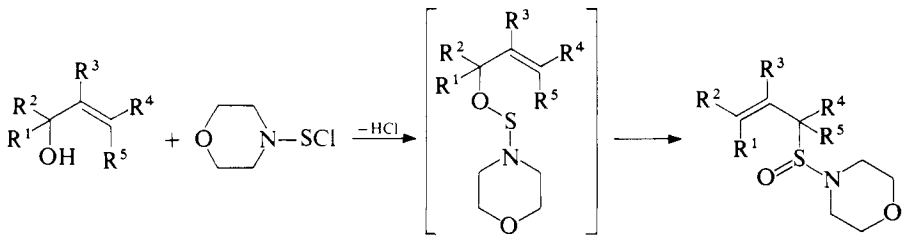
SCHEME 80

When the nucleophile is a silyl-protected thiol, it was possible to isolate compounds of type **313**, i.e. **316**, without the addition of bases[333] (equation 107). Indeed, in this reaction, protic acids able to break the sulphur–nitrogen bond of **316** are not formed.



(316) (107)

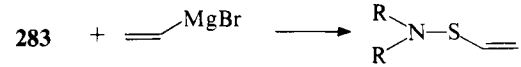
The reaction of allyl alcohols with morpholine-1-sulphenyl chloride allowed an easy synthesis of allylic sulphinamides **317**[257a] (equation 108).



(317) (108)

The sulphinamide **317** is thought to arise from an intermediate sulphenate ester via a 2,3-sigmatropic rearrangement (see Section IV for a more detailed discussion of this reaction).

The reaction of aminosulphenyl chlorides (**283**) with 1-ethynyl or vinyl lithium and that with the corresponding Grignard derivatives are examples of the reactivity of this class of compounds with carbon nucleophiles[338,339] (equations 109 and 110). The unsaturated sulphenamides **318** and **319** obtained by this route turned out to be valuable intermediates for a new synthesis of the indole ring system[338,339].



(318) (109)

(319) (110)

VI. SULPHENAMIDES

Sulphenamides are the amino derivatives of sulphenic acids and in this respect are analogous to carbon amides (equation 111).

They may be regarded also as sulphenyl cation carriers associated with very strong bases (R_2N^-) and, as the other members of this family, may be attacked at sulphur by strong nucleophiles; however, some form of acid catalysis is required to complete the substitution reaction (equation 112).

$$RSOH + NH_3 \longrightarrow RS{-}NH_2 + H_2O \quad (111)$$

$$R{-}S{-}NR_2 + B^- \longrightarrow RS{-}B + HNR_2 + X^- \quad (112)$$

Since sulphenic acids are weak acids and the electronegativities of sulphur and nitrogen are quite similar, the basic properties of nitrogen are largely preserved and sulphenamides react with Brønsted or Lewis acids to give the conjugate acid (Scheme 81).

$$RSNH_2 + HX \rightleftharpoons R{-}S{-}\overset{+}{N}H_3 + X^-$$

$$RSNH_2 + L.A. \rightleftharpoons R{-}S{-}NH_2LA$$

SCHEME 81

Furthermore, the weakness of the sulphur–nitrogen bond[340] makes the homolytic dissociation rather facile, thus enriching the chemistry of these compounds (Scheme 82).

$$R{-}S{-}NR'_2 \longrightarrow RS\cdot + \cdot NR'_2$$

$$R{-}S{-}\overset{+}{N}R_3 \longrightarrow RS\cdot + \cdot NR_3^+$$

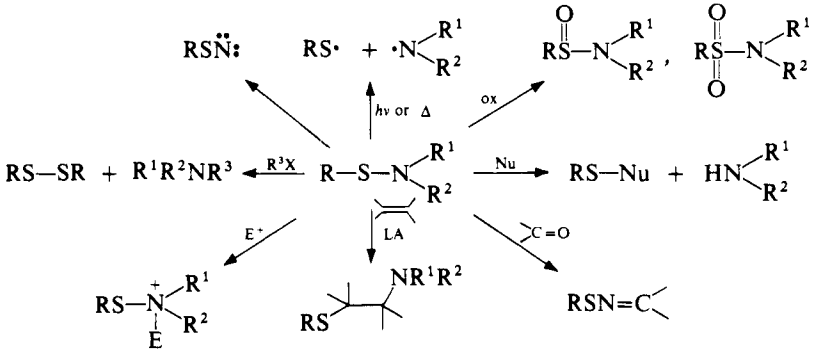
SCHEME 82

Finally, the reactivity of the amino group and of the sulphide sulphur is preserved to a large extent, further increasing the versatility of sulphenamides.

Indeed, they have been used in the synthesis of sulphides[341], disulphides[99, 342], trisulphides[343], sulphenate esters[344], sulphenimines[345], sulphenamides[346], β-amino sulphides[347, 348], aminocarbo-trithioates[349], etc.

Moreover, some sulphenamides have found industrial applications as pesticides and as accelerators in the vulcanization of rubber, as documented by the patent literature.

It follows that considerable attention has been devoted to the preparation[16, 350–353] and even more to synthetic applications of sulphenamides[350] (Scheme 83).



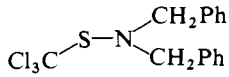
SCHEME 83

The most important and recent developments in both theoretical and experimental studies will be reported in this section, while for earlier work reference must be made to previously published articles[16, 17].

A. The Sulphur–Nitrogen Bond and the Structure

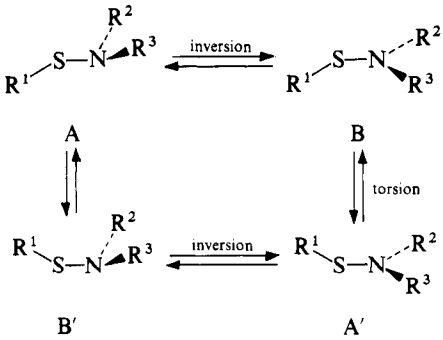
The nature of the sulphur–nitrogen bond in sulphenamides presents interesting theoretical aspects[354-357]. The chemical and stereochemical behaviour of this class of compounds have been associated with the interaction of a lone pair of either sulphur or nitrogen atoms with an antibonding orbital on the adjacent atom. This interaction is thought to be responsible for torsional preferences (the gauche effect), enhanced nitrogen barrier of inversion (conjugative destabilization) and increased nucleophilicity (the α-effect).

More than twenty years ago it was observed[358] that benzyl protons in sulphenamide **320** are diastereotopic, which implies that the nitrogen is chiral.



(**320**)

The topomerization, that is, the interconversion of one enantiomer into the other one, requires the intervention of two different processes: rotation around the sulphur–nitrogen bond and pyramidal inversion at nitrogen (Scheme 84).

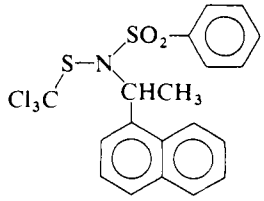


SCHEME 84

Detailed studies[359, 360] allowed one to distinguish which of the two equilibria represents the slow step in the topomerization process which is responsible for the coalescence of the signals observed by ^{1}H NMR. The two processes are affected in different ways by structural variations[359, 360]: the nitrogen inversion barrier becomes higher in going from acyclic to cyclic derivatives (sulphenylaziridines) and from large to small and strained rings. On the other hand, the barriers for sulphur–nitrogen bond rotation are higher for the acyclic sulphenamides than for the cyclic ones. The torsional barrier is also increased by bulky substituents at the nitrogen atom[361], and by strong electronegative groups at the sulphenyl sulphur[362].

The X-ray structure determination of the *N*-alkylsulphonylsulphenamide **321**, taken as a representative example, provides evidence for the existence of a partial double bond between sulphur and nitrogen involving the nitrogen lone pair[363].

The experimental and theoretical analysis of the system[328, 361, 364-368] leads to the conclusion that there are several contributions to the sulphenamide torsional barrier: overlap repulsion between non-bonding electrons on sulphur and nitrogen, steric



(321)

hindrance at the transition state, dependence of the sulphur–nitrogen bond strength on the dihedral angle, and polar substituent effects. The torsional barrier ranges, for sulphenamides with different substituents, from 12 to 20 kcal mol^{-1}.

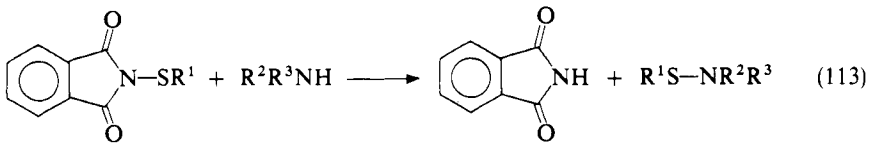
The understanding of the stereoelectronic features of sulphenamides allowed the unambiguous configurational assignment, by NMR spectroscopy, of the *meso* and *dl* diastereomers of secondary amines after their conversion to sulphenamides by reaction with a sulphenyl chloride[369].

B. Reactions with Nucleophiles

The reactions of sulphenamides with Grignard reagents[370], thiols[371, 101] and amines[372] effect displacement at sulphur and give sulphides, disulphides and new sulphenamides, respectively.

1. Amines

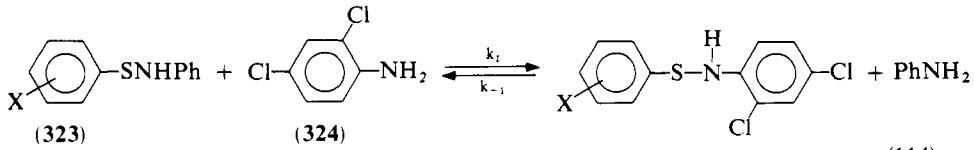
The reaction of sulphenamides with amines allowed the synthesis of substituted sulphenamides[372–374]. Alkyl sulphenamides, which are difficult to obtain by using standard methods, have been prepared by this route. For example, reaction of thiophthalimides **322** with both primary and secondary amines gives excellent yields (81–100%) of the corresponding sulphenamides[373] (equation 113). *N*-thio-substituted lactams can also be used instead of thiophthalimides to perform the same transformation[375].



(322)

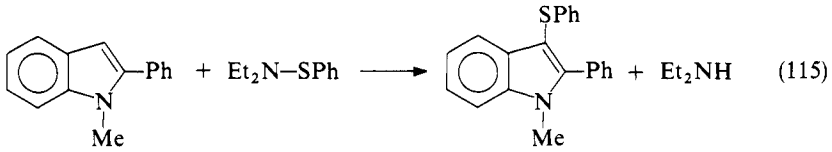
R^1 = Et, Bu, $PhCH_2$

A mechanistic investigation on the reaction of *N*-phenyl-substituted arenesulphenamides **323** with the aniline **324** (equation 114) shows that the reaction rates are correlated by σ^- constant with a negative ρ value[376]. It has been suggested that it is not a simple S_N2 reaction.



(323) (324) (114)

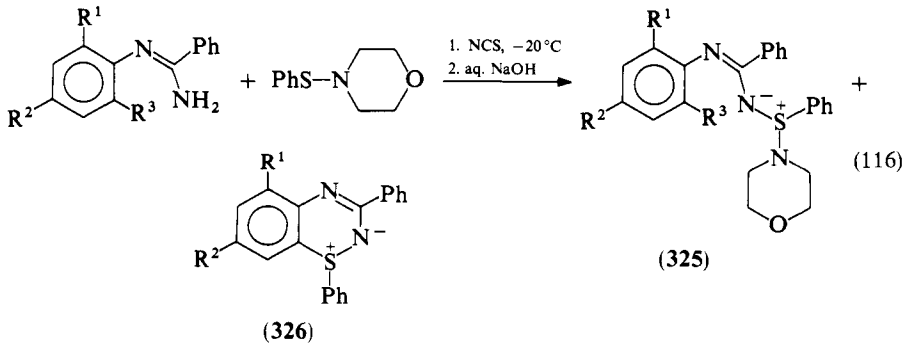
It was also suggested that these sulphenylation reactions may be an electron-transfer processes[377]. Indeed, reactions such as those reported in equation 115 carried out in the cavity of an ESR spectrometer allowed one to detect an unresolved signal.



(115)

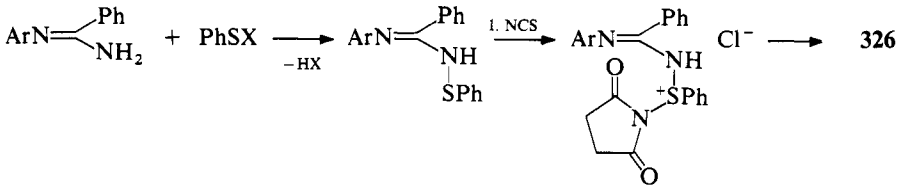
This is in agreement with the finding that sulphenamides can be oxidized to the corresponding sulphenamide radical cations which were detected by ESR spectroscopy[378].

When the amino functionality is part of a more complex molecule, further transformations may occur. Thus, for instance, the reaction of *N*-arylbenzamidines with phenylthiomorpholine (equation 116) leads to sulphinimides **325**[379].



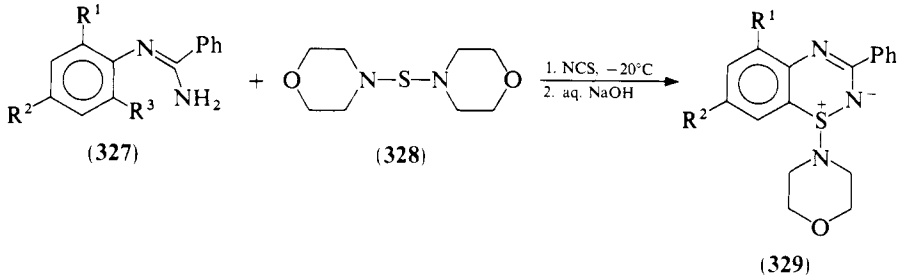
(326) (325) (116)

Depending on the substituents, compound **326** can be also isolated as a minor product. The mechanism suggested and partially proved is reported in Scheme 85.



SCHEME 85

Similar reactions of **327** with the bis-aminosulphide **328** yield cyclic ylides of type **329**[379, 380] (equation 117).



(117)

2. Thiols and alcohols

The reactions of sulphenamides with thiols, alkoxide ions, Grignard reagents and with compounds which have acidic methylene groups give rise in all cases to the sulphenylation of the nucleophile.

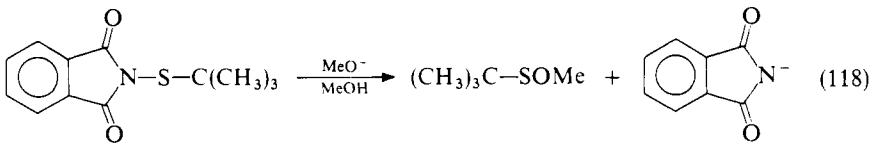
The reaction of sulphenamides with thiols allows the synthesis of both symmetric or unsymmetric disulphides. This reaction is also used as a mild method to cleave the sulphur–nitrogen bond in sulphenamides derived from the amino groups of peptides. This aspect will be discussed later in Section VI.C.

Depending on the nature of the sulphenamides, the reaction can be carried out under neutral conditions or may require Lewis acid catalysis. Reactive sulphenamides like those derived from amides undergo cleavage of the sulphur–nitrogen bond just mixing the two reagents[101].

By this method symmetrical alkyl or aryl disulphides as well as aryl alkyl disulphides have been prepared in good yields[381]. However, the synthesis of unsymmetrical aromatic disulphides following this procedure presents some problems since a rapid thiol–disulphide exchange may lead to a mixture of symmetric and unsymmetric disulphides[99, 342a].

When aromatic sulphenamides are used, acid catalysis to facilitate the cleavage of the sulphur–nitrogen bond is necessary[382]. In the presence of thiols, asymmetric aromatic disulphides are formed together with variable amounts of the two symmetric disulphides[382]. Statistical distribution of the three disulphides was obtained in the reaction of thiophenol with 4-methylbenzene-*N*-(4-nitrophenyl)sulphenamide; higher chemoselectivity for the asymmetric disulphides was observed when 4-chloro- or 4-nitrothiophenol was used[382].

The addition of the sulphenamide **330** to a solution of sodium methoxide in methanol yields the corresponding sulphenate ester **331**[344] (equation 118).



(330) (331) (118)

3. Carbon nucleophiles

Sulphenylation of Grignard reagents was reported for the benzenesulphenamides **332**. It reacts with phenylmagnesium bromide in toluene to give diphenyl sulphide[370] (equation 119).

$$PhSNEt_2 + PhMgBr \xrightarrow[70°C,\ 10h]{\text{Toluene}} PhSPh + EtNH_2 \qquad (119)$$

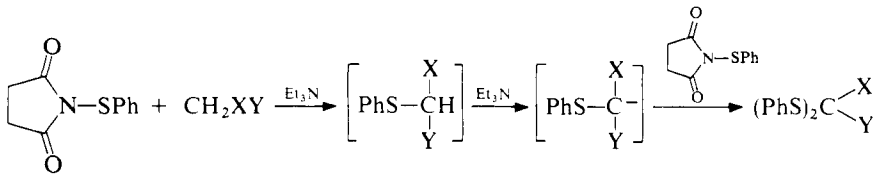
(**332**)

Sulphenamides like *N,N*-diethylbenzenesulphenamide, *N*-(phenylthio)pyrrolidine or *N*-(phenylthio)piperidine react with reactive methylene compounds in methylene chloride to give monosulphenylated products **333** in good yields[383, 384] (equation 120).

$$RS{-}NR^1R^2 + CH_2XY \longrightarrow \underset{\displaystyle SR}{YX\overset{-}{C}\cdot H_2\overset{+}{N}R^1R^2} \xrightarrow{HCl} \underset{\displaystyle (\mathbf{333})}{RS{-}CHXY} + R^1R^2NH{\cdot}HCl \qquad (120)$$

X, Y = EWG groups

The bis-sulphenylation of active methylene compounds in the presence of a base can be obtained with more acidic derivatives like the *N*-(phenylthio)succinimide (equation 121).



(121)

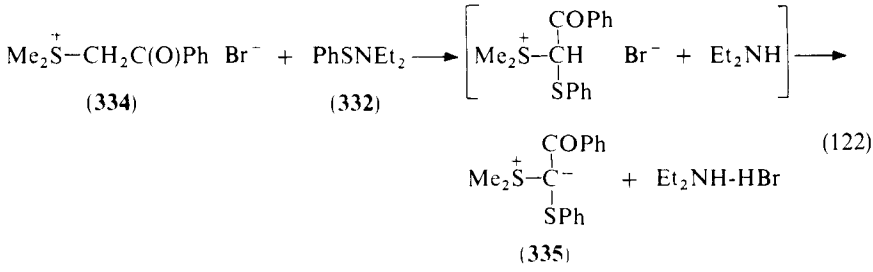
N-(Phenylthio)phthalimide is also able to give α-sulphenylation of enamines and bis-sulphenylation is obtained only in the presence of base[383, 384].

Enolizable ketones can be similarly mono-sulphenylated by sulphenamides but bis-sulphenylation is obtained in the presence of a base[383, 384]. The reaction with α-alkylated ketones occurs at the most substituted carbon[383, 384]. However, the same results may be obtained simply by mixing sulphenyl chlorides and ketones in methylene chloride (Section III).

The activation of the α-methylenic protons of ketones by the introduction of a sulphonium group allowed the sequential functionalization of the α-carbons[385]. This is the case of the reaction of methylphenacylsulphonium bromide (**334**) with *N,N*-diethylbenzenesulphenamide (**332**), which yields 2-phenylthio-2-(dimethylsulphuramylidene)acetophenone (**335**) (equation 122). The ylid **335** can be quenched in the usual way and then the resulting sulphonium salt further functionalized[385].

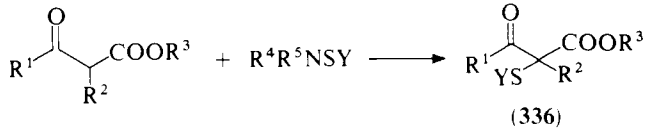
Similar results have been obtained when the activating sulphonium moiety is substituted by a pyridinium group[386].

The α-sulphenylation of β-ketoesters was carried out by sulphenamides in refluxing methanol or in aprotic solvents such as benzene or methylene chloride. In all cases the sulphenylated ketoesters **336** were obtained in good yields[384] (equation 123).



(334) (332) (335)

(122)

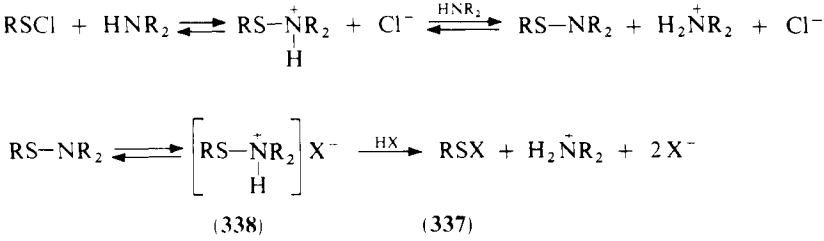


(336)

(123)

C. Acid-catalyzed Reactions

Sulphenamides are usually prepared by reaction of an appropriate sulphenyl derivative, usually a sulphenyl halide, with ammonia or primary and secondary amines as shown in Scheme 86.



(338) (337)

SCHEME 86

The reaction is reversible and therefore sulphenamides may react with excess of Brønsted acids to give a sulphenyl derivative and an ammonium salt whenever the conjugate base of the Brønsted acid (HX) yields a sulphenyl derivative **337** more stable than the protonated sulphenamide **338**.

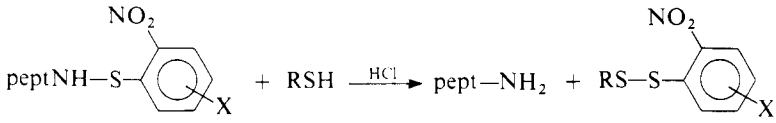
However, the sulphenamides are rather weak bases and the reactions shown in Scheme 86 may require rather strong acids particularly when the amino moiety is by itself a weak base. Sulphenamides are also rather weak electrophiles and hence some of them may be rather stable versus both acids and bases. This property has been exploited in organic synthesis for the reversible protection of amino groups[101].

The large spectrum of reactivity of the sulphenyl derivatives, as already discussed in Sections I and II, applies also to sulphenamides and hence the appropriate reagent may be selected as a function of the specific needs of the synthetic target.

Peptide synthesis is certainly an area where this methodology has found wide application. In this field the S-2-nitrobenzene derivatives have acquired a particular interest for their specific properties.

As sulphenylating reagents of the amino functionality, the sulphenyl chlorides are the most used class of compounds because of their reactivity and easy preparation. However, as discussed in previous sections, the 2-nitro substituent in the benzenesulphenyl chloride decreases significantly the reactivity of sulphur so that sulphenyl chlorides bearing this substituent are quite stable and easy to purify. Moreover, they react only very slowly with hydroxylic solvents, including water, so that they can be reacted with the amino functionality of amino acids or peptides in mixed polar solvents, where these compounds are soluble, giving the corresponding sulphenamides in almost quantitative yields. The 2-nitrobenzenesulphenamides have also the advantage of being coloured and high melting compounds, which facilitate their isolation and detection.

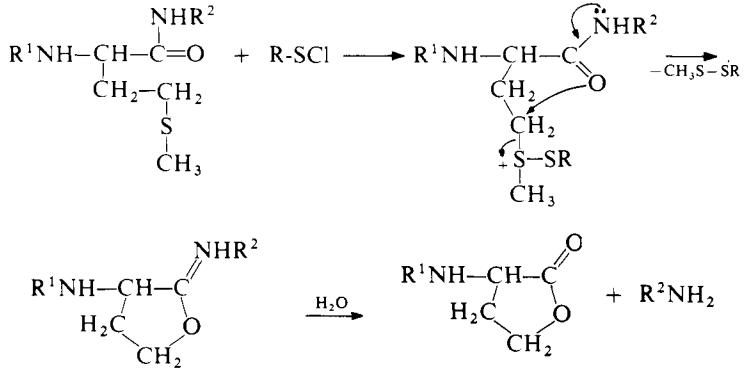
The weak basicity of these sulphenamides ensures good stability of the protected amino functionality even in rather strong acidic conditions, which are needed to carry out the removal of other protecting groups of either amino- or carboxy-functionalities. The deblocking of the amino group protected as sulphenamide is usually carried out by hydrochloric acid[17, 25, 387, 388]. Sometimes this reaction is accomplished in the presence of thiols[371] to avoid the formation of sulphenyl chlorides, which may react with sensitive amino acids like triptophane (equation 124). 2-Nitrobenzenesulphenamides can be also cleaved by 2-mercaptopyridine[389] or by catalytic desulphurization with Raney Nickel[390]. In other cases the benzenesulphenamides of cephalosporins were cleaved by sodium iodide[391].



(124)

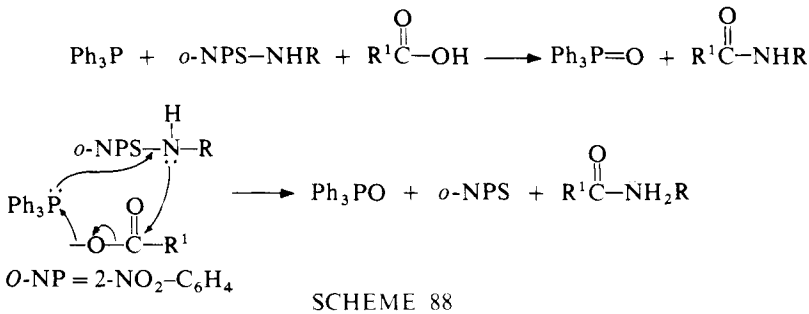
Albeit the 2-nitrobenzenesulphenyl chloride is the most widely used protecting reagent, a few other weakly reactive sulphenyl halides, such as 2,4-dinitrobenzene-, pentachlorobenzene- and 2-pyridinesulphenyl chlorides and even the simple benzenesulphenyl chloride, have been used for this purpose[101]. More recently *N*-(2-nitrobenzenesulphenyl)-saccharine, an even less reactive and more stable reagent, was proposed as a substitute for the 2-nitrobenzenesulphenyl chloride[392].

Related to this aspect of the sulphenyl derivative chemistry is the ability of 2-nitrobenzenesulphenyl chloride to cleave the peptide bond in proteins at the level of methionine, a reaction which presents some advantages over the more known cyanogen bromide procedure[393] (Scheme 87).



SCHEME 87

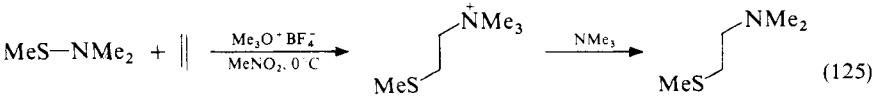
Among the several other applications of this reagent in peptide synthesis, mentioned may be made of the peptide bond formation, which can be obtained as shown in Scheme 88[393].



SCHEME 88

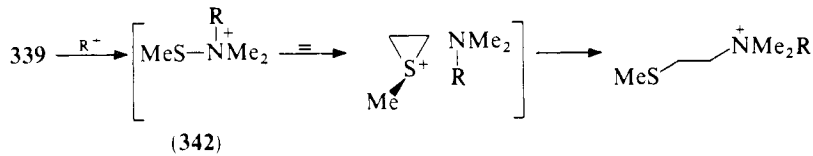
The reaction of either Lewis or Brønsted acids, like trifluoromethanesulphonic acid, whose conjugate base is a very weak nucleophile, transforms the weakly electrophilic sulphenamide in a rather strong electrophile which may react with weak nucleophilic species like alkenes and alkynes and even with acetonitrile when it is used as a solvent.

For example, sulphenamide **339** reacts with the Meerwein reagent and adds stereospecifically *anti* to alkenes giving the methylthioammonium salt **340**, which can be demethylated by triethylamine to the aminosulphide **341**[348] (equation 125).



(339) (340) (341) (125)

This reaction corresponds to the azasulphenylation of alkenes. Azasulphenylation of a double bond can be obtained by *in situ* formation of the thiiranium ion followed by dimethylamine ring opening[394] (Scheme 89). This synthetic procedure was applied to several olefins showing that the scope of the reaction is quite broad. It was suggested that the (alkylthio)ammonium ion **342** is the transient reactive species which generates the intermediate thiiranium ion.

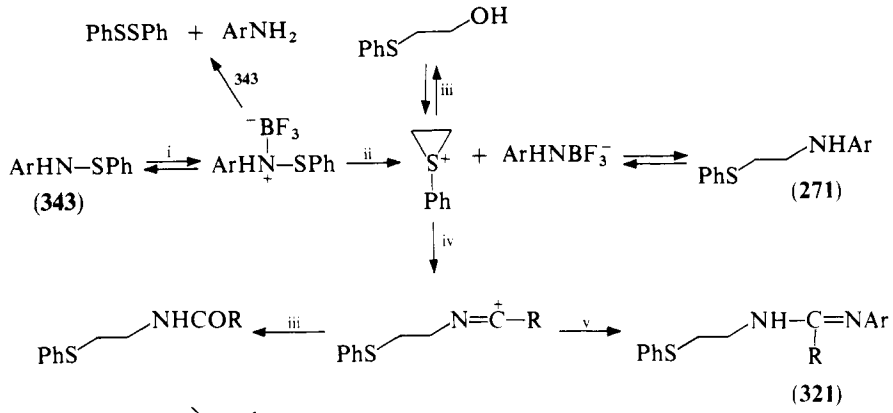


(342)

SCHEME 89

As might be expected sulphenylanilides **343** also present similar reactivity[347, 395–397]. They react with alkenes[395] and alkynes[347, 397] in the presence of the boron trifluoride–diethylether complex. The reaction affords in a highly stereoselective fashion and in fairly good yields the corresponding β-amino sulphides. Depending on the

solvent[347, 395], different products might be formed but always with *anti* stereochemistry. This is shown in Scheme 90 for the reaction of alkenes.

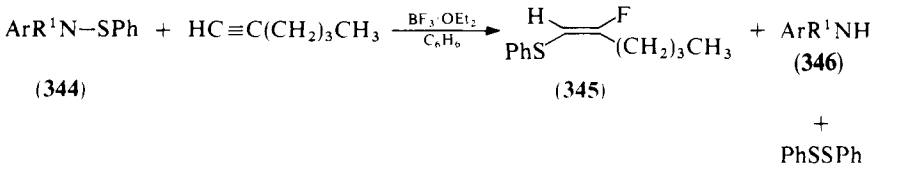


SCHEME 90

The aminosulphenylation reaction of unsaturated hydrocarbons is very sensitive to the *N*-aryl substituent of the sulphenamides as far as the yield of the products is concerned. Thus, the yield of the resulting adducts strongly decreases with increasing electron-donating character of the substituent. It was also reported that activation of benzenesulphenamide can be achieved by trifluoromethansulphonic acid or by trimethylsilyl trifluoromethanesulphonate under acid catalysis[396].

The addition of sulphenamides to the carbon–carbon triple bond[347, 397] in the presence of a Lewis acid seems to be a more sluggish reaction.

A large spectrum of products can be obtained depending on the solvent and reaction conditions. However, it is noteworthy that in the reaction of **344** with 1-hexyne using benzene as solvent, the fluoro adduct **345** is formed in appreciable amounts together with the aniline **346** and diphenyl disulphide[347] (equation 126).

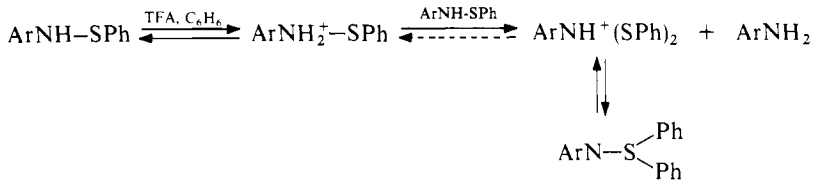


(344) (345) (346)

(126)

The complex course of this reaction is not surprising since the conjugate acid of the sulphenamide, irrespective of its formation via protonation, alkylation or Lewis acid complexation, may be electrophilic enough to react with alkenes and alkynes to form other reactive species.

If they cannot be quenched by an appropriate nucleophile either because their activity is depressed by the excess of acid added or because they are not present, they will evolve in pathways not easy to predict. Indeed, sulphenamides are reported to 'decompose' in the presence of Lewis acids[398] (Scheme 91).



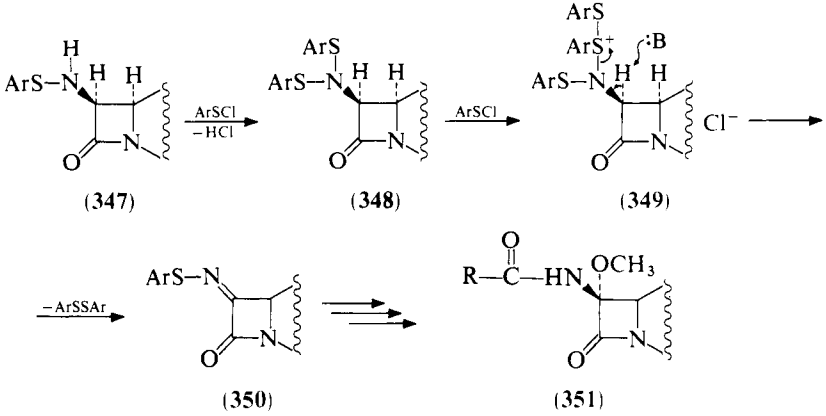
Ar = Ph, 4-An,4-Tol, 4-ClC_6H_4, 4-$NO_2C_6H_4$,

3-$NO_2C_6H_4$, 3-An, 3-$(PhCH_2CH_2)C_6H_4$, 2-PhC_6H_4

SCHEME 91

Other interesting synthetic applications of the chemistry of sulphenamides have been exploited.

For example, cephalosporins **347** may be transformed into 7-α-methoxy cephalosporins[399] by the reaction of the sulphenamides **348** with excess sulphenyl halide that gives **349**, which is then transformed to **350** (Scheme 92). Further simple transformations of **350** lead to the methoxycephalosporine derivative **351**. All these reactions occur under very mild conditions, are stereospecific and give high yields of the product.



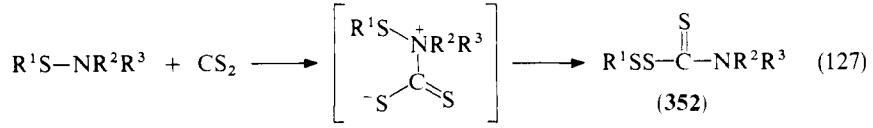
(347) (348) (349) (350) (351)

SCHEME 92

D. Reactions with Electrophiles

1. *Carbon disulphides and isocyanates*

Carbon disulphide[349, 350, 389] behaves as an electrophile in the reaction with sulphenamides and gives rise to the formation of aminecarbotrithioates **352** (equation 127). Some of the aminecarbotrithioates 352 synthesized by this method are reported in Table 20.



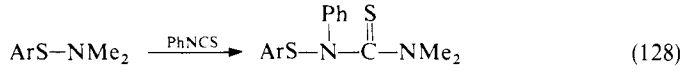
(127)

TABLE 20. Reaction of sulphenamides with carbon disulphide compounds, conditions and yields of **352** (see equation 127)

R^1	R^2, R^3	t(°C), [a] time	Yield (%) of **352**	Ref.
CH_3	$-(CH_2)_5-$	RT, 5 min	88	349
CH_3	$(CH_2)_2O(CH_2)_2$	reflux, 45 min	98	349
CH_3CH_2	$(CH_2)_2O(CH_2)_2$	reflux, 4 h	83	349
CH_3	C_2H_5, C_2H_5	reflux, 4 h	76	349
C_6H_5	$(CH_2)_2O(CH_2)_2$	75, 4 h	36	349
$CH_3S(CH_2)_2$	$-(CH_2)_5-$	reflux, 4 h	77	349
$CH_3S(CH_2)_2$	CH_3, H	reflux, 4 h	89	349
$(CH_3)_3C$	$-(CH_2)_5-$	RT, 21 d	50	350
C_2H_5	$-(CH_2)_5-$	RT, 30 min	95	350
$AcNH(CH_2)_2$	$(CH_2)_2O(CH_2)_2$	RT, 30 min	100	350

[a] RT = room temperature.

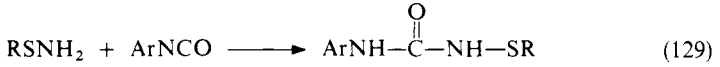
By a similar mechanism sulphenamides react with isothiocyanates[350] and give *N*-sulphenylthioureas **353** (equation 128).



(128)

(**353**)

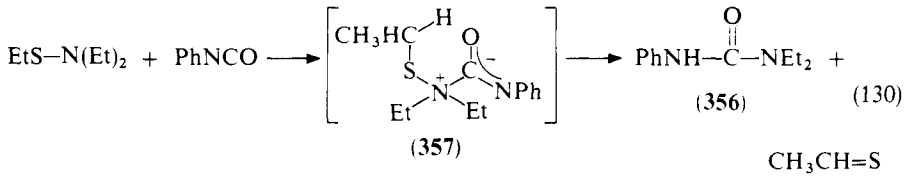
Other similar reactions have been reported. For example, sulphenylamides **354** react with aryl isocyanates to give the substituted ureas **355**, which are addition products of the primary sulphenamide **354** to the carbon–nitrogen multiple bond of the isocyanate[400–402] (equation 129).



(129)

(**354**) (**355**)

However, when the sulphenamide is disubstituted, the reaction takes a different course[350, 400, 401] (equation 130). The urea **356** and the thioacetaldehyde which are the reaction products probably derive from **357** by hydrogen shift and elimination of the thioaldehyde.



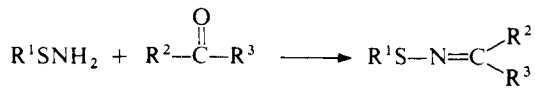
(130)

(**357**) (**356**)

$CH_3CH{=}S$

2. Carbonyl compounds

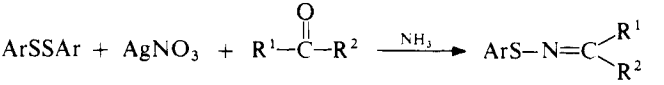
The condensation of a sulphenamide with an aldehyde or a ketone is the general route to the synthesis of sulphenimines[345, 352, 402–405] (equation 131).



(131)

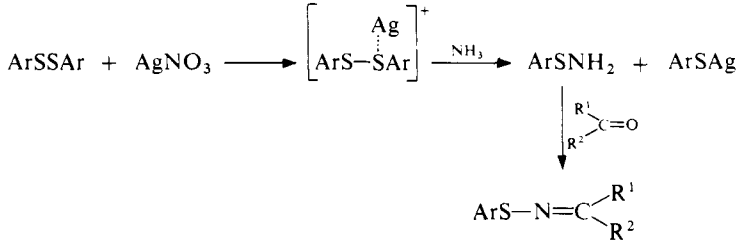
R^1, R^2 = Alkyl or Aryl; R^3 = Alkyl, Aryl or H

In principle, the reaction may be catalyzed either by base or acid; however, to avoid formation of disulphides from decomposition of the sulphenamide in the presence of acids even in traces, the condensation is usually carried out under base catalysis in alcoholic solutions. Potassium carbonate has been used with aromatic aldehydes, but stronger bases, like alcoholates, are required for ketones and aliphatic aldehydes[403b]. Other procedures employ pyridinium *p*-toluensulphonate in very dry solvents[404] and the formation of the sulphenamide *in situ* from disulphide and liquid ammonia under silver ion catalysis[345, 352, 405] (equation 132).



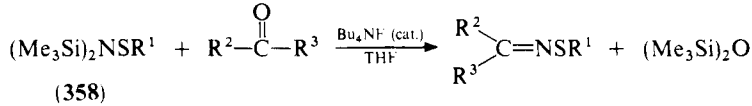
(132)

As shown in Scheme 93, the silver ion forms a complex with a lone pair of the sulphur. Nucleophilic attack by ammonia on the activated disulphide bond gives the sulphenamide. The resulting sulphenamide condenses with the carbonyl compound to yield the product sulphenimine. This approach, however, is limited to aromatic disulphides, and gives low yields of sulphenimines.



SCHEME 93

A more general synthesis of sulphenimines which takes advantage of the easy silicon–nitrogen bond breaking in *N*,*N*-bis(silyl)sulphenamides (**358**) is shown in equation



(**358**)

(133)

R^1 = Me, Ph; R^2 = H, Me, Ph

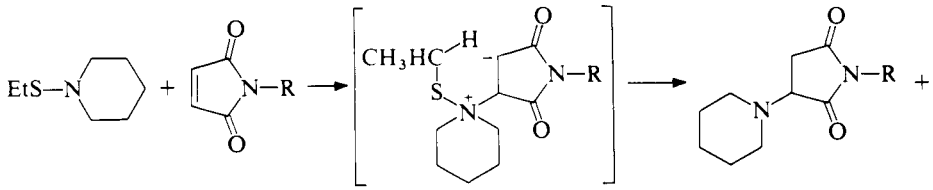
R^3 = Me, Cy, Ph, Ar, PhCH = CH, PhCO (Cy = Cyclohexyl)

R^2–R^3 = $-(CH_2)_5-$

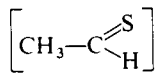
133. *N,N*-Bis(silyl)sulphenamides (**358**) produce sulphenimines in yields higher than 80% using tetrabutylammonium fluoride as catalyst to activate the silicion–nitrogen bond[406].

3. *Alkylation and thioalkylation*

Formation of new carbon–nitrogen bonds is possible by the reaction of alkanesulphenamides with electrophilic double bonds[350]. Alkanesulphenamides give reactions similar to those with carbonyl compounds already described in equation 131. The amino moiety is transferred to the olefinic carbon and oxidative elimination of the alkylthio residue as thioaldehyde leads to **359**, which formally corresponds to the addition product of an amine to the double bond[350] (equation 134).

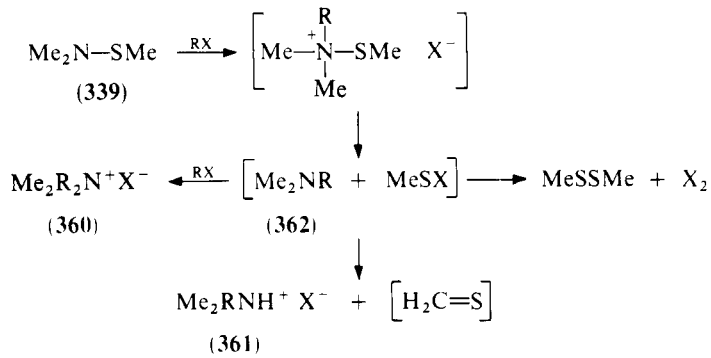


(359)



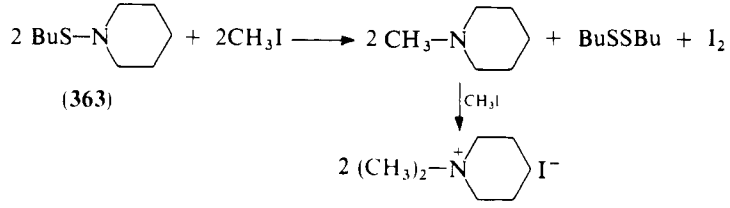
(134)

Attempts to alkylate *N,N*-dimethyl-methylsulphenamide (**339**) and to isolate the primarily formed thioammonium or azasulphonium salts were unsuccessful and lead only to ammonium salts[348, 350, 407]. For example, the reaction of **339** with alkyl iodides allowed one to isolate only dimethyl disulphide, the quaternary ammonium salts **360** and the tertiary ammonium salt **361** which probably is formed by hydrogen abstraction of the intermediate methanesulphenyl iodide by the free amine **362**[407] (Scheme 94).



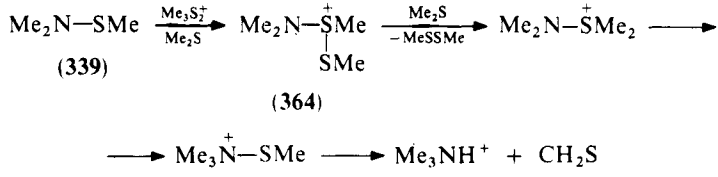
SCHEME 94

A similar behaviour is exhibited by the sulphenamide **363**, which gives dibutyl disulphide and the dimethylpiperidinium salt upon reaction with methyl iodide[348, 350] (equation 135).



(135)

Alkanethiolation of sulphenamides by dimethyl(methylthio)sulphonium tetrafluoroborate gives products similar to those obtained by alkylation[407] (Scheme 95). However, the mechanism of their formation probably implies the initial thioalkylation at sulphur. Although reversible attack at nitrogen cannot be excluded, attack at sulphur leads to the formation of thiosulphonium ions **364**, which further react with **339**. Anyhow, the only identified sulphur-containing products were dimethyl sulphide and dimethyl disulphide.



SCHEME 95

D. Oxidation

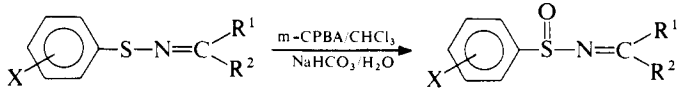
Oxidation of sulphenamides **365a** with potassium permanganate afforded the corresponding sulphonamides but in low yield[408]. However, the oxidation carried out with two equivalents of 3-chloroperbenzoic acid (m-CPBA) gave much higher yields of the oxidized derivatives[409] (equation 136).

(365)

(a) $R^1 = 4\text{-Cl-}C_6H_4$, $R^2 = H$
(b) $R^1 = C_6H_{13}$, $R^2 = H$
(c) $R^1 = s\text{-}C_4H_9$, $R^2 = H$
(d) $R^1 = t\text{-}C_4H_9$, $R^2 = H$
(e) $R^1 = i\text{-}C_3H_7$, $R^2 = i\text{-}C_3H_7$

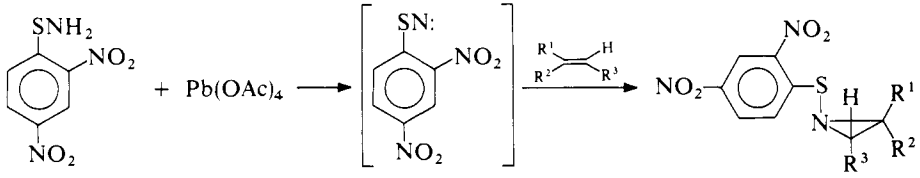
(136)

3-Chloroperbenzoic acid can also oxidize sulphenimines **366** to the corresponding S-oxides **367**[410]. The reaction, carried out using one equivalent of the oxidant in the two-phase system chloroform–water and in the presence of sodium bicarbonate, allowed the synthesis of *N*-alkylidenesulphenamides **367** (equation 137).

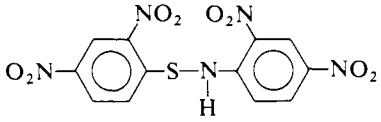


(366) (367) (137)

The oxidation of unsubstituted sulphenimines takes a different course likely involving a nitrene as intermediate. The oxidation products of 2,4-dinitrobenzenesulphenamide with lead tetracetate were trapped with electron-rich alkenes as *N*-(2,4-dinitrophenylsulphenyl)aziridines **368**[411] (equation 138). This reaction was carried out as a probe of formation of the sulphenylnitrene **369**. When the oxidation of the sulphenamide **370** was carried out in the absence of any trapping reagent, the sulphenamide **371** was isolated. This product probably derives by attack of the initially formed nitrene **369** at the nitrogen atom of a second molecule of **370** followed by two consecutive Smiles rearrangements[411].

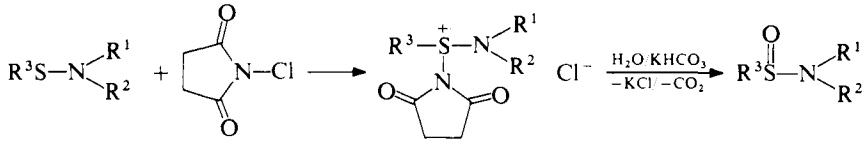


(370) (369) (368) (138)



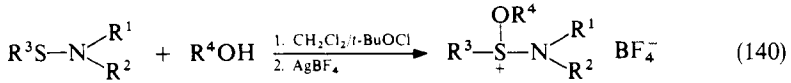
(371)

A quite simple method to oxidize sulphenamides to sulphinamides is the reaction with *N*-chlorosuccinimide[412] (equation 139). The reaction occurs with the intermediacy of aryl or alkyl-dialkylamino-succinimido sulphonium salts **372**. These salts are stable and isolable as chlorides or tetrafluoroborates and can easily be obtained by reaction of sulphenamides with *N*-chlorosuccinimide in non-hydrolytic conditions[413].



(372) (139)

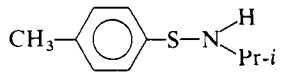
A different oxidative process of sulphenamides using *t*-butyl hypochlorite in the presence of alcohols and silver tetrafluoroborate results in the synthesis of aza-oxysulphonium salts **373**[414] (equation 140).



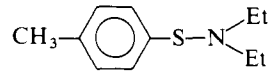
(140)

(373)

The structural features of sulphenamides allowed asymmetric oxidation of the sulphur atom. This was performed by using the complex $Ti(OPr\text{-}i)_4/(+)\text{-DET}/H_2O$ (1:2:1) DET = diethyltartrate and *t*-BuOOH at −20°C in methylene chloride[415]. The reaction is quite slow (three days for **374** and seven days for **375**) and the sulphinamides were isolated in low yield, 28 and 60%, and show a low enantiomeric exces.



(374)



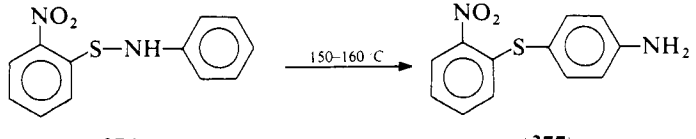
(375)

Recently, a variety of *N*-substituted 2-nitrophenylsulphenylimines **367** were obtained in good yield by direct and indirect electrochemical oxidation of the corresponding sulfinimines[416] or by using stoichiometric amounts of triarylamine radical cation salts in the presence of 2,6-dimethylpyridine as proton acceptor[416]. In both the reactions the yields of sulphinylimines were quite good, ranging from 67 to 95%.

E. Rearrangement and Radical Reactions

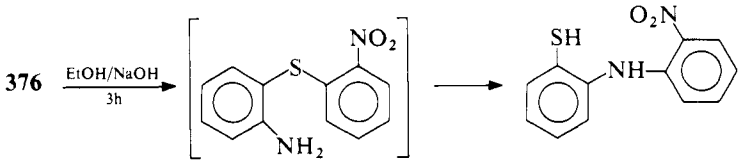
Rearrangements of sulphenamides have been known for many decades[417–419]. The thermal stability of sulphenamides increases with the number of substituents at the nitrogen and with increasing the electron-withdrawing power of substituents at sulphur.

The sulphenamide **376** can be thermally transformed into the isomeric sulphide **377**[418] (equation 141). When the reaction is carried out in the presence of aniline, the yield of the rearranged product increases up to 70%. In alcoholic sodium hydroxide solution the sulphenamide **376** gives the substituted thiol **378** (equation 142), which probably arises from intermediate sulphide **379**[419]. On the other hand, 4-nitrobenzenesulphenanilide is quite stable in the basic conditions used in equation 142[420] and neither thiols of type **378** nor rearranged sulphides were found in the reaction mixture.



(141)

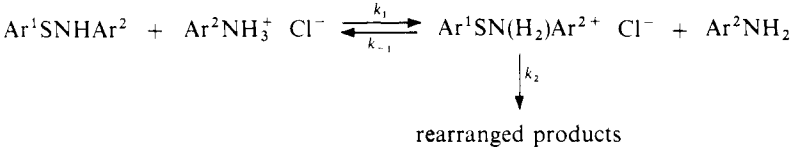
(376) (377)



(142)

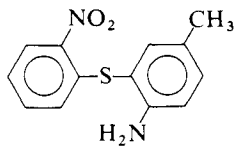
(379) (378)

A more detailed study of this type of rearrangement[421] shows that electron-donating groups favour a radical reaction giving thiyl- and amino-radicals, which lead to aryl disulphides and azobenzene derivatives, whereas electron-withdrawing groups favour the benzidine-type rearrangement. The rearrangement is favoured by secondary and primary aromatic amines used as solvents. Acid catalysis by the amine hydrochloride has also been observed. These findings led to the proposed mechanism reported in Scheme 96[421].

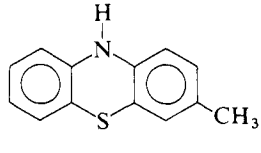


SCHEME 96

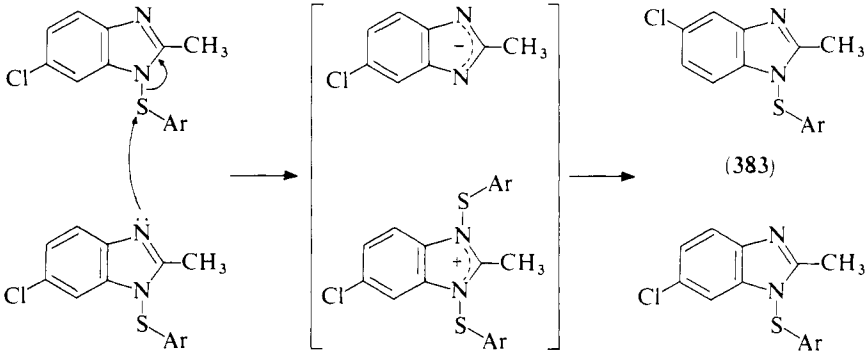
Rearrangement of **376**, using 4-methylaniline as solvent, gave crossover products such as **380** or **381**. This result was interpreted as a proof of an intermolecular rearrangement but no conclusive tests were offered to confirm the intervention of this mechanism only[422]. It may be that intermolecular and intramolecular mechanisms are competing and both are operative. Indeed, trapping experiments with *N,N*-dimethylaniline allowed one to conclude that, at least in part, the rearrangement occurs intermolecularly[423].



(380)



(381)



SCHEME 97

Relevant to this point is the study of the rearrangement of the sulphenamide **382** which, on heating, undergoes rearrangement to **383**[424]. Albeit an intramolecular mechanism can be easily conceived, detailed kinetic studies showed that the formation of **383** occurs intermolecularly as shown in Scheme 97.

VII. CONCLUSIONS

The chemistry of sulphenyl halides, sulphenamides and analogous reagents began with rather limited scope, but quickly attracted the attention of several research groups for the peculiar mechanistic aspects while gradually acquiring importance for the transformations that the reaction products could undergo and for their utility in organic synthesis.

These parallel the growing importance of sulphur-containing modified synthones, due to the ability of sulphur in the various oxidation states to influence the chemistry of the proximal functionality and to induce, often, high stereoselectivity.

Under the unifying description of these compounds as sulphenylium cation carriers there are compounds highly reactive (bisthio-sulphonium ions, sulphenyl chlorides) which allow the formation of sulphur–carbon, sulphur–nitrogen and, in general, sulphur–M bonds where M may be any one of a large variety of mono- or polyvalent atoms. On the other hand, there are others like disulphides, thiosulphonates so stable that react only with strong nucleophiles. It follows that it is possible to select from a large variety of reagents with vastly different properties the one most suited to the specific transformation under study.

Beside that, the very extended mechanistic work lead to improved general knowledge of the electrophilic additions to double and triple carbon–carbon bonds and by the isolation of the 'reaction intermediates', the thiiranium and thiirenium ions, helped to put on more solid bases the description of these important reactions.

The extremely high stereoselectivity and the confinement of the reaction to a single π-system in polyenes or polynes allow the selected functionalization of a chosen unsaturated centre with two groups of different intrinsic properties which may be the sites of different transformations.

As the chemistry of these reagents is expanding in every direction at a fairly high pace, it has not been possible to cover in this chapter all the vast literature related to this field. We have therefore been forced to make a selection either for type of reagents or for type of reactions of each specific reagent. The guidelines have been to select the most informative reactions under a mechanistic point of view or the sulphenyl derivatives most widely utilized in organic synthesis.

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The Chemistry of Sulphenic Acids and their Derivatives
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CHAPTER **11**

Photochemistry and radiation chemistry

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I. INTRODUCTION

For the purpose of this review the compounds included are those containing divalent sulphur bonded to a hetero atom as in C–S–X, where X can be Br, Cl, I, O, N or N=. The

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photochemical reactions covered involve, in the main, S–X bond fission, although some processes are included where rearrangement of the C–S–X concatenation takes place. The photochemistry of this grouping is very poorly reviewed and referenced and material is scattered throughout the literature in a variety of guises, often difficult to locate by conventional scanning techniques. The review by Block[1] is reasonably comprehensive for the literature prior to 1969. Other useful review articles are the appropriate chapters in *Photochemistry*[2].

II. SULPHENYL HALIDES

A. Haloalkanesulphenyl Chlorides

This group of compounds is represented by the general formula RSX where X can be bromine, iodine, but is more usually chlorine. The UV/visible absorptions of the RSCl group is typified by the parent of the series, methanesulphenyl chloride (CH_3SCl), and shows maxima at 355 ($\varepsilon = 24.5$) and 205 ($\varepsilon = 235$)[3]. Changes in substitution on the carbon do not appear to influence either the position or the intensity of the bands as shown by CF_3SCl, which has low intensity maxima at 333 nm ($\varepsilon = 25$) and 214 nm ($\varepsilon = 235$) in the gas phase and maxima at 322 ($\varepsilon = 10$) and 324 ($\varepsilon = 12$) in petroleum or chloroform[4].

The most common photoreaction observed for the sulphenyl halides is fission of the S–X bond and the production of the corresponding sulphur-centred radical and halogen atoms. The chemistry, thereafter, is of the free radical type. Trifluoromethanesulphenyl chloride is typical and decomposes on irradiation through quartz to afford CF_3Cl and sulphur chlorides[4]. γ-Radiolysis of Me_2CHSCl is also reported to bring about fission of the S–Cl bond[5]. Harris[6] has studied the irradiation (UV through Pyrex or X-ray) of trifluoromethanesulphenyl chloride in the presence of alkenes. This allows the trapping of the radical species ($CF_3S^{\cdot}$ and chlorine atoms) produced. Typically, addition to 1,1,2-trifluoroethene yields the two adducts **1** and **2** in the yields shown. The formation of the

TABLE 1. Photoaddition of trifluoromethanesulphenyl chloride to alkenes[6].

Alkene	Time (h)	Products	Yield (%)
$CF_2{=}CFH$	2.75	CF_3SCF_2CFHCl (**1**) $CF_3SCFHCF_2Cl$ (**2**)	50 11
$CF_2{=}CFCF_3$	3 days	$CF_3SCF_2CFClCF_3$ $CF_3SCF(CF_3)CF_2Cl$ $CF_3SCF_2CF(CF_3)SCCl_3$ $Cl(C_3F_6)_2Cl$ CF_3SSCF_3	 26.4 Total 10
$ClCF{=}CF_2$	26	$CF_3SCFClCF_2Cl$ $CF_3SCF_2CFCl_2$	42 12
$CH_2{=}CHCl$	16	$CF_3SCF_2CFCl_2$ $CF_3SCHClCH_2Cl$	12 73
$CH_3OCF{=}CF_2$	10 min	$CH_3OCF(SCF_3)CF_2Cl$ $CH_3OCFClCF_2SCF_3$ $CH_3OCF(SCF_3)CF_2SCF_3$ CF_3SSCF_3	16 26 11 31
$CH_2{=}CF_2$	9.75	$CF_3SCF_2CH_2Cl$ $CF_3SCF_2CH_2Cl$ CF_3SSCF_3	40 11 12

$R^1R^2R^3CSX$

(4) (a) $R^1 = R^2 = R^3 = F$, $X = Cl$

(b) $R^1 = R^2 = F$, $R^3 = Cl$, $X = Cl$

(5) (a) $R^1 = F$, $R^2 = Cl$, $R^3 = Br$, $X = Br$

(b) $R^1 = R^2 = F$, $R^3 = Br$, $X = Br$

(6) $R^1 = R^2 = R^3 = X = Cl$

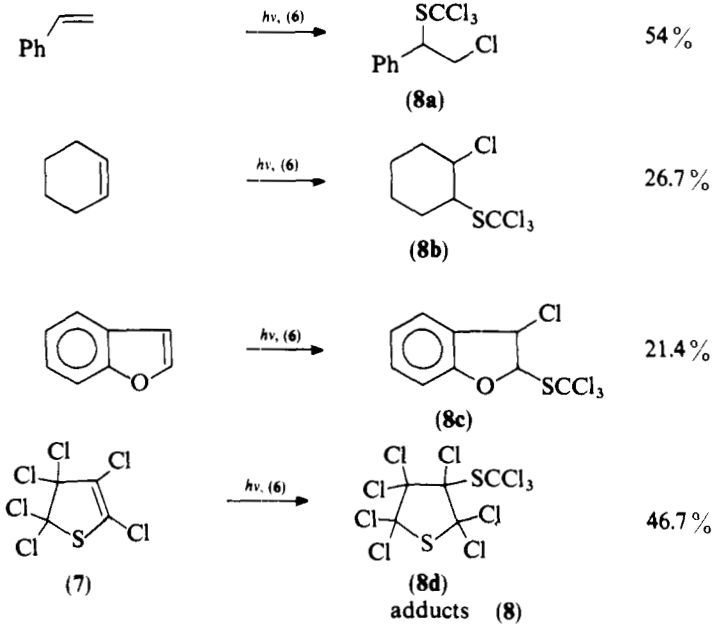
products arises by the addition of the chlorine atom as the key step. Assuming this to be the case, the predominance of the adduct **1** is readily explained. The addition to other alkenes follows the same path and the results are tabulated (Table 1)[6].

Haas and Klug[7] have also described the photochemical behaviour of CF_3SCl and its use in the synthesis of the disulphides **3** which can be prepared in high yield by the photochemical addition of the sulphenyl chlorides **4** and sulphenyl bromides **5** to CF_2S and CFClS; again the reaction involves the homolytic fission of the S–halogen bond. The products and the yields are shown in Table 2.

TABLE 2. Additions of sulphenyl halides to XYC=S compounds[7].

Sulphenyl halide	Substrate	Product (3)	Yield (%)
CF_3SCl	F_2CS	F_3CSSCF_2Cl	72
FClBrCSBr	F_2CS	$FClBrCSSF_2Br$	78
$F_2BrCSBr$	F_2CS	$F_2BrCSSF_2Br$	100
CF_3SCl	FClCS	$F_3CSSCCl_2F$	56
CF_2ClSCl	FClCS	$F_2ClCSSCFCl_2$	62
FClBrCSBr	FClCS	FClBrCSSCBrClF	75

The photochemical reactions of trichloromethanesulphenyl chloride (**6**) follow a similar reaction path. Thus the chloride **6** can be added to alkenes such as styrene, cyclohexene, benzofuran and the chlorinated thiophene (**7**) to afford the adducts (**8**) shown in Scheme 1[8]. The identity of the styrene adduct presented some difficulty but Kloosterziel[9] has suggested that, since the trichloromethylthiyl radical should add first to afford the more stable radical, the correct identity should be as shown in **8a**. Other alkenes have also served as substrates[10]. The reactivity of these compounds again involves homolytic fission. Prey and coworkers[11] also examined the hydrogen abstracting potential of the chloride **5** in reactions with cyclohexane where high yields (80%) of cyclohexyl chloride are obtained. Photoreactions of a variety of sulphenyl halides (Scheme 2) in other hydrocarbons have shown that reasonable yields of the corresponding disulphides can be obtained [12]. Later work by Kloosterziel[13a] demonstrated that trichloromethanesulphenyl chloride (**6**) is a highly selective chlorinating agent where the $Cl_3CS^{\cdot}$ was the hydrogen abstracting species and chlorination of pentane occurs in a ratio of 1:0.31 for secondary: primary attack while that for 2,3-dimethylbutane shows a ratio of 3.36:0.03 for tertiary: primary. There is a further enhancement of this selectivity when the reactions are carried out in benzene. A further paper supplemented this work by a study of chlorination of 1-chlorobutane and 1-chloropropane[13b].



SCHEME 1

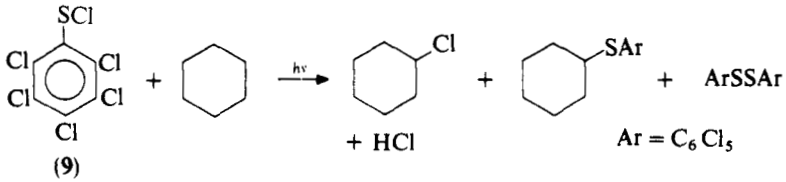
$$RSCl \xrightarrow{h\nu} RSSR$$

(a) R = Pr	(a) 39.4%
(b) R = Bu	(b) 58%
(c) R = Ph	(c) 24.8%
(d) R = 4-Tol	(d) 51.7%

SCHEME 2

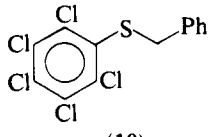
B. Arenesulphenyl Chlorides

Pentachlorobenzenesulphenyl chloride (**9**) reacts in sunlight with cyclohexane to yield the products shown in Scheme 3. It is interesting to note that both chlorine and arylsulphenyl substitution takes place but that the latter is dominant. The reaction is somewhat different when irradiation is carried out in toluene where the process is



SCHEME 3

dominated by the formation of the sulphide **10**, a preference explained by the involvement of a charge transfer interaction between the sulphenyl chloride and the toluene. Benzoquinone has also been used as a substrate for reaction and the products **11** and **12** are isolated[14]. A novel reaction occurs affording the thiophene **13** when the sulphenyl chloride **9** is irradiated in carbon tetrachloride[15, 16]. The suggested mechanism is a photochemical loss of sulphur dichloride to afford tetrachlorobenzyne, followed by reaction with the sulphenyl chloride to yield **14** from which the final compound is obtained.



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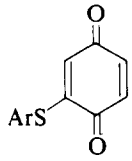
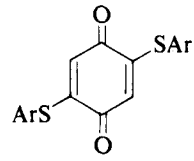
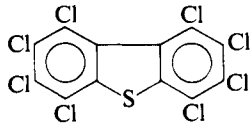


(11)



(12)

Ar = C_6Cl_5



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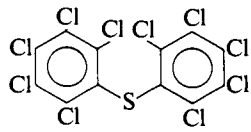
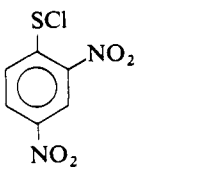


(14)

Several accounts have been given regarding the photochemical oxygen transfer reaction taking place from an *o*-nitro group. Perhaps the earliest report of this involved 2,4-dinitrobenzenesulphenyl chloride (**15**), which on irradiation in water/acetic acid afforded a high yield of 2-amino-4-nitrobenzenesulphonic acid (**16**)[17]. A similar result was also reported by Barton and his coworkers[18]. This reaction is not restricted only to the dinitro derivatives and Pillai[19] has reported the conversion of 2-nitrobenzenesulphenyl chloride (**17**) into 2-aminobenzenesulphonic acid (**18**) in 80% yield. One possible mechanism for this reaction is shown in Scheme 4. Here, conversion of the sulphenyl chloride to the sulphenic acid takes place followed by irradiation during which oxygen is transferred from the *o*-nitro group to the sulphenic acid group. This yields a nitrene which picks up hydrogen from the medium.



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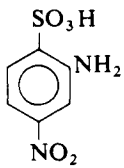

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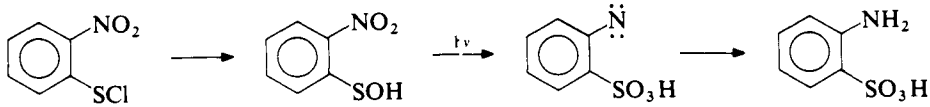


(17)

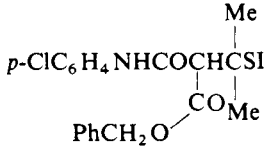
(18)

SCHEME 4

The homolytic fission of the S–Cl bond of sulphenyl chlorides has been studied as a means of making photodegradable polymers. However, often these (e.g. **15**) are found to be poor additives for the purpose[12].

C. Sulphenyl Iodides

Sulphenyl iodides have been postulated as intermediates in reactions but few have been obtained as isolable compounds. Field and White[21] have reported that the stable iodide **19** is photochemically reactive and decomposes on irradiation under unspecified conditions to yield the disulphide **20**. Similar behaviour is reported for the sulphenyl iodide **21** which yields the corresponding disulphide and iodine in a zero-order process[22].



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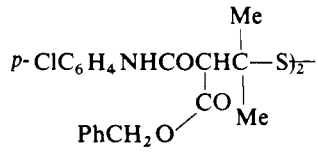

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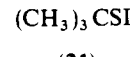


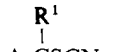
(21)

D. Miscellaneous Sulphenyl Chlorides

Bacon and his coworkers[23, 24] studied the photochemical reactions of the sulphenyl chloride **22**. This is also subject to S–Cl bond fission affording the thiyl radical **23** and a chlorine atom. Irradiation of **22** through pyrex in alkyl-substituted arenes affords the products **24** by a path involving hydrogen abstraction by the chlorine atom. A study of the photochemical decomposition of Captan (**25**) and Difolotan (**26**), fungicides for fruit and vegetables, in hexane and ethanol using 254 nm has shown that reaction in ethanol is faster. Captan and Difolotan yield *cis*-cyclohex-4-ene-1,2-dicarboximide as the main product in both solvents[25]. Previous studies had reported that these compounds readily decomposed on exposure to sunlight[26].

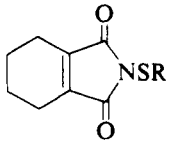
(22)

(23)



(24)

$R^1 = R^2 = H$, Ar = Ph
$R^1 = H$, $R^2 = Me$, Ar = Ph
$R^1 = R^2 = Me$, Ar = Ph
$R^1 = H$, $R^2 = Ar$ = Ph
$R^1 = R^2 = Ar$ = Ph



(25) R = CCl_3

(26) R = CCl_2CHCl_2

III. SULPHUR–NITROGEN SYSTEMS

A. Sulphenamides

Sulphenamides are commonly used as thermal vulcanization accelerators where homolytic fission of the S–N bond results in the production of free radicals. Various

studies have demonstrated that this type of compound is also photochemically reactive. Thus irradiation of the sulphenamides **27** in out-gassed benzene solution affords the radicals **28**. This reaction occurs via a path involving the fission of the S–N bond yielding the radicals **29** and **30**. Reaction of **29** with the sulphenamide **27** yields the radical **28** and *t*-butylamine[27]. These radicals can also be produced directly by hydrogen abstraction using *t*-butoxy radicals. An ESR study of the radicals **28** was carried out[27]. A similar reaction path is observed with the benzoyl sulphenamides **31** which, on irradiation, afford the radicals **32**. Again, these are presumed to be formed by S–N fission and abstraction of hydrogen from **31** by the amidyl radical **33**[28]. The ESR study shows that the electron is unpaired and resides on the nitrogen.

$(CH_3)_3CNHSAr$

(27) Ar = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$

$(CH_3)_3\dot{C}NSAr$ **(28)** $(CH_3)_3C\dot{N}H$ **(29)** $ArS^{\cdot}$ **(30)**

$RC(=O)NHSAr$

(31) R = Ph, Ar = Ph, *p*-ClC_6H_4 or C_6D_5
R = *p*-$MeOC_6H_4$ or *p*-$NO_2C_6H_4$, Ar = *p*-ClC_6H_4
R = $(CH_3)_3C$, Ar = Ph or *p*-ClC_6H_4

$RC(=O)\dot{N}SAr$ **(32)** $RC(=O)\dot{N}H$ **(33)**

Bayfield and Cole[29] have demonstrated that diffuse sunlight can also bring about S–N fission. This was demonstrated by the irradiation of a mixture of the sulphenamides **34a** and **35a** whereby the exchange products **34b** and **35b** are produced. Several examples of this process were carried out: e.g. **34b**, **35b** yields **34a**, **35a**; **34c**, **35c** yields **34a**, **34d**; and **34b**, **35d** yields **34c**, **35c**. The yields of exchange products are dependent on the dose of irradiation. Fission of the S–N bond is also observed on irradiation of the phosphoranylidene derivative **36**. In this case only a low yield (11%) of the disulphide **37** was formed as well as triphenylphosphine (61%) and tar[30]. Interestingly no oxygen transfer from the

R^1SNHR^2

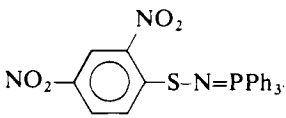
(34)

	R^1	R^2
(a)	*p*-Tol	Ph
(b)	Ph	Ph
(c)	*p*-ClC_6H_4	Ph

R^3SNHR^4

(35)

	R^3	R^4
(a)	Ph	*p*-Tol
(b)	*p*-Tol	*p*-Tol
(c)	Ph	*p*-ClC_6H_4
(d)	*p*-ClC_6H_4	*p*-ClC_6H_4



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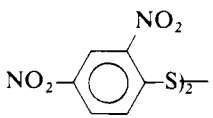
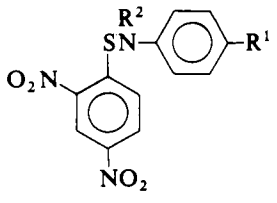


(37)

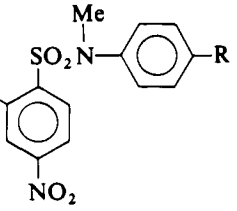
o-nitro group to the sulphur was detected. However, this was observed with the sulphenamides **38** which, on irradiation in benzene, yielded the sulphonamides **39** in low yield[31]. Oxygen transfer of this type has already been discussed in the section dealing with sulphenyl chlorides. When the nitrogen of the sulphenamide is not methylated as in **40**, the oxygen transfer is suppressed and only N–S bond fission occurs affording azobenzene (34%) by a free radical path[31]. Free radical fission is also predominant in the irradiation of the sulphenamide **41** in pentane. Using weak sunlight is sufficient to afford the products shown in Scheme 5. The structurally simpler sulphenamide **42** is also reactive under the same conditions affording the photo-Fries-type products **43** (15%), **44** (14%). In addition *N*-Methylaniline (21%) and diphenyl disulphide (39%) are formed confirming the involvement of a free radical process[32].

The ease of cleavage of the S–N bond has also been exploited in the design of radioprotective agents. Thus the sulphenamides **45** and **46** have been synthesized and shown to offer weak protection in mice[33].

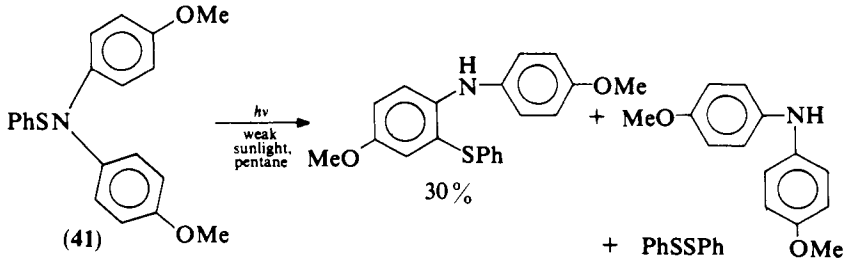


(**38**) R^1 = Me or H, R^2 = Me

(**40**) R^1 = Me or H, R^2 = H

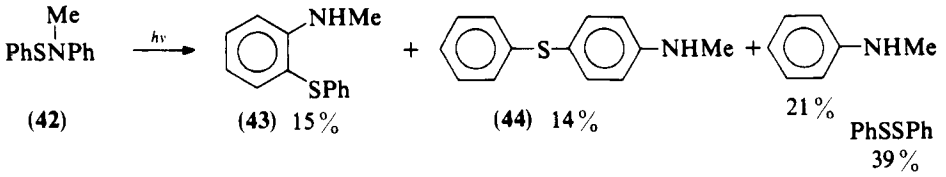


(**39**)

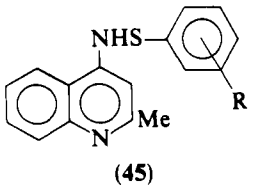


(**41**)

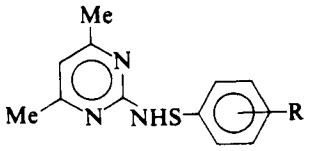
SCHEME 5



(**42**) (**43**) 15% (**44**) 14% 21% PhSSPh 39%



(**45**)



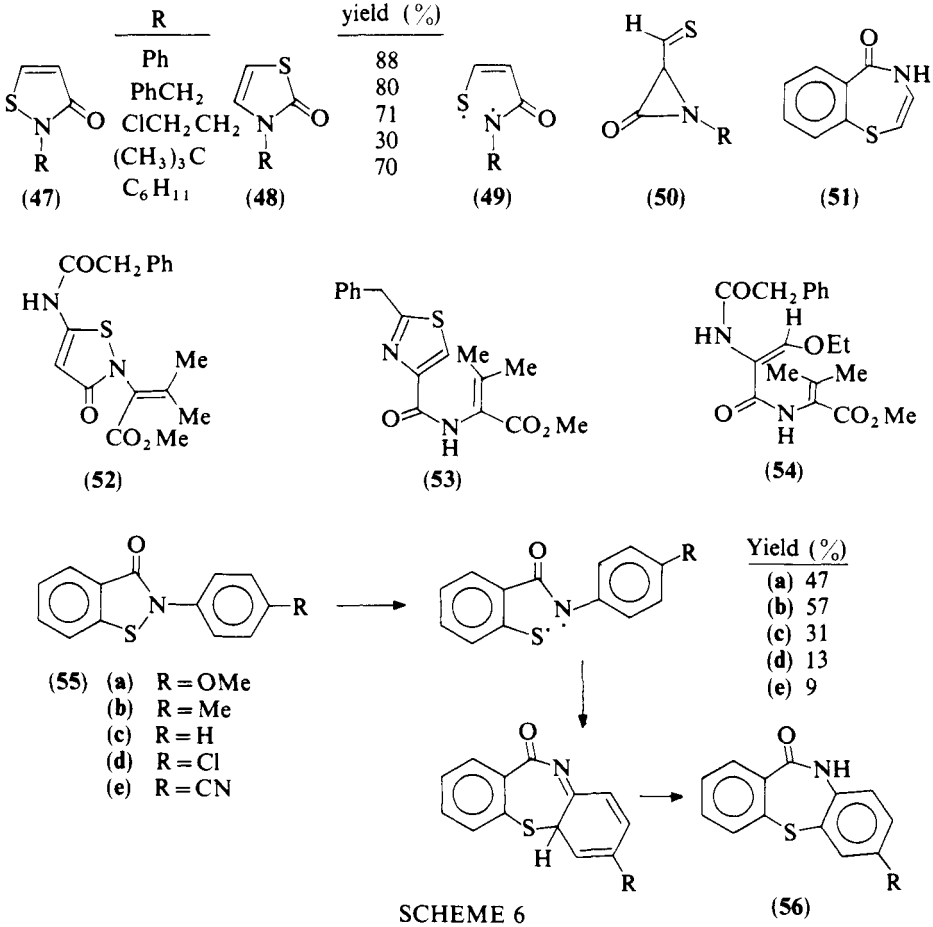
(**46**)

R = 2-or 3-NO_2

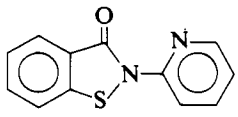
R = 2,4-$(NO_2)_2$

B. Isothiazolones

The isothiazole group of compounds is related to the sulfenamides. The photochemistry of such systems is again dominated by the weakest bond in the system and usually irradiation brings about S–N bond fission to afford radicals from which the products are obtained. A typical reaction is shown by the irradiation of the isothiazol-3(2*H*)-ones **47** which affords the isomeric compounds **48** in the yields shown. The initially formed biradical **49** ring closes to the aziridinone **50** from which the final products are obtained. The intermediacy of the biradical **49** gets support from the isolation of the product **51** via bonding at the *ortho* site of the *N*-phenyl group[34]. It is likely that the transformation of the derivative **52** follows the same path yielding **53** and **54**[35]. Analogous behaviour is reported for the 2-aryl-1,2-benzisothiazol-3(2*H*)-ones **55** which, on irradiation through Corex or Pyrex, affords the products **56** by the path shown in Scheme 6[36]. This free radical path, cyclization and 1,7-hydrogen migration is common to a variety of derivatives such as the pyridyl **57**[37], pyrazinyl **58**[37] and naphthyl **59**[38] analogues. All of these rearrange efficiently to yield the corresponding thiazepinones **60**, **61** and **62**, respectively.



SCHEME 6



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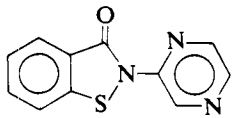

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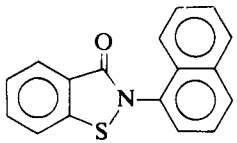

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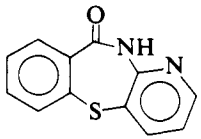

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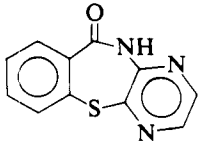

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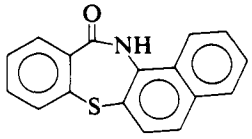

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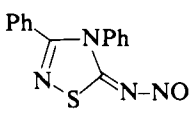

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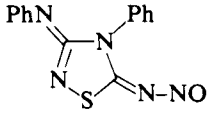
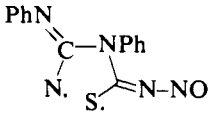


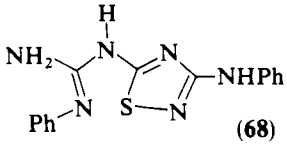
(64)



(65)

PhNHCN (66)

PhNHCONH$_2$ (67)

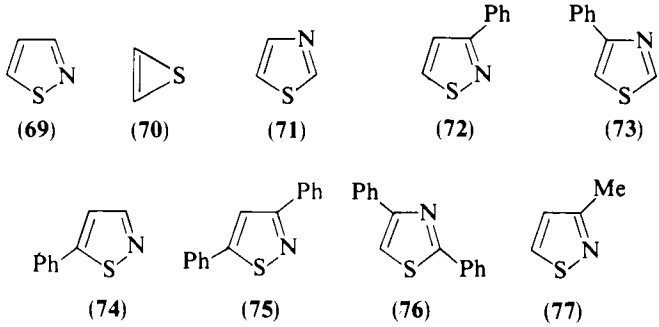


(68)

The *N*-nitrosoimines **63**, **64** are loosely related to the isothiazolones. However, **63** is only poorly photochemically reactive under a variety of conditions while the bis-imine **64** undergoes S–N fission to afford a biradical **65** from which the products **66–68** are produced[39].

C. Isothiazoles

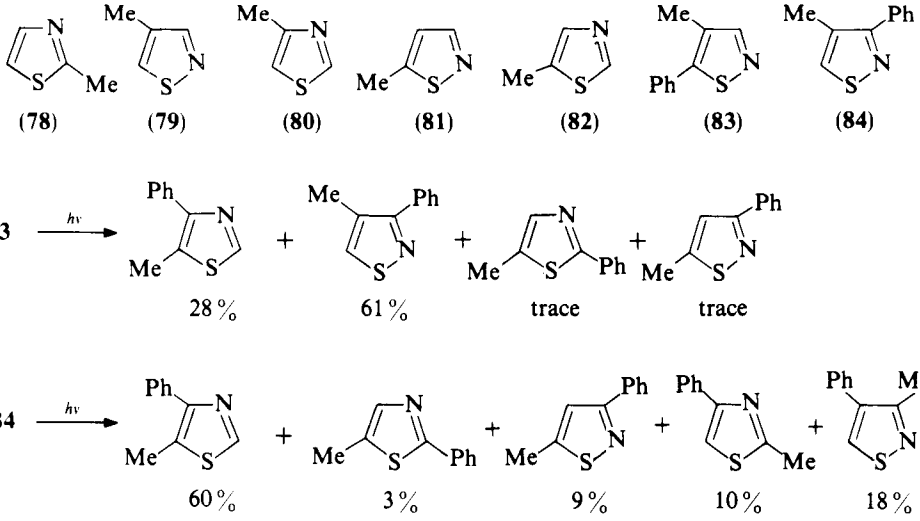
Photofission of the S–N bond is not common in the irradiation of isothiazoles. However, there is one report that the parent isothiazole **69** on irradiation in an argon matrix affords the thiiren **70**[40, 41]. The formation of this species will be discussed in more detail later. Generally, the photoreactivity of the isothiazoles is one where ring rearrangement brings about conversion into a thiazole **71**. Typical of this is the irradiation of the parent base, isothiazole **69**, which gives thiazole **71** in 7% yield when the irradiation is carried out in propylamine or 1% when carried out in ether[42]. Several unidentified products are also formed. The rearrangement is more successful when substituted derivatives are studied. Thus irradiation at 254 nm in ether of 3-phenylisothiazole **72** yields 4-phenylthiazole (**73**, 12%) and recovered starting material (72%) while 5-phenylisothiazole (**74**) yields 3-phenylisothiazole (**72**, 2.3%) and starting material (35%) under the same conditions[43]. Better yields of product are obtained with heavier substitution and 3,5-diphenylisothiazole (**75**) is converted into 2,4-diphenylisothiazole (**76**, 48%)[43] respectively. Vernin and coworkers[44] have also studied the photorearrangement of the 3-phenylisothiazole (**72**). Other detailed studies on the photochemistry of isothiazoles and thiazoles have shown that there is a decreasing order of reactivity as



(69) (70) (71) (72) (73)

(74) (75) (76) (77)

follows: 2-phenylthiazole or 5-phenylisothiazole > 5-phenylthiazole or 3-phenylisothiazole > 4-phenylthiazole or 4-phenylisothiazole[45]. The methyl isothiazole derivatives are also photoreactive and afford a mixture of products dependent on the position of the substituent. Thus irradiation of 3-methylisothiazole (**77**) yields 2-methylthiazole (**78**); 4-methylisothiazole (**79**) yields 4-methylthiazole (**80**) and 5-methylisothiazole (**81**); and 5-methylisothiazole (**81**) yields 5-methylthiazole (**82**), 4-methylisothiazole (**79**) and 3-methylisothiazole (**77**)[46]. In general, as was observed by Ohashi's group[43], disubstitution gives better yields of product. This has also been observed by Vernin and his coworkers in a study of the 4-methyl-5-phenylisothiazole (**83**) and 4-methyl-3-phenylisothiazole (**84**) derivatives[47], shown in Scheme 7. The mechanistic details of the mechanism for the rearrangement are not clear, although two main views have been expressed based upon the products formed and the results from irradiation in the presence of deuterium oxide. Vernin and his coworkers[45, 47] summarized by Lablache-Combier[48] favour the route shown in Scheme 8, where S–N bond fission is an important step. They argue that the

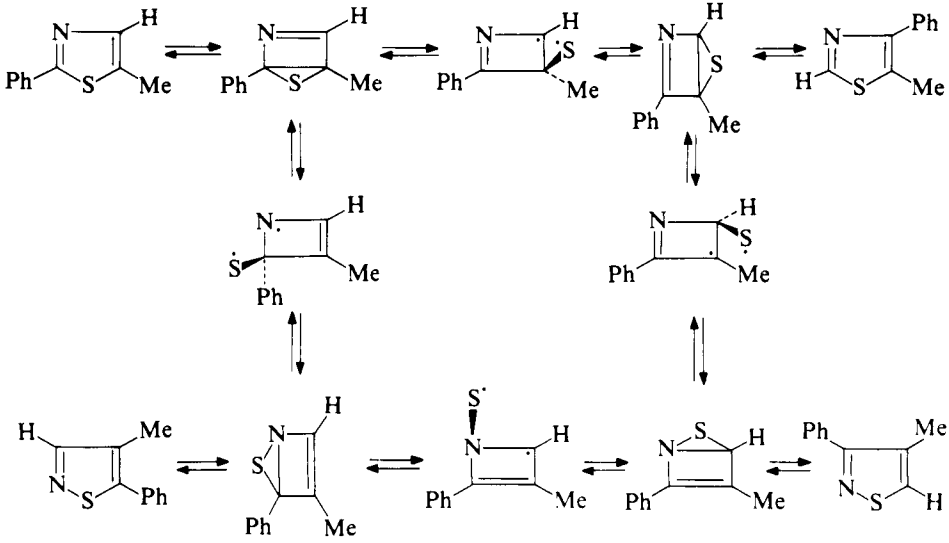


(78) (79) (80) (81) (82) (83) (84)

83 —hν→ 28% + 61% + trace + trace

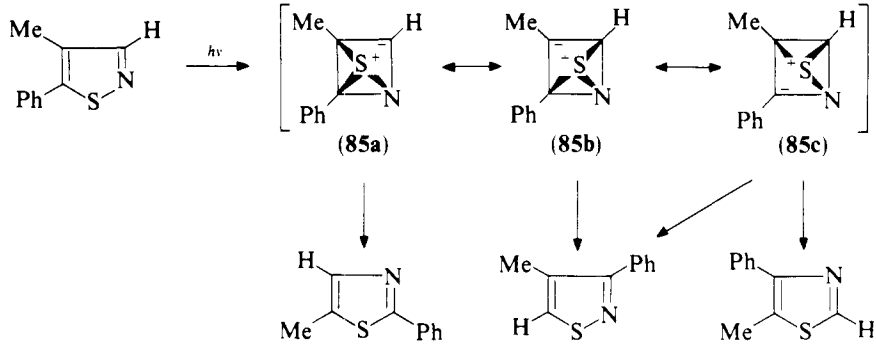
84 —hν→ 60% + 3% + 9% + 10% + 18%

SCHEME 7



SCHEME 8

major products result from bicyclic intermediates, *Dewar-type*, where the double bonds are conjugated with phenyl groups. It is also stated[48] that such intermediates are supported by calculation. An alternative route has been proposed by Kojima and coworkers[49, 50] and by Ohashi and collaborators[43, 51], who have studied the rearrangement of the phenylisothiazoles. Thus the irradiation of 5-phenylisothiazole (**74**) in ether/deuterium oxide affords 3-phenylisothiazole (**72**) with deuterium incorporated at C-4. Other experiments show that the deuterium incorporation is a photochemical process. They[49] suggest that this result implicates the tricyclic sulfonium species **85** shown in Scheme 9. They also reason that the involvement of these cations places the rearrangement of the isothiazoles into thiazoles together with the reverse rearrangement where such cations have also been implicated[52–55]. MO calculations have been carried out on the rearrangement of isothiazoles into thiazoles[56].

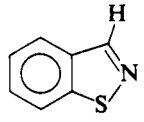


SCHEME 9

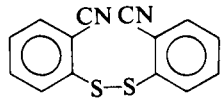
γ-Radiolysis studies have been carried out on isothiazole (**69**)[57] and pulse radiolysis studies on 4-nitroisothiazole[58].

D. Benzoisothiazoles

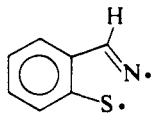
Fusion of the isothiazole to a benzene ring re-introduces the S–N fission path on irradiation of the benzoisothiazole **86**[59]. Thus irradiation in ether affords the disulfide (**87**, 12%) via the radical **88** formed on bond fission. Benzoisothiazole **86** also undergoes photochemical addition to dimethyl acetylenedicarboxylate affording the adducts **89** and **90**[60]. A further examination of the system has shown that addition can also take place to



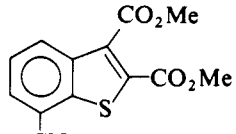
(**86**)



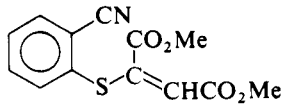
(**87**)



(**88**)

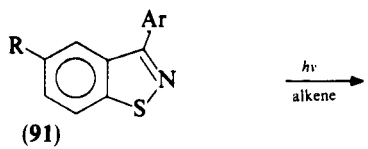


(**89**)



(**90**)

the derivatives **91**. Using a variety of alkenes, the adducts shown in equation **1** were obtained on irradiation. In this case the mechanism of the addition is more complex and it is proposed that the reaction involves a solvent-sensitive exciplex which dissociates to a radical cation radical anion pair **92**, which subsequently collapses to afford the final products in a regio- and stereo-specific fashion[61, 62]. Alternatively it has been proposed that the charge separated resonance form **93** could contribute to the process and addition to this would lead to a product in which the stereochemistry of the alkene was preserved[63]. The isomeric system **94** is photoreactive by N–S cleavage. Irradiation of the parent **94a** in benzene/diethylamine affords the aminoaldehyde **95** (19%) after acylation. The chloro derivative **94b** exhibits two types of reaction and in benzene/diethylamine the derivative **96** (10%) and the ring-opened compound **97** (26%) are obtained. These compounds are not interconvertible on irradiation and must therefore arise by independent paths. In methanol **94b** again affords a product **98** (8%) arising by substitution of the chlorine and a ring-opened product **99** (28%). In this case **98** can be photochemically converted into **99**[64].



(**91**) (1)

(**a**) R = H, Ar = Ph

(**b**) R = H, Ar = *p*-MeC_6H_4

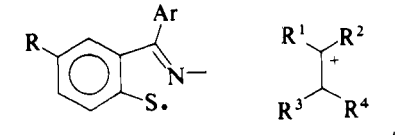
(**c**) R = Cl, Ar = Ph

$R^1 = R^2 = R^3 = R^4 = Me$

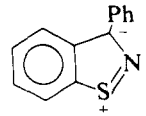
R^1 = OEt, R^2–R^4 = H

$R^1 = R^3 = Me$, $R^2 = R^4 = H$ (from *cis* but-2-ene)

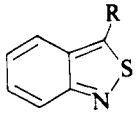
$R^1 = R^4 = Me$, $R^2 = R^3 = H$ (from *trans* but-2-ene)



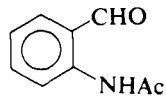
(92)



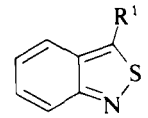
(93)



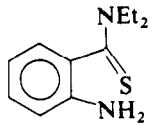
(94) (a) R = H
(b) R = Cl



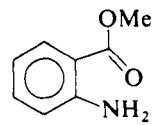
(95)



(96) $R^1 = NEt_2$
(98) R^1 = MeO

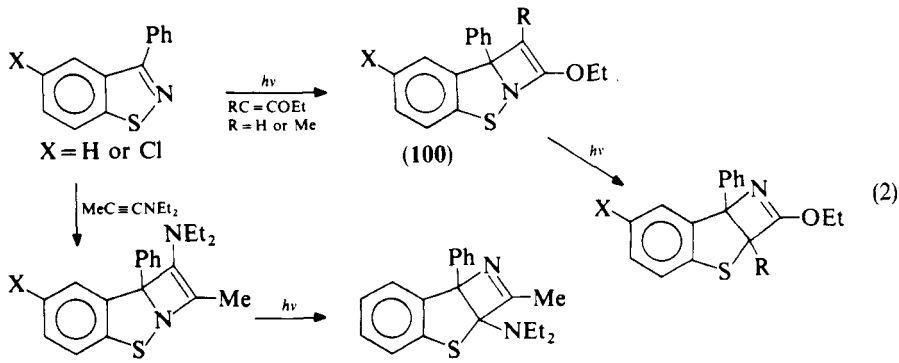


(97)



(99)

In at least one instance the S–N bond of the benzoisothiazole initially remains intact. Thus the irradiation of 3-phenyl-1,2-benzisothiazole (**90a**) in the presence of electron-donating alkynes (ethoxyethyne and diethylaminoethyne) the bicyclic compounds (e.g. **100**) are obtained by (2+2) addition and rearrangement[65]. The rearrangement involves the fission of the S–N bond in the initial (2+2)-cycloadduct by a second photon and rebonding as shown in equation 2.

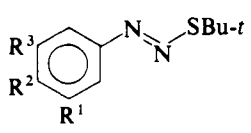


(2)

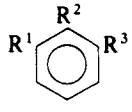
E. Thiadiazoles

1. *Diazosulphides*

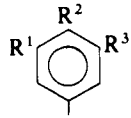
Irradiation at wavelengths > 400 nm of the diazosulphides **101** leads to interconversion of the *Z–E* isomers of the azo group. Irradiation at wavelengths > 365 nm brings about decomposition of the *Z*-isomer affording the products **102**, **103** and **104**[66].



(101)



(102)



(103)

t-BuSSBu-*t*

(104)

(a) $R^1 = R^3 = H$, $R^2 = CN$, NO_2 or Me_2N

(b) $R^1 = R^3 = Cl$, $R^2 = H$

2. *1,2,3-Thiadiazoles*

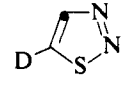
Krantz and Laureni and coworkers[40, 41, 67] have studied in considerable detail the photochemical reactivity of the parent 1,2,3-thiadiazole **105** in an argon matrix. Irradiation at 290 nm brought about loss of nitrogen and the formation of a species which was identified as the thiiren **106**. The identification of the reactive species **106** was aided by the use of ^{13}C and deuterium-labelled 1,2,3-thiadiazines **107**, **108** and **109**, respectively. The study has shown that irradiation affords thioketene and ethynethiol in addition to the thiiren. The labelled starting materials have enabled the identification of two paths of reaction. Thus with **107** irradiation induces the processes illustrated in Scheme 10, where

(105)

(106)

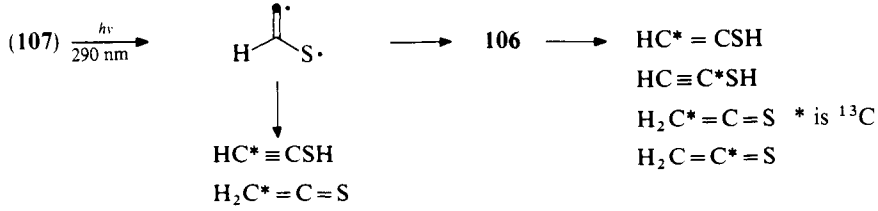
(107)

(108)



(109)

• is ^{13}C

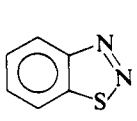


SCHEME 10

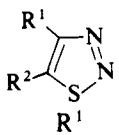
loss of nitrogen affords a biradical from which the two products can be formed. Ring closure of the biradical affords the thiiren **106**, which can ring-open to yield the same products but with the label distributed as shown. Meier and Kolshorn[68] have studied the ring opening of the thiiren **106** from a kinetic-modelling and energy-profile standpoint. Other workers[69] have also studied this process using a series of thiadiazoles **110–113**. The parent **105** in an argon matrix at 8 K using 265 nm yields detectable quantities of the thioketene and the ethyne. Irradiation at 215 nm gives evidence for the thiiren. The study of derivatives **111–113** also shows the presence of the corresponding thiirens and, in addition, the substitution plays an important part in that the formation of the thiiren is enhanced by the presence of electron-withdrawing substituents. Some criticism of the band assignments made in the foregoing has been made by Krantz and Laureni[70]. Further substantiation for the influence of electron-withdrawing substituents comes from the irradiation of the matrix isolated 4,5-disubstituted thiadiazole **114** which gives a quantitative yield of the thiiren **115**[71]. 1,2,3-Thiadiazole **105** is also reactive in the gas

phase on irradiation at wavelengths >220 nm. Again, loss of nitrogen occurs quantitatively along with formation of a small amount of carbon disulphide and the corresponding alkyne (12.6%). The methyl derivatives (**116**, **117**) follow the same path yielding nitrogen, carbon disulphide, methane and the alkyne **118** (14.4 and 16.1%). Interestingly irradiation of **116** and **117** with hexafluorobut-2-yne affords the same thiophene **119** in 12.3 and 12.5%. This result is evidence for the generation of the thiiren **120** as a common intermediate in the gas phase[72].

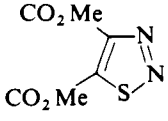
The influence of substituents is also observed on irradiation at 265 nm of the thiadiazole **121** in an argon matrix. This affords the carbene **122** which converts into the thiiren **123**[73]. It is interesting to note that an ESR study of the photochemical decomposition of 4,5-diphenyl-1,2,3-thiadiazole **124** has identified the triplet biradical **125**[74]. A path involving radicals had been identified following a study of the irradiation of 1,2,3-thiadiazoles **105**, **110**, **112**, **126a** by ESR spectroscopy[75].



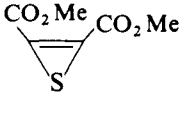
(**110**)



	R^1	R^2
(**111**)	CF_3	H
(**112**)	Me	CO_2Et
(**113**)	CO_2Et	Me
(**116**)	Me	H
(**117**)	H	Me
(**121**)	COMe	Me
(**124**)	Ph	Ph

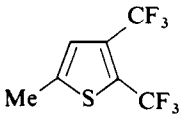


(**114**)

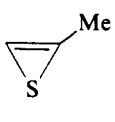


(**115**)

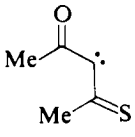
(**118**)



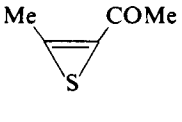
(**119**)



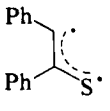
(**120**)



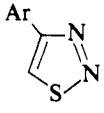
(**122**)



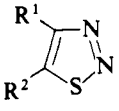
(**123**)



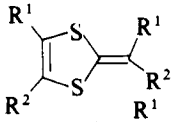
(**125**)



(**126**) Ar = Ph
p-biphenylene
1-naphthyl
2-naphthyl



(**127**) $R^1 = R^2 = Ph$
(**128**) $R^1 = CO_2Me$, $R^2 = Ph$

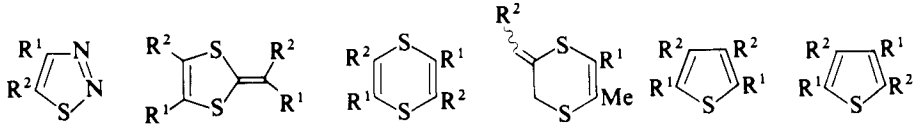


(**129**)

R^1	R^2
Ph	H
p-biphenylene	H
1-naphthyl	H
2-naphthyl	H
Ph	Ph
CO_2Me	Ph

One of the earliest studies on the photochemical reactivity of substituted 1,2,3-thiadiazoles was carried out by Kirmse and Horner[76]. They studied photochemical conversion of the 5-aryl substituted thiadiazoles **126** and the disubstituted derivatives **127**,

128 into the dithiafulvenes **129**. Later work by Zeller and coworkers[77] has extended the scope of the procedure. The compounds **130** are all photochemically reactive on irradiation into the $\pi\pi^*$ long-wavelength absorption. The compounds formed by the loss of nitrogen are to some extent dependent on the nature of the substituents as can be seen from Scheme 11.



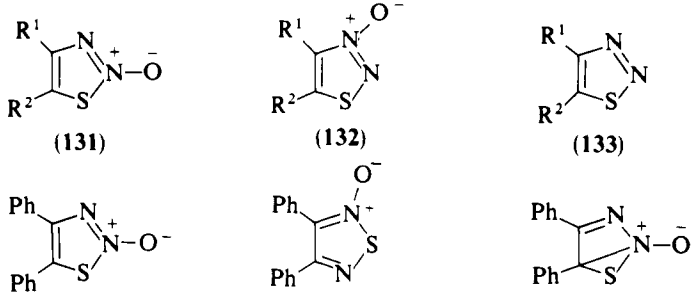
(130)

	R^1	R^2					
(a)	Me	CO_2Et	100	—	6	—	—
(b)	Me	COPh	—	—	35	100	65
(c)	H	Ph	100	—	—	—	—
(d)	Ph	Ph	100	25	—	—	—
(e)	Ph	CO_2Me	10	—	—	100	—
(f)	benzo		—	100	—	—	—

Relative yields of products

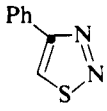
SCHEME 11

The photoactivity of the thiadiazole oxide **131** has also been studied but reactions do not involve S–N bond fission. Thus irradiation affords the products **132** and **133**. The diphenyl derivative **134** behaves somewhat differently and gives a low yield of **135** which is thought to arise via the bicyclic intermediate **136**[78]. The search for a thiiren intermediate has also been carried out in the aryl-substituted thiadiazoles. Thus the ^{13}C labelled 4-phenyl- and 5-phenyl-1,2,3-thiadiazole (**137**, **138**) on irradiation at >230 nm in benzene affords the corresponding dithiafulvenes (**139**, **140**). Irradiation in alcohols affords the thioesters **141** and **142** by trapping of the corresponding thioketenes. There is no evidence from work with thiadiazole **137** that a thiiren is involved. However, the 5-phenyl-1,2,3-thiadiazole is thought to yield a thiiren **143** by loss of nitrogen[79]. The thiadiazole **143** loses nitrogen on irradiation and yields the three products which are formed by the route shown in Scheme 12 and verified by labelling studies[80]. The influence of ring size on the process has been studied and the products obtained are shown in Scheme 13[81].

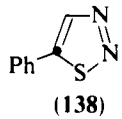


(131) **(132)** **(133)**

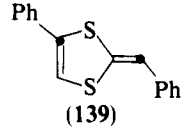
(134) **(135)** **(136)**



(137)

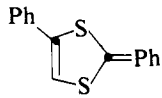


(138)



(139)

● is ^{13}C



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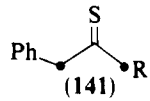

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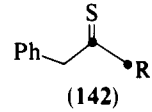
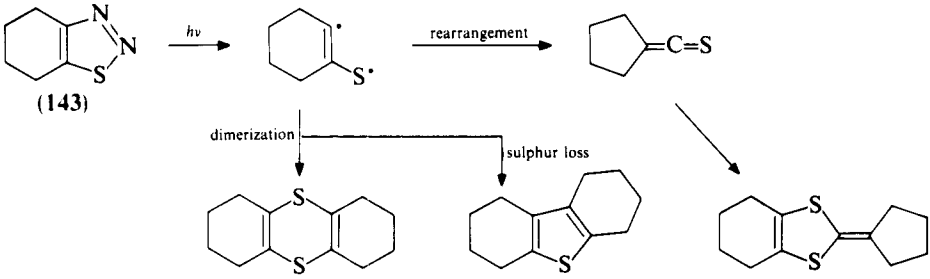
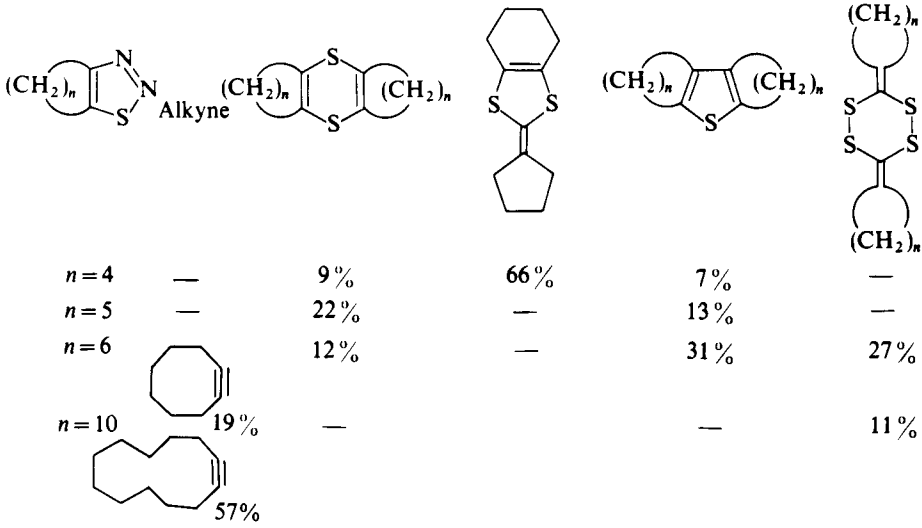


(142)



(143)

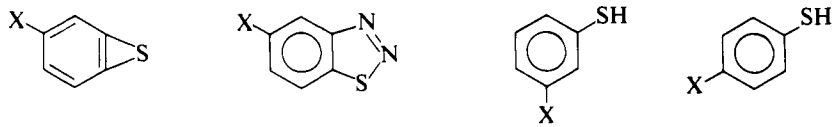
SCHEME 12



	Alkyne				
$n=4$	—	9%	66%	7%	—
$n=5$	—	22%	—	13%	—
$n=6$		12%	—	31%	27%
$n=10$	19%	—		—	11%
	57%				

SCHEME 13

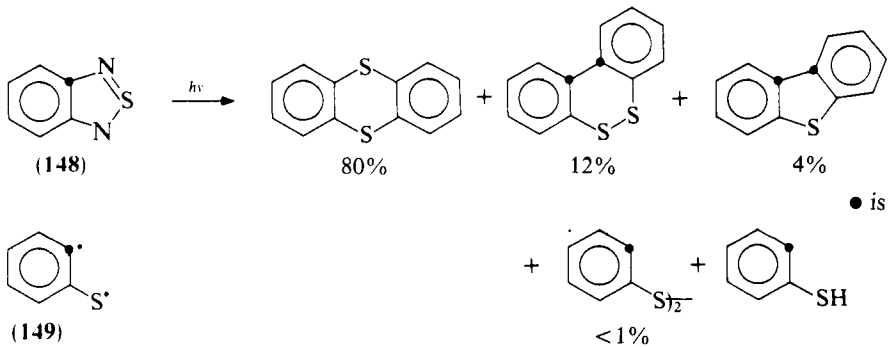
Earlier it was mentioned that benzo-1,2,3-thiatriazole (**110** ≡ **130f**) is converted photochemically[77] and is converted into a dithiadioxin derivative (Scheme 11). Others have sought to demonstrate the involvement of a thiiren in the rearrangement of the benzothiadiazoles. Thus White and collaborators[82] have shown that the presence or absence of a thiiren **144** in the photoreaction of the benzothiazoles **145** was dependent upon substitution. The irradiation of **145a** affords only *m*-methoxythiophenol (100%) using Pyrex filtered light. The other derivatives behave differently and yield mixtures of *m*- and *p*-substituted thiophenols (**146**, **147**) in the yields shown. The scrambling of the position of the sulphur was taken as evidence for the thiiren. However, a later study using the benzothiadiazole **148** labelled as shown with ^{13}C fragments on irradiation affords the products shown in Scheme 14. An analysis of the labelling pattern in the products clearly shows that benzothiiren is not an intermediate in this reaction and that the biradical **149** is the intermediate produced on loss of nitrogen from **148**[83].



(**144**) (**145**) (**146**) (**147**)

(**a**) X = MeO
(**b**) X = Cl
(**c**) X = CO_2Me
(**d**) X = Me

(**b**) 77% (**b**) 23%
(**c**) 69% (**c**) 31%
(**d**) 83% (**d**) 17%



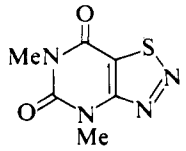
(**148**) 80% 12% 4%

● is ^{13}C

(**149**) <1%

SCHEME 14

Senga and coworkers[84] report that the thiadiazole **150** also loses nitrogen on irradiation in ethanol. This affords the biradical **151** which abstracts hydrogen from the solvent. The resultant thio radical dimerizes to yield the disulphide **152** in 50% yield. Loss of nitrogen from 4-vinyl-5-methyl-1,2,3-thiadiazole (**153**) has been used as a method for cross-linking in polymer chains[85, 86]. Thus the polymerization of the thiadiazole affords a polymer with a backbone of the type shown in **154**. Irradiation brings about loss of nitrogen and cross-linking yielding sulphur bridges of the type shown in **155** and **156**. These systems are commonly produced on irradiation of monomeric thiadiazoles. Cross-linking of polymer chains can be achieved by the elimination of nitrogen from copolymers incorporating 5-vinyl-1,2,3-thiadiazoles[86]. Pesticides incorporating the thiadiazole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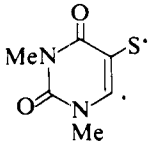
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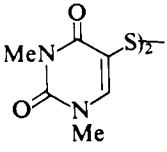
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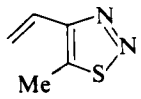
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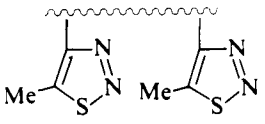
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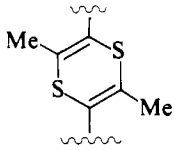
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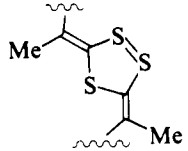
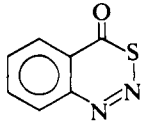

(156)

grouping have also been synthesised and a method for testing the photochemical decomposition of *Thidiazuron* samples sprayed on earth has been published[87].

3. Thiadiazines and 1,2,5-thiadiazoles

The loss of nitrogen on photolysis of the thiadiazine **157** affords the thiobenzpropiolactone **158** detected spectroscopically[88]. Such an intermediate has been detected previously by irradiation of other starting materials[89]. This intermediate thermally yields the final products **159** and 160 of the reaction. When irradiation of **157** is carried out in butan-1-ol, the ester **161** is the major product again as a result of involvement of the propiolactone **158**. 1,2,5-Thiadiazoles (**162**) undergo photochemical fission to yield nitriles and elemental sulphur[90].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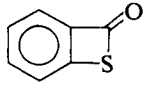
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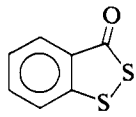
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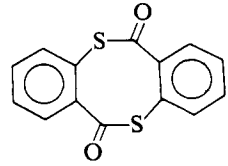
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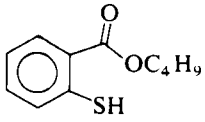
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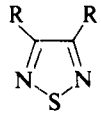
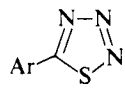
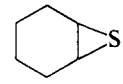

(162) R = Ph or Me

F. 1,2,3,4-Thiatriazoles

1,2,3,4-Thiatriazoles also have S–N bonding and can be classified as a type of sulphenamide. Some of the early photochemical studies have been reviewed[91]. Several accounts have appeared over the years of the photochemical elimination of nitrogen from these compounds. The first report is probably that of Kirmse[92] who observed that aryl cyanides, aryl cyanates and sulphur are formed on irradiation of 5-arylthiatriazoles (**163**).

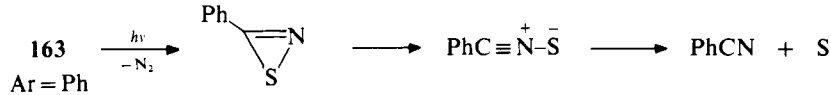


(163)



(164)

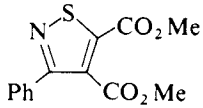
The photolysis of 5-phenyl-1,2,3,4-thiatriazole (**163**, R = Ph) and 5-amino-1,2,3,4-triazole in cyclohexene was studied by Okazaki's group[93] and it was found that the episulphide **164** was formed in low yield. The addition to 2,3-dimethylbut-2-ene was also examined. The process was thought to involve the generation of a nitrene from which sulphur was extruded. There is little doubt, however, from this early work that the triplet state of the thiatriazole was unreactive and that an excited singlet state was involved in the extrusion of nitrogen. Holm and coworkers[94] have studied the decomposition of 5-phenyl-1,2,3,4-thiatriazole (**163**, R = Ph) in considerable detail. Like Okazaki and coworkers[93] they[94] observed that the singlet state was reactive and fragments on photochemical excitation to afford phenyl isothiocyanate (5–8%). Benzonitrile (65–76%) and sulphur are also formed via the thiazirine **165** and the nitrile sulphide **166** as shown in Scheme 15. The extruded



SCHEME 15

nitrogen has been shown by labelling studies to arise from the N(2)–N(3) nitrogens and no evidence for nitrogen scrambling was found. The thiazirine **165** is stable at 10–15 K when embedded in PVC[95]. The formation of the benzonitrile sulphide has been studied by laser flash photolysis and can be trapped by a variety of substrates, e.g. as the isothiazole **167** by dimethyl acetylenedicarboxylate. This work has also demonstrated that the amount of benzonitrile sulphide formed is independent of the conditions of the reaction[94]. Interestingly, other species have been observed from the photolysis of 5-phenyl-1,2,3,4-thiatriazole (**163**, R = Ph) in an Argon matrix. An IR analysis of the matrix following irradiation at 310 nm or 254 nm has shown the presence of dinitrogen sulphide (N_2S)[96].

An extension of this work has examined the irradiation of a series of derivatives of the 5-phenyl-1,2,3,4-thiatriazole system (**163**, R = Ph). All of these undergo loss of nitrogen to yield the phenylthiazirine **165** and benzonitrile. When the irradiations are carried out in neat dimethyl acetylenedicarboxylate the 1,3-dipole **166**, formed from the thiazirine **165**, is trapped as an isothiazole[97]. The influence of a substituent on the aryl group of **163** has been investigated and again efficient formation of the thiazirine and the dipole **166** takes place[98]. Machida and collaborators[99] have observed an alternative photochemical path to arylthiazirines. Thus irradiation of the thioamides **168** in the presence of oxygen affords the thiazirines **169** which, like the others mentioned above, ring-open to the corresponding thionitriles.



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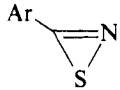
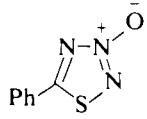


(169)

Ar = Ph, 3- or 4-pyridyl, 2-furyl or 2-thienyl

The related 3-*N*-oxide (**170**) also yields phenyl isothiocyanate (65%) and benzonitrile (3%) on irradiation in methylene chloride at 254 nm. Irradiation under argon has no effect on the reaction and it is presumed that a singlet state is involved[100]. Radiolysis of the parent 1,2,3,4-thiatriazole has been carried out and the products studied[101].



(170)

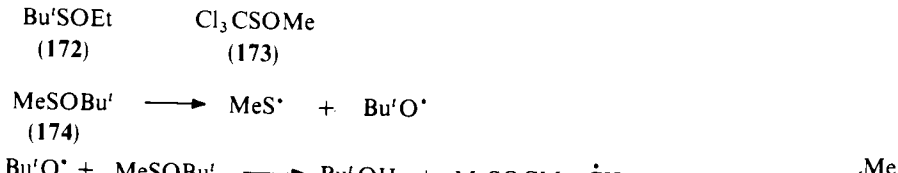
IV. SULPHENIC ACIDS

Only a very few sulphenic acids are stable although many have been identified as intermediates in thermal reactions[102]. One stable derivative which has been examined in considerable detail is *t*-butyl derivative **171**. The photochemistry has not been studied although the production of the *t*-butylsulphinyl radical has been identified following irradiation of **171** in the presence of di-*t*-butyl peroxide in toluene or isopentane at -40 to $-60\,^{\circ}$C. This reaction is not the result of photohomolysis of the sulphenic acid but is due to hydrogen abstraction by a *t*-butoxy radical[103]. However, irradiation of the sulphenic acid **171** in an isopentane glass has been reported to yield the same radical[5].

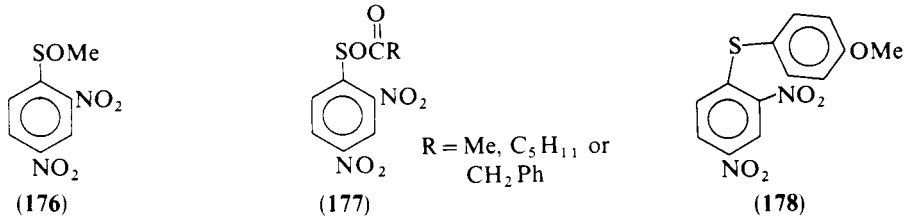
t-BuSOH
(**171**)

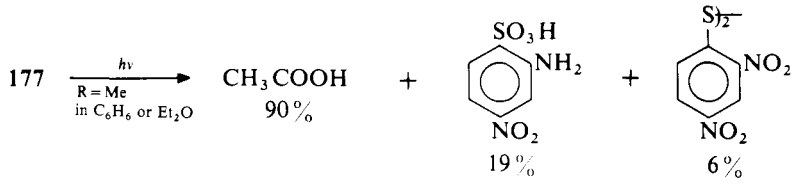
V. SULPHENATES

The sulphenate ester **172** exhibits a weak absorption ($\varepsilon = 70.5$) at 265.5 nm and a similar absorption is reported for the ester **173**[104]. Irradiation of these has not been reported. However, Kochi and his coworkers[105] and Gara and collaborators[106] have reported the results of irradiation of the closely related *t*-butyl methanesulphenate (**174**). This treatment brings about fission of the weak S–O bond. The resultant radicals (methanethiyl and *t*-butoxy) react according to the mechanism shown in Scheme 16 ultimately leading to the final product, isobutylene, and the alkylsulphinyl radical **175** detected by ESR. Aryl derivatives of sulphenates have been studied in more detail. Thus the irradiation of the aryl derivative **176** has shown that these compounds, which are considered to be more like ethers than esters[104], are inert to irradiation[18]. More usually this type of sulphenate ester is photolabile as demonstrated by Barton and his coworkers[18, 107], who studied the sulphenate esters represented in **177**. These derivatives are photolabile on irradiation in benzene or ether and again the products result from the cleavage of the S–O bond as illustrated in Scheme 17. However, unlike the above report,



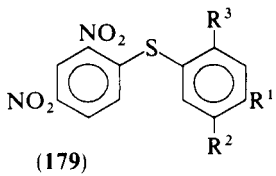
SCHEME 16





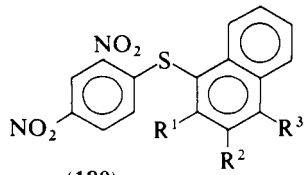
SCHEME 17

the photocleavage in this system follows an ionic rather than a radical path. This was demonstrated by irradiation of **177** in a mixture of benzene and anisole whereby no 2,4-dinitrophenyl sulphide was obtained and the product was the methoxy derivative **178**. It is argued that there is no difference between the rates of radical attack on anisole or benzene, and the difference lies in the rate of electrophilic attack with the preference being for attack on anisole, so leading to the observed product. The scope of this electrophilic process affording products **179–181** has been studied and the results are tabulated in Table 3[31].



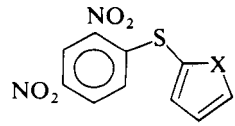
(**179**)

(**a**) $R^1 = H$, $R^2 = R^3 = H$
(**b**) $R^1 = MeO$, $R^2 = R^3 = H$
(**c**) $R^1 = Cl$, $R^2 = R^3 = H$
(**d**) $R^1 = H$, $R^2 = R^3 = MeO$
(**e**) $R^1 = NMe_2$, $R^2 = R^3 = H$
(**f**) $R^1 = H$, $R^2 = NMe_2$, $R^3 = Me$



(**180**)

(**a**) $R^1 = R^2 = R^3 = H$
(**b**) $R^3 = H$, $R^2 = R^1 = (CH{=}CH)_2$
(**c**) $R^1 = H$, $R^2 = R^3 = (CH{=}CH)_2$



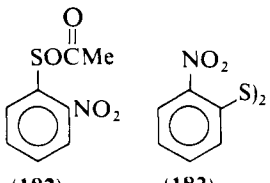
(**181**)

(**a**) X = S
(**b**) X = O

The *o*-nitrobenzenesulphenyl acetate **182** is also photochemically reactive, and irradiation in benzene affords the disulphide **183** while in anisole irradiation yields the derivative **184** in 55% yield[31]. Aryl esters such as the tolyl, phenyl, and benzyl esters (**185**) undergo photochemical fission into radicals. Evidence was gathered for the free radical nature of this process by the formation of Pummerer's ketone from the irradiation of the tolyl ester **185a**. Such a product must arise from dimerization of the *p*-tolyloxy radical. The principal product in each case was the aminosulphonic acid **186** where oxygen had been transferred intramolecularly from the *o*-nitro function to the sulphur[31]. This type of reactivity is

TABLE 3. Photo-Friedel–Crafts reaction of dinitrobenzenesulphenyl acetate[31].

Acetate (mmol)	Substrate	(mmol)	Solvent	(ml)	Time (min)	Product	Yield (%)
1.0	Benzene	6	Benzene	125	60	**179a**	73
1.0	Anisole	1.0	Benzene	125	60	**179b**	74
2.0	ClPh	6	ClPh	100	60	**179c**	14
1.9	1,4-diMeO Benzene	1.9	Benzene	100	20	**179d**	55
2.0	*N*,*N*-diMe Aniline	4	Benzene	150	70	**179e**	27
2.0	*N*,*N*-diMe *p*-toluidine	3.3	Benzene	150	40	**179f**	23
2.0	Naphthalene	2.0	ClPh	100	15	**180a**	40
1.0	Anthracene	1.0	ClPh	15	15	**180b**	74
1.0	Phenanthrene	1.0	ClPh	15	10	**180c**	82
2.0	Thiophene		Neat	9	45	**181a**	13
2.0	Furan		Benzene	110	60	**181b**	28



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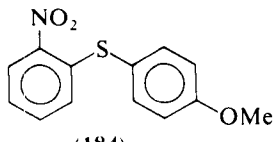
(183)



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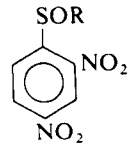
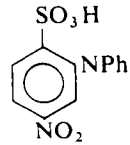


(185)

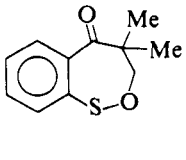
(a) R = *p*-Tol
(b) R = Ph
(c) R = CH_2Ph



(186)

analogous to that described by Kaluza and Perold[17] for the reaction of 2,4-dinitrobenzenesulphenyl chloride.

Sulphenates are also important intermediates in the photochemical rearrangement of sulphoxides. One of the more common reactions of sulphoxides involves racemization involving fission and rebonding of an S–C bond[108]. This presumably involves a biradical. Alternative bonding routes are possible, such as rebonding to yield a sulphenate by a process formally analogous to the formation of oxacarbenes from ketones[109]. Secondary photolysis of the sulphenate would result in S–O bond fission and, via the resultant biradicals, provides a route to a variety of products. The involvement of sulphenates was initially reported by Still and Thomas[110], who isolated the ester **187** from the irradiation of **188**. Prolonged irradiation of the sulphenate yields the aldehyde **189**. Interestingly, substitution at the 3-position of the aromatic ring in **190** prevents the desulphurization and affords ring-contracted thiaindanones. Shultz and Schlessinger[111] also observed that direct irradiation of the *cis*-sulphoxide **191** affords the *trans*-pyran **192**, the *cis*-pyran **193** and the ketone **194** in 18, 2 and 52% yields. The *trans*-sulphoxide yields the same three products but in different yields (2, 8 and 13%, respectively). The pyrans **193**, **194** results from the transformation of the sulphoxide into the sulphenate **195** followed by secondary irradiation in which loss of sulphur occurs. The sulphoxide **196** is also reactive and irradiation provides a low yield of the sulphide **197** by way of the sulphenate **198**[112]. In



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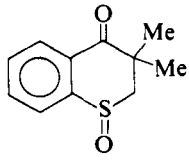

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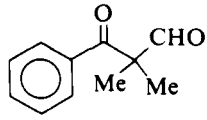

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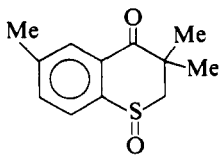

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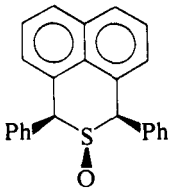

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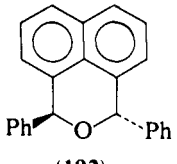

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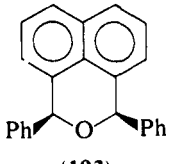

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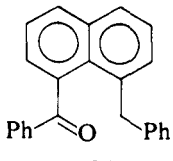

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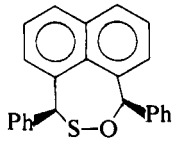
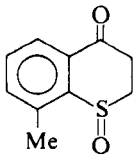


(195)

later work Still and his coworkers[113] have cited further examples of the photorearrangement of the sulphoxides proceeding via a sulphenate ester intermediate. Several examples (e.g. **190**) were studied including deuterio analogues (Scheme 18). The irradiation of the thiin-1-oxide **199** also follows this path and affords the isomeric 1,3-dithioles



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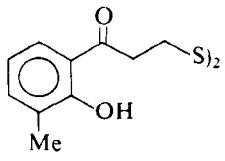

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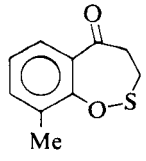

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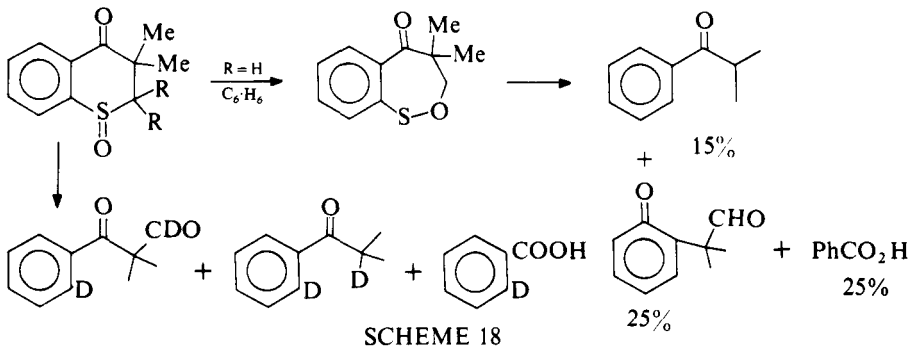
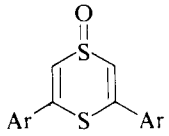


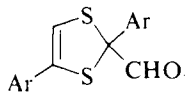
SCHEME 18

200 and **201**[114, 115]. The formation of these is thought to involve the isomerization of **199** by C–S bond fission and cyclization of the biradical into the cyclic sulphenate esters **202** and **203**. Proof of this reaction path has been supplied by Kobayashi and Mutai[115] and by Gajurel[116] who isolated the ester (**202**, R = Ph) in low yield from the irradiation of the sulphoxide (**199**, Ar = Ph) in dimethyl sulphoxide. The esters are photolabile and S–O bond fission produces radicals from which the final products are formed[114]. A sulphenate **204** is also implicated in the products obtained from the sulphoxide **205** from which the dimer **206** is produced on irradiation[117]. The mechanism was followed using ^{18}O labelling. The episulphoxide **207** is also photoreactive and, on irradiation, is converted into benzil and thiobenzil[118, 119]. The route to these products is presumed to involve conversion into the sulphenate **208** prior to fragmentation. Sulphenates can appear in odd situations as in the photodecomposition of the thiolone **209**. This yields the transient mono-thio-*o*-benzoquinone (**210**) which on irradiation at 77 K is converted into the photo-unstable benzoxathiete, a sulphenate (**211**)[120].



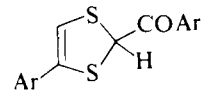
(**199**)

(**a**) Ar = *p*-ClC_6H_4
(**b**) Ar = C_6H_5
(**c**) Ar = *p*-MeC_6H_4



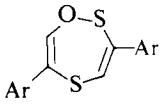
(**200**)

(**a**) 38%
(**b**) 32%
(**c**) 79%

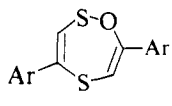


(**201**)

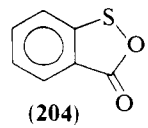
(**a**) 56%
(**b**) 46%
(**c**) 13%



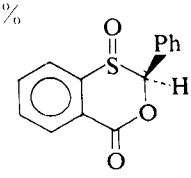
(**202**)



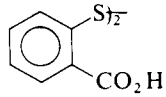
(**203**)



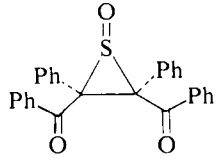
(**204**)



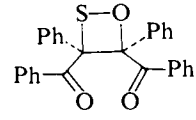
(**205**)



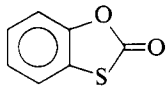
(**206**)



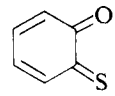
(**207**)



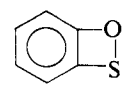
(**208**)



(**209**)



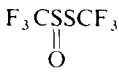
(**210**)



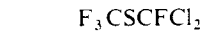
(**211**)

The sulphenyl carboxylates **212** are also related to the sulphenates and likewise have a photolabile S–O bond. Thus Haas and Oh[121] have shown that the derivative **212a** undergoes photochemical conversion into trifluoroacetic anhydride and the sulphide **213**, while the derivative **212b** yields the sulphide **214** and carbon dioxide.

(212) (a) X = F
(b) X = Cl



(213)

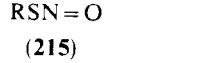


(214)

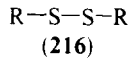
VI. MISCELLANEOUS SULPHENYL SYSTEMS

A. *S*-Nitroso Compounds

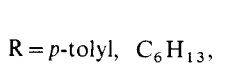
The *S*-nitroso derivatives, thionitrites, can also be classed as related to the general class of sulphur–nitrogen systems. They are also photolabile, although not much work has been carried out in this area. One of the simplest processes to occur in such systems is the reversible interconversion of two rotational isomers of methyl thionitrite in an argon matrix at 12 K[122]. Others have demonstrated that the S–N bond of methyl thionitrite is labile and can be readily cleaved by irradiation in the 300–400 nm range in the gas phase to produce NO and thiyl radicals from which dimethyl disulphide is formed[123]. This work has been re-examined in the 450–470 nm range and it has been confirmed that both methyl thionitrite and *t*-butyl thionitrite undergo S–N bond fission to the corresponding radicals[124]. Other studies have examined the behaviour in dilute hexane solutions of the *S*-nitrosothiols **215** which undergo ready fission of the S–N bond on irradiation at 365 nm. The resultant thiyl radicals dimerize to yield the corresponding disulphides (**216**)[125]. A further study has examined irradiation at 365 nm of the *S*-nitrosohexane **217** which, in methanol, affords the corresponding disulphide. The bis nitroso compound **218** is also photochemically reactive under the same conditions and yields the tetrathio compound **219**[126]. An ESR study of the photochemical decomposition of the thionitrite ester **220** in the presence of alkenes has shown that the thiyl radicals produced by the S–N bond fission add to the alkenes. The process is terminated by the addition of NO in what is a synthetically useful synthetic path to nitroso compounds[127]. A more complex thionitrite **221** has also been synthesized and shown to be photochemically labile[128].



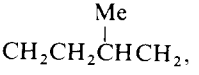
(215)



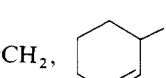
(216)



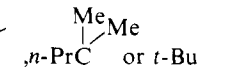
(217) R = H
(218) R = SNO



(219)



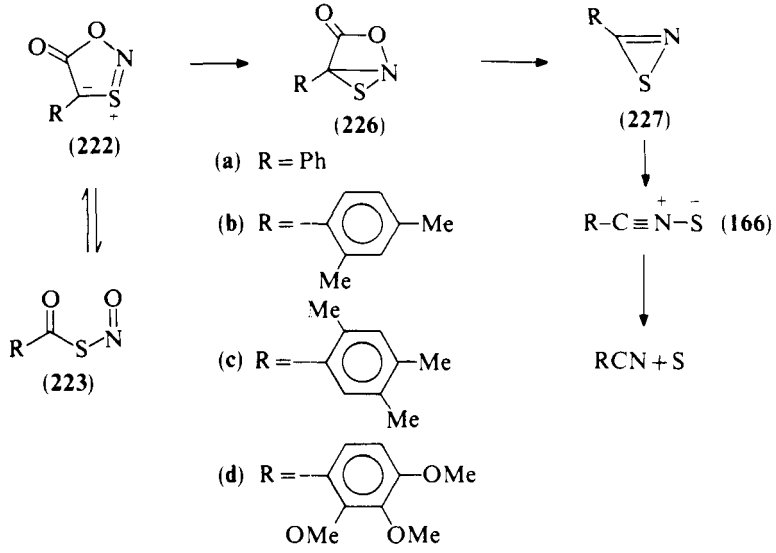
(220)



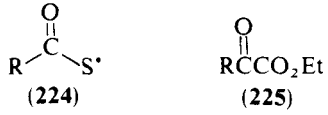
(221)

B. Mesionic Compounds

It is interesting to note that *S*-nitroso compounds are obtained on irradiation of the mesionic compound **222**. The identification of the intermediate **223** (see Scheme 19) was achieved by irradiation of the mesionic compound in a matrix where **223** and the benzonitrile sulphide **166** were shown to be primary photochemical products[95, 129, 130]. The *S*-nitroso intermediate **223** photochemically loses NO to afford the thio radical **224**



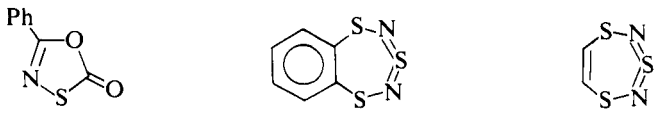
SCHEME 19



which, in the presence of oxygen, is converted into the pyruvate **225**. The conditions of the reaction are important, since the formation of **166** is favoured in polyvinyl chloride while **223** is formed preferentially in solid nitrogen. The interconvertibility of **223**, **166** and **222** was studied. Earlier studies had examined the photochemical behaviour in solution where it was found that irradiation of **222a** with 404.5–407.8 nm light produces a bicyclic compound **226** which loses carbon dioxide to afford the thiaaziridine **227**. This ring opens to the dipole **166** which, in the absence of dipolarophiles, fragments to sulphur and cyanobenzene[131, 132]. Other examples of the process using **222b–d** have also been published[133].

The lactone **228**, related to the above system, is unreactive on irradiation at 300 or 340 nm. However, photolysis at 254 nm brings about decomposition and the formation of cyanobenzene, sulphur and carbon dioxide[134].

The 1,3,5,2,5-trithiadiazepines (**229**, **230**) undergo extensive decomposition on irradiation (300 or 350 nm) in light petroleum[135].



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The Chemistry of Sulphenic Acids and their Derivatives
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CHAPTER **12**

Free radical chemistry of sulfenic acids and their derivatives

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I. INTRODUCTION

Most of the material included in this chapter has never been reviewed, although extensive survey articles have recently appeared on sulfur-containing radicals[1]. However, due to the difficulty of selecting adequate material for this chapter, this survey is not meant to be exhaustive but rather to reflect the scientific interest of the author. Therefore, a few words about the pattern of organization of this chapter will be useful.

Section II is concerned with the structure and chemical reactions of radicals in which the central sulfur atom is bonded to three ligands, **1**, the so-called sulfuranyl radicals. This section deals with only sulfuranyl radicals that *in principle* can be obtained from reactions involving sulfenic acids or their derivatives. However, most of the available data on the subject have been obtained by alternative routes.

The Chemistry of Sulphenic Acids and their Derivatives
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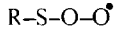
(1)



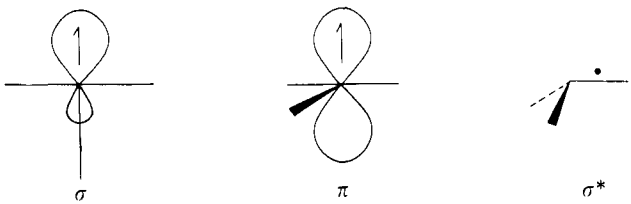
(2)

Section IV examines the alkanethiylperoxyl radicals, (**2**), which resemble sulfenic acids and their derivatives. Most of the work in this area is very recent and, to a certain extent, this class of radicals represents the expansion and importance of organosulfur reactive intermediates in a number of branches of chemistry. Some of the general concepts of free radical chemistry are introduced at appropriate points throughout the review without reference.

II. SULFURANYL RADICALS

A. Structural Characteristics

Sulfuranyl radicals and their structures have been the subject of various investigations. On the basis of ESR spectroscopic and optical absorption studies, several bonding models have been advanced to describe sulfuranyl radicals having different ground state electronic structures (see Scheme 1). These systems have been classified as 9-*S*-3 sulfuranyl radicals, i.e. nine electrons are formally associated with sulfur to which three ligands are bound, and have been called three-center, three-electron (3c, 3e) bond, three-center, four-electron (3c, 4e) bond and two-center, three-electron (2c, 3e) bond for σ-, π- and σ^*-type radicals, respectively[2, 3].

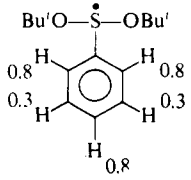


SCHEME 1

Careful analysis of the ESR spectrum of $F_3S^\bullet$ in $SF_3^+ \ ^-BF_4$ single crystals led Morton and collaborators[4] to postulate a σ-type structure. In such a structure, the sulfur atom and its three nearest neighbors adopt a T shape with the unpaired electron localized in an orbital which is in the plane of those atoms. They assumed that the ground state structure would be unaffected by changes in the ligands and therefore contested the suggestion made by Roberts and his coworkers[5, 6] that the structures of the related radicals $(RO)_3S^\bullet$ and $R\hat{S}(OBu^t)_2$ (where R = alkyl) were of π-type with the unpaired electron in an orbital which was perpendicular to the plane defined by the sulfur and its three nearest neighbors (Scheme 1). The electronic spectra due to sulfuranyl radicals $(RO)_3S^\bullet$ have also been obtained by laser flash photolysis and show absorption maxima at 330 nm[7].

Although it is generally difficult to discriminate between the σ and π structures, there is good evidence from ESR spectra that the π structure is adopted by the sulfuranyl $Ph\hat{S}(OBu^t)_2$[6] and other aryl substituted sulfuranyls[8, 9] (see Table 1). Hydrogen hyperfine splittings in these radicals has been detected from the ring protons, and their magnitude implies delocalization of the unpaired electron into the π orbital of the benzene ring. It

TABLE 1. ESR spectra of aryl substituted sulfuranyl radicals (a_H in gauss)



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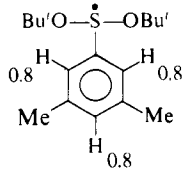

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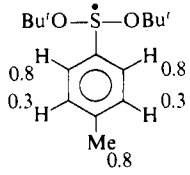

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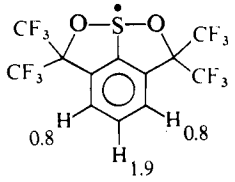
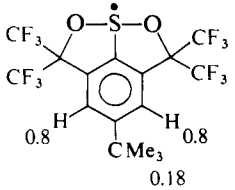


(6)[b,c]

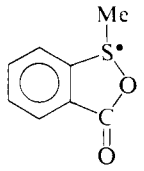


(7)[b,c,d]

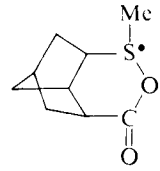
[a] From Reference 8.
[b] From Reference 9.
[c] Fluorine splitting of 0.63 G and carbon-13 splitting of 9.9 G are observed.
[d] A sulfur-33 splitting of 15.7 G is observed.

can, of course, be argued that this observation does not resolve the σ *vs* π question in a broad sense, since the aryl substituent would be bound to perturb the system so as to favor the π state. However, the hyperfine splittings involved were extremely small, indicating that the unpaired electron was effectively localized at sulfur and suggesting that perturbations induced by the aryl group were negligible. Unfortunately, an attempt to obtain the absorption spectrum of $PhS(OBu^t)_2$ has been unsuccessful[7]. Thus, while $F_3S^\bullet$ may have the σ structure, it is possible that sulfuranyls with less electron-withdrawing substituents may adopt the π configuration.

In the σ^*-type structure, the configuration about the sulfur atom is pyramidal and the unpaired electron is located in an antibonding orbital associated with the bond between the sulfur and one of its ligands. The distinction between the σ and σ^* structures is fairly subtle, since the transition from the former to the latter simply requires a change from a planar to a pyramidal configuration about the sulfur atom. For example, the spectrum of radical **8** has been established by extensive CINDP[10] and ESR[2] investigations to be of the σ- or σ^*-type. Although the distinction between π- and σ- or σ^*-types was unequivocal, a precise assignment of σ and σ^* for **8** could not be made since this would have required a definition of exact configuration of sulfur, i.e. planar *vs* pyramidal. On the basis of calculations Martin and his coworkers[2] suggest that the radical **8** is best described as a slightly distorted T-shape species with a (3c, 3e) bond, i.e. a σ-sulfuranyl radical. Further support for the above discussion came from the electronic spectra. The absorption spectrum of **8** shows a maximum at 385 nm[7] similar to the $\lambda_{max} = 390$ nm reported by Glass and coworkers[11] for the radical **9**, indicating that the phenyl group has no influence on the absorption band.



(8)



(9)

The ESR spectra of the adducts $R_2\hat{S}OSiMe_3$ have been detected by addition of $Me_3SiO^\bullet$ radical to corresponding dialkyl sulfides[12]. On the basis of the spectrum of $(MeCH_2)_2\hat{S}OSiMe_3$ which exhibits splitting from two pairs of equivalent protons from CH_2 even at relatively high temperature, the authors concluded that the α-methylene protons are diastereotopic and therefore nonplanar arrangement of bonds to sulfur with the unpaired electron is probably confined to a σ^*_{S-O} orbital.

The σ^*-type bonding model is found to describe the structure of radicals $R_2\hat{S}X$ (where X = halogen). That is, two-center, three-electron (2c, 3e) bonds can be formed by reactions of electrophilic radicals with nucleophiles via two-orbital three-electron interactions which are usually bonding in nature, viz. Figure 1. Therefore, these (2c, 3e) bonds result from an interaction of the unpaired p electron on $R_2S^{+\bullet}$ with a free p electron pair of the X^- and consist of two bonding σ-electrons and one antibonding σ^*-electron.

Symons and Petersen[13] reported an ESR study of R′R″S—X radicals, where R′ and R″ are alkyl groups and X = Cl, Br and I. They found that exposure to ^{60}Co γ-rays of methanolic or acidic aqueous glasses containing halide salts together with organic sulfides

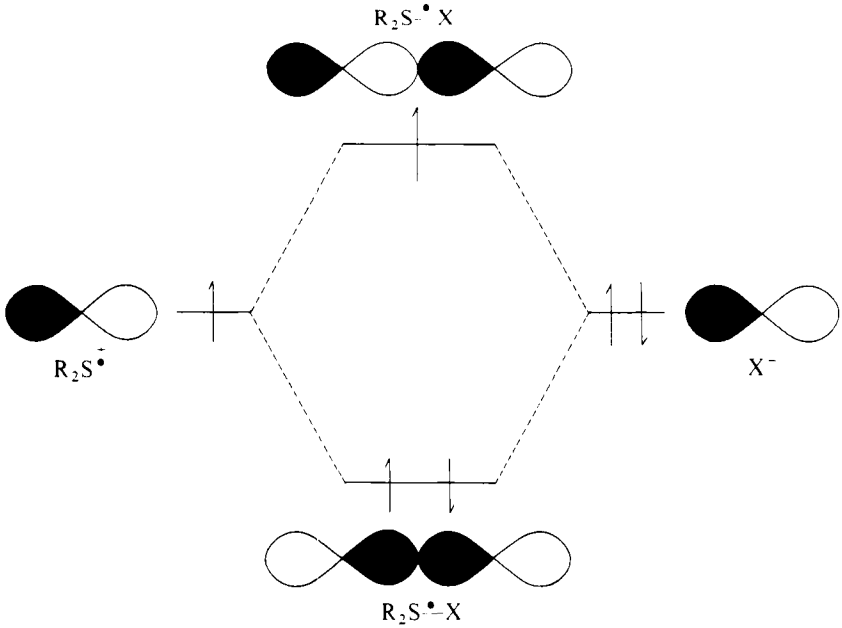


FIGURE 1

gave the electron loss center $R'R''S^{+\bullet}$ which reacted with halide ions to give a sulfuranyl radical. The identification of the species is based on the hyperfine coupling constants of the halogen atom, i.e. ^{35}Cl, ^{81}Br, ^{127}I, as well as on the g-values. Relatively poor signal-to-noise ratios in all cases ruled out the chance of detecting ^{33}S satellites. The anisotropic and isotropic components of the halogen in these radicals have been analyzed to estimate the percent occupancy of the halogen s and p orbitals by the unpaired electron. Using appropriate parameters from Reference 14, details of the analysis are given in Table 2. The data show that on going from chlorine to bromine, there is a clear gain in the spin density as expected for an electron in an antibonding orbital; differences between bromide and iodine are not considered to be significant, remembering that the original results have large errors.

TABLE 2. Characteristics of the orbital containing the unpaired electron in $R_2S^{\bullet}$–X radicals calculated from the halogen coupling constants

	$R_2S^{\bullet}$–Cl	$R_2S^{\bullet}$–Br	$R_2S^{\bullet}$–I
%ns	4.2	2.0	1.7
%np	19.3	29.6	28.3
%(ns + np)	23.5	31.6	30.0

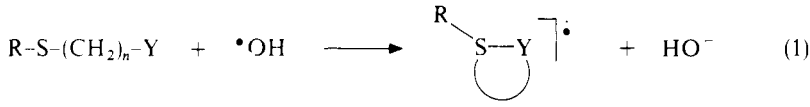
The optical absorption spectra of $R_2S^{\bullet}$–X, measured by means of liquid phase pulse radiolysis[15, 16], show broad structureless absorption bands. Maxima are observed around 400 nm (see, for example, Table 3) and have been assigned to a $\sigma \rightarrow \sigma^*$ electronic transition in the $S^{\bullet}$–X three-electron bond. Stabilization of (2c, 3e) bonds between two different heteroatoms seems to become increasingly effective the smaller the differences in electronegativity. Thus, a two-center, three-electron bond between sulfur and iodine is very stable, but not between sulfur and fluorine, and such a bond is of marginal stability between sulfur and chlorine. In fact, *ab initio* molecular orbital calculations[17] for the $H_2S^{\bullet}$–Cl radical at the HF/4-31G and MP2/4-31G levels show it to be a very weakly bound Van der Waals' complex in which the three-electron bond is not significant. There is, however, a large discrepancy between spin densities calculated for the gas-phase structure and those observed for analogous radicals in matrices or in solution.

TABLE 3. Optical absorption spectra of $Me_2S^{\bullet}$–X radicals

Radical	λ_{max} (nm)	ε_{max} ($M^{-1}\,cm^{-1}$)
$Me_2S^{\therefore}$–Cl	390	8000
$Me_2S^{\therefore}$–Br	400	6700
$Me_2S^{\therefore}$–I	410	5700

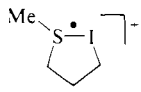
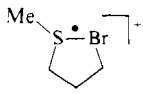
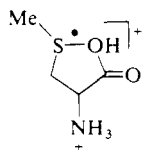
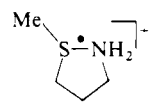
Asmus and coworkers[18] have also measured the optical absorption spectra of $R_2S^{\bullet}$–Br for various substituents R. They found a linear free-energy correlation between λ_{max} and Taft's inductive parameter; such an approach allowed them to quantify the inductive effect as well as to evaluate the influence of steric hindrance on the stability of the three-electron bond. In other words, the optical properties of such species are a sensitive measure of the strengths of their three-electron bonds.

Intramolecularly formed three-electron bonded radical cations have been identified as transient intermediates in the HO• radical induced oxidation of a variety of substituted alkylthioalkanes[19, 20] (equation 1). Their formation is based on the addition of the electrophilic •OH to the sulfur atom as the initial step which is followed either by a concerted formation of the final radical product or by a stepwise mechanism with the intermediate formation of the $R_2S^{+\bullet}$ radical. In both cases the result is an intramolecular sulfur–heteroatom bond which contains two bonding σ-electrons and one antibonding σ^*-electron. Some data are collected in Table 4. All these radical cations exhibit optical absorptions in the visible and near-UV with extinction coefficients of *ca.* 4000–6000 $M^{-1}\,cm^{-1}$.



(1)

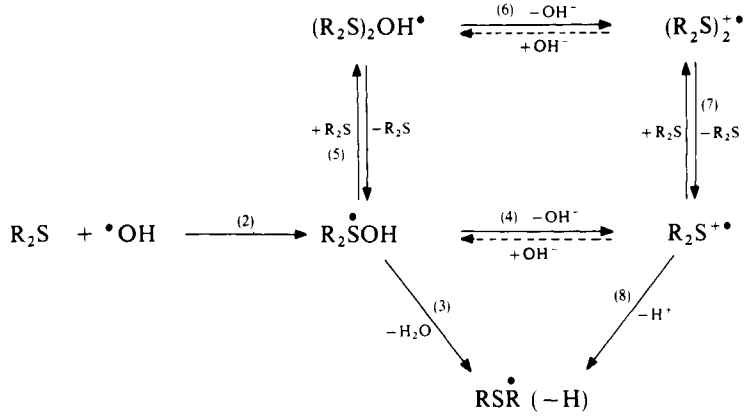
TABLE 4. Data of transient radical cations obtained by pulse radiolysis via reaction 1

Radical	λ_{max} (nm)	ε_{max} ($M^{-1}\,cm^{-1}$)	$t_{1/2}$ (μs)
	440	5100	110
	370	5300	20
	385		27
	385	4500	600

B. Chemical Properties

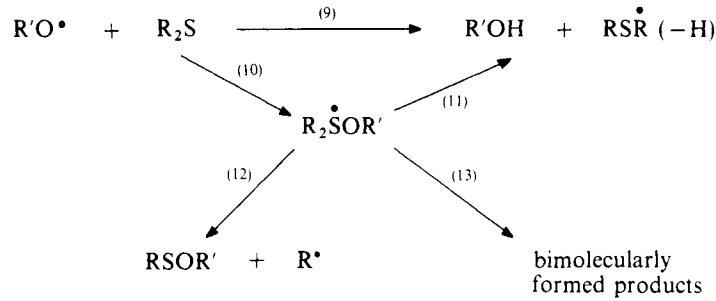
The oxidation of a variety of sulfides by hydroxyl radicals in aqueous solution has been the subject of a number of studies in the last two decades, particularly by means of pulse radiolysis[21–23] and ESR spectroscopy[24–26]. Detailed pulse radiolysis investigations have shown that hydroxyl radicals add to sulfides to give an adduct radical, $[R_2\dot{S}OH]$, with rate constants controlled by diffusion at room temperature. These sulfuranyl intermediate species have not been observed directly up to now. However, at low sulfide

concentrations the adduct eliminates either H_2O or OH^- (cf. reactions 3 and 4, respectively, in Scheme 2), whereas at high sulfide concentrations this species reacts with another R_2S molecule to form presumably a new sulfuranyl radical which dissociates to $(R_2S)_2^{+\bullet}$ and OH^-. The radical cation $R_2S^{+\bullet}$, which is also formed by dissociation of the relatively stable 'dimer' cation (equation 7), can lose a proton with formation of a carbon-centered radical $RS\dot{C}(-H)$[25, 27]. Nearly all these species are in equilibrium with each other, although in some cases the equilibrium lies strongly on one side as indicated by the full vs. the dashed arrows.



SCHEME 2

The reactions of photochemically generated $Me_3CO^\bullet$ and $Me_3SiO^\bullet$ radicals with dialkyl sulfides have been studied by means of ESR spectroscopy[6]. These oxidizing species react by abstraction of hydrogen from an α-C–H group (reaction 9) or by a competing addition to sulfur to form a sulfuranyl radical (reaction 10 in Scheme 3). For $Me_3CO^\bullet$, although an intermediate sulfuranyl radical has never been detected, some secondary product radicals $RS\dot{C}(OBu^t)_2$ have been observed. It appears that formation of $RSOBu^t$ occurs to some extent, probably by alkoxydealkylation of the sulfides (reaction 10 and 12) and, particularly with thietan, this is the only reaction detected by ESR spectroscopy[28]. The existence of a large kinetic isotope effect (at 198 K $k^H/k^D = 7.0$) for production of $RS\dot{C}X_2$ (X = H or D) is strong evidence against the formation of α-alkylthioalkyl radicals by loss



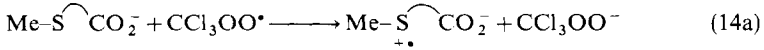
SCHEME 3

of *tert*-butyl alcohol from a short-lived sulfuranyl radical, although it does not preclude the possibility of formation of $R_2\hat{S}OBu^t$ in a rapid pre-equilibrium (reaction 10) followed by rate-determining loss of *tert*-butyl alcohol (reaction 11).

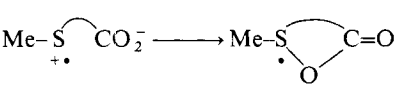
The situation is clearer in the $Me_3SiO^\bullet$ radical case, since sulfuranyl radical adducts have been observed. On the basis of kinetic ESR data, Roberts and his coworkers[12] concluded that the reaction of $Me_3SiO^\bullet$ with R_2S involves two independent but competing pathways, i.e. reactions 9 and 10, and that reaction 11 does not occur due to the second-order decay process of sulfuranyl radicals. The actual reaction 13 responsible for this second-order decay has not been identified.

The mechanistic differences discussed above between $RO^\bullet$ and $HO^\bullet$ radicals may result from the greater electrophilicity of $HO^\bullet$ and consequent faster addition to the electron-rich sulfur, coupled with the nature of the solvent (water for $HO^\bullet$, organic solvents for $RO^\bullet$) which facilitates loss of water from $R_2\hat{S}OH$. Electrophilicity is expected to increase in the order $Me_3CO^\bullet < Me_3SiO^\bullet < HO^\bullet$, in parallel with the yields of products derived by attack at S rather than H.

A pulse radiolysis study of the oxidation of organic sulfides containing carboxylate groups by $CCl_3OO^\bullet$ has been reported[29]; the resulting radical intermediates have been characterized as sulfuranyls (see equations 14a and 14b). Significant sulfur–oxygen interaction seems to occur only if both heteroatoms are separated by three or four carbon atoms in the unoxidized molecule which enables favorable five- or six-membered ring structures in the radical intermediates. This geometric effect can additionally be favored by minimizing the free rotation of the functional groups through rigid molecular structures, e.g. in norbornane derivatives. For two of these radicals, Table 5 reports optical absorption data and rate constants for their formation, k_{14}, and unimolecular decay as well as their proton- and hydroxide-assisted decays. The bond strength of the sulfur–oxygen interaction is estimated to be of the order of 12 kcal mol^{-1} as deduced from the temperature dependence of its dissociation[29].

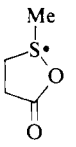
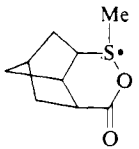


(14a)

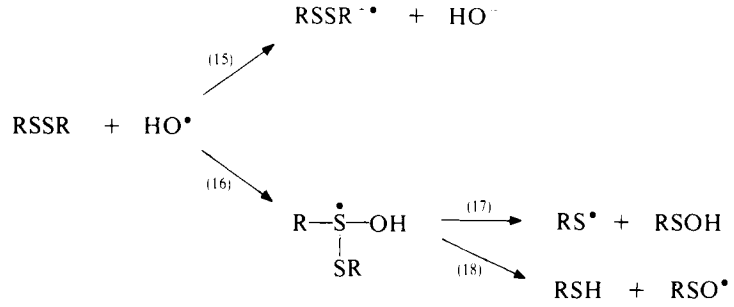


(14b)

TABLE 5. Optical absorption spectra and kinetic data of radical species formed in the oxidation of organic sulfides containing carboxylate groups (reaction 14)

		
λ_{max} (nm)	410	390
ε_{max} (M^{-1} cm^{-1})	3200	3900
k_{14} (M^{-1} s^{-1})	1×10^8	1×10^8
k_{decay} (s^{-1})	3×10^3	1×10^4
k_{H^+} (M^{-1} s^{-1})	9.8×10^5	3.0×10^7
k_{OH^-} (M^{-1} s^{-1})	1.2×10^7	8.0×10^6

The reaction of hydroxyl radicals with aliphatic disulfides in water occurs essentially in a diffusion-controlled process and leads to an electron transfer or HO• attachment with about equal probability[30] (see reactions 15 and 16 in Scheme 4). The existence of the OH• adduct radical is supported by both ESR[31] and pulse radiolysis studies[30], and its chemical



SCHEME 4

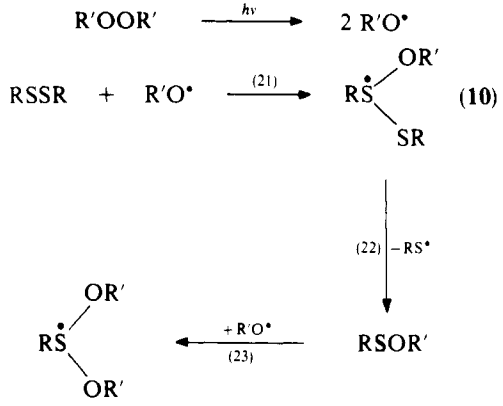
fate depends on the pH of the solution and the structure of the aliphatic groups of the disulfide. That is, in neutral solution the adduct primarily decays via reaction 17 leading to an RS• radical and a sulfenic acid, whereas in acidic and basic solutions the decay to thiols and sulfinyl radicals predominates (reaction 18). Asmus and his coworkers have also discussed the reaction[19] as a possible alternative in the intermediate pH range, followed by the deprotonation of $RSOH^{+\bullet}$ to give RSO• radical[30]. The ESR parameters of aromatic sulfinyl radicals have been obtained during the reaction of hydroxyl radical with diaryl disulfides; reaction 20 is believed to be the most probable mechanism for such oxidations[32].

$$RSSR^{+\bullet} + RSOH \longrightarrow RSSR + RSOH^{+\bullet} \tag{19}$$

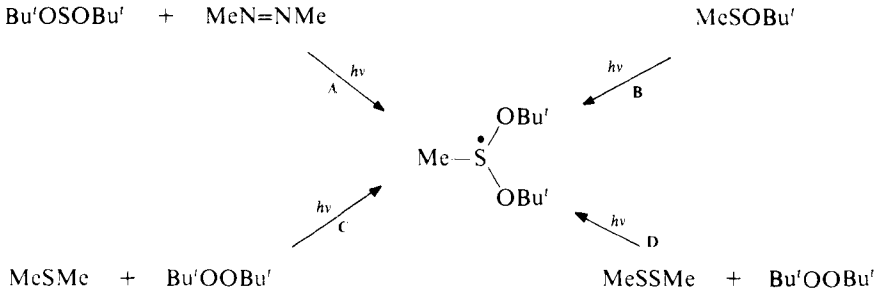
$$ArSSAr \xrightarrow{+OH^{\bullet}} Ar\dot{S}(OH)SAr \xrightarrow{-H^{+},\,-ArS^{-}} ArSO^{\bullet} \tag{20}$$

On the basis of ESR experiments, the mechanism which has been proposed for the production of dialkoxysulfuranyl radicals, $R\dot{S}(OR')_2$, from photolysis of dialkyl disulfides and peroxides is outlined in Scheme 5[6]. Although the intermediate species **10** has not been observed directly up to now, it is generally believed that the formation of alkyl alkanesulfenates, RSOR', is a two-step process (reactions 21 and 22) rather than a concerted S_H2 reaction. However, ESR spectra for a series of dialkoxysulfuranyl radicals, $R\dot{S}(OR')_2$, have been obtained by a variety of methods. Scheme 6 summarizes the four different approaches for the formation of the $Me\dot{S}(OBu^t)_2$ radical[6]. Methods **A** and **B** are straightforward addition of alkyl and alkoxyl radicals to the appropriate reagents. The mechanistic details of methods **C** and **D** are represented by reactions 10, 12, 23 and by reactions 21, 22, 23, respectively. Similarly, $Ar\dot{S}(OR)_2$ radicals have been obtained by photolysis of diaryl disulfides or alkyl arenesulfenates and peroxides (methods **D** and **B**)[8].

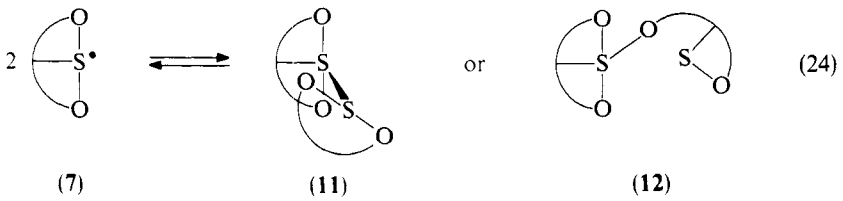
Spectroscopic data (ESR, NMR) show that the persistent sulfuranyl radical **7** (see Table 1) is in equilibrium with a dimer[33]. This accurate work of Perkins and Martin[33] indicates the mixture of two dimers as shown in equation 24. At 173 K, 20% of dimer is the S^{IV}–S^{IV} bisulfuranyl **11** and 80% is the alkoxysulfurane S^{IV}–O isomer **12**; at high temperature **11** is a still smaller fraction of the mixture of dimers. The equilibrium constant for the Dimer$\rightleftharpoons$2 Monomer reaction varies from 4.7×10^{-4} at



SCHEME 5



SCHEME 6



233 K to 3.53×10^{-1} M at 313 K. The values of ΔS° and ΔH° for the dissociation of the dimer are determined to be 13 ± 3 eu and 12.0 ± 0.7 kcal mol^{-1}, respectively. No evidence was found for the existence of an O–O dimer. The value of the S^{IV}–S^{IV} bond dissociation energy was calculated to be *ca* 14 kcal mol^{-1}.

Roberts and his coworkers[5] using ESR spectroscopy show that UV irradiation of dialkyl sulfoxylates, ROSOR, generates alkoxyl radical, which adds to the parent sulfoxylate with a high degree of stereoselectivity, the incoming group taking up an apical site in the trialkoxysulfuranyl radicals. Laser flash photolysis experiments show that

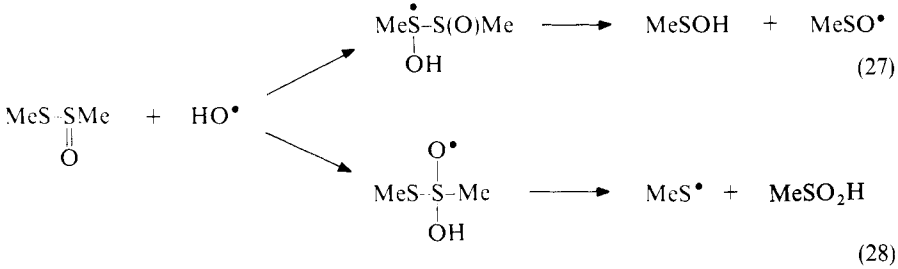
(13) (25)

reaction 25 is a diffusion-controlled process and that the cyclic sulfuranyl radical **13** disappears with clean first-order kinetics represented by the following expression[7]:

$$\log(k\ (s^{-1})) = (11.66 \pm 0.24) - (8.84 \pm 0.36)/\theta \tag{26}$$

in which $\theta = 2.3RT$(kcal mol^{-1}). Equation 26 describes all the possible modes of fragmentation of **13**, i.e. both α and β cleavage.

Reaction of hydroxyl radicals with methyl methanethiosulfinate has also been studied by Gilbert and coworkers[34]. Evidence for the occurrence of both reactions 27 and 28 was obtained.



(27)

(28)

An ESR study of the reaction of $NH_3^{+\bullet}$, generated from the Ti^{III}–NH_2OH couple, with sulfides and other sulfur compounds has been reported[35]. The data indicate a behavior similar to the corresponding HO• reactions; that is, the results are consistent with the formation of short-lived adduct $[R_2\overset{\bullet}{S}NH_3^+]$ which can then undergo a variety of reactions, including substitution and several types of fragmentation. Intramolecularly formed S–N sulfuranyl radical cations have been identified as transient intermediates in the HO• radical-induced oxidation of 3-(methylthio)propylamine, methionine and methionine ethyl ester (cf. equation 1 and Table 4).

Bonifačić and Asmus[15] have studied in detail the chemical behavior of $R_2S^{\bullet}$–X radicals. The formation of $R_2S^{\bullet}$–Cl and $R_2S^{\bullet}$–Br was obtained by the reaction of $X_2^{\bullet-}$ with dialkyl sulfides with rate constants ranging from 2.0×10^9 to 4.7×10^{10} $M^{-1}s^{-1}$. The corresponding reaction with $I_2^{\bullet-}$ was too slow to be observed on the time-scale of these experiments. However, $R_2S^{\bullet}$–I were obtained by the diffusion-controlled reaction of $(R_2S)_2^{+\bullet}$ with I^- ions. The $R_2S^{\bullet}$–X radicals in aqueous solution, produced either by oxidation of sulfides with $X_2^{\bullet-}$ or by reaction of $(R_2S)_2^{+\bullet}$ and halide ion, have been shown to exist in a number of equilibria (equations 29–32). Data are availabe for sulfuranyl radicals derived from Me_2S, Et_2S and methionine. The equilibrium constants for the ethyl-substituted derivatives are given in Table 6.

$$X^{\bullet} + R_2S \rightleftharpoons R_2S^{\bullet}\text{–}X + X^- \tag{29}$$

$$R_2S^{\bullet}\text{–}X + R_2S \rightleftharpoons (R_2S)_2^{+\bullet} + X^- \tag{30}$$

$$R_2S^{\bullet}\text{–}X \rightleftharpoons R_2S + X^{\bullet} \tag{31}$$

$$R_2S^{\bullet}\text{–}X \rightleftharpoons R_2S^{+\bullet} + X^- \tag{32}$$

TABLE 6. Equilibrium constants for $Et_2S^{\bullet}$—X radicals[15]

	K_{29}	K_{30}	K_{31}	K_{32}
$Et_2S^{\bullet}$—Cl	$\gg 10^4$	9.09×10^2	$\ll 10^{-10}$	1.6×10^{-1}
$Et_2S^{\bullet}$—Br	8.3×10^3	1.43	5.5×10^{-10}	4.1×10^{-4}
$Et_2S^{\bullet}$—I	4.5×10^{-1}	$\ll 1$	2.0×10^{-5}	$\ll 10^{-4}$

III. HYDROGEN ABSTRACTION REACTIONS

Sulfenic acids undergo hydrogen atom transfer to free radicals readily (equation 33). For example, *tert*-butylsulfinyl radical has been obtained by the reaction of the corresponding

$$RSOH + X^{\bullet} \longrightarrow RSO^{\bullet} + HX \tag{33}$$

acid with *tert*-butoxyl radical at low temperatures (173 K) and its bimolecular self-reaction has been studied by kinetic ESR spectroscopy[36]. Evidence has been given, also by ESR spectroscopy, showing that the sequence of the following reactions occurs rapidly during the oxidation of aliphatic[31] or aromatic[32] thiols by the Ti^{III}–H_2O_2 couple:

$$RS^{\bullet} + H_2O_2 \longrightarrow RSOH \xrightarrow{OH^{\bullet}} RSO^{\bullet} \tag{34}$$

Koelewijn and Berger[37] estimated the rate constants for the reactions of peroxyl radicals derived from tetralin with *tert*-butylsulfenic and anthraquinone-1-sulfenic acids to be at least 10^7 $M^{-1}s^{-1}$ at 333 K. It has also been suggested that the marked antioxidant activity of most thiosulfinates[38] as well as the main inhibiting action of dialkyl sulfoxides or related compounds in the autoxidation of hydrocarbons[37] derives from their ability to form transient sulfenic acids by thermal decomposition.

A number of extensive review articles have recently appeared on sulfinyl radicals; therefore, the reader is referred to those reports[39, 40] for the collection and discussion of the material pertinent to this class of radicals.

A large number of substituted *N*-thioaminyl (or sulfenaminyl) radicals, $RS\overset{\bullet}{N}R'$, has been studied by Miura and his coworkers using ESR spectroscopy. Generally, these radicals have been obtained from the corresponding sulfenamides through hydrogen abstraction by *tert*-butoxyl radicals (equation 35) generated either by thermolysis of di-*tert*-butyl diperoxyoxalate or by photolysis of di-*tert*-butyl peroxide[41, 42, 44, 45]. How-

$$RSN(H)R' + Bu^tO^{\bullet} \longrightarrow RS\overset{\bullet}{N}R' + Bu^tOH \tag{35}$$

ever, other methods of generation have also been employed; for example, the oxidation of *N*-arylarenesulfenamides with lead dioxide and potassium carbonate[45-47] is the most effective for the generation of $ArS\overset{\bullet}{N}Ar'$ radicals whereas this method is quite unsuitable for the generation of alkyl derivatives[41]. Another method which is very efficient for the generation of mixed *N*-thioaminyl radicals, i.e. $RS\overset{\bullet}{N}Ar$[42] or $ArS\overset{\bullet}{N}R$[43], is the photolysis of the corresponding *N*,*N*-bis(alkylthio)anilines or *N*,*N*-bis(arylthio)alkylamines. The (*o*-nitrophenylthio)aminyl radical, $ArS\overset{\bullet}{N}H$, has been obtained by thermal dissociation of the parent hydrazine in toluene; the ESR data at 330 K are $a_N = 11.0$ G and $g = 2.0076$[48].

Tables 7 and 8 show ESR parameters and spin density distribution, respectively, for some representative *N*-thioaminyl radicals obtained by Miura and coworkers[41-43, 46]. The decrease of nitrogen hfs constants when there is a change from *N*-alkyl to *N*-aryl substituent is obviously due to the extent of the delocalization of the unpaired electron onto the benzene ring. The large g values found for these radicals relative to other nitrogen-centered radicals are attributable to the considerable delocalization of the

TABLE 7. ESR parameters for some selected *N*-thioaminyl radicals in benzene at room temperature

	a_N	a_S	a_{other}	g
Bu^{t}SNBu^t	12.37	5.9[a]	6.2(^{13}C)[a, b]	2.0074
Bu^{t}SNPh	9.92	4.66[e]	3.75(*o*-H), 1.27(*m*-H), 4.10(*p*-H)[c]	2.0065
PhSNBu^t	11.78	6.1	1.0(*o*- and *p*-H)[d]	2.0070
PhSNPh	9.59	4.62[e]	3.70(*o*-H), 1.26(*m*-H), 4.18(*p*-H)[c] 0.78(*o*-H), 0.27(*m*-H), 0.84(*p*-H)[d]	2.0059

[a] Observed at 203 K.
[b] Assigned to the *N*-*tert*-butyl quaternary carbon.
[c] *N*-phenyl ring protons.
[d] *S*-phenyl ring protons.
[e] Sulfur-33 hfs constants are referred to *N*-(3,5-*tert*-butylphenyl) derivative.

TABLE 8. Estimated spin density distribution in some *N*-thioaminyl radicals[a]

	N	*N*-Phenyl	S	*S*-Phenyl
Bu^{t}SNBu^t	0.74[b]	—	0.26[b]	—
Bu^{t}SNPh	0.451	0.339	0.202	—
PhSNBu^t	0.535	—	0.270	0.074
PhSNPh	0.436	0.339	0.210	0.069

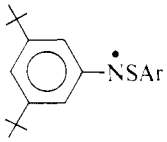
[a] The spin densities were derived from the experimental hfs constants reported in Table 7.
[b] The delocalization of the unpaired electron onto the alkyl groups has been neglected.

unpaired electron onto the sulfur and sulfur has a large spin–orbit coupling parameter. In fact, the data in Table 8 reveal that the spin density on the sulfur atom is between 20 and 30%, depending on the nature of the substituent. Thus, the aminyls bearing a divalent sulfur atom adjacent to the radical center are significantly stabilized by resonance contributions shown in equation 36. Miura's group[42, 43] also observed that the magnitude of the nitrogen hfs constant is slightly increased when the substituent in the *S*-phenyl ring is electron-withdrawing. This has been interpreted in terms of an increase in the relative importance of the resonance from **14**. On the other hand, when more powerful electron-accepting substituents are introduced in the *N*-phenyl ring, the polar form **15** becomes more important, resulting in a reduction of the spin density on the central nitrogen with an increase in the spin density on the sulfur. *Ab initio* molecular orbital calculations on a model radical, HSNH, predict a *trans*-coplanar structure as the most stable conformation, which is 1.5 kcal mol^{-1} lower than the *cis*-coplanar structure and with a barrier of rotation of 9.8 kcal mol^{-1} [41].

$$\underset{\textbf{(14)}}{-\dot{N}-\ddot{S}-} \longleftrightarrow \underset{\textbf{(15)}}{-\ddot{N}^{-}-\dot{S}^{+}-} \tag{36}$$

N-Thioaminyl radicals are fairly persistent when they have no active hydrogen atoms (e.g. β-hydrogen atoms). Thus, the Bu^{t}SNBu^t radical is extremely persistent in oxygen-free hydrocarbon solvents and showed no tendency to dimerize even at low temperature[41]. However, in the presence of air the radical concentration was rapidly reduced in constrast to aryl-substituted *N*-thioaminyl radicals, i.e. ArSNAr', ArSNBu^t and Bu^{t}SNAr, which persisted even in the presence of oxygen. *N*-(arylthio)-*tert*-butylaminyls[44] and *N*-(*tert*-butylthio)arylaminyls[42] have been found to exist in equilibrium with a dimer. For a

collection of rate constants on thioaminyl radicals, see Reference 49. Among ArSNAr', the particularly interesting ones are (arylthio)(3,5-di-*tert*-butylphenyl)aminyls, (**16**), which can be isolated as pure crystalline dimers that dissociate into the original radicals in solution at room temperature with large equilibrium constants (0.94×10^{-4}–4.59×10^{-4} M)[46] and [(4-nitrophenyl)thio](2,4,6-tri-*tert*-butylphenyl)aminyl (**17**), which has been isolated as pure dark brown needles[47]. Radical **17**, whose structure has been determined by X-ray diffraction analysis, is stable as a solid in the presence of oxygen, but it reacts with oxygen when in solution to give the corresponding nitroxide with rate constant 3.6×10^{-2} $M^{-1} s^{-1}$ at 292 K. Radical **17** shows a visible band with a maximum around 600 nm[46].



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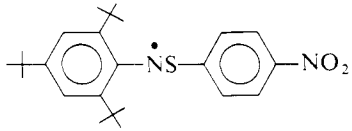


(17)

Similarly, *N*-thioaminyl radicals obtained from sulfenamides such as Bu^{t}SN(H)COR[50], ArSN(H)COR[51], ArSN(H)SAr[52], ArSN(H)C(Ar')=NSAr[53], ArSN(H)SOAr'[54] and Bu^{t}SSN(H)COR[50] have also been studied by Miura and his coworkers using ESR spectroscopy.

IV. ALKANETHIYLPEROXYL RADICALS

Alkanethiylperoxyl radicals, RSOO•, are adducts of alkanethiyl radicals (RS•) to molecular oxygen. In the recent literature some authors have represented alkanethiyl peroxyl radicals as $RSO_2^•$ rather than RSOO• and this fact has already caused some inconvenience. In alkanesulfonyl radicals, $RSO_2^•$, the sulfur atom is understood to be bonded to two oxygen atoms as well as to R; the unpaired electron does not reside on one particular atom but rather it extends over all atoms of the SO_2 group[55].

Alkanethiylperoxyl radicals are reactive transient species; it is believed that they play important roles in the atmospheric sulfur cycle and in biological systems. Most of the work on alkanethiylperoxyl radicals has been published during the last decade and consequently no attempt to review this subject has appeared so far. However, the following summary reveals how insufficient our current knowledge still is on the chemistry and structural characteristics of RSOO• radicals.

A. Gas Phase

There is a fairly compelling body of evidence from indirect studies which show that the tropospheric oxidation of a variety of organosulfur compounds can lead to the production of thiyl radicals in the atmosphere[56]. However, the reaction

$$CH_3S^• + O_2 \longrightarrow \text{products}$$

which is considered to be the most important in atmospheric photooxidation, has only recently received the necessary attention. Thus, although there is qualitative agreement that the oxidation of the simple methyl derivatives of sulfur-containing compounds (i.e. CH_3SH, CH_3SCH_3, CH_3SSCH_3) lead to SO_2, CH_3SO_3H and HCHO via a $CH_3S^•$ radical, the mechanistic schemes proposed are still rather confused.

The photooxidation of CH_3SH, CH_3SCH_3 and CH_3SSCH_3 in air has been performed with alkyl nitrites as a source of OH• radicals by Hatakeyama and Akimoto[57]. They

suggest that the major pathway for the distribution of the products should be the formation of methanesulfonyl radicals:

$$CH_3S^{\bullet} + O_2 \longrightarrow CH_3SOO^{\bullet} \longrightarrow CH_3SO_2^{\bullet} \quad (37)$$

Grosjean studied the photooxidation of organsosulfur compounds under atmospheric conditions[58]. He found that the simple methyl derivatives of sulfur-containing compounds catalyze the conversion of NO to NO_2 and the relative rate coefficient to be *ca* 2×10^6 for the reaction of $CH_3S^{\bullet}$ with NO_2 and O_2. Balla and Heicklen photolyzed CH_3SSCH_3 in the presence of O_2 at room temperature with light of 253.7 nm and found that SO_2 was produced by a chain mechanism[59]. They proposed that molecular oxygen adds to $CH_3S^{\bullet}$ to form an adduct which does not decompose to give SO_2 but can add further to O_2, finally yielding SO_2 and $HO^{\bullet}$ radical (equations 38–41). They concluded that the reaction of oxygen with $MeS^{\bullet}$ dominates over $MeS^{\bullet}$ radical recombination and found a rate coefficient greater than $1.2 \times 10^5\ M^{-1}\,s^{-1}$.

$$CH_3S^{\bullet} + O_2 \longrightarrow CH_3SOO^{\bullet} \quad (38)$$

$$CH_3SOO^{\bullet} + O_2 \longrightarrow CH_3SO_4^{\bullet} \quad (39)$$

$$CH_3SO_4^{\bullet} \longrightarrow HO^{\bullet} + CH_2O + SO_2 \quad (40)$$

$$HO^{\bullet} + CH_3SSCH_3 \longrightarrow CH_3S^{\bullet} + CH_3SOH \quad (41)$$

Following the discovery by Suzuki and collaborators[60] of the laser-induced fluorescence spectrum of $CH_3S^{\bullet}$ radical, three independent groups directly measured the rate coefficients for the reaction of $CH_3S^{\bullet}$ with O_2 and found it to be less than 1.2×10^5, 1.2×10^4 and $1.5 \times 10^3\ M^{-1}\,s^{-1}$, respectively[61–63]. The recent lowest value of Tyndall and Ravishankara[63] obtained from the absence of observable $CH_3S^{\bullet}$ loss in the presence of O_2 indicates that the reaction either is very slow or is fast and reversible, and that the adduct does not react on the time scale of their experiments. In fact, Tyndall and Ravishankara conclude that $CH_3S^{\bullet}$ and O_2 do not form an adduct or that such an adduct must be very weakly bound. Furthermore, one explanation for the discrepancy between the upper limit and the lower limit rate coefficients is that $CH_3S^{\bullet}$ does form an adduct with molecular oxygen and that the chemistry of this adduct is rate limiting in the continuous photolysis experiment. Indeed, the mechanism proposed by Balla and Heicklen[59] relies on the addition of a second O_2 molecule in contrast with Tyndall and Ravishankara's experiment, which shows that even if an adduct is formed it cannot react rapidly with O_2. These considerations suggest to the present author the following tentative mechanism in continuous photolysis comprising equations 42–45. Thermodynamic arguments based on some rather gross assumptions suggest that $CH_3SOOSCH_3$ has very weak (or even negative) O–O bond strength[39]. The oxidation of $CH_3SO^{\bullet}$ to $CH_3SO_2^{\bullet}$ may occur by different pathways, i.e. there is evidence that $CH_3SO^{\bullet}$ adds to molecular oxygen[64]. Recently, reaction 44 has been studied in the liquid phase and a rate constant of *ca* $1 \times 10^9\ M^{-1}\,s^{-1}$ was obtained, indicating that the addition of a sulfonyl radical to molecular oxygen is a very fast process[8].

$$CH_3S^{\bullet} + O_2 \rightleftharpoons CH_3SOO^{\bullet} \quad (42)$$

$$CH_3SOO^{\bullet} + CH_3S^{\bullet} \longrightarrow [CH_3SOOSCH_3] \longrightarrow 2CH_3SO^{\bullet} \quad (43a)$$

$$CH_3SO^{\bullet} \xrightarrow{ox} CH_3SO_2^{\bullet} \quad (43b)$$

$$CH_3SO_2^{\bullet} + O_2 \longrightarrow CH_3SO_2OO^{\bullet} \quad (44)$$

$$CH_3SO_2OO^{\bullet} \longrightarrow SO_2 + HCHO + HO^{\bullet} \quad (45)$$

It is worth mentioning that *ab initio* calculations at the 6-31G level have been performed for the $CH_3SOO^{\bullet}$ radical; the optimized geometry predicts bond lengths of 1.80, 1.71 and 1.29 Å for C–S, S–O and O–O, respectively, and angles 94° and 111° for $\widehat{CSO}$ and $\widehat{SOO}$, respectively[65].

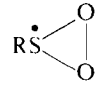
The reactions of other alkylthiyl radicals with oxygen under atmospheric conditions have also recently been reported. Thus, $EtS^{\bullet}$ and *i*-$PrS^{\bullet}$ with oxygen seem to behave similarly to the $MeS^{\bullet}$ radical discussed above[66]. Recently, the reaction rate constant of thiophenoxyl radical with O_2 at room temperature has been determined to be $1.5 \times 10^9\ M^{-1}\,s^{-1}$ [67].

In conclusion, although more experiments remain to be done, the above proposed mechanistic scheme seems to accommodate all the experimental data obtained so far.

B. Liquid Phase

Thiols have been known for some time to defend cells from damage by free radical attack. Two different processes have been identified, so-called 'protection' and 'repair'[68]. The protective mechanism involves competitive scavenging of the attacking reactive free radical before the reaction with a biological target occurs. The repair mechanism is believed to involve donation of the thiol hydrogen to a carbon-centered free radical on a biomolecule, resulting in restoration of the biomolecule to its original structure prior to fixation of the damage by further action of the carbon-centered radical. Both of these defensive processes yield thiyl radicals ($RS^{\bullet}$) which could undergo a variety of reactions within biochemical environments. Recently, the effect of thiols on the oxygen enhancement ratio for cell death in irradiated cells has been the focus of considerable effort[69, 70]. As a result of these studies the reactions of thiyl radicals with molecular oxygen have became of considerable interest.

Pulse radiolysis studies indicate that thiyl radicals generated from a variety of substituted alkanethiols react with molecular oxygen to form a product radical which absorbs at *ca* 550 nm. However, a problem encountered in all optical absorption studies is to identify the transient species responsible for the transient absorption band. Several different groups have suggested that the radical produced has the structure **18**[71–73] while von Sonntag[68] has recently pointed out that such a visible absorption is unknown for the alkylperoxyl radicals and has proposed two alternative structures for the observed species. However, structure **20** must be excluded on the basis of recent studies of the optical absorption spectra of sulfonyl radicals which show an absorption band with its maximum at 350 nm[74].



$RSOO^{\bullet}$ $RS^{\bullet}(O)_2$ $RSO_2^{\bullet}$

(**18**) (**19**) (**20**)

As far as the kinetics of the addition of $RS^{\bullet}$ radicals to molecular oxygen are concerned, all the available data have been obtained from pulse radiolysis experiments and seem to be somehow muddled. Measurements of the rate constants, k_{46}, have been achieved either by direct methodology or by using a competitive reaction. Direct measurements encounter appreciable problems owing to the lack of a strong absorption for both $RS^{\bullet}$ and $RSOO^{\bullet}$ species. However, rate constants for thiyl radicals derived from penicillamine[75] and glutathione[71] were found to be 4.0×10^7 and $2.0 \times 10^9\ M^{-1}\,s^{-1}$ respectively, by following the disappearance of $RS^{\bullet}$ and/or the growth of $RSOO^{\bullet}$ radicals. With other thiols, competition reactions have been employed in order to be able to work with reasonably high extinction coefficients. These have involved either the use of thiolate to complex the thiyl radical[71, 76] (equation 47) or an electron donor such as ascorbate[27] (equation 48) in competition to reaction 46. By monitoring the strong absorption of

$$RS^{\bullet} + O_2 \longrightarrow RSOO^{\bullet} \quad (46)$$

$$RS^{\bullet} + RS^{-} \longrightarrow RSSR^{\bullet -} \quad (47)$$

$$RS^{\bullet} + AH^{-} \longrightarrow RS^{-} + A^{\bullet -} + H^{+} \quad (48)$$

$RSSR^{\bullet -}$ at around 410 nm, bimolecular rate constants have been obtained for the thiyl radicals derived from ethanethiol[75] ($3.4 \times 10^8\ M^{-1}s^{-1}$), 2-mercaptoethanol[75] ($2.7 \times 10^8\ M^{-1}s^{-1}$), 2-methylpropanethiol[75] ($7.8 \times 10^8\ M^{-1}s^{-1}$), cysteine[75] ($8.1 \times 10^9\ M^{-1}s^{-1}$) and glutathione[76] ($1.6 \times 10^9\ M^{-1}s^{-1}$), respectively. From the competition between $RS^{\bullet}$ reacting with O_2 and ascorbate, Asmus and coworkers[27] obtained rate constants of the order of 10^7–$10^8\ M^{-1}s^{-1}$ for thiyl radicals derived from cysteine, penicillamine, homocysteine, cysteamine, thiopropionic acid and glutathione. Therefore, the values obtained for O_2 addition to the thiyl radicals from glutathione and cysteine differ by about two orders of magnitude. Asmus and coworkers[27] pointed out that the addition of molecular oxygen to $RS^{\bullet}$ radicals may be of a complex nature and, if the diffferences in rate constants are real, this may be due to reaction 46 being reversible. Furthermore, Tamba and coworkers[71] have found that there is no linear relationship between the rate of build-up of the $RSOO^{\bullet}$ radical adduct and the oxygen concentration, concluding that there must be an equilibrium involved in the glutathione system,

$$GS^{\bullet} + O_2 \rightleftharpoons GSOO^{\bullet} \quad (49)$$

the rate constants for the forward and reverse reaction being $2.0 \times 10^9\ M^{-1}s^{-1}$ and $6.2 \times 10^5\ s^{-1}$, respectively. It thus appears that the question regarding the rate constant for the reaction of oxygen with thiyl radicals in the liquid phase is by no means settled, although the early conclusion[77] that thiyl radicals add to molecular oxygen irreversibly and with diffusion-controlled rates cannot be accepted anymore.

Tamba and coworkers[71] also found that (i) the decay of the product radicals at 540 nm, i.e. $GSOO^{\bullet}$, is a complex process and cannot be described in terms of simple first- or second-order kinetics, and (ii) evidence for electron transfer from ascorbate to the $GSOO^{\bullet}$ radical has been obtained and the respective rate constant has been determined to be $1.7 \times 10^8\ M^{-1}s^{-1}$.

Products from radiolysis of oxygenated solutions of thiols are mainly the disulfides and hydrogen peroxide, but sulfinic and sulfonic acids have also been reported[78, 79]. The intermediacy of sulfenic acid, RSOH, has been postulated, but it has never been isolated. At present, most of the mechanistic concepts are highly speculative and therefore we refer the reader to previous reports on the subject[68, 73].

It is worth mentioning that Ito and Matsuda[80], using flash photolysis, have found the rate constant of the additon of the oxygen to *p*-chlorobenzenethiyl radicals to be *ca* $9 \times 10^4\ M^{-1}s^{-1}$ in cyclohexane at room temperature. Again, it may be impossible to deny the reversibility of the reaction, which will give a small rate constant in the flash photolysis.

C. Frozen Solution

An electron spin resonance investigation of the irradiation of thiols with methyl, butyl and *tert*-butyl groups, cysteine, cysteamine, glutathione and penicillamine in a number of aqueous and organic matrices in the presence of molecular oxygen has clearly shown the production of sulfinyl radicals[65, 81],

$$R'S^{\bullet} + O_2 \longrightarrow [R'SOO^{\bullet}] \longrightarrow R'SO^{\bullet} \quad (50)$$

The identity of sulfinyl radicals has been confirmed using ^{17}O-labelled molecular oxygen. Two mechanistic schemes have been proposed by Sevilla and coworkers[65] for this conversion. The first involves the formation of thiyl and thiyl peroxyl radicals as

intermediates:

$$ROO^{\bullet} + R'SH \longrightarrow ROOH + R'S^{\bullet} \quad (51)$$

$$R'S^{\bullet} + O_2 \longrightarrow R'SOO^{\bullet} \quad (52)$$

$$R'SOO^{\bullet} + R'SH \longrightarrow R'SO^{\bullet} + R'SOH \quad (53)$$

The other, possibly competitive mechanism may involve a direct bimolecular reaction:

$$ROO^{\bullet} + R'SH \longrightarrow [ROO\overset{\delta+}{S}(H)R'^{\delta-}] \longrightarrow R'SO^{\bullet} + ROH \quad (54)$$

which has been estimated to be exothermic (*ca* 245 kJ).

In a recent communication using ESR spectroscopy Sevilla and collaborator[82] presented evidence that indicates, again not unequivocally, the formation of the thiyl-peroxyl radical from cysteine (CysSOO•) at 160 K in dilute aqueous glasses. According to this report, although the CysSOO• radical shows a typical peroxyl ESR spectrum, unlike carbon-based peroxyl radicals it has a violet color ($\lambda_{max} = 540$ nm) in contradiction to their *ab initio* calculations at the 6-31G level which predict very similar physical parameters for methylperoxyl and methanethiylperoxyl radicals[65]. However, the presumed CysSOO• radical either forms a new radical showing a singlet ESR spectrum when photobleached with visible light, or it reacts to form CysSO• radicals when the glass is warmed to 165 K.

In conclusion, it should be stressed that the chemistry of RSOO• radicals has not been studied in sufficient detail to characterize them conclusively.

V. MISCELLANEOUS

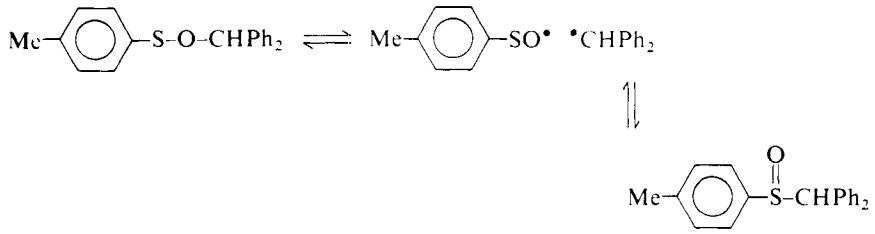
Using pulse radiolysis techniques, Packer[83] presented evidence for the formation of a complex between the thiyl radical derived from cysteine and a halide ion, viz.

$$CyS^{\bullet} + X^{-} \rightleftharpoons CyS{-}X^{\bullet -} \quad (55)$$

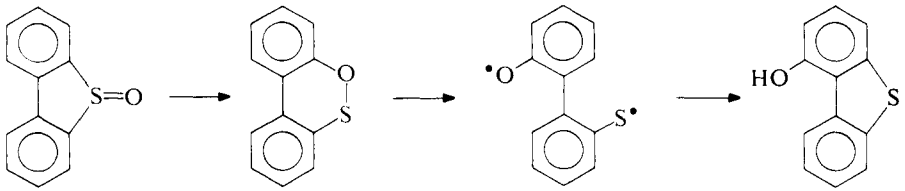
On the basis of the optical properties of these adducts, it has been suggested that they contain three-electron bonds. Some reactions of these species have also been discussed and equilibrium constants have been estimated for equations 55 and 56.

$$CyS{-}X^{\bullet -} + CyS^{-} \rightleftharpoons CySSCy^{\bullet -} + X^{-} \quad (56)$$

There are several mechanisms proposed for sulfoxide–sulfenate rearrangements, including radical pair, ion pair, and concerted mechanisms. For example, a study on the thermal decomposition of benzhydryl *p*-toluenesulfenate and benzhydryl *p*-tolyl sulfoxide indicates that equilibrium is established between them at a very early stage in the reactions and that this rearrangement occurs through a radical pair, at least partly (equation 57)[84]. Pyrolysis at 900°C of dibenzothiophen-5-oxide (**21**) gives 1-hydroxy-



(57)



(21) (22) (23) (24)

(58)

dibenzothiophene (**24**) in 55% yield. Davis and coworkers[85] suggested that the key step was a sulfoxide–sulfenate rearrangement following homolytic cleavage of the S–O bond in the sulfenate ester with the formation of biradical **23**.

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CHAPTER **13**

Electrochemistry of sulfenic acids and their derivatives

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I. POLAROGRAPHIC REDUCTION OF ESTERS OF ARENESULFENIC ACIDS

A. Methyl Benzenesulfenate

The polarogram of methyl benzenesulfenate (**1**) in 50% aqueous ethanol at pH 7.6 shows three reduction waves[1,2]. The half-wave potentials ($E_{1/2}$) of the first and second waves of **1** (0.2 mM) are −0.12 and −0.51 V vs. an aqueous saturated calomel electrode

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(SCE). With increasing concentration of **1**, the wave height of the first wave reaches a limiting value. On the other hand, the total height of the three waves is proportional to the concentration and to the square root of the mercury pressure. Thus the first wave has adsorption and the total wave diffusion properties. The appearance of a prewave is associated with the formation of a readily reducible substance on the mercury surface. The third wave corresponds to the postwave appearing in the reversible reduction of the strongly adsorbed mercaptide.

Controlled-potential coulometry on the first plateau gives a coulometric n value of 0.96 $\pm$0.03, and that on the total limiting current gives an n value of 1.9 $\pm$ 0.1.

$$\underset{(\mathbf{1})}{\mathrm{PhSOMe} + \mathrm{e} + \mathrm{H}^+ + \mathrm{Hg}} \longrightarrow \mathrm{HgSPh} + \mathrm{MeOH} \tag{1}$$

$$\mathrm{HgSPh} + \mathrm{e} + \mathrm{H}^+ \rightleftharpoons \mathrm{PhSH} + \mathrm{Hg} \tag{2}$$

Equations 1 and 2 are proposed for the polarographic reduction of **1** in aqueous ethanol. The first step consists of a reductive fission of the S–O bond giving methanol and a strongly adsorbed mercaptide, and the mercaptide is further reduced to thiophenol in the second step. HgSPh also undergoes dimerination, followed by disproportionation.

Controlled-potential coulometry of **1** in DMF and DMSO in the absence of a proton donor gives an n value of less than two, and the value decreases with increasing initial concentration of **1**. Analysis of the products of the electrolysis shows that thiophenolate ion, methanol and benzenesulfinate ion are formed.

$$\mathrm{PhSOMe} + 2\mathrm{e} \longrightarrow \mathrm{PhS}^- + \mathrm{MeO}^- \tag{3}$$

$$\mathrm{MeO}^- + \mathrm{H_2O} \rightleftharpoons \mathrm{MeOH} + \mathrm{OH}^- \tag{4}$$

$$2\mathrm{PhSOMe} + 2\mathrm{OH}^- \longrightarrow \mathrm{PhSO_2^-} + \mathrm{PhS}^- + 2\mathrm{MeOH} \tag{5}$$

Equations 3–5 are proposed for the polarographic reduction of **1** in DMF and DMSO. During the course of the reduction methoxide ion is produced at the cathode, which reacts with the residual water to give hydroxyl ion. Under strongly basic conditions hydroxyl ion reacts with **1** to give a benzenesulfinate ion.

B. Methyl 2-Nitro-, 4-Nitro- and 2-Nitro-4-chloro-benzenesulfenates

Substituted methyl benzenesulfenates [2-nitro (**2**), 4-nitro (**3**), 2-nitro-4-chloro (**4**)] in anhydrous DMF show two waves on the polarograms, and the first wave is approximately half the height of the second[3]. Both waves are of a diffusion type. The half-wave potentials of the first and second waves in DMF containing 0.1 M Et_4NI are: (**2**) 0.92 and 1.72 V, (**3**) 1.20 and 1.85 V, (**4**) 0.82 and 1.60 V vs. SCE. The first step corresponds to a two-electron reduction, while the second corresponds to a transfer of four to six electrons.

A partial preparative electrolysis of **2** in DMF on a mercury cathode at -1.0 V gives, after treatment of the electrolyzed solution with MeI, a mixture of **2** and 2- nitrothioanisole. The products corresponding to the reduction of the nitro group are not detected. Thus the sulfenic ester group is reduced earlier than the nitro group. The specific interaction of the sulfur-containing group with the surface of the mercury electrode is considered to have an influence on the sequence of the reduction.

II. ELECTROCHEMICAL REDUCTION OF BENZENESULFENYL CHLORIDES

Electrochemical reduction of substituted benzenesulfenyl chlorides at a platinum electrode was first studied by Kalinkin and coworkers[4]. However, they used DMF containing 0.1 M Bu_4NI as solvent, in which the decomposition rates of the sulfenyl chlorides are unsuitably high, and hence the half-wave potentials reported do not refer to the reduction of the sulfur–chlorine bond but rather to the corresponding disulfides.

Bontempelli and coworkers[5] studied the electrochemical reduction of benzenesulfenyl chloride (**5**) in acetonitrile containing 0.1 M Bu_4NClO_4, in which the rate of the decomposition is slow enough to allow voltammetric and coulometric measurements. The cyclic voltammogram of **5** in acetonitrile at a platinum sphere electrode shows three anodic peaks at −0.04, −0.72 and −1.85 V vs. SCE. On reversing the direction of a scan at −0.3 or −2.1 V, an anodic peak at +1.1 V is observed, which has been found to be associated with the first reduction process. The peak potential (E_p) of the third peak coincides with that of diphenyl disulfide (**6**), while E_p of the anodic peak equals that of chloride ion.

Controlled-potential coulometry carried out at a platinum gauze electrode at potentials corresponding to the first reduction process gives an n value ranging from 0.5 to 0.7, depending on the concentration of **5**. The highest n value is obtained with the lowest concentration **5**. Coulometry carried out at potentials corresponding to the second reduction process gives an n value of 1.0. **6** and Cl^- are detected in the solution after electrolysis.

$$\underset{(\mathbf{5})}{2PhSCl} + 2e \longrightarrow \underset{(\mathbf{6})}{PhSSPh} + 2Cl^- \tag{6}$$

$$2PhSCl + H_2O \xrightarrow{Cl^-} \underset{(\mathbf{7})}{PhS(O)SPh} + 2HCl \tag{7}$$

$$2PhS(O)SPh \longrightarrow PhSSPh + \underset{(\mathbf{8})}{PhSO_2SPh} \tag{8}$$

Equation 6 is proposed for the first cathodic process. Chloride ion formed in reaction 6 then catalyzes the reaction of **5** with the traces of water still present in the nominally anhydrous solvent to give phenyl benzenethiosulfinate (**7**) (reaction 7). **7** undergoes a spontaneous decomposition, induced by light, to give phenylbenzenethiosulfonate (**8**) (reaction 8). Formation of **7** and **8** is confirmed by preparative electrolysis at a potential corresponding to the first cathodic process. The reason why the coulometric n value is less than one and decreases with increasing initial concentration of **5** can be explained by reaction 7. The higher the initial concentration of **5**, the higher the concentration of Cl^-; consequently the catalytic action of Cl^- will be more effective. The second cathodic peak is attributable to the reduction of hydrogen chloride formed in reaction 7.

Johansson and Persson also studied electrochemical reduction of **5** and *p*-methylbenzenesulfenyl chloride in acetonitrile containing 0.1 M Et_4NClO_4 at a glassy carbon electrode[6]. The results are similar to those obtained by using a platinum electrode, except for the absence of the cathodic peak attributed to the reduction of hydrogen chloride.

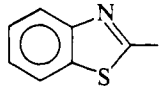
In situ electrochemical reduction of 4-nitro-, 2-nitro- and 2-nitro-4-chlorobenzenesulfenyl chlorides in acetonitrile containing Bu_4NClO_4 shows well-resolved electron spin resonance (ESR) spectra, which are assigned to those of the anion radicals of the nitrobenzenethiolate[7].

III. ELECTROCHEMICAL REDUCTION OF SULFENAMIDES AND SULFENIMIDES

A. Benzo-1,3-thiazole-2-sulfenamides and *N*-Thioalkyl (or Thioaryl)succinimides

The polarographic half-wave potentials of five benzo-1,3-thiazole-2-sulfenamides [NR^2R^3 = *t*-BuNH–, *c*-HexNH–, $(c\text{-Hex})_2N$–, Et_2N–, $O(CH_2CH_2)_2N$–] are 2.00, 1.73, 1.89, 1.80 and 1.60 V vs. SCE, respectively[8]. Electrochemical reduction of the sulfenamides at a mercury pool cathode gives the corresponding thiols and amines; the S–N bond is broken in the manner shown in equation 9.

$$R^1SN(R^2)R^3 + 2e + 2H^+ \longrightarrow R^1SH + R^2R^3NH \qquad (9)$$

$R^1 =$ 

The values of $E_{1/2}$ of three sulfenimides, *N*-benzylthiosuccinimide, *N*-phenylthiosuccinimide and *N*-*c*-hexylthiosuccinimide, are 0.40, 0.94 and 1.84 V vs. SCE, respectively[8], and the electrochemical reduction of the sulfenimides gives the corresponding thiols and succinimide.

B. *p*-Nitrobenzenesulfenamides

In situ electrolysis of *p*-nitrobenzene sulfenamide and *N*,*N*-dimethyl-*p*-nitrobenenesulfenamide in acetonitrile at a mercury pool electrode shows well-resolved ESR spectra, which are assigned to those of the anion radicals of the parent sulfenamides[9]. Their ESR parameters are close to the corresponding values for the anion radicals of *p*-nitroanilines.

The half-wave potential of *N*-(*p*-nitrophenylthio)-2,4,6-tri-*t*-butylaniline in acetonitrile at a rotating platinum disc electrode is -1.08 V vs. SCE[10], which is close to that for nitrobenzene. A cyclic voltammogram of the isolable *N*-(*p*-nitrophenylthio)-2,4,6-tri-*t*-butylphenylaminyl radical shows both cathodic and anodic waves[10]. On the cathodic scan, a reversible peak at -0.68 V is found and, on the reversal scan at -0.90 V, a reoxidation peak of equal magnitude is found at -0.61 V. On the anodic scan, a partially reversible peak at $+0.78$ V is found, which indicates that the intermediate cation, 2,4,6-tri-*t*-BuC_6H_2–$N{=}S^+$–$C_6H_4NO_2$-*p*, produced on the anodic scan, is relatively unstable.

C. *N*-(Phenylthio)quinoneimines

N-(Phenylthio)quinoneimines are reduced in acetonitrile at a dropping mercury electrode in two successive one-electron stages[11]. A good linear relationship (equation 10) exists between the half-wave potentials of the first waves of seven *N*-(2- and/or 4-substituted phenylthio)quinoneimines and the Hammet σ constants of the substituents, which indicates that the lowest unoccupied molecular orbital is localized mainly on the quinoneimine fragment.

$$E_{1/2} = -0.7 + 0.10\sigma \text{ V vs. SCE } (r = 0.997) \qquad (10)$$

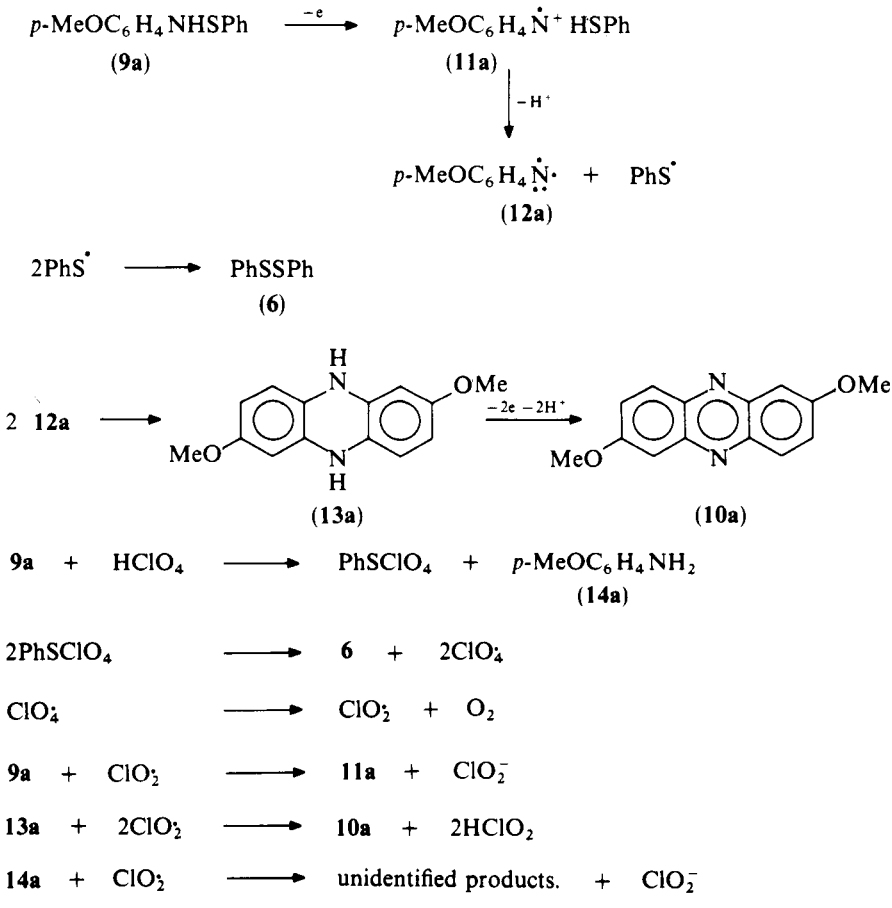
IV. ANODIC OXIDATION OF SULFENAMIDES

A. 4′-Substituted Benzenesulfenanilides

Benzenesulfenanilides [4′-OMe (**9a**), 4′-Me (**9b**), 4′-Cl (**9c**), 4′-H (**9d**)] are easily oxidized at a glassy-carbon anode in acetonitrile[12]. The peak potentials (E_p) of the first waves of **9a–d** are listed in Table 1. The values of $i_p \cdot c^{-1}$ of **9a–d**, where i_p is the peak current and c is the concentration of **9a–d**, decrease with increase in c. This dependence is ascribed to the acid hydrolysis of **9a–d** at the surface of the anode, since the anolyte becomes acidic in the neighborhood of the anode and the acidity increases with increase in the electricity consumed.

Controlled-potential electrolysis of **9a–c** in acetonitrile containing 0.1 M $NaClO_4$ gives 2,7-disubstituted phenazines [OMe (**10a**), Me (**10b**), Cl (**10c**)] and diphenyl disulfide (**6**), whereas that of **9d** does not. The results of electrolysis are also summarized in Table 1.

The mechanism shown in Scheme 1 has been proposed for the anodic oxidation of **9a**. The nitrene (**12a**) is considered to be an intermediate for the formation of the phenazine



SCHEME 1

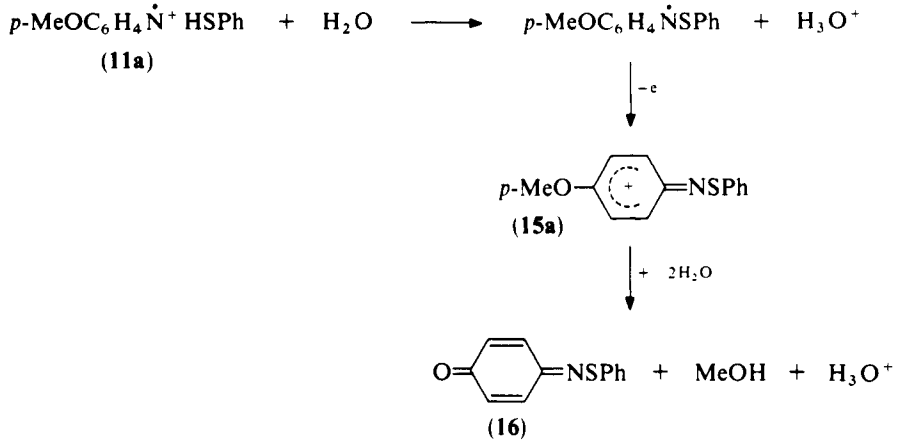
TABLE 1. Results of cyclic voltammetry and controlled-potential electrolysis of 4′-substituted benzenesulfenanilides (4′-XC_6H_4NHSPh) in acetonitrile containing 0.1 M $NaClO_4$. Reproduced by permission of the Pharmaceutical Society of Japan from Ref. 12.

Compd. No.	4′-X	E_p (V)[a]	Applied potential (V)[a]	*n* Value	Products identified	Yield (mol%)[b]
9a	OMe	0.75	0.75	0.67	2,7-dimethoxyphenazine	39.4
					diphenyl disulfide	99.1
					p-anisidine	0.8
9b	Me	0.88	0.90	0.69	2,7-dimethylphenazine	42.0
					diphenyl disulfide	98.4
9c	Cl	0.94	1.00	0.70	2,7-dichlorophenazine	13.6
					diphenyl disulfide	53.1
					p-chloroaniline	64.0
9d	H	0.88	0.97	0.66	not identified	

[a] All potentials were measured against an aqueous saturated calomel electrode.
[b] Yield based on 2 moles of the anilide forming 1 mole of the phenazine and 1 mole of diphenyl disulfide.

(**10a**). Since **9a** is unstable in acidic solution and the anolyte becomes acidic with the progress of the electrolysis, a fairly large amount of **9a** and of the perchlorate decomposes to **6**, *p*-anisidine (**14a**), chlorine dioxide and oxygen without being oxidized at the anode. The chlorine dioxide thus formed oxidizes **9a**, **14a** and 2,7-dimethoxy-5,10-dihydrophenazine (**13a**) to produce **10a** and unidentified resinous compounds.

Addition of water (1%) to the solution of **9a–d** increases the value of $i_p \cdot c^{-1}$, especially at $c = 1$ and 2 mM. Electrolysis of **9a** in the presence of water (1%) gives *N*-phenylthio-*p*-quinoneimine (**16**) in addition to **10a**. Reaction 11 is proposed for the formation of **16**. The water molecule abstracts a proton from the cation radical (**11a**), and the *N*-(phenylthio)-*p*-methoxyphenylaminyl radical formed is oxidized further to the cation (**15a**) at the applied potential, and then **15a** is immediately hydrolyzed to give **16** and methanol.



(11)

Electrolysis of **9b** and **9c** is considered to be analogous with that of **9a**. The reason why electrolysis of **9d** does not give phenazine will be discussed later.

B. 4′-Substituted 2-Nitrobenzenesulfenanilides

The peak potentials (E_p) of the first anodic wave of 2-nitrobenzenesulfenanilides [4′-OMe (**17a**), 4′-Me (**17b**), 4′- Cl (**17c**), 4′-H (**17d**)] in acetonitrile containing 0.1 M $NaClO_4$ are 0.10–0.22 V more positive than those of **9a–d**, respectively[13]. The values of $i_p \cdot c^{-1}$ of **17a–d** are 1.4–2.0 times those of **9a–d**. Addition of water (1%) to the solution of **17a** increases the value of $i_p \cdot c^{-1}$ at $c = 5$, 10 and 30 mM, whereas at $c = 2$ mM it does not. When ethyltributylammonium trifluoromethanesulfonate (ETBT) is used as the supporting electrolyte, the value of $i_p \cdot c^{-1}$ is not affected by the addition of water.

Controlled-potential electrolysis of **17a–c** in acetonitrile containing 0.1 M $NaClO_4$ gives the corresponding 2,7-disubstituted phenazines (**10a–c**), 2,2′-dinitrodiphenyl disulfide (**18**) and 2-nitrobenzenesulfonic acid (**19**). In addition, *p*-anisidine (**14a**) and *N*-(2-nitrophenylthio)-*p*-benzoquinoneimine (**20**) are obtained in the electrolysis of **17a**. The results of controlled-potential electrolysis are summarized in Table 2.

When $NaClO_4$ is replaced by ETBT, the electrolysis of **17a–d** does not give **19**. Instead, the yield of the disulfide **18** increases. These results indicate that the perchlorate anion does act as an oxidant in the anodic oxidation of **17a–d**, and that **19** is formed through one-step two-electron transfer followed by reaction of the dication with perchlorate anion. The introduction of the 2-nitro group is considered to elicit the one-step two-electron transfer.

Addition of trifluoroacetic acid (TFA) to the solution of **17a–c** in acetonitrile containing 0.1 M ETBT improves the yields of **10a–c** considerably[14]. Furthermore, although electrolysis of 4′-ethoxycarbonyl- and 4′-acetyl-2-nitrobenzenesulfenanilides [4′-COOEt (**17e**), 4′-COMe (**17f**)] in the absence of TFA does not give the corresponding phenazines at all; in the presence of TFA (1%) it does. On the other hand, electrolysis of **17d** and 4′-nitro-2-nitrobenzenesulfenanilide (**17g**) does not give the corresponding phenazines even in the presence of TFA. The results are summarized in Table 3.

Electrolysis of 2′-(*p*-chlorophenyl)amino-4′-chloro-2-nitrobenzenesulfenanilide (**21c**) in acetonitrile containing 0.1 M ETBT and 1% TFA gives 2,7-dichlorophenazine (**10c**) in good yield[15].

Electrolysis of **17a–d** in the presence of pyridine (1%) gives the corresponding 2′-pyridinated sulfenanilides (**27**), while that of **17e** and **17f** gives the corresponding 4,4′-disubstituted azobenzenes (**28**)[14].

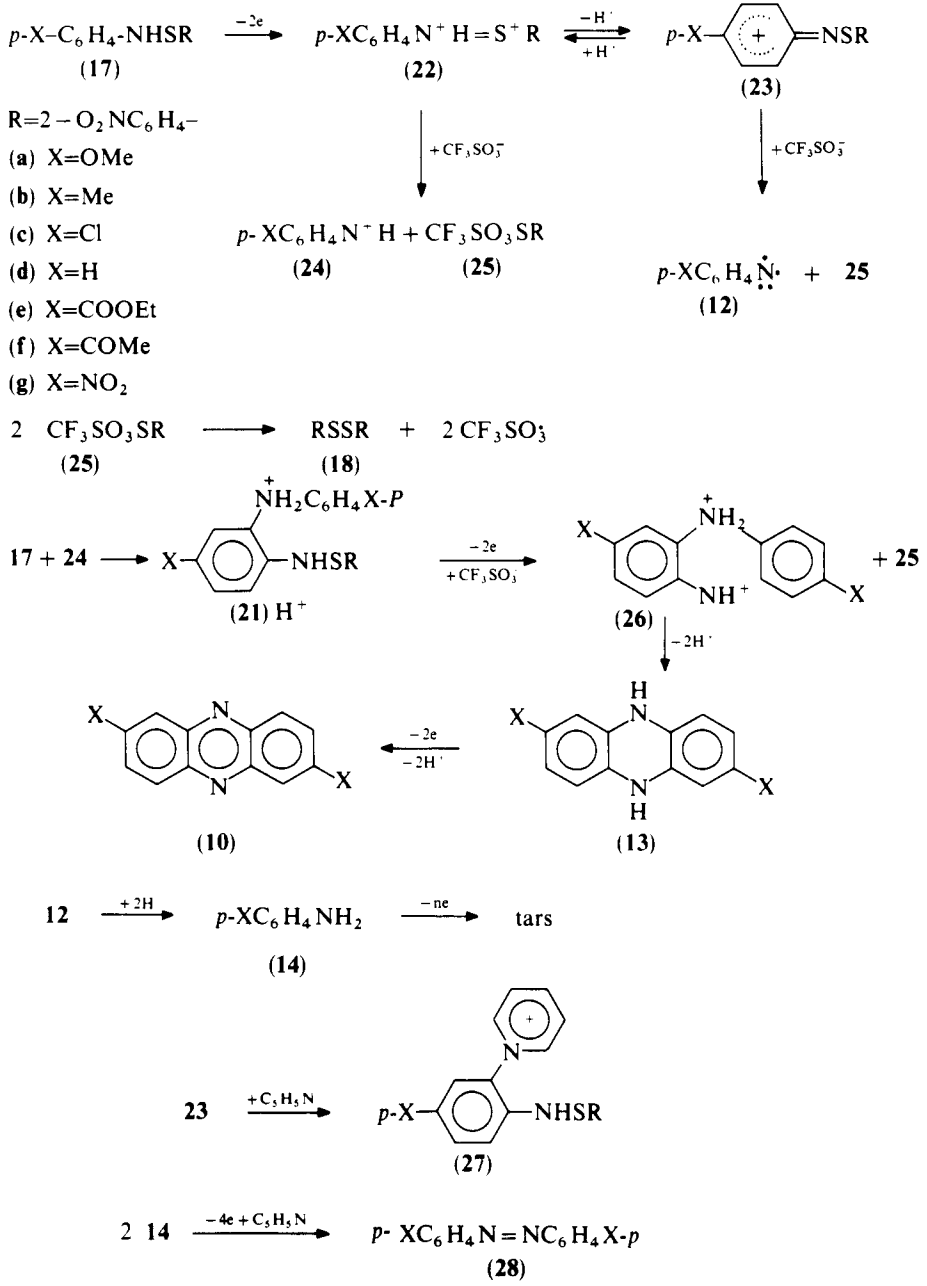
Scheme 2 was proposed for the anodic oxidation of the 4′-substituted 2-nitrobenzenesulfenanilides (**17**) in acetonitrile containing 0.1 M ETBT in the presence of TFA or pyridine[14,15]. The dication **22** is formed through one-step two-electron oxidation of **17**. In the presence of TFA, **22** reacts with trifluoromethanesulfonate ion and gives the nitrenium ion (**24**). **24** binds to the 2′-position of **17** to form the protonated *N*,*N*′-disubstituted *o*-phenylenediamine derivative (**21**), which is oxidized further to *o*- and *p*-disubstituted nitrenium ion (**26**) and then to the 2,7-disubstituted phenazine (**10**). An electron-attracting substituent at the 4′-position increases the dissociation of **22** and decreases the concentration of **24** and thus decreases the yield of **10**. Addition of TFA to the solution suppresses the dissociation of **22** and thus increases the yield of **10**. However, this suppression is considered to be incomplete for the electrolysis of **17g**, whose 4′-substituent has the largest Hammett σ value among **17a–g**, and hence electrolysis of **17g** does not give **10g** even in the presence of TFA.

In the presence of pyridine, **22** is deprotonated immediately to **23**, and a part of **23** reacts with pyridine and gives the 1-substituted pyridinium derivatives (**27**). The rest of **23** reacts with trifluoromethanesulfonate ion and gives the nitrene **12**, which abstracts two hydrogen atoms from the solvent or **17** and gives the *p*-substituted anilines (**14**). **14** (except for **14g**, which has the highest oxidation potential among **14a–g**) is oxidized further to the corresponding 4,4′-disubstituted azobenzenes (**28**) and/or tars. Electron-donating substi-

TABLE 2. Results of controlled-potential electrolysis of 4′-substituted 2-nitrobenzenesulfenanilides (10 mM) in acetonitrile. Reproduced by permission of the Pharmaceutical Society of Japan from Ref. 13.

Compd. No.	Applied potential (V)	*n* Value	Supporting electrolyte	Yield (mol%)				
				2,7-Disubstituted phenazine (**10**)	2,2′-Dinitrodiphenyl disulfide (**18**)	Amine (**14**)	2-Nitrobenzene sulfonic acid	Quinoneimine (**20**)
17a	0.85	0.63	$NaClO_4$	29.4	3.0	27.0[a]	40.8	2.3
17a	0.85	1.35	ETBT[b]	29.2	44.2	15.2[a]	0	2.0
17b	1.03	0.69	$NaClO_4$	29.0	11.0	0	38.2	0
17b	1.03	1.95	ETBT	40.0	19.7	0	0	0
17c	1.18	1.04	$NaClO_4$	25.0	1.5	0	30.6	0
17c	1.18	1.97	ETBT	37.3	22.5	0	0	0
17d	1.13	1.03	$NaClO_4$	0	trace	0	35.1	0
17d	1.13	2.15	ETBT	0	3.0	0	0	0

[a] *p*-Anisidine.
[b] Ethyltributylammonium trifluoromethanesulfonate.


p-X-C6H4-NHSR
(17)
-2e
p-XC6H4N+H=S+R
(22)
-H·
+H·
p-X
NSR
(23)
R=2-O2NC6H4-
(a) X=OMe
(b) X=Me
(c) X=Cl
(d) X=H
(e) X=COOEt
(f) X=COMe
(g) X=NO2
+CF3SO3-
p-XC6H4N+H + CF3SO3SR
(24) (25)
p-XC6H4N· + 25
(12)
2 CF3SO3SR
(25)
RSSR + 2 CF3SO3-
(18)
17 + 24
NH2C6H4X-P
NHSR
(21) H+
-2e
+CF3SO3-
+25
(26)
-2H·
(10)
(13)
12
+2H
p-XC6H4NH2
(14)
-ne
tars
23
+C5H5N
p-X
NHSR
(27)
2 14
-4e + C5H5N
p-XC6H4N=NC6H4X-p
(28)

SCHEME 2

TABLE 3. Results of cyclic voltammetry and controlled-potential electrolysis of 4′-substituted 2-nitrobenzenesulfenanilides (10 mM) in acetonitrile containing 0.1 M ETBT, 1% trifluoroacetic acid (TFA) and 1% trifluoroacetic anhydride (TFAH). Reproduced by permision of the Pharmaceutical Society of Japan from Ref. 14

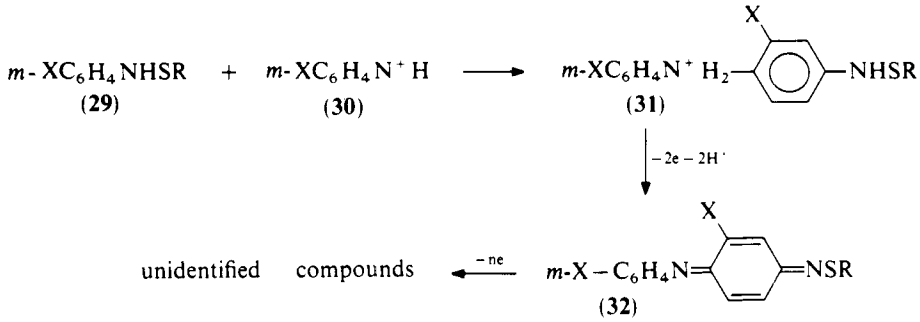
Compd. No.	E_p(V)[a]	Applied potential (V)[a]	n Value	Yield (mol%) 2,2′-Dinitrodiphenyldisulfide (**18**)	Yield (mol%) 2,7-Disubstituted phenazine (**10**)	Hammett σ_p of substituent
17a	0.97	1.10	0.88	64.0	45.9 (29.2)[b]	−0.268
17b	1.12	1.23	1.58	54.5	46.8 (40.0)	−0.170
17c	1.23	1.33	1.35	64.0	57.2 (37.3)	+0.227
17d	1.18	1.18	1.40	26.0	0 (0)	0.0
17e	1.15	1.45	1.85	51.0	45.8 (0)	+0.45
17f	1.34	1.48	1.17	47.0	7.6 (0)	+0.502
17g	1.37	1.48	0.52	0	0 (0)	+0.778
21c	1.23	1.33	2.32	75.0	55.0 (0)	

[a] All potentials were measured against an aqueous saturated calomel electrode.
[b] Numbers in parentheses are yields of the phenazines without addition of TFA and TFAH.

tuents at the 4′-position of **17** stabilize **23** and increase the yields of 1-substituted pyridinium derivatives (**27**).

C. 3′- and 2′-Substituted 2-Nitrobenzenesulfenanilides

Since the 4′-position of the sulfenanilides is vacant, most of the nitrenium ion (**30**) formed binds to the 4′-position to give *N*,*N*′-disubstituted *p*-phenylenediamine derivatives (**31**). **31** is oxidized to the *p*-quinonediimine derivative (**32**) at the applied potential, and most of **32** formed is oxidized further to unidentified resinous compounds (reaction 12)[15].



(12)

Therefore, electrolysis of 3′- and 2′-substituted 2-nitrobenzenesulfenanilides [3′-OMe (**29a**), 3′-Me (**29b**), 3′-Cl (**29c**), 3′-NO_2 (**29g**), 2′-Me (**33b**)] in acetonitrile containing 0.1 M ETBT and 1% TFA gives no appreciable amount of the corresponding phenazines[15].

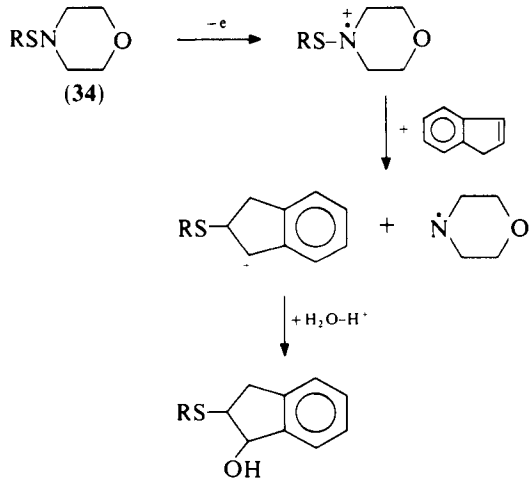
The experimental fact that the electrolysis of **9d** and **17d** in acetonitrile does not give phenazine can be explained by the same mechanism as above.

D. *N*-(*o*-Nitrophenylthio)alicyclic Amines

Cyclic voltammograms of *N*-(*o*-nitrophenylthio)alicyclic amines [morpholine (**34**), thiomorpholine (**35**), piperidine (**36**), pyrrolidine (**37**)] in acetonitrile show two or three anodic waves[16]. Voltammetric data are summarized in Table 4. On reversing the direction of a scan just beyond the potentials of the first waves, **34**, **36** and **37** show a relatively large cathodic counterpart, respectively. The differences in potential between the anodic and cathodic peaks are 70 mV. Therefore, the first step in the anodic oxidation of the sulfenamides is considered to be a quasi-reversible one-electron transfer to form the sulfenamide radical cations.

Formation of the radical cations is confirmed by electron spin resonance (ESR) spectroscopy. Although **35** gives no cathodic counterpart in the voltammogram, *in situ* electrolysis of **35** shows the ESR spectrum of the radical cation. However, the radical cation of **35** is most unstable among those of the sulfenamides. ESR studies on the radical cations of *N*-(*o*-nitrophenylthio)alicyclic amines generated electrochemically have been carried out in acetonitrile or propionitrile at various temperatures, and the rate of conformational exchange of these radicals has been discussed[17].

Electrolysis of **34**–**37** in acetonitrile containing 0.1 M $NaClO_4$ gives no definite product except 2,2′-dinitrodiphenyl disulfide[18]. When indene is added to a solution of **34**–**36** prior to electrolysis, 2-(*o*-nitrophenylthio)indan-1-ol (**38**) is obtained on electrolysis of **34**–**36**[16]. Reaction 13 is proposed for the formation of **38**[16].



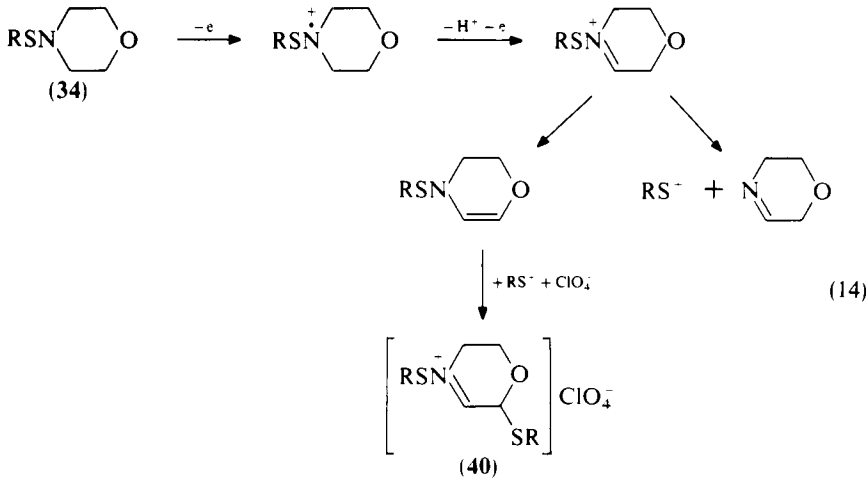
(34) (38) R = *o*-nitrophenyl (13)

Electrolysis of **34**–**37** in methanol containing 0.1 M $NaClO_4$ at 1.2 V gives methyl 2-nitrobenzenesulfenate (**39**) in 21.0, 56.0, 23.0 and 36.6% yields, respectively[18]. **39** is considered to be derived from the reaction of the sulfenylium ion with methanol (reactions 14 and 15). A yellow powder is precipitated from the electrolyzed solution in the last stage of electrolysis of **34** in methanol (yield 74.2%). This compound was identified as 2,4-bis(*o*-nitrophenylthio)-5,6-dihydro-2*H*-1,4-oxazinium perchlorate (**40**), which is formed through the reaction of the sulfenylium ion with 4-(*o*-nitrophenylthio)-5,6-dihydro-1,4-oxazine.

TABLE 4. Results of cyclic voltammetry of *N*-(*o*-nitrophenylthio)amines (2 mM) in acetonitrile containing 0.1 M $NaClO_4$ at a scan rate of 50 mV s^{-1}. Reproduced by permission of the Pharmaceutical Society of Japan from Ref. 16

Compd. No.	First wave E_{pa} (V)[a]	Second wave E_{pa} (V)[a]	Reverse wave E_{pc} (V)[a]	First wave i_{pc}/i_{pa}
34	1.21	1.67	1.14	0.60
35	1.20	1.31[b]	*c*	*c*
36	1.12	1.70	1.05	0.58
37	1.07	1.65	1.00	0.70

[a] All potentials were measured against an aqueous saturated calomel electrode.
[b] A third wave was also recognized at 1.45 V.
[c] No reverse wave was recognized.



(14)

$$RS^+ + MeOH \longrightarrow \underset{(39)}{RSOMe} + H^+ \qquad (15)$$

E. Trialkylsulfenamides

Cyclic voltammograms of 1-(methylthio)pyrrolidine (**41**), 1-(methylthio)piperidine (**42**), (methylthio)diisopropylamine (**43**), 9-(methylthio)-9-azabicyclo[3.3.1]nonane (**44**), (*t*-butylthio)dimethylamine (**45**), 1-(*t*-butylthio)pyrrolidine (**46**), (*t*-butylthio)diisopropylamine (**47**) in a acetonitrile containing 0.1 M Bu_4NClO_4 at gold electrode show a one-electron oxidation wave at 0.7–1.0 V[19]. The anodic peak for each is nearly electrochemically reversible at fast scan rates (up to 100 V s^{-1}). The oxidation–reduction peak separations are 0.06–0.09 V. The observed order of increasing stability of the radical cations is **45** < **42** < **41**, **46** < **47** < **43** < **44**. Addition of 6.8 mM of pyridine to the solution of **41** decreases the size of the cathodic counterpart relative to the oxidation peak, and no cathodic peak is observed at a scan rate of 0.5 V s^{-1}.

F. *N,N*-Disubstituted 2-Nitrobenzenesulfenamides

Voltammetric data on *N*-(2-nitrophenylthio)dibenzylamine (**48**) and six *N*-alkyl-2-nitrobenzenesulfenanilides [*N*-Me, 4′-Me (**49**); *N*-Me, 4′-*t*-Bu (**50**); *N*-Me, 4′-COOEt (**51**); *N*-Me (**52**); *N*-Et (**53**); *N*-CH_2Ph (**54**)] in acetonitrile containing 0.1 M $NaClO_4$ are summarized in Table 5[20]. The voltammetric behavior of the sulfenamides is classified into two groups. One shows a quasi-reversible anodic wave, and the other shows an irreversible anodic wave whose peak height is nearly twice that of the former. The former comprises **48** and the 4′-substituted sulfenanilides (**49**, **50** and **51**), and the latter comprises the 4′-unsubstituted sulfenanilides (**52**, **53** and **54**).

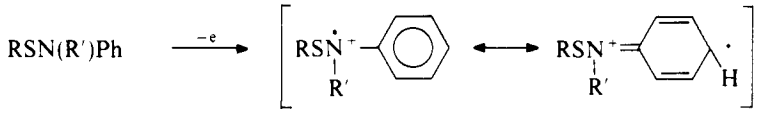
TABLE 5. Results of cyclic voltammetry of the *N,N*-disubstituted 2-nitrobenzenesulfenamides (2 mM) in acetonitrile containing 0.1 M $NaClO_4$. Reproduced by permission of the Pharmaceutical Society of Japan from Ref. 20

Compd. No.	Sulfenamide[a]	E_p^b	$i_{pa} \cdot C^{-1} \cdot v^{-1/2}$ [c]	i_{pc}/i_{pa} [d]
48	$RSN(CH_2Ph)_2$	1.31	2.3	0.5
49	$RSN(Me)C_6H_4Me$-*p*	1.15	2.6	0.7
50	$RSN(Me)C_6H_4(t$-Bu)-*p*	1.15	2.2	0.8
51	$RSN(Me)C_6H_4COOEt$-*p*	1.43	2.6	0.4
52	RSN(Me)Ph	1.17	5.1	0
53	RSN(Et)Ph	1.16	4.9	0
54	$RSN(CH_2Ph)Ph$	1.25	4.6	0

[a] R = 2-nitrophenyl.
[b] Anodic peak potential in V vs. SCE, sweep rate 50 mV s^{-1}.
[c] i_{pa}, anodic peak current in μA; *C*, concentration in mM; *v*, sweep rate in mV s^{-1}.
[d] i_{pc}, peak current of the cathodic counterpart obtained by reversal of the scan.

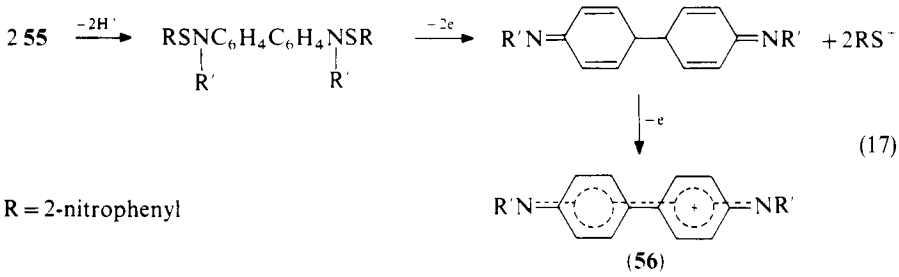
In situ electrolysis of **48**, **49**, **50** and **51** in acetonitrile at room temperature gives fairly unstable radicals whose ESR spectra can be assigned to the radical cations of the parent sulfenamides, whereas that of **52**, **53** and **54** gives very stable radicals whose ESR spectra cannot be simulated by ESR parameters expected for the radical cations of the sulfenamides. The latter radicals have been identified as the radical cations of *N,N*-dialkyldiphenoquinonediimines (**56**) formed by dimerization of the sulfenamide radical cations (**55**) and further oxidation of the dimers.

Reactions 16 and 17 are proposed for the formation of **56**. The dimerization is considered to take place before the cleavage of the S–N bond in the sulfenamide radical cations (**55**).



(**52**) R′ = Me
(**53**) R′ = Et
(**54**) R′ = $PhCH_2$

(**55**) (16)



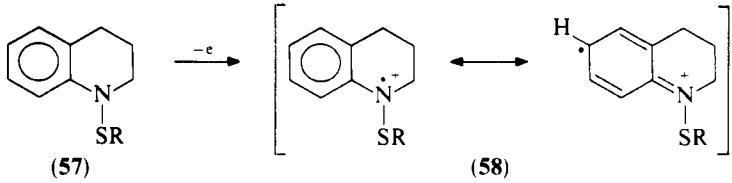
(17)

R = 2-nitrophenyl

(56)

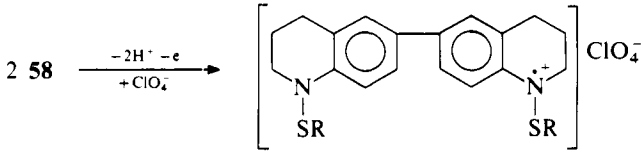
G. *N*-(2-Nitrophenylthio)-1,2,3,4-tetrahydroquinoline and *N*-(2-Nitrophenylthio)-1,2,3,4-tetrahydroisoquinoline

The cyclic voltammogram of *N*-(2-nitrophenylthio)-1,2,3,4-tetrahydroquinoline (**57**) in acetonitrile shows an anodic peak at 1.02 V[21]. Upon reversal of the scan direction at 1.3 V, a cathodic wave is observed at 0.7 V, which indicates that the anodic wave is irreversible. *In situ* electrolysis of **57** in acetonitrile gives a stable radical whose ESR spectrum does not correspond to that of the radical cation of the parent sulfenamide. The perchlorate of 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-di(2-nitrophenylthio)-6,6′-biquinoline radical (**59**) is precipitated as a black powder from the solution during the electrolysis of **57** (5 mM) in acetonitrile containing 0.1 M $NaClO_4$ at a glassy-carbon anode at 1.0 V. Reactions 18 and 19 are proposed for the formation of **59**.



(18)

(57) (58)



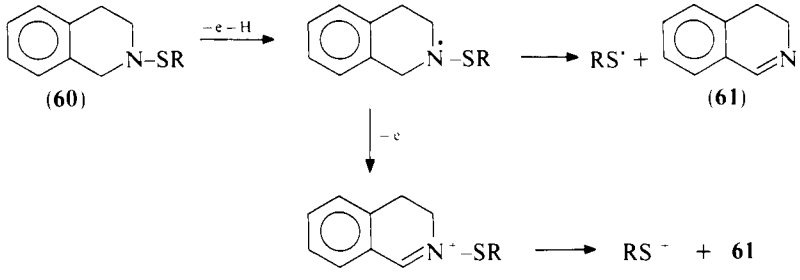
(19)

(59)

R = 2-nitrophenyl

The voltammogram of *N*-(2-nitrophenylthio)-1,2,3,4-tetrahydroisoquinoline (**60**) shows two irreversible anodic waves at 1.19 and 1.70 V. No cathodic counterpart is observed upon reversal of the scan direction. *In situ* electrolysis of **60** in acetonitrile shows no ESR signal even at −40°C. Electrolysis of **60** (10 mM) in acetonitrile at 1.19 V gives 3,4-dihydroisoquinoline (**61**) and a trace amount of 2,2′-dinitrodiphenyldisulfide. Electrolysis of **60** (10 mM) in methanol at 1.19 V gives an almost quantitative yield of **61** and a 56% yield of methyl 2-nitrobenzenesulfenate (**39**). Reactions 20, 21 and 22, which are

similar to those proposed for the electrolysis of **34**, are suggested for the formation of **61** and **39**.



(20)

$$RS^- + MeOH \longrightarrow \underset{(39)}{RSOMe} + H^+ \qquad (21)$$

$$2RS^{\cdot} \longrightarrow RSSR \qquad (22)$$

R = 2- nitrophenyl

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **14**

Syntheses and uses of isotopically labelled sulphenic acid derivatives

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

Sulphenic acid chemistry celebrated in 1970 one hundred years since the synthesis by Rathke[1] of trichloromethanesulphenyl chloride, Cl_3CSCl. Various reviews appeared on that occasion[2-9] and contain many leading references to creative studies in this rapidly developing new branch of organic chemistry[8,9]. The large body of accumulated data initiated formulations of general mechanistic schemes concerning reaction paths, charge distributions in substrates and in transition states as well as concerning structures of transition states. Many of the controversies on the mechanisms of formation of sulphenic acid derivatives could be solved by the synthesis of isotopically labelled substrates and by carrying out appropriate tracer or isotope effect experiments, but there are only few isotope effect studies aimed at clarifying the transition states involved. The latter are reviewed thoroughly in Section IV. Sulphenic acid derivatives labelled with stable and especially radioactive isotopes are also helpful in structure elucidations and in analytical determinations in biological systems. The sensitivity of radiodeterminations of isotopically labelled sulphenyl derivatives surpasses the limits of accuracy of the conventional analytical methods. Practical medical aims also contributed greatly to the development of the isotopic sulphenic acid chemistry.

II. SYNTHESES OF LABELLED SULPHENIC ACID DERIVATIVES

Halogenolysis of sulphides, thiol esters, esters of thioacids, P=S and C=S double bonds, some aromatic sulphinic acids, disulphides and trisulphides at low temperature is a synthetic procedure used for preparation of aliphatic, aromatic and heterocyclic sulphenyl halides and their derivatives[2-4,10,11]. Numerous syntheses of the isotopically labelled starting compounds have been reviewed[12]. Sulphenic acid appears as the fast reacting intermediate in the course of oxidative cleavage of compounds containing divalent sulphur. This class of organic compounds are important in biological processes in agriculture and in medicine and has been reviewed in Section II.C. Labelled compounds containing divalent sulphur obtained in the course of exchange studies are reviewed in Section III.

A. Syntheses of Deuterium and Tritium Labelled Sulphenic Acid Derivatives and Related Compounds

1. *Syntheses of deuterium labelled sulphenic acid derivatives and related compounds*

a. Synthesis of deuterated symmetrical N,N′-bis (trifluoromethanesulphenyl) urea and deuterated asymmetrical N,N-bis(trifluoromethanesulphenyl) urea. The deuterated symmetrical compound **1** has been prepared by reaction of trifluoromethanesulphenyl isocyanate with D_2O (equation 1)[13]:

$$CF_3SN{=}C{=}O + D_2O = CF_3SND{-}\underset{\underset{O}{\|}}{C}{-}NDSCF_3 + CO_2 \quad (1)$$

(1)

The deuterated asymmetrical compound **2** was obtained in the course of the hydrolysis of the *N,N*-bis(trifluoromethanesulphenyl) carbamoyl isocyanate, **3** (equation 2):

$$(CF_3S)_2N{-}\underset{\underset{O}{\|}}{C}{-}N{=}C{=}O + D_2O = (CF_3S)_2N{-}\underset{\underset{O}{\|}}{C}{-}ND_2 + CO_2 \quad (2)$$

(3) **(2)**

The compound **3** is the liquid dimeric by-product (*ca* 25% yield) in the reaction of trifluoromethanesulphenyl chloride with silver cyanate (equation 3), which gives at room temperature the trifluoromethanesulphenyl isocyanate as the main product (*ca* 75%).

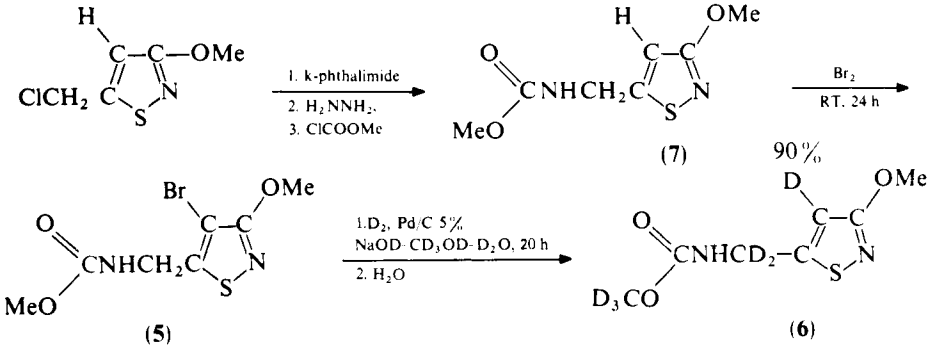
$$3\ CF_3SCl + 3\ AgOCN \xrightarrow{RT,\ 1\ h} CF_3SNCO + \mathbf{3} + 3AgCl \qquad (3)$$

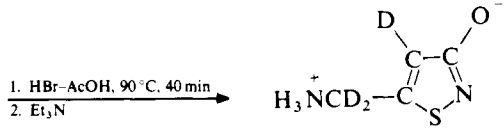
Deuteration helped greatly to identify the structure of **3**. Replacement of hydrogen by deuterium shifted the 3480–3280 cm^{-1} absorption to 2590–2430 cm^{-1}, which coincides with the absorption at 2604–2421 cm^{-1} found in deuterated urea. The cyclic structure **3a** should give the symmetrical disubstituted urea upon hydrolysis (equation 4).

$$\begin{array}{l} CF_3SN\text{–}C{=}O \\ \quad\ |\ \ | \\ O{=}C\text{–}N\text{–}SCF_3 \\ \quad\ \mathbf{(3a)} \end{array} + D_2O \longrightarrow (CF_3SND)_2C{=}O + CO_2 \qquad (4)$$

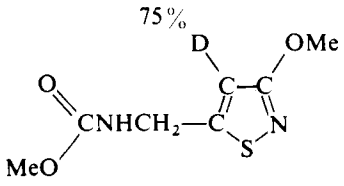
The infrared spectra of **1** and **2** have been determined and interpreted[14]. The $\nu NH_2(as) = 3480\ cm^{-1}$ in $(CF_3S)_2NCONH_2$ shifts upon deuteration to the $\nu ND_2(as) = 2500\ cm^{-1}$ in **2**. The $\nu NH_2(sym)$ at 3350 cm^{-1} and 3290 cm^{-1} shift to $\nu ND_2(sym) = 2430\ cm^{-1}$. νNH in $(CF_3SNH)_2CO$ equal to 3280 cm^{-1} shifts to νND in $(CF_3SND)_2CO$ equal to 2440 cm^{-1}. The $\nu C{=}O = 1679$ in $(CF_3SNH)_2CO$ shifts slightly upon deuteration to 1672 cm^{-1} in **1**. The frequencies 1727 cm^{-1} and 1687 cm^{-1} corresponding to $\nu C{=}O$ in $(CF_3S)_2NCONH_2$ shift to 1715 and 1682 cm^{-1} in **2**. The angle deformation vibrations of the NH_2 group, $\delta(NH_2) = 1605\ cm^{-1}$ in $(CF_3S)_2NCONH_2$ and $\delta(NH_2) = 1605\ cm^{-1}$ in $CF_3NHCONH_2$, disappear in the corresponding deuterated compounds because of coupling with other fundamentals such as C–N skeletal stretching modes. One of the three additional new bands appearing in the case of **2** is located at 990 cm^{-1}. $\delta(NH) = 1507\ cm^{-1}$ found in $(CF_3SNH)_2C{=}O$ disappears also on deuteration, but a new coupled vibration at 1209 cm^{-1} appears due to interaction of N–D deformation vibration with other modes of vibration. It is interesting to note that ν(C–N), ν(C–F)(as) and ν(C–F)(sym) of $(CF_3SNH)_2C{=}O$, at 1370 cm^{-1}, 1173 cm^{-1} and 1107 cm^{-1}, shift to 1394 cm^{-1}, 1180 cm^{-1} and 1125 cm^{-1} upon deuteration. The deuteration of $(CF_3S)_2NCONH_2$ shifts the ν(CN), $\nu(C\text{–}F)_{as}$ and $\nu(C\text{–}F)_{sym}$ from 1353, 1175 and 1104 cm^{-1} to 1357, 1173 and 1105 cm^{-1} respectively. Frequencies appearing in the range 670 cm^{-1} to 469–460 cm^{-1} have been recorded and assigned as γNH, NH_2 twisting, δCF_2 asym, γNH_2 wagging and C–S stretching.

b. Synthesis of deuterium labelled GABA agonist thiomuscimol. Continuing a programme on isotopic labelling[15,16] and on receptor binding studies[17–19] of GABA agonists (GABA = 4-aminobutyric acid, central inhibitory neurotransmitter concerned with the control of neuronal activity in the mammalian central nervous system, involved in the pathophysiology of neurological and psychiatric disorders[20]), deuterium labelled thiomuscimol (**4**) has been synthesized[21] by catalytic deuteration of (*N*-methoxycarbonylaminomethyl)isothiazole (**5**) (equation 5). Acid catalyzed deprotection of the reduction product **6**, followed by treatment with triethylamine, gave pure **4** in 69% yield from **6**. The product **4** so obtained had an R_f value identical with the R_f of an authentic sample of thiomuscimol. Reduction of **5** with low pressure D_2, catalysed by Pd/C 5%, afforded **6a** deuterated only in the ring $C_{(4)}$ position and the hydrogenated analogue **7**.





(5)



c. Synthesis of deuterated (−)-(R)-benzyl-α-d p-toluenesulphenate and related deuterated sulphoxides. The compound **8** has been prepared[22] from *p*-toluenesulphenyl chloride and (−)-(R)-benzyl-α-d alcohol (equation 6).

$$p\text{-}MeC_6H_4SCl + PhCHDOH \longrightarrow p\text{-}TolSOCHDPh \quad (6)$$

(**8**) 59% yield

The distilled deuterated, light yellow product **8** was *ca* 90% pure by NMR.

The synthesis of (+)-benzyl-α-d *p*-tolyl sulphoxide **9**, carried out according to equation 7, as well as the synthesis of *p*-Tols(O)CD_2Ph (**10**) and of (−)-benzyl-α-d *p*-tolyl

$$PhCHDOH \xrightarrow{COCl_2} PhCHDCl \xrightarrow{p\text{-}TolSNa} p\text{-}TolSCHDPh \xrightarrow{NaIO_4} p\text{-}TolS(O)CHDPh \quad (7)$$

(**9**)

sulphoxide (**11**) have been performed to reject, on the basis of low-temperature optical studies, the pyramidal inversion mechanism of thermal racemization of benzyl tolyl sulphoxide, requiring temperatures of 180–250°C, and to formulate the relatively fast homolytic scission mechanism of racemization of **9** via the achiral radical pair (equation 8)

$$p\text{-Tol-}\overset{\overset{O}{\|}}{S}\text{-}CH_2Ph \rightleftharpoons p\text{-TolSO}^{\cdot} + PhCH_2^{\cdot} \rightleftharpoons p\text{-Tol-}\overset{\overset{O}{\|}}{S}CH_2Ph \qquad (8)$$

(−)-(S) (+)-(R)

due to stability of both the large benzyl radical and the arenesulphenyl radical. The possibility of the alternative mechanism of racemization of **9** involving the intramolecular migration of the benzyl group of **9** from S to 0, formation of the achiral benzyl *p*-toluenesulphenate (**8**) and racemization of **9** by a reverse intramolecular O → S shift of the benzyl group has been excluded by kinetic and optical studies[22] presented in Section IV.C.

d. Synthesis of dimethyl trisulphide-d_6, **12**, has been prepared on the 2 mmol scale according to the route shown in equation 9[23]. Methane thiol-d_3 (**13**) has been generated from methyl isothiourea sulphate-d_6 (**14**) by heating it in a $NaOD/D_2O$ solution. In the subsequent oxidation step the product **12** was obtained with 21% yield. The sulphur transfer reagent bis-phthalimido sulphide (**15**) converts thiol **13** into the trisulphide **12** only in the presence of imidazole as catalyst.

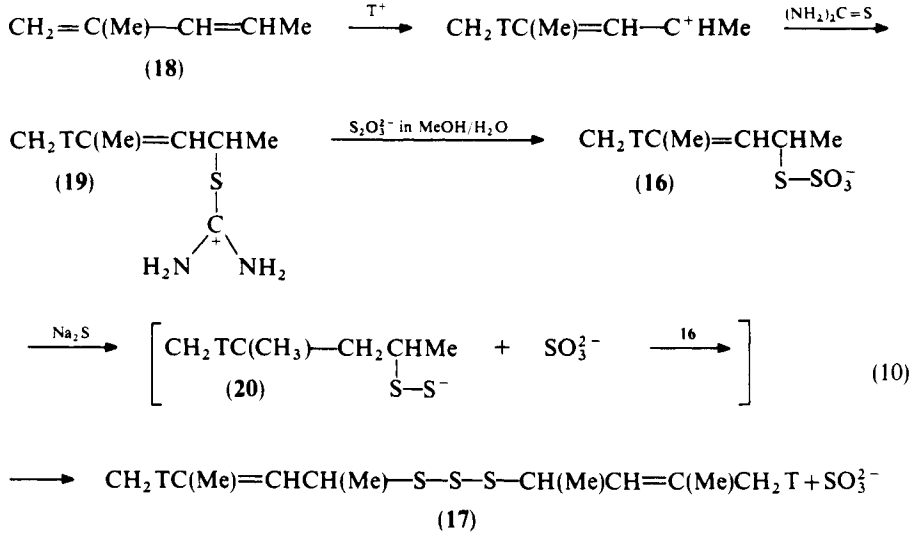
$$2(H_2N)_2C{=}S + (CD_3)_2SO_4 \longrightarrow \underset{\textbf{(14)}}{\left(H_2N\text{-}\overset{\overset{SCD_3}{|}}{C}{=}NH\right)_2 \cdot H_2SO_4} \longrightarrow \underset{\textbf{(13)}}{2CD_3SH}$$

$$\xrightarrow[\text{imidazole, RT, 20 h}]{\text{(15) in pentane}} \underset{\begin{array}{l}\textbf{(12)}\ 98.7\%\ \text{deuteration}\\ >99\%\ \text{purity}\end{array}}{CD_3SSSCD_3} \qquad (9)$$

2. *Syntheses of tritium labelled sulphenic acid derivatives*

a. Synthesis of tritium labelled Bunté salt and related tritium labelled trisulphide $A_1S_3A_1$. The tritium labelled salt **16** has been obtained as the intermediate in the course of the synthesis of trisulphide **17**, structurally related to sulphur crosslinks in vulcanized natural rubber (equation 10)[24]. Nucleophilic attack on the cation **19**, *S*-(1,3-dimethylbut-2-enyl[4-$^3H_1$])thiouronium bromide, by thiosulphate yields the Bunté salt **16**, and nucleophilic attack by the perthio-anion **20** (obtained in the reaction of one half of **16** with sodium sulphide) on the unreacted part of **16** proceeded with an overall yield of about 10%.

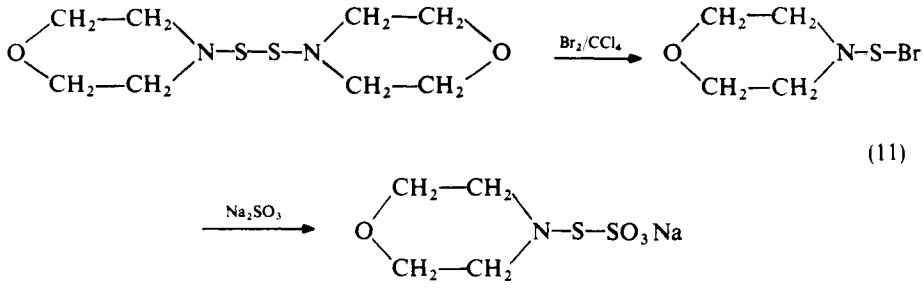
The measured activity of the trisulphide **17** indicates that it contains only 10% of the expected amount of tritium, taking into account only the isotopic dilutions and exchanges occurring in the course of the procedure in equation 10. This 'loss' of tritium has been attributed to a tritium isotope effect in the initial reaction of the diene **18** leading to the introduction of tritium into the terminal methyl group of the A_1 moiety in $A_1S_3A_1$, **17**. The rate of protonation was 8–10 times faster than the rate of tritionation, similarly to that found[25,26] in the case of hydration of isobutene and of propene where the specific activities of the products *t*-BuOH and *i*-PrOH respectively were 6.9 and 4.5 times smaller than the specific activity of the reaction medium. Obviously, formation of the new carbon–hydrogen bond in these reactions proceeds at a higher rate than formation of carbon–deuterium or carbon–tritium bonds. The authors'[24] suggestion, that this is the



(10)

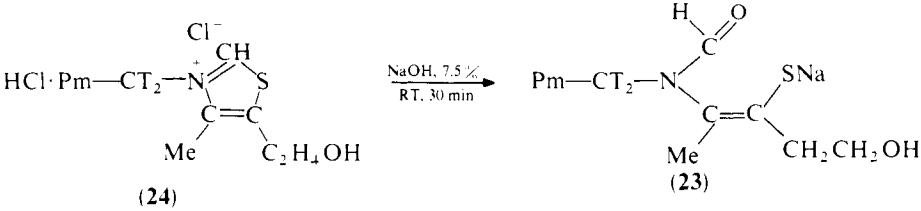
manifestation not of the kinetic but largely of a thermodynamic isotope effect[27], probably needs reconsideration in view of the results of extensive isotopic studies with vinyl ethers[12]. The deuterium isotope effects observed in the hydrolysis of simple vinyl ethers were ascribed to proton transfer from a hydronium ion to the double bond. The secondary solvent (D_2O) deuterium isotope effects, k_{H_2O}/k_{D_2O}, were located in the range 0.65–0.66. The measured tritium isotope effects obeyed the Swain relation. The rates following the Gross–Butler predictions may be reconciled with either a slow proton transfer or a protonation pre-equilibrium[27]. The dependence of the velocity constant k_n on the atom fraction of deuterium in D_2O/H_2O mixed solvent is not sensitive to differences between mechanisms of acid catalysis[27].

b. Synthesis of N-methylene-^3H thiamine 1-adamantyl trisulphide hydrochloride, **21**, has been carried out (equations 11–13) to investigate its metabolism in animals[28] and to study the mechanism of its self-radiolysis by self-β-radiation. Sodium morpholino thiosulphate, **22**, has been prepared according to equation 11. The tritium labelled substrate **23** has been prepared from [*N*-methylene-^{3}H]thiamine chloride hydrochloride **24** (equation 12). **21** has been synthesized via the disulphide **25** according to equation 13.



(11)

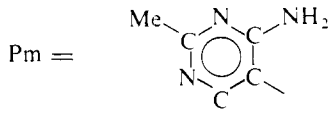
(22)

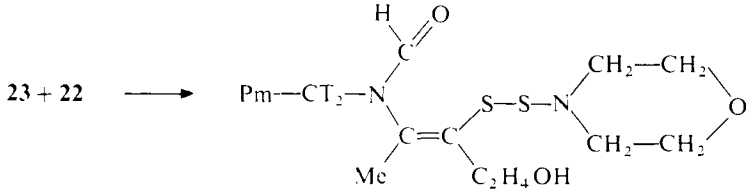


(24)
1.1 Ci/mmol

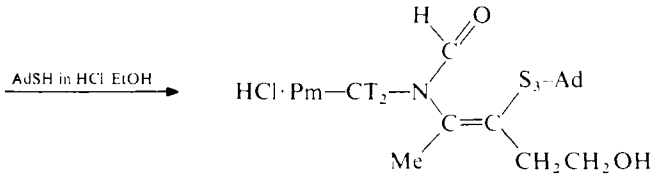
(23)

(12)



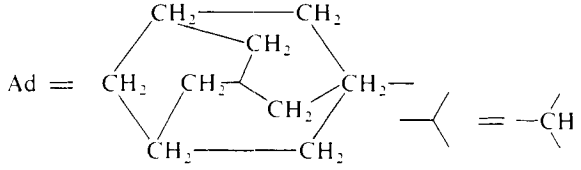


(25)

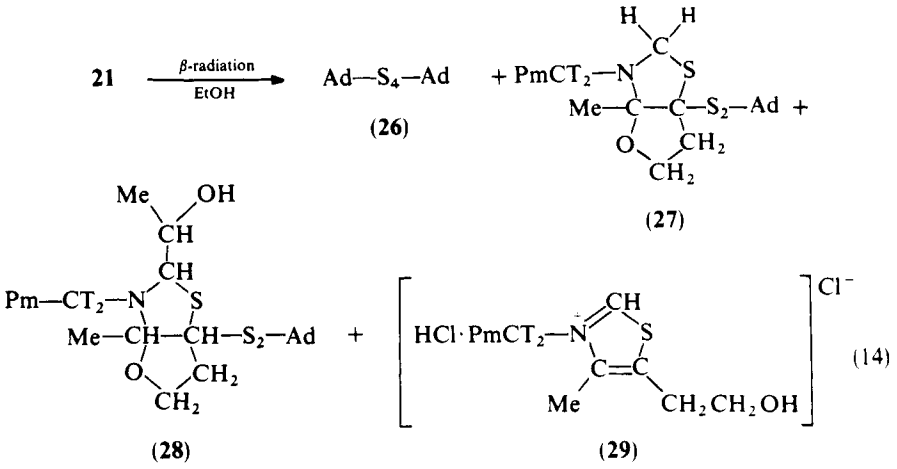


(21) 649 mCi

(13)

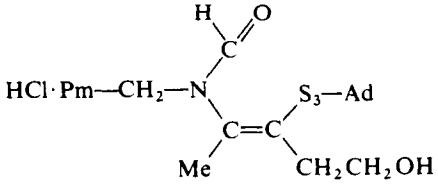


The product **21** was obtained in 59% yield based on **24**, had a specific radioactivity of 1056. 7 mCi/mmol and R_f identical with a sample of normal isotopic composition. Self-radiolysis of crystalline **21**, containing 17 mol% ethanol, showed that after 12 and 17 months storage at −20 °C the purity of **21** decreased from 98% to 63 and 45%, respectively. Radiochromatography and high-speed liquid chromatography permitted one to identify four products of decomposition: **26**, **27**, **28** and **29** (equation 14), chemically identical with the four products of γ-radiolysis of trisulphide **21b** of natural isotopic composition. Calculations showed that under these experimental conditions less than 0.18% of **21** decomposes due to the internal primary decay of tritium into helium-3. The destruction of **21** is caused by β-particles emitted by tritium which are completely



absorbed by the crystalline **21**. $G(-\mathbf{21}) = 3.4$ was computed from self-irradiation effects. In the γ-radiolysis of ethanolic argon saturated solution of the free base of **21b**, $G = 3.2$.

Solvated electrons and hydrogen atoms attacking selectively the trisulphide bond cause the decomposition of **21b** both with crystalline **21b** and with its ethanolic solutions. Tritium/hydrogen exchange in **21** and tritium exchange between **21** and EtOH caused by self-β-radiation have not been investigated, although the latter could be easily and exactly followed by measuring tritium activity of EtOH vapours as was done[29,30] in the $CH_3CHTCOONa$–H_2O–NaOH exchange system, where the exchange was observed by detecting changes in the specific activity of water vapour.

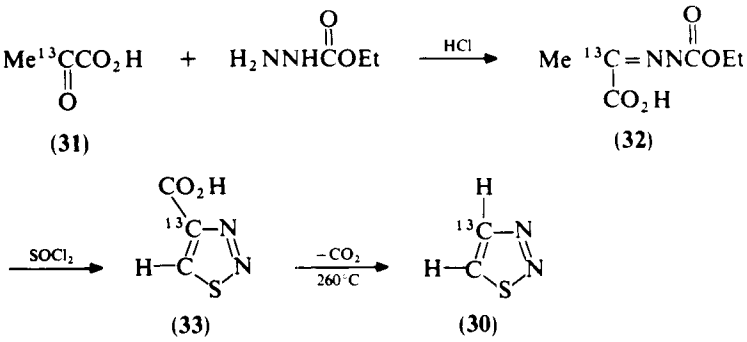


(**21b**)

B. Syntheses of Isotopic Heavy Atom Labelled Sulphenic Acid Derivatives and Deuterium and Carbon-13 Doubly Labelled Sulphenic Acid Derivatives

1. Syntheses of deuterium and ^{13}C labelled thiadiazoles

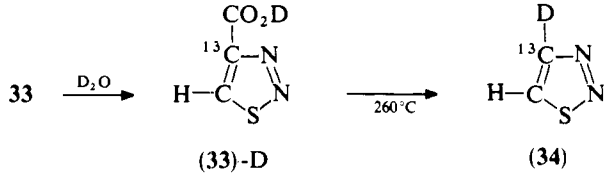
a. Synthesis of 4-^{13}C-1,2,3-thiadiazole, **30**, has been obtained[31] following the reaction scheme 15. ^{13}C-labelled pyruvic acid with carboethoxyhydrazine gave the α-*N*-carboethoxyhydrazonopropionic acid-2-^{13}C, **32**, which in turn yielded with thionyl chloride 4-carboxy-4-^{13}C-1,2,3-thiadiazole (**33**). This undergoes vigorous decarboxylation producing **30** in 58% yield.



(31) (32)

(15)

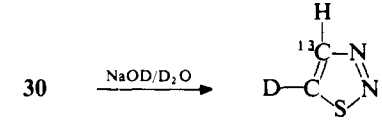
b. Synthesis of 4-deuterio-4-^{13}C-1,2,3-thiadiazole[31], **34**, was obtained in 62% yield by exchanging the carboxyl hydrogen of **33** with deuterium oxide and subsequent violent decarboxylation of the acid **33**-D (equation 16).



(33)-D (34)

(16)

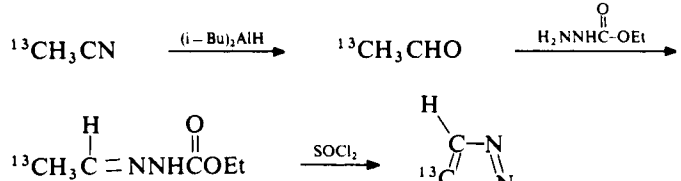
c. Synthesis of 5-deuterio-4-^{13}C-1,2,3-thiadiazole[31], **35**, has been prepared on a mmol scale by deuterium exchange of **30** with excess of NaOD (equation 17), followed to completion by NMR.



(35) 76% yield

(17)

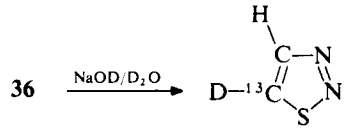
d. Synthesis of 5-deuterio-5-^{13}C-1,2,3-thiadiazole, **36**, has been obtained according to scheme 18 on a 10 mmol scale. The intermediate acetaldehyde-2-^{13}C-carboethoxyhydrazone, **37**, on reaction with thionyl chloride gave **36** in 45% yield.



(37) 55% yield (36)

(18)

e. Synthesis of 5-deuterio-5-^{13}C-1,2,3-thiadiazole, **38**, has been carried out by the H/D exchange reaction 19 following the procedure of Olofson and coworkers[32]. The ^{13}C and deuterium labelled thiadiazoles were synthesized to investigate the mechanism of the thiirene formation in the course of the photochemical decomposition of **30**, **34**, **35** and **38**[33].

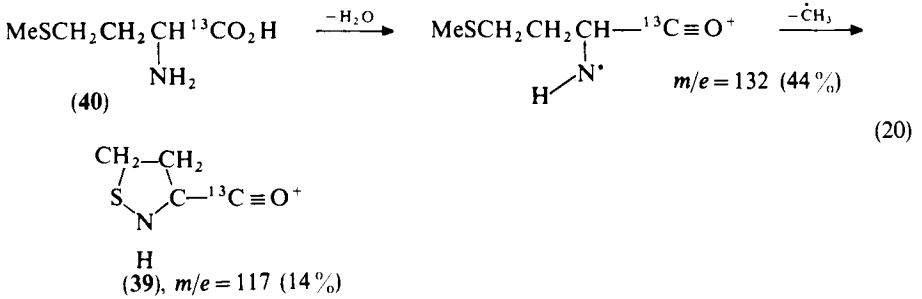


(19)

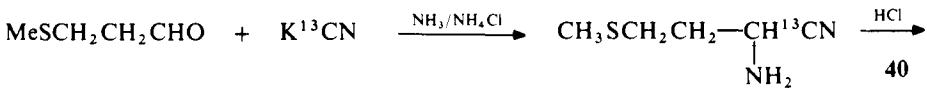
(**38**) 66% yield

2. Synthesis of D,L-1-^{13}C-methionine

^{13}C labelled cyclic sulphenylimide fragment ion **39** has been identified in the mass spectrum of methionine-1-^{13}C, **40** (equation 20). **40** was obtained according to equation 21[34].



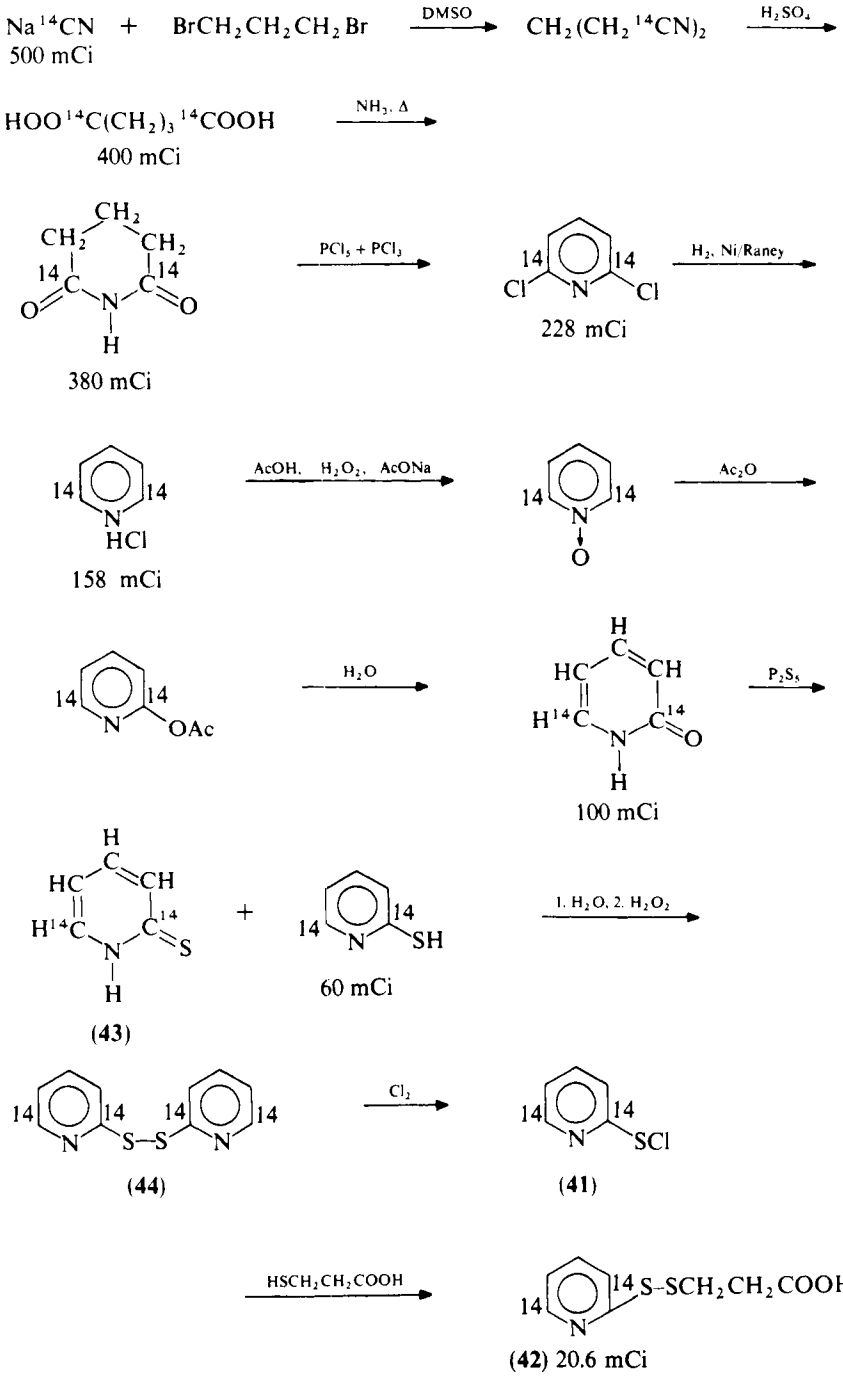
(20)



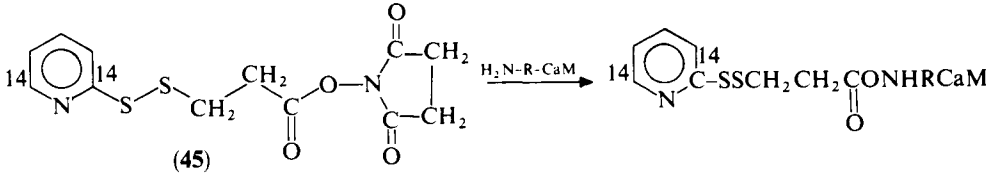
(21)

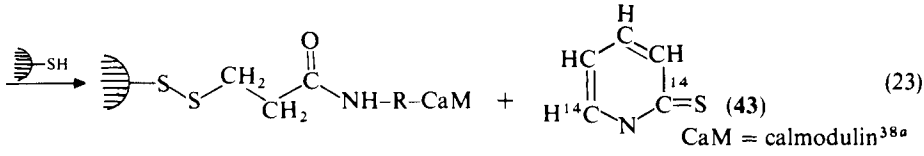
3. Synthesis of [2,6-^{14}C]2-pyridinylsulphenyl chloride and 3-([2,6-^{14}C]2-pyridinyldithio)propanoic acid

Synthesis of this compound (**41**) and its derivative (**42**), specific activity 55 mCi/mmol and 98.7% radiochemical purity, has been accomplished by Noel and Pichat[35] with an overall yield of 4% based on sodium cyanide/500 mCi, following a 12-step scheme[36] (equation 22). The reactive intermediate **41** was obtained without isolation by chlorination of [2,6-^{14}C]2-dipyridinyldisulphide (**44**) and with 3-mercaptopropanoic acid produced the final product **42** in 98.7% purity. The latter dissolved in butanol (1 mCi/cc) and, when stored at 0 °C, did not undergo visible radiodecomposition during 1 week but, dissolved in CH_2Cl_2 and kept under similar conditions, gave 2% radiolysis. The high specific activity of **42** permits one to detect by radioanalytical methods small quantities of **43** (equation 23) produced in the course of coupling of proteins, present in very small quantities in the medium, when spectrophotometric determination of **43** is insufficient[37,38] to follow the coupling reaction.


Na14CN + BrCH2CH2CH2Br
500 mCi
DMSO
CH2(CH2 14CN)2
H2SO4
HOO14C(CH2)3 14COOH
400 mCi
NH3, Δ
380 mCi
PCl5 + PCl3
228 mCi
H2, Ni/Raney
158 mCi
AcOH, H2O2, AcONa
Ac2O
H2O
100 mCi
P2S5
(43)
60 mCi
1. H2O, 2. H2O2
(44)
Cl2
(41)
HSCH2CH2COOH
(42) 20.6 mCi

(22)

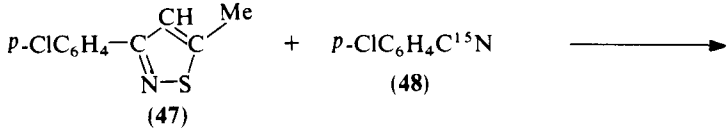


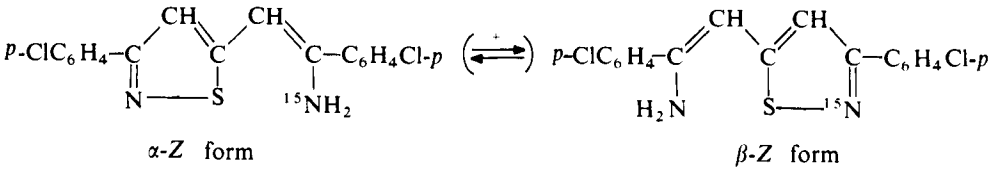


(23)

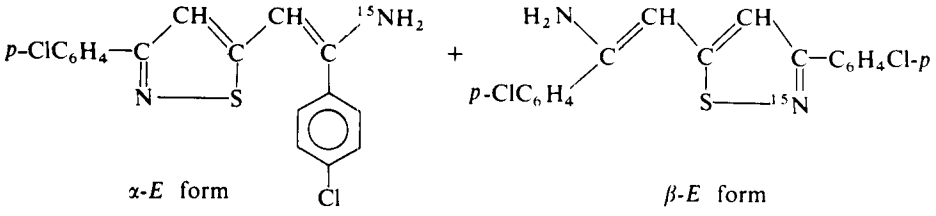
4. Synthesis of ^{15}N-labelled. 5-[2-amino-2-(p-chlorophenyl)vinyl]-3-(p-chlorophenyl)-isothiazole

Compound **46** has been prepared[39] in 57% yield by coupling 3-(*p*-chlorophenyl)-5-methylisothiazole (**47**) with ^{15}N-labelled *p*-chlorobenzonitrile (**48**). The level of ^{15}N enrichment of **46** was > 97% (equation 24). The ring transformation (equation 24) has been confirmed by the ^1H and ^{15}N NMR spectra of **46**. The possibility of the appearance of *E* forms of **46** in reaction 24 has been eliminated by synthesizing **49** in the *Z* form by treating 3-(*p*-chlorophenyl)-5-[(*t*-butyldimethylsilyl)methyl]isothiazole (**50**) with n-BuLi and adding ^{15}N-labelled *p*-chlorobenzonitrile (**48**) at the same temperature (equation 25). Desilylation of **49**-*Z* with tetrabutylammonium fluoride (TBAF) yielded the α-*Z* form of **46** when quenched quickly by stirring with water at −78°C. Heating the benzene-d_6 solution of **46**-α-*Z* at 50 °C during 50 h produced the 1:1 mixture of **46**-α-*Z* and **46**-β-*Z* forms, the ^1H NMR spectrum of which was identical with the ^1H NMR spectrum of the mixture of the α-*Z* and β-*Z* forms obtained in reaction 24. The coincidence of the ^1H NMR spectra of products obtained by scheme 24 and according to scheme 25 is a second confirmation of the bond switching equilibrium 26. The symmetrical sulphurane structure **51** is involved as the intermediate ('non-polar transition state') in this rearrangement of heterocycles **46**.

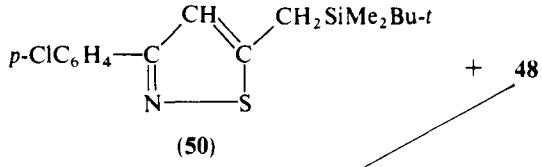




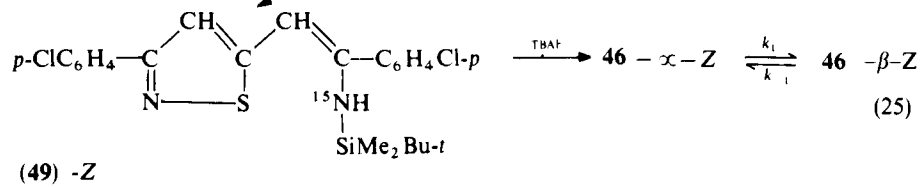
(24)



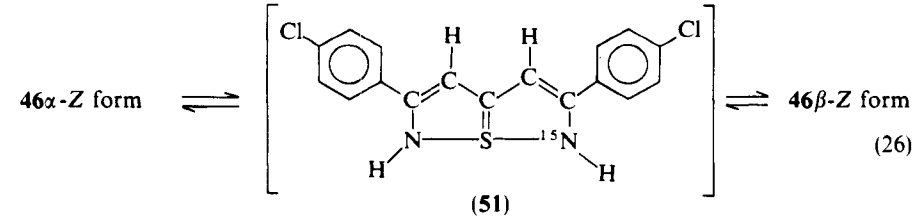
α-*E* form (46) β-*E* form



(50) + 48



(49) -*Z* (25)



(51) (26)

A kinetic study of transformation 26, carried out in benzene-d_6, using the ratio of NH_2 and $^{15}NH_2$ proton signals showed that reaction 26 follows reversible first-order kinetics. Arrhenius plots corresponding to the

$$\alpha \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \beta$$

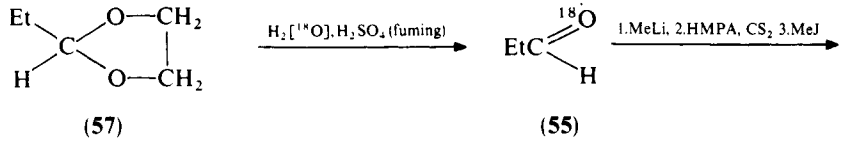
process gave the following activation parameters and rate constants standardized for 25 °C: $\Delta H^{\neq} = 12.2 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\neq} = -41.0 \pm 0.5$ e.u., $\Delta G^{\neq} = 24.4 \pm 0.8$ kcal mol^{-1}, correlation coefficient 0.999, k (25 °C) = $6.21 \cdot 10^{-6}$ s^{-1} (value extrapolated from activation parameters).

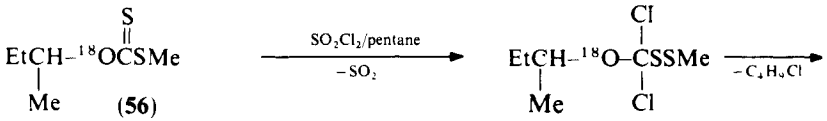
5. *Synthesis of [^{18}O]-chlorocarbonylsulphenyl chloride*

This compound (**52**), a versatile bifunctional reagent, has been synthesized by two different preparative methods[40]. One approach was by controlled hydrolysis of trichlor-

omethanesulphenyl chloride (**53**) with [^{18}O] water (equation 27). The yield of **52** (on a 0.25 mmol scale) was 88%, but the isotopic purity was only 17 atom% ^{18}O because of the dilution caused by complete ^{18}O exchange of [^{18}O] water with [^{16}O] sulfuric acid. In principle [^{18}O]-enriched sulfuric acid could be used in this synthetic route but, because of the high price of this reagent, **52** was synthesized with 92% isotopic purity in a three-step sequence (equation 28). The yield of **52** was 81% according to an *N*-methylaniline assay (equation 29).

$$Cl_3CSCl \underset{(53)}{} + H_2[^{18}O] \xrightarrow[50°C,\ 7h]{H_2SO_4} \underset{(52)}{ClC[^{18}O]SCl} + 2\,HCl \qquad (27)$$





$$Cl\text{-}\overset{\overset{^{18}O}{\|}}{C}\text{-}SSMe \xrightarrow[-SO_2]{SO_2Cl_2} \underset{(52)}{Cl\text{-}\overset{\overset{^{18}O}{\|}}{C}\text{-}SCl} + MeSCl \left(\xrightarrow[-SO_2]{SO_2Cl_2} \underset{(54)}{ClCH_2SCl}\right) \qquad (28)$$

$$52 + PhNHMe \longrightarrow PhN(Me)\overset{\overset{O}{\|}}{C}SNPhMe \qquad (29)$$

The crude **52** was contaminated with chloromethanesulphenyl chloride (**54**) identified similarly by reaction 29a.

$$ClCH_2SCl \xrightarrow{PhNHCH_3} ClCH_2SN(Me)Ph \qquad (29a)$$

The yields of the intermediates [^{18}O]-propanal (**55**), [^{18}O]-*O*-1-methylpropyl *S*-methyl dithiocarbonate (**56**) and of the final product (**52**) were 57%, 49% and 40%, respectively. The starting material (**57**), 2-ethyl-1,3 dioxolane, was prepared from propanal and 1,2-ethanediol (equation 30).

$$EtC(=O)H + HOCH_2CH_2OH \longrightarrow \mathbf{57} \qquad (30)$$

6. Synthesis of oxygen-18 labelled phenyl benzenethiosulphinate

This compound (**58**) was achieved according to sequence 31[41]. Bright yellow crystals of **58** were isolated with 40% overall yield (m.p. 69 °C, 1.48 atom% ^{18}O).

$$PhSH + 2Cl_2 \longrightarrow PhSCl_3 + HCl$$

$$PhSCl_3 + MeC^{18}O_2H \longrightarrow PhS(^{18}O)Cl + MeC(^{18}O)Cl + HCl$$

$$PhS(^{18}O)Cl + PhSH \longrightarrow Ph\text{-}S\text{-}S(^{18}O)Ph + HCl \quad (31)$$

(58)

7. *Synthesis of ^{17}O and ^{18}O labelled α-thiophosphoryl trifluoroacetate and α-phosphoryl thiotrifluoroacetate*

These (**59**) were synthesized to study the mechanism of formation of α-phosphoryl thiotrifluoroacetate and to reveal which oxygen of the trifluoroacetate group in **59** exchanges with sulphur of the α-thiophosphoryl group (equation 32)[42].

$$PhCMe(OMe)_2 + H_2[^{18}O] \xrightarrow{H^+} PhC(^{18}O)Me \xrightarrow{H\text{-}P(S)(OEt)_2,\ Et_3N}$$

$$PhC(MeS)(=S)\text{-}P(OEt)_2 \xrightarrow[(CF_3CO)_2O]{} Ph\text{-}C(Me)(S)\text{-}P(OEt)_2 \xrightarrow{NaOAc\ in\ (AcOH\text{-}1\%(AcO)_2)}$$

$$PhC(^{18}OH)(=S)\text{-}P(OEt)_2 \quad (61) \qquad Ph\text{-}C(Me)(^{18}O\text{-}C(O)CF_3)\text{-}P(OEt)_2 \quad (59)$$

$$Ph\text{-}C(Me)(S\text{-}C(O)CF_3)\text{-}P(^{18}O)(OEt)_2 + Ph\text{-}C(Me)(S\text{-}C(^{18}O)CF_3)\text{-}P(O)(OEt)_2 \quad (32)$$

(60)

80% (liquid NH_3) $\rightarrow CF_3\text{-}C(=O)\text{-}NH_2$

20% (liquid NH_3) $\rightarrow CF_3\text{-}C(=^{18}O)\text{-}NH_2$

^{17}O and ^{18}O labelled acetophenones have been prepared by acid catalysed hydrolysis of acetophenone dimethyl ketal with $H_2{}^{17}O$ (23% enriched) and $H_2{}^{18}O$ (97% enriched). The labelled acetophenones with hydrogen diethylthiophosphite gave labelled **61**, which were converted to the trifluoroacetates, **59**-^{17}O and **59**-^{18}O. Rearrangement of **59** gave **60** in 63% yield. Cleavage of **60** with ammonia produced the amide which has a sharper ^{17}O signal than the broad ^{17}O signal of the carbonyl group of compound **60**.

8. Synthesis of cysteine-^{35}S-sulphate

Chromatographically pure cysteine ^{35}-S-sulphate (**62**) has been prepared[43] by a rapid and easy exchange method, which can be used for microquantity synthesis on a μmole scale (equation 33). 80% yield of cysteine-^{35}S-sulphate has been obtained when the ratio of cysteine-^{35}S- to cysteine-S-sulphate was 1:4 and the incubation of the reactants has been carried out in anaerobic conditions under nitrogen during 30 min. Excess of unlabelled cysteine-*S*-sulphate lowers the specific activity of **62** and necessitates the use of the cysteine-^{35}S of high specific activity. **62** has been utilized to study the mechanism of its destructive action on the neurons in the rat central nervous system, its distribution in the brain and its relation with childhood neurodegenerative disease. Cysteine-S-sulphate is an abnormal urinary and plasma metabolite associated with sulphite oxidase deficiency.

$$R^{35}SH + RS\text{–}SO_3^- \longrightarrow R^{35}SSR + HSO_3^-$$

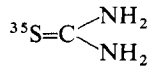
$$R^{35}SSR + RSSO_3^-; \quad \begin{matrix} \xrightarrow{k_{35_s}} R^{35}SSO_3^- + RSSR \\ \quad\quad (\mathbf{62}) \\ \xrightarrow{-k_{32_s}} RSSO_3^- + R^{35}SSR \end{matrix} \qquad (33)$$

$$R = -CH_2CH(NH_2)COOH$$

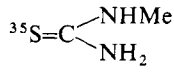
C. Syntheses and Biological, Agricultural or Medical Applications of Isotopically Labelled Organic Compounds Containing Divalent Sulphur

1. Synthesis of ^{35}S labelled thiourea and its derivatives

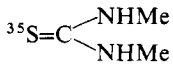
For uses in synthetic organic chemistry and in diagnostics, ^{35}S-labelled thiourea and its *N*-alkyl and *N*-aryl derivatives[44] **63**–(**70**) have been obtained by homogeneous exchange of the corresponding unlabelled substrates with radiosulphur-35 diluted with elementary sulphur (specific activity 9 mCi/mg, concentration 1×10^{-3} M) carried out in dry isoamyl alcohol (or in pyridine in the case of thiourea), 80–130°C in glass ampoules sealed under argon.



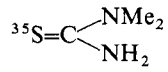
(**63**)



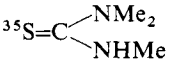
(**64**)



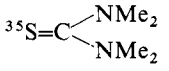
(**65**)



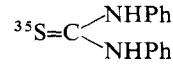
(**66**)



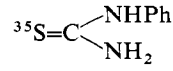
(**67**)



(**68**)

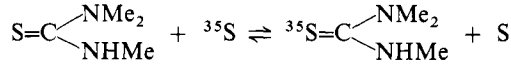


(**69**)



(**70**)

The ^{35}S exchange was followed by paper chromatography. A detailed synthetic procedure has been elaborated for the preparation of ^{35}S-labelled thiourea (**63**) and *N,N,N'*-trimethylthiourea (**67**) (see equation 34).

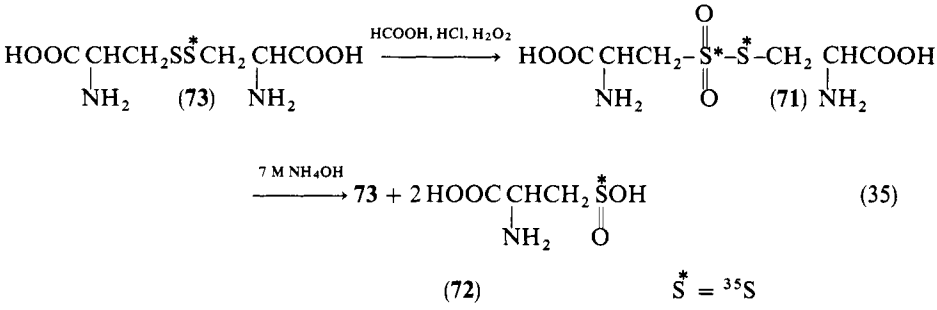


(34)

67 was obtained in 79.5% chemical yield and in 50.4% radiochemical yield (specific activity 25.8 μCi/mg). The highest (50.8%) extent of ^{35}S exchange was achieved with **68** and the lowest (12%) with **65**.

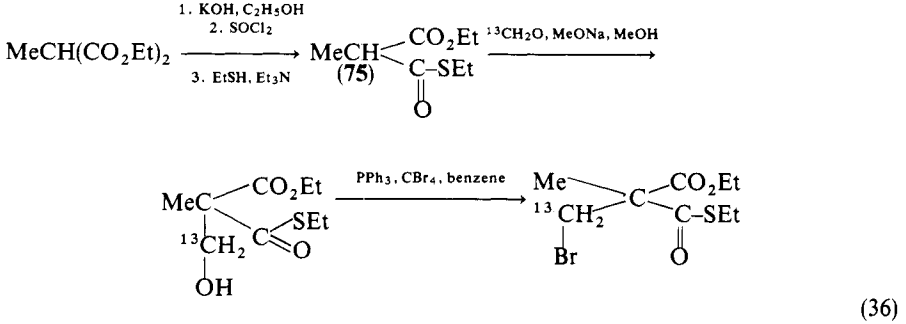
2. Synthesis of ^{35}S labelled thiosulphonate

The ^{35}S-labelled compound **71** has been obtained as an intermediate in the synthesis of L-[^{35}S]cysteinesulphinic acid (**72**) from S-[^{35}S]cystine (**73**) according to scheme 35[45]. **72** was separated from **73** by cellulose thin-layer plate chromatography. The starting material **73** recovered in 25–40% yield was used to prepare a second portion of **71**, increasing the overall yield of **72** to 65–70%. Use of an excess of oxidizing reagent leads to the oxidation of thiosulphonate **71** to cysteic acid[45].



3. Synthesis of O,S-diethyl-2-(bromomethyl-^{13}C)-2-methylthiomalonate

Compound **74**[46] needed in the course of model studies of the coenzyme B_{12} dependent mutase reactions has been prepared by condensing paraformaldehyde-^{13}C with *O,S*-diethyl methylthiomalonate (**75**) (equation 36), and conversion of the ^{13}C-alcohol **76** to the bromo compound **74**.



(36)

4. Synthesis of 1-α-methylallylthiocarb-^{14}C-amoyl-2-methylthiocarbamoylhydrazine

This compound MATCH (**77**), which inhibits the pituitary gonadotrophic function and is an effective estrus synchronizing agent in swine, has been $^{14}C_{(1)}$ labelled in the reaction sequence 37[47].

$$CH_3CH{=}CHCH_2Cl + KS^{14}CN \xrightarrow{DMF} CH_3CH{=}CH{-}CH_2S^{14}CN$$

(78)

$$\xrightarrow{\text{heat}} CH_2{=}CHCH(Me)N{=}{}^{14}C{=}S \xrightarrow{H_2NNHC(=S)NHMe \text{ in EtOH}}$$

(79)

$$CH_2{=}CHCH(Me)NH{}^{14}C(=S)NHNHC(=S)NHMe \quad (37)$$

(77)

5. *Synthesis of ^{14}C labelled thiocarbamate, EPTC*

S-Ethyl-*N*,*N*-dipropylthiocarbamate (EPTC **80**), a herbicide widely used in modern agricultural practice, has been labelled with ^{14}C in the carbonyl moiety by the reaction of lead mercaptide, $Pb(SC_2H_5)_2$, with *N*,*N*-dipropylcarbamoyl chloride carbonyl ^{14}C (**81**) in chlorobenzene at 140–150°C under argon atmosphere (equation 38)[48]. 27% radiochemical yield of **80** was attained (388.5 MBq, specific activity 1.0 GBq/g, radiochemical purity better than 99.8%). The chemical yield (on a mmol scale) in the last synthetic step was 73.1%. **80** was synthesized with the aim of investigating its metabolism, mode of action and environmental fate.

$$Pr_2NH + {}^{14}CO_2 \rightarrow (Pr_2N{-}{}^{14}C(=O){-}O^-)(H_2\overset{+}{N}Pr_2)$$

$$\xrightarrow{(Me)_3SiCl} Pr_2N{}^{14}C(=O)Si(Me)_3 \xrightarrow{PCl_5} Pr_2N{}^{14}C(=O)Cl \xrightarrow{Pb(SEt)_2} EtS{}^{14}C(=O)NPr_2 \quad (38)$$

(81) (80)

6. *Synthesis of [2,3-^{14}C]-2,3-dimercapto succinic acid (DMSA)*

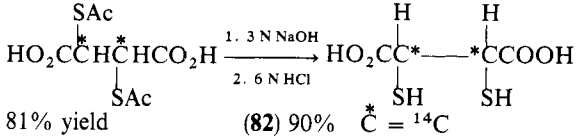
This compound (DMSA, **82**), a chelating agent for technetium 99 m (^{99m}Tc, $t_{1/2} = 6$ h, $E_{\gamma(90\%)} = 0.140$ Mev), clinically useful for studies of renal functions by scintillographic imaging, has been synthesized on a mmol scale (equation 39)[49]. The starting [2,3-^{14}C]succinic acid (specific activity 1.8 mCi/mmol) yielded ^{14}C-DMSA in 57% overall yield. The product **82** (specific activity 1.64 mCi/mmol) was used to study the mechanism of its fixation in the renal system.

$$HO_2C\overset{*}{C}H_2\overset{*}{C}H_2CO_2H \xrightarrow{Br_2, HBr} HO_2C\overset{*}{C}HBr\overset{*}{C}HBrCO_2H$$

3 mCi 79%

$$\xrightarrow[2.\ H_2SO_4]{1.\ KOH \text{ in MeOH}} HO_2C{-}\overset{*}{C}{\equiv}\overset{*}{C}{-}CO_2H \xrightarrow{AcOEt + AcSH}$$

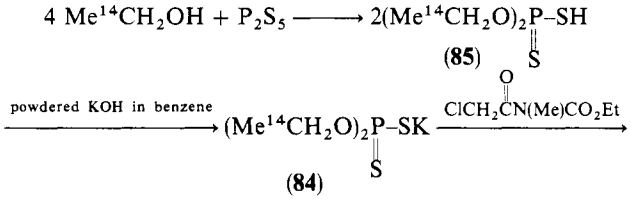
99%

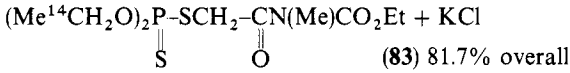


81% yield (**82**) 90% $\overset{*}{C} = {}^{14}C$ (39)

7. *Synthesis of carbon-14 labelled mecarbam* (**83**)

O,O-di-[1-^{14}C]-ethyl *S*-[*N*-ethoxycarbonyl-*N*-methylcarbamoylmethyl] phosphorothiolothionate (**83**), used for the protection of olives, citrus fruits, rice and for control of a number of root larvae, has been labelled with ^{14}C in the ethyl group (equation 40)[50] to investigate its metabolism.



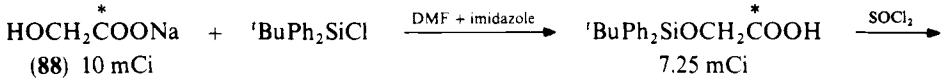


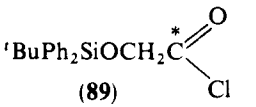
(**83**) 81.7% overall yield (40)

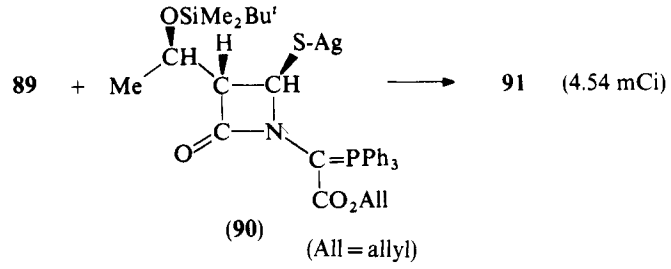
specific activity 1.97 mCi/mmol

8. *Synthesis of ^{14}C labelled antibiotics FCE 22101 and FCE 22891*

Synthesis of [^{14}C]PENEM antibacterials: (5*R*,6*S*)-6-[(1*R*)-hydroxyethyl]-2-carbamoyloxymethylpenem-3-carboxylate, FCE 22101 (**86**) [2-^{14}C] and its acetoxymethyl ester [2-^{14}C]FCE 22891 (**87**) combining structural features of both penicillins and cephalosporins, has been realized in eight steps using sodium [1-^{14}C]glycolate (**88**) as the starting key compound (equation 41)[51]. *t*-Butyldiphenylsilyloxy-[1-^{14}C]acetyl chloride (**89**) reacted with the silver mercaptide (**90**) to yield (3*S*)-[(1*R*)-*t*-butyldimethylsilyloxyethyl]-(4*R*)-*t*-butyldiphenylsilyloxy-[1-^{14}C]acetylthio-1-(1-allyloxycarbonyl-triphenylphosphoranylidenemethyl)azetidin-2-one (**91**). Wittig ring closure of **91** and deprotection of the hydroxyl group of **92** gave the [2-^{14}C]penem system **93** in 72% radiochemical yield. **93** in turn yielded intermediate **94** and then product **95** with an unmasked carbamoyl and a secondary hydroxyl group. $Pd(PPh_3)_4$ catalyzed deallylation of **95** gave [2-^{14}C]FCE 22101 (**86**) in overall 21% yield based on **88**. Finally, the acetoxymethyl (5*R*,6*S*)-6-[(1*R*)-hydroxyethyl]-2-carbamoyloxymethyl-[2-^{14}C]penem-3-carboxylate (**87**) was obtained by alkylation of **86** with bromomethylacetate in 41% radiochemical yield.

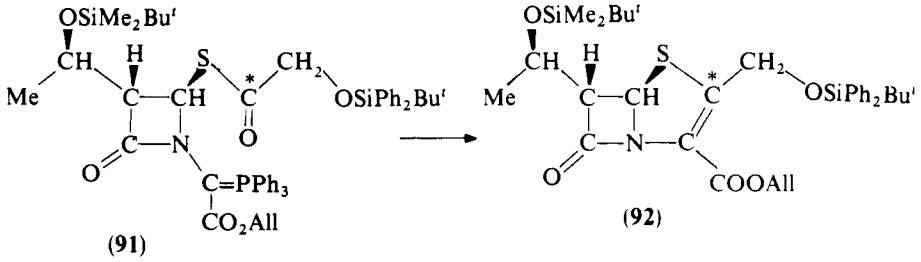




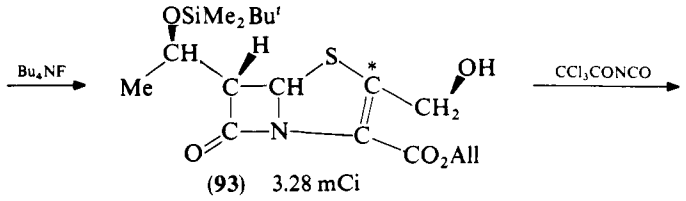


(90)

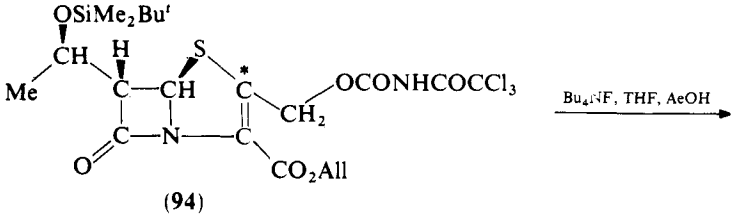
(All = allyl)



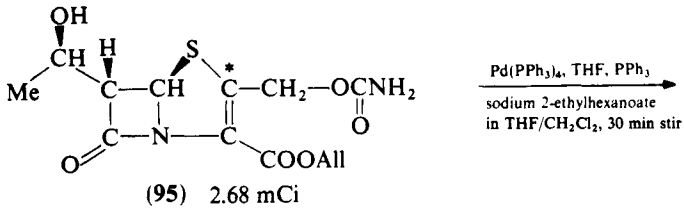
(91) (92)



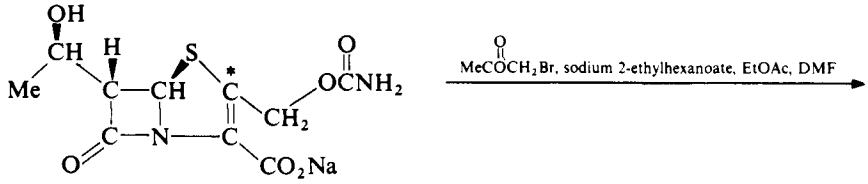
(93) 3.28 mCi



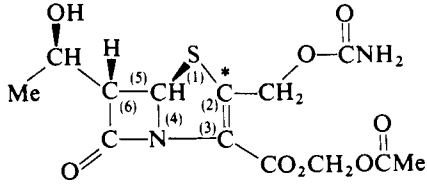
(94)



(95) 2.68 mCi



(**86**) 2.131 mCi, 98% radiochemical purity

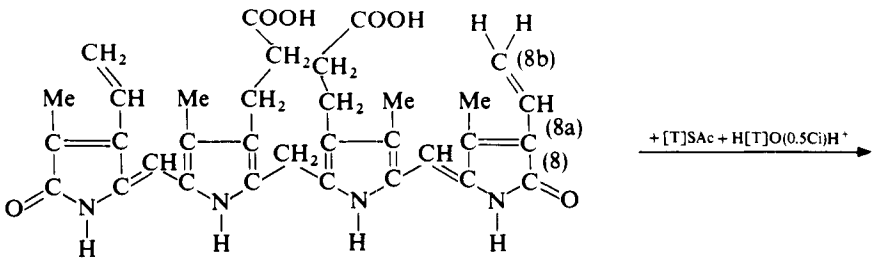


(41)

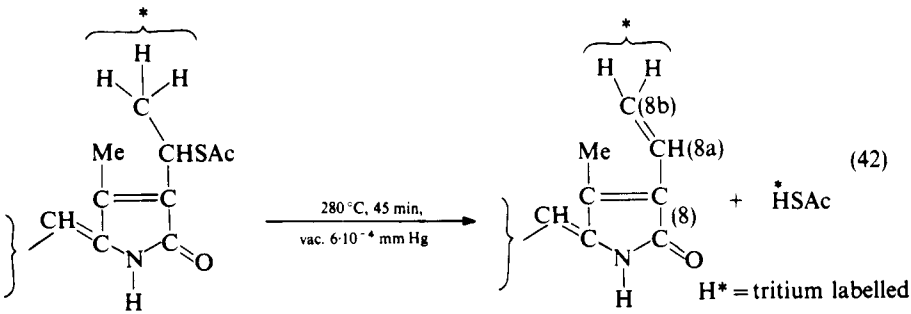
(**87**) 97% radiochemical purity, specific activity 4.56 mCi/mmol

9. Synthesis of bilirubin labelled by tritium at the exo-vinyl group

The tritium-labelled pigment bilirubin **96** with a high specific activity has been prepared[52] in a one-step addition of thioacetic acid-carboxyl-T to bilirubin, tritiated in all labile positions by exchange with tritiated water, and subsequent vacuum thermal elimination of the isotopically diluted thioacid from the adduct **97** leading to the required 8b-[$^3H_2$]bilirubin **96** (equation 42).



(**96**)



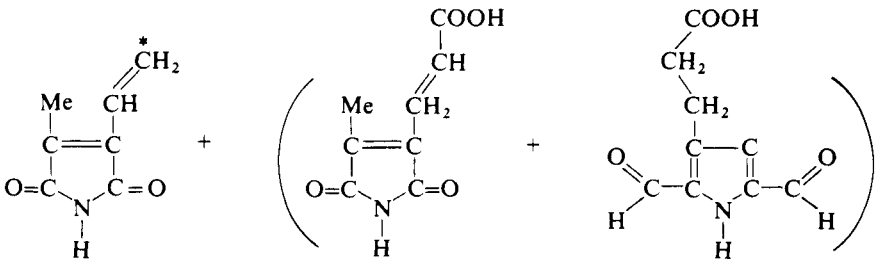
(42)

(**97**) 1·525·10^6 Bq/mmol

(**96**) – [^{3}H]

Since tritium is removed from labile positions of the adduct **97** in the course of the work-up, the specific activity of the product **96** was only about half that of **97**. The specific activity of the adduct **97** is about 8.6 times smaller than the theoretical specific activity of this adduct calculated under the assumption that there is no thermodynamic and kinetic fractionation of tritium at room temperature in the course of addition of ^{3}HSAc to the double bond of bilirubin at the 8a and 8b positions. This may be partly caused by dilution of the tritiated water with traces of water of natural isotopic composition present in the chloroform used as the solvent. The observed decreases in the tritium activity of **97** and of **96** devalue slightly the synthetic applicability of scheme 42 for tritium labelling of **96**, but it makes the reaction scheme 42, as such, interesting from the standpoint of quantitative mechanistic exchange and kinetic studies.

The possibility of significant randomization of tritium during labelling of **96** was excluded by synthesis of **96** specifically deuterated in the 8b position by preliminary equilibration of bilirubin and HSAc with D_2O (99.5% D) and by MS and NMR investigation of the deuterated product **96**. Additional evidence of nearly exclusive tritium labelling of **96** in the exo-vinyl group was obtained by chromate degradation[53] of the **96** complex with $FeCl_3 \cdot H_2O$. More than 97% of the tritium activity was found in the oxidation product **98**, methylvinylmaleimide, and only less than 3% of the tritium activity was located in the mixture of hematimide **99** and pyrrole-2,5-dicarbaldehyde **100**.



(98) **(99)** **(100)**

10. Synthesis of ^{35}S-, ^{14}C- and ^{3}H-labelled di[(chloro-2-ethyl)-2-N-nitroso N-carbamoyl]-cystamine ('CNCC')

The compound CNCC (**101**), showing great oncostatic activity and tested experimentally on tumors implanted in animals[54], has been labelled with ^{35}S, ^{14}C and tritium in three positions[55].

a. ^{35}S labelling has been achieved according to reaction scheme 43 using commercially available ^{35}S labelled cystamine hydrochloride (**102**), 17 mCi, as the precursor. Product **101** had 4. 15 mCi/mmol specific activity ($1.535 \cdot 10^8$ Bq/mmol).

b. Introduction of the ^{14}C label into CNCC has been accomplished following the reaction sequence 44. ^{14}C labelled silver isocyanate, $AgN{=}\overset{*}{C}{=}O$, specific activity 1.66 mCi/mmol ($6.14 \cdot 10^7$ Bq/mmol), has been prepared from ^{14}C labelled urea (50 mCi) with $AgNO_3$. The radiochemical yield of ^{14}C–CNCC was 7% with respect to ^{14}C urea used, specific activity 3.3 mCi/mmol ($1.22 \cdot 10^8$ Bq/mmol).

c. Tritium labelled CNCC has been obtained using, in the reaction scheme 44, tritiated 1-chloro-2-ethylamine hydrochloride (**106**), specific activity 2.5 mCi/mmol

$$HCl \cdot H_2NCH_2CH_2\overset{*}{S}\text{–}\overset{*}{S}CH_2CH_2NH_2 \cdot HCl \xrightarrow[2.\ O{=}C{=}NCH_2CH_2Cl,\ 0°C]{1.\ Et_3N/H_2O,\ 0°C}$$

$\overset{*}{S}$= ^{35}S label position

(**102**)

$$\begin{array}{l} \overset{*}{S}\text{–}CH_2CH_2NHC(=O)NHCH_2CH_2Cl \\ | \\ \overset{*}{S}\text{–}CH_2CH_2NHC(=O)NHCH_2CH_2Cl \end{array} \xrightarrow{HCOOH/H_2O,\ NaNO_2,\ 0°C}$$

(**103**) 90% yield

$$\begin{array}{l} \overset{*}{S}CH_2CH_2\text{–}N(NO)\text{–}C(=O)NHCH_2CH_2Cl \\ \overset{*}{S}CH_2CH_2\text{–}NH\text{–}C(=O)\text{–}N(NO)CH_2CH_2Cl \end{array} + \begin{array}{l} \overset{*}{S}CH_2CH_2N(NO)\text{–}C(=O)NHCH_2CH_2Cl \\ \overset{*}{S}CH_2CH_2N(NO)\text{–}C(=O)CH_2CH_2Cl \end{array}$$

65% (**101**) CNCC 35%

60% radiochemical and chemical yields. (43)

$$HOCH_2CH_2S\text{–}SCH_2CH_2OH \xrightarrow{TosCl} TosOCH_2CH_2S\text{–}SCH_2CH_2OTos \xrightarrow{NaJ}$$

(**104**)

$$ICH_2CH_2S\text{–}SCH_2CH_2I \xrightarrow[140°C,\ toluene\ reflux]{AgN{=}\overset{*}{C}{=}O} \begin{array}{l} SCH_2CH_2N{=}\overset{*}{C}{=}O \\ | \\ SCH_2CH_2N{=}\overset{*}{C}{=}O \end{array}$$

(**105**)

$$\xrightarrow[90\%\ yield]{HCl \cdot H_2NCH_2CH_2Cl/benzene} \begin{array}{l} SCH_2CH_2NH\overset{*}{C}(=O)NHCH_2CH_2Cl \\ | \\ SCH_2CH_2NH\overset{*}{C}(=O)NHCH_2CH_2Cl \end{array}$$

(**103**) – ^{14}C

$$\xrightarrow{HCOOH/H_2O,\ NaNO_2} \textbf{101}\text{–}^{14}C \quad (44)$$

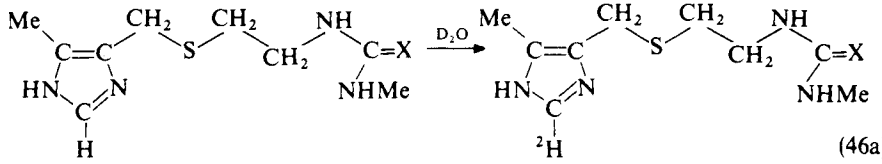
($9.25 \cdot 10^7$ Bq/mmol), prepared by reaction 45. The specific activity of the final product, ^{3}H-CNCC, was 5 mCi/mmol. 90% chemical yield has been achieved by reacting **105** with tritiated **106**. The overall radiochemical yield was 44% with respect to ^{3}H-2-aminoethanol (**107**).

$$\underset{\textbf{(107)}\ 15\ \text{mCi},\ 6.5\ \text{mmol}}{HCl\cdot NH_2\overset{*}{C}H_2CH_2OH} \xrightarrow{SOCl_2} \underset{\textbf{(106)}\ 6.2\ \text{mmol}}{HCl\cdot H_2N\overset{*}{C}H_2CH_2Cl} \qquad (45)$$

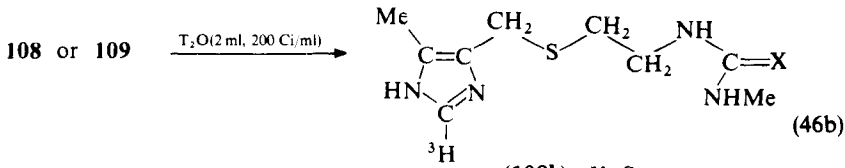
$^* H = {}^3H$ label

11. Synthesis of deuterium, tritium and ^{35}S labelled methiamide and cimetidine

The imidazole derivatives methiamide (**108**) and cimetidine (**109**)[56] are potential H_2-receptor antagonists, inhibiting gastric secretions, and have been labelled with deuterium and tritium at the $C_{(2)}$ position by refluxing **108** and **109** in D_2O and in ^3H_2O (400 Ci) (see equations 46a and 46b). Deuteration at C-2 was better than 97%. The half-life of tritiated compound **108b** was 2.4 days at 37°C. Tritium was removed from labile positions by exchange with MeOH, which was distilled off. The theoretical specific activity of **108b** was 1 Ci/mmol.

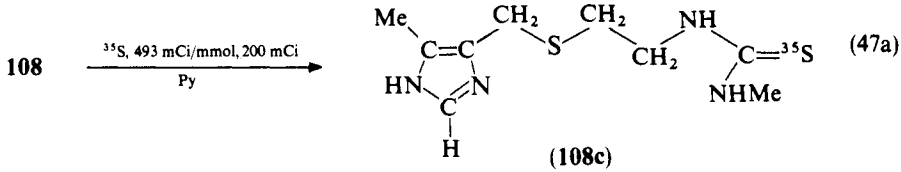


(108) X=S **(108a)**
(109) X=NCN **(109a)** (46a)

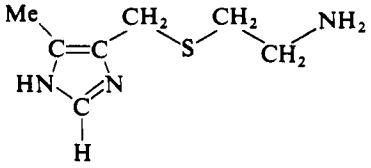


(108b) X=S
(109b) X=NCN (46b)

^{35}S labelled **108c** (labelled in the thiourea moiety) has been prepared[56] by treating **108** with elemental sulphur-35 in pyridine under reflux (equation 47a) or by reacting **110**, 2[(4-methyl-5-imidazolyl)methylthio]ethylamine, with methyl isothiocyanate-^{35}S (equation 47b). The radiochemical purity of **108c** after purification by preparative thin-layer chromatography was greater than 99%.



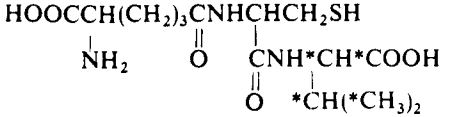
(108c) (47a)



(110) (47b)

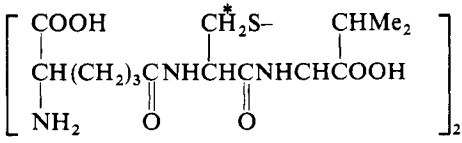
12. Synthesis of ^{14}C and tritium labelled tripeptides

^{14}C and tritium labelled tripeptides[57] bis-6-(L-2-aminoadipyl)-L-cystinyl-bis-L-valine-$^{14}C(U)$† (**111**) and bis-6-L-2-aminoadipyl-L-cystinyl-3,3′-T-bis-L-valine (**112**), as well as corresponding tritiated dipeptides, L-cystinyl-3,3′-T bis-L-valine (**113**) and L-cystinyl-bis-L-valine-$^{14}C(U)$ (**114**), structurally related to isopenicillin N (**115**), have been synthesized using as the starting labelled compounds L-valine-^{14}C (U) (450 μCi, specific activity 14.9 mCi/mmol) and L-cystine-3,3′-T(3 mCi, specific activity 200 mCi/mmol). The dipeptides **113** and **114** were obtained by modifying the procedure of Roeske[58–60] and using dicyclohexylcarbodiimide for coupling di-*N*-carbobenzyloxy-L-cystine (**116**) with L-valine *t*-butyl ester **117**.



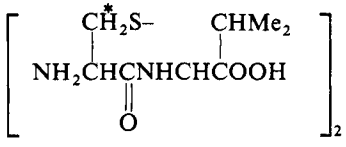
$\dot{C}$ = ^{14}C labelled positions
specific activity 87.3 μCi/mmol

(**111**) 600 mg

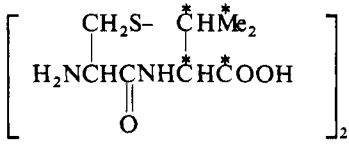


(**112**) 465 μCi

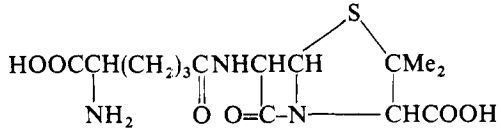
$\overset{*}{H}$ = tritium labelled position



(**113**) 350 μCi/mmol



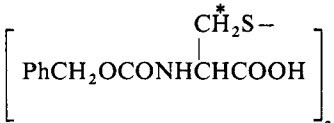
(**114**) specific activity 86.7 μCi/mmol



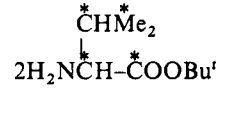
(**115**)

†In structures **111**, **114** and **117** $^{14}C(U)$ means uniform ^{14}C-labeling in the L-valine moiety only.

Tripeptides **111** and **112** are considered as possible intermediates in the biosynthesis of the β-lactam antibiotics in the mycelia *Penicillium* and *Cephalosporium*[61].



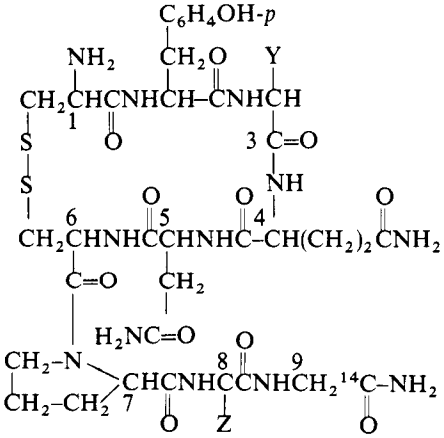
(**116**)



(**117**)–^{14}(U)

13. Synthesis of ^{14}C labelled arginine-vasopressin, lysine vasopressin and oxytocin

[9-glycinamide-1-^{14}C]-arginine-vasopressin (^{14}C-AVP) (**118**), [9-glycinamide-1-^{14}C]-lysine-vasopressin (^{14}C-LVP) (**119**) and [9-glycinamide-1-^{14}C]-oxytocin (^{14}C-OT) (**120**) of 30, 25 and 30 mCi/mmol specific activities, respectively, have been prepared[62] by a stepwise solid-phase synthesis, ideal for labelling naturally occurring biopolymers due to insolubility of intermediates attached to the solid support and application of automatic repetitive synthetic cycles[63–65]. Ring tritiated N^{α}-*t*-butyloxycarbonyl-phenylalanine ('Boc protected-phenylalanine', 2 mCi) has been incorporated[66] into position 3 of [8-arginine]-vasopressin and the ^{3}H-antidiuretic hormone so obtained was used to elucidate the mechanism of its action by studying its binding to isolated kidney cell membranes.



(**118**) 8-arginine-vasopressin(found in man, ox, rat and other mammals), Y = Bz, Z = $-(CH_2)_3NHCNH_2$ (NH)

(**119**) 8-lysine-vasopressin(found in pig and hippopotamus), Y = Bz, Z = $-(CH_2)_4-NH_2$

(**120**) oxytocin, Y = $-$CHEt(Me), Z = $-CH_2^{i}Pr$

14. Synthesis of tritium labelled oxytocin and vasopressin of very high specific radioactivity

a. Tritium labelled oxytocin and lysine vasopressin of very high specific activity, having one tritium atom per molecule, have been synthesized[67, 68] using as the source of label L-tyrosine-3-^{3}H, prepared by hydrogenolysis of L-3-iodotyrosine with tritium gas. The

tritiated hormones (specific activity 2.9 Ci/mmol), prepared by coupling the tritiated tyrosine with heptapeptides of oxytocin and lysine-vasopressin, were used extensively in vivo.

b. Tritium labelled 8-lysine vasopressin (LVP) of very high specific radioactivity, 10 Ci/mmol, has been prepared[69]. An especially fast method [70–72] includes the following steps: Iodination of LVP hydrochloride (tyrosyl residue) with iodine monochloride, [^{125}I]Cl, when about two iodine atoms were incorporated per peptide molecule (80% yield), followed by reduction of the lyophylized iodo derivative with 10 Ci of pure tritium in the presence of 10% Pd on alumina catalyst and removal of the tritium from labile positions by several exchanges with excess of distilled water, and finally separation of all by-products by affinity chromatography on sepharose-bound neurophysins. A single peak of ^{3}H radioactivity comprised *ca* 50% of the total tritium. Biotests have shown that the tritiated LVP retains the ability to bind neurophysins and the biological activity of native hormone.

c. Lysine-vasopressin (LVP) tritium labelled in the tyrosine and phenylalanine residues has been prepared subsequently by solid-phase peptide synthesis of 3,5-dibromotyrosine and 4-chlorophenylalanine derivatives of LVP and catalytic reduction of the incorporated halogen-containing amino acids with carrier-free tritium gas. The protected peptides were cleaved from the styrene–divinylbenzene copolymer by ammonolysis and deprotected with liquid hydrogen fluoride. The disulphide bridges were formed by oxidation with hydrogen peroxide and aeration[73]. In a similar manner, the octapeptide, DG-LVP (des-9-glycinamide-8-lysine-vasopressin), tritium-labelled in the tyrosine and phenylalanine residues, has been synthesized[74]. The radiolabelled DG-LVP, free of endocrine effects of LVP, permits one to study the binding and mechanism of neurotropic action of the octapeptide.

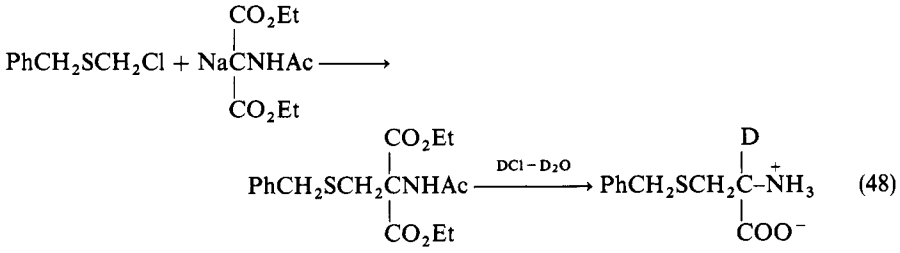
A suggestion that LVP is attached at its receptor site through a covalent bond, formed in a displacement reaction between disulphide groups of LVP and the thiol groups of the receptor protein, was given additional support[75] by showing that ^{3}H-LVP, obtained by the Wilzbach method[76], is bound to the kidney receptor protein through the disulphide bond and is released from the kidney protein by treatment with cysteine solution at pH 8.

15. Synthesis of specifically deuterated S-benzylcysteines and oxytocin

Amino acids, peptides and proteins labelled with deuterium[77] at non-exchangeable positions and with ^{13}C are very useful for studying their physical and dynamic properties, the microdynamical behavior of specific segments of the peptide hormones by deuteron magnetic resonance spectroscopy[78, 79] and ^{13}C NMR[80], their possible conformational structures, their modes of binding to carrier proteins and for tracing their biochemical reaction paths in living organisms[77a]

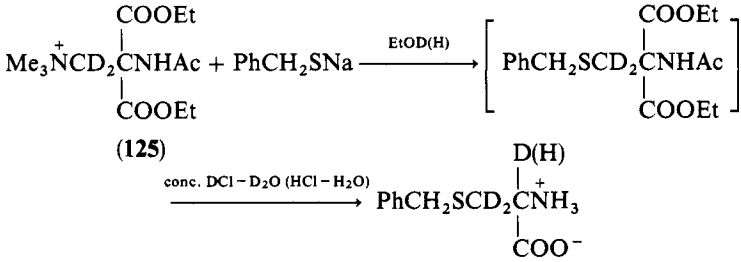
Fourier transform ^{1}H NMR spectroscopic studies of the hydrogen-deuterium exchange of the amide protons of oxitocin with D_2O showed that there are apparent barriers to exchange of the order of 0.5 and 0.6 kcal/mol for Asn^5 and Cys^6 peptide NH, respectively. These are explained by steric hindrance to solvent access in the case of Asn^5 and by intramolecular hydrogen bond participation in the case of Cys^6. The exchange data did not demonstrate the noncovalent association of the tocin ring with the tripeptide tail of the hormone.

a. Synthesis of S-benzylcysteine deuterated in the α position, *S*.-benzyl-DL-[α-$^{2}H_1$] cysteine (**121**), has been prepared as outlined in equation 48. The DL stereoisomers were separated by N-acylation and treatment with hog renal acylase[81].



(122) (121) 97% of D, 65% yield (48)

b. S-benzyl-DL-[β, β-$^2H_2$] *cysteine* (**123**) and *S-benzyl-DL-*[α, β, β-$^2H_3$] *cysteine* (**124**) were prepared according to equation 49[77]. **123** and **124** were resolved into their enantiomers as above by N-acetylation and subsequent reaction with hog renal acylase.

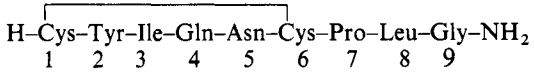


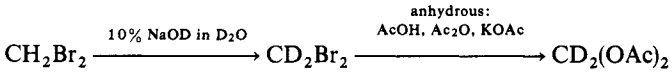
(**123**) > 97% D

(**124**) > 97% D at β position

> 95% D at α position (49)

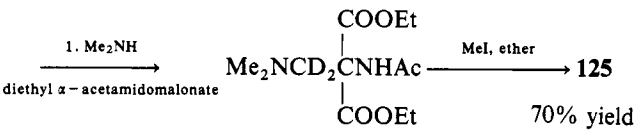
The β-deuterated starting material **125** was obtained following scheme 50. **123** and **124** were utilized[80a, b] in the preparation of several deuterated oxytocin analogues, such as a nonapeptide amide containing deuterium in 1-hemicystine or in the 6-hemicystine residue,





49% yield,

> 95% D,



70% yield (50)

*16. Synthesis of S-benzyl-DL-[1-^{13}C] cysteine (**126**) and its incorporation into oxytocin and 8-arginine vasopressin*

126 has been prepared[81] using Na^{13}CN as the source of ^{13}C, following the procedure of Gawron and Glain[82] shown in equation 51. Reaction of **126** with *t*-butyloxycarbonyl azide produced the protected N-Boc-S-benzyl-DL-[1-^{13}C] cysteine **129**[83]. **129** was incorporated into one of the six positions of the oxytocin derivatives and 8-arginine vasopressin hormone derivatives **130** by total solid-phase synthesis[84].

$$NaHSO_3/H_2O \xrightarrow[2.\ Na^{13}CN(90\%\ ^{13}C\ enriched)]{1.\ PhCH_2SCH_2CHO} PhCH_2SCH_2\underset{\displaystyle OH}{\underset{|}{C}}H^{13}CN$$

(**127**) 88% yield

$$\xrightarrow{NH_3} PhCH_2SCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}H^{13}CN \xrightarrow{37\%\ HCl}$$

(**128**) 40% yield

$$PhCH_2SCH_2\underset{\displaystyle {}^{+}NH_3}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}{}^{13}COO^- \xrightarrow{t\text{-}BuOCN_3} PhCH_2SCH_2\underset{\displaystyle NHCOBu\text{-}t}{\underset{|}{C}}H^{13}COOH \qquad (51)$$

(**126**) 50% yield (**129**) 83% yield

H–Cys–Tyr–Phe–Gln–Asn–Cys–Pro–Arg–Gly–NH_2

1 2 3 4 5 6 7 8 9

(**130**)

17. Synthesis of tritiated insulin of very high specific radioactivity

Semisynthetic [Phe^{B}1–^{3}H] insulin[85], free of some of the disadvantages of a radioiodinated product[86] (protein can suffer 'iodination damage', since the iodine atom is large and may affect the behaviour of the molecule), has been prepared using pig insulin and ^{3}H phenylalanine, L-[4-^{3}H] phenylalanine and L-phenyl[2,3-^{3}H]-alanine at specific radioactivities between 1 Ci/mmol and 20 Ci/mmol. The disulphide bridges were kept intact in the course of synthesis.

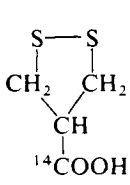
18. Synthesis and applications of [1-^{14}C] acetyl enzyme-glyceraldehyde-3-phosphate dehydrogenase

Reaction of glyceraldehyde-3-phosphate dehydrogenase (the enzyme catalysing the reversible oxidation and phosphorylation of aldehyde substrate to the corresponding acyl

phosphates) with *p*-nitrophenyl-[1-^{14}C]acetate yielding the [1-^{14}C]acetyl enzyme[87] helped greatly to identify the products of the hydrolytic decomposition of the [1-^{14}C]acetyl enzyme with pepsin in 0.02 N hydrochloric acid. Separation of the pepsin digest on a Sephadex column and ^{14}C monitoring of the acetic acid effluent permitted one to separate the large basic peptides from smaller neutral and acidic ones in the hydrolysate. Subsequent paper ionophoretic separations of the fractions, their oxidation with performic acid and hydrolysis with HCl of the major peptide P4, permitted one to establish the amino acid composition and the amino acid sequence around the reactive cysteine residue in the glyceraldehyde-3-phosphate dehydrogenase, and to draw the conclusion that each enzyme molecule contains at least three structurally equivalent 'catalytic centres' ('polypeptide chains'). Each 'active centre' contains in turn a reactive SH group (cysteine residue), which forms a covalent bond with a substrate or with inhibitors of the enzyme.

19. Biosynthesis of isotopically labelled sulphur compounds (1,2-dithiolanes)

The mechanism of formation of naturally occurring 1,2-dithiolanes such as *asparagusic acid*, **131** (a plant growth inhibitor possessing potent nematicidal activity, produced by *Asparagus officinalis*[88, 89], the alkaloids : gerrardine **132** and brugine **133** (isolated from *Rizophoraceae* plants) and nereistoxin **134** (found in marine annelid[90]) as well as the widely distributed α-(+)-lipoic acid **135** (functioning as an essential coenzyme in many organisms[91]) has been investigated using ^{14}C, $^{3}_{1}$H and ^{35}S as radioactive traces[92, 93].



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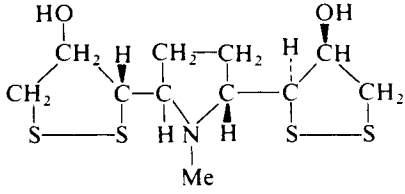

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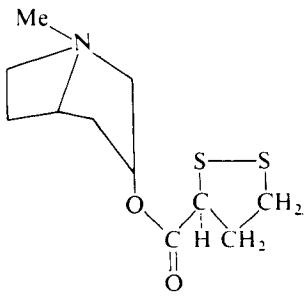

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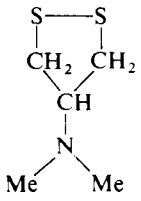

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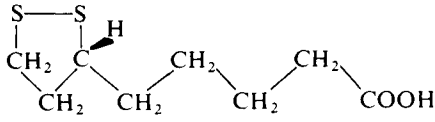
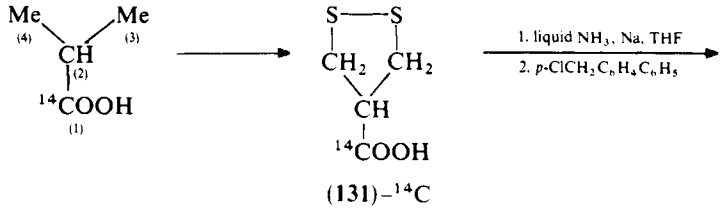


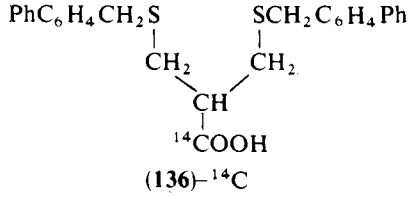
(135)

Administration of [1-^{14}C]-isobutyrate to young *Asparagus officinalis* plants by the cottonwick method yielded ^{14}C-carboxyl labelled asparagusic acid (**131**)-^{14}C, derivatized as the bis *p*-phenylbenzyl thioether **136** (equation 52). The specific incorporation of isobutyric acid into asparagusic acid has been documented by the degradation of **136** which gave isopropylamine, derivatized as crystalline benzamide **137** devoid of radioactive ^{14}C (equation 53).

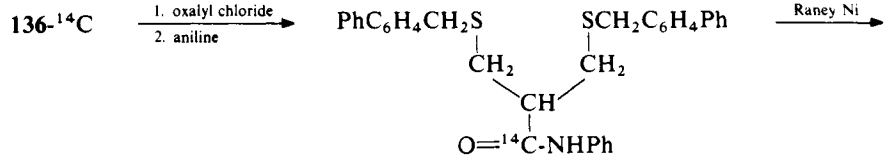
The mechanism governing the introduction of sulphur into the isobutyrate molecule has been investigated by synthesizing [3,4-^{3}H] and [2-^{3}H] isobutyrates, and mixing them with [1-^{14}C]isobutyrate, followed by administration of the doubly labelled isobutyrates

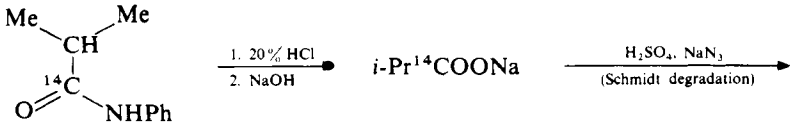


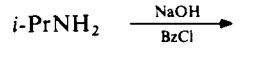
(131)-^{14}C



(136)-^{14}C (52)



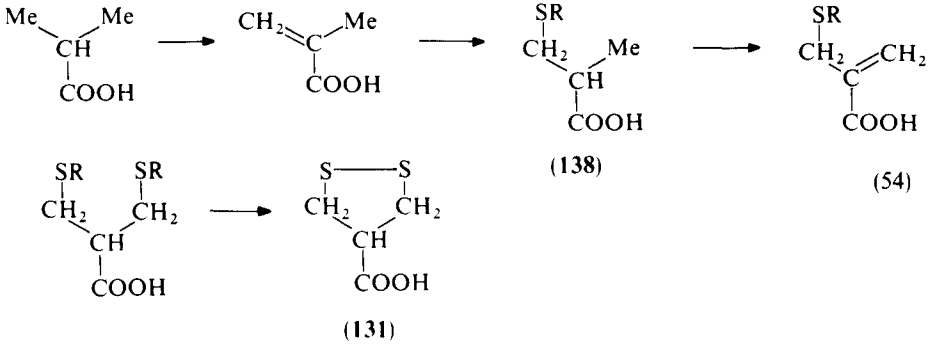




(137) (53)

to *Asparagus*, isolation and derivatization of the asparagusic acid produced by the plant. Biological experiments have shown that [3,4-^{3}H]isobutyrate is incorporated into asparagusic acid practically without tritium loss (probably due to the large tritium isotope effect in the removal of the hydrogen atom from the methyl group of isobutyrate), but complete loss of the tritium label occurs in the course of incorporation of the [2-^{3}H]isobutyrate into asparagusate. It has been suggested that [2-^{3}H]isobutyrate undergoes dehydrogenation to methacrylic acid. Specific incorporation of 1-^{14}C methacrylate into *Asparagus* plant strengthened this explanation. The results of these experiments suggest that the biosynthesis of 1,2-dithiolanes in *Asparagus officinalis* proceeds according to equation 54.

The possibility of the appearance of the 2-methyl-3-mercaptopropanoic acid (**138**) as an intermediate in the pathway shown in equation 54 has been evaluated by incorporation experiments using two pairs of doubly labelled sodium 2-methyl-3-mercaptopropanoates,

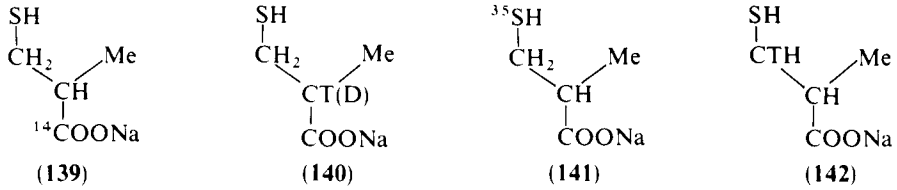


(138)

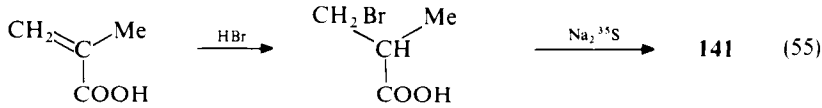
(54)

(131)

139+**140** and **141**+**142**. [1-^{14}C] **139** was prepared from [1-^{14}C]methacrylic acid with thiolacetic acid. **140** was synthesized similarly, but using tritiated water (or D_2O). **141** was obtained by the scheme[94] shown in equation 55. [3(*R*,*S*)-^{3}H]-2-methyl-3-mercaptopropanoate **142** was prepared by treating (*z*)-[3-^{3}H]-2-methylprop-2-enoic acid with thiolacetic acid, followed by basic hydrolysis of the thioester.



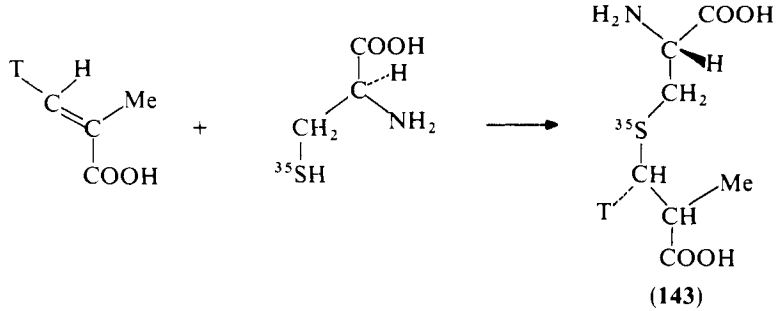
(139) (140) (141) (142)



(55)

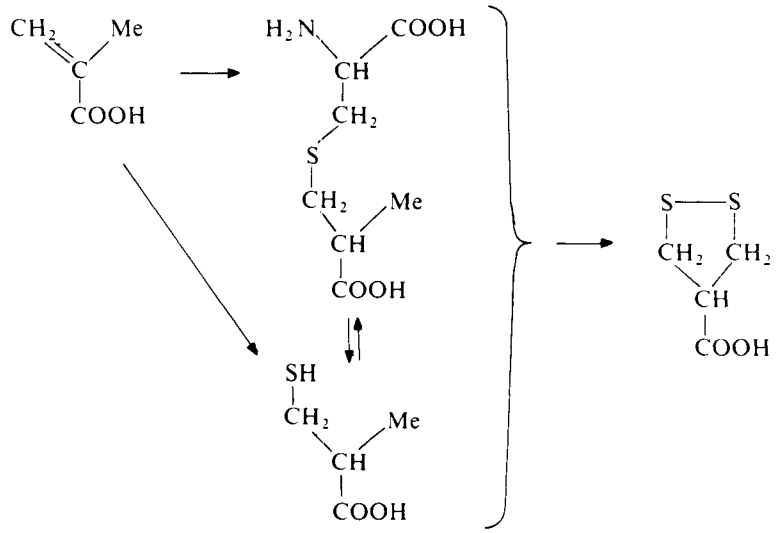
The two doubly labelled precursors were administered to *Asparagus* plants and the percentage incorporation, isotope ratios, labelling patterns and isotope retention in the asparagusic acid isolated from the plant material were investigated. The isotopic data obtained showed that **138** is the true specific precursor of asparagusic acid. Complete retention of ^{35}S from **138** in product **131** is observed and the double bond is formed between $C_{(2)}$ and $C_{(4)}$. Further isotopic experiments have revealed that cysteine is the donor of at least one of the sulphur atoms (equation 56) of asparagusic acid, while (−)-*S*-(2-carboxypropyl)-L-cysteine (**143**) plays a significant role in the biosynthesis of asparagusic acid and is also the progenitor of the lacrymatory principle in onions[95]. It has been suggested that the second step in equation 54 may be represented by scheme 57.

Synthesis of tritium labelled (2*S*)- and (2*R*)-[3-^{3}H]isobutyrate, their incorporation into *Asparagus* plant, subsequent isolation of the bioproduced *S*-(2-carboxy-n-propyl)-L-cysteine, degradation of *N*-benzoyl-*S*-2-carboxypropyl-L-cysteine (**144**) by two methods showed that tritium is located at $C_{(3)}$. This implies that from two enantiotopic 2-pro-*R* and 2-pro-*S* methyl groups of isobutyrate, the 2-pro-*S* methyl group is biooxidized exclusively in the conversion of isobutyrate to methacrylate in Asparagus plants, followed by addition of the sulphur nucleophile. A similar stereochemistry was found in the oxidation of isobutyrate to methacrylate by the procaryote, *Pseudomonas putida*[96].



(56)

(143)



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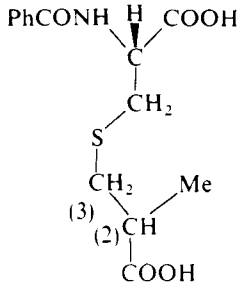
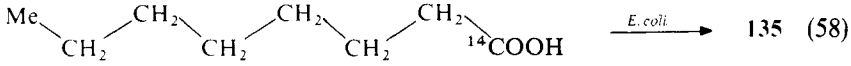


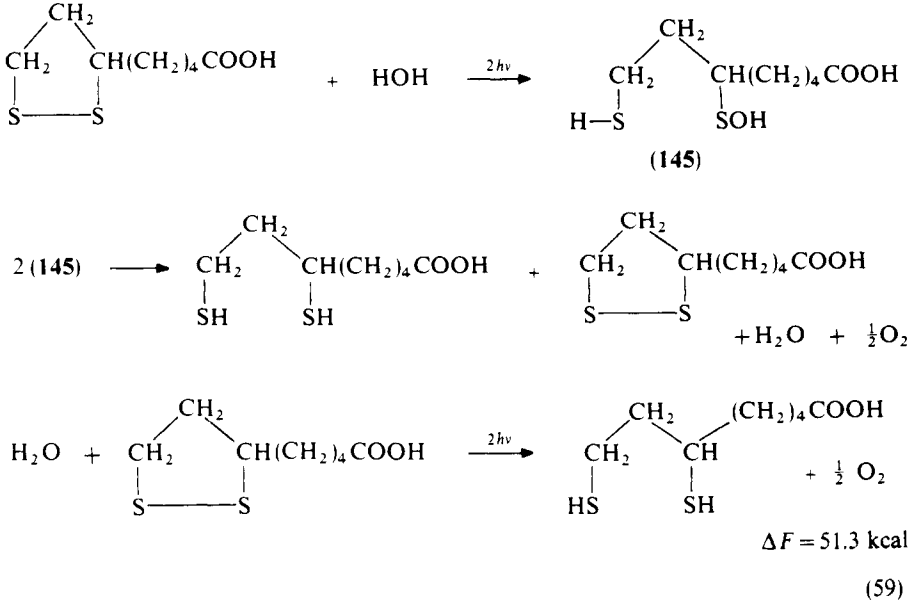
(144)

In contrast, lipoic acid (6,8-thiooctic acid, **135**) is biosynthesized in *E. coli* by direct introduction of sulphur at $C_{(6)}$ and $C_{(8)}$ of octanoic acid without involvement of $C_{(5)}$ and $C_{(7)}$, with inversion of configuration at $C_{(6)}$ (equation 58)[97]. Degradation of 6,8-thiooctic acid proved that octanoic acid is its specific precursor. Equation 58 was supported by



synthesizing octanoic acid, specifically tritiated at $C_{(5)}$, $C_{(6)}$, $C_{(7)}$ and $C_{(8)}$, from the corresponding tritiated alcohols, mixing each sample of the tritiated sodium octanoate with sodium[1-^{14}C]-octanoate, administration of the doubly labelled octanoates to *E. coli* in feeding experiments, isolation of the lipoic acid and its detailed degradation accompanied by the tritium/carbon-14 ratio determinations of the degradation products. The above results were corroborated also by feeding deuterium labelled precursors, [U-$^{2}H_{15}$]-octanoate, to *E. coli* and by MS analysis of the bioproduced lipoic acid, which showed that biosynthesized labelled lipoic acid contains thirteen deuterium atoms. This result implies that sulphur atoms are inserted into octanoic acid with loss of two deuterium atoms only. Additional tracer studies revealed that hydroxylated compounds are not intermediates in the sulphur insertion processes[98, 99].

In the course of tracer studies of the reduction of carbon-14 dioxide to hexose-^{14}C, taking place in photosynthesizing plants, it has been suggested[100] that a sulphenic acid intermediate **145** should appear if the mechanism of water photolysis involves thiooctic acid (equation 59). 63% of the energy of two light quanta ($\lambda = 7000$ Å, $2E_{h\nu} = 2 \times 40.7 = 81.4$ kcal) stored in the dithiol molecule is subsequently used indirectly for reduction of 3-phosphoglyceric acid (PGA,Ⓟ$OCH_2CHOHCOOH$), synthesis of ATP from ADP and formation of reduced forms of coenzymes.



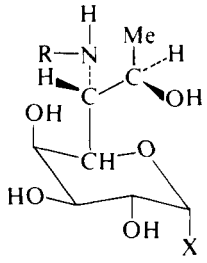
(59)

20. Biosynthesis of ^{2}H- and ^{13}C-labelled lincomycins

The clinical and pharmaceutical importance of the antibiotic lincomycin A (**146**), produced by *Streptomyces lincolnensis*, prompted biotechnological studies of the fermentation process leading from glucose to **146** and to **147**, MTL. The mechanism of the

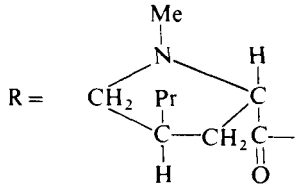
biosynthetic production of **146** has been studied [101, 102] by a combination of the NMR (^{13}C–^{13}C spin–coupling patterns) and mass spectral analysis with deuterium and ^{13}C enriched lincomycin and MTL, isolated from feeding experiments in which specifically deuterated tyrosine, DOPA, methionine, ($^{13}C_6$) glucose (98% enriched), D-(1-^{13}C) glucose, D-(6-^{13}C) glucose, (1-^{13}C) pyruvate, (2-^{13}C) glycerol and (1, 3-$^{13}C_2$) glycerol had been added to the fermentation broth.

The biosynthetic pathway proposed by Hurley and coworkers, leading to lincomycin A, involves the biosynthesis of a propylhygric acid unit **148** produced from tyrosine (equation 60) and biosynthesis of the aminooctose moiety, α-methylthiolincosaminide

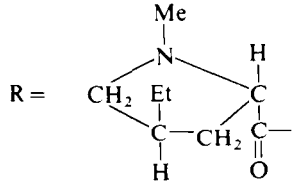


(**146**)

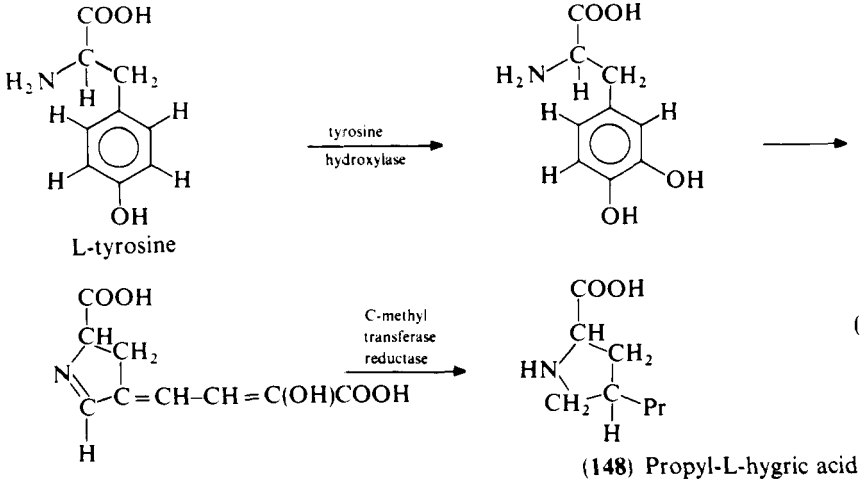
Lincomycin A: X = SMe



Lincomycin B: X = SMe



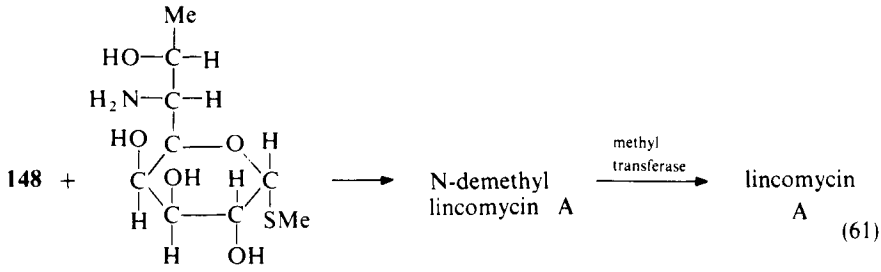
(**147**), MTL, X = SMe
R = H



(60)

(**148**) Propyl-L-hygric acid

(MTL, **147**), assembled through condensation of the pentose unit (C-5) and (C-3) unit derived also from glucose in the set of different biochemical transformations. Condensation of **147** with propylproline (**148**) and methylation of the adduct gives lincomycin A (equation 61).



(61)

21. Isotopic studies of the metabolism of DL-[β-^{14}C] and [-^{35}S] cystine in rats

DL-[β-^{14}C]cystine, DL-(HOOCCH(NH_2)$^{14}CH_2$S-)$_2$ and DL-[^{35}S]cystine, DL-(HOOCCH(NH_2)$CH_2{}^{35}$S-)$_2$ fed to rats were metabolized enzymically into pyruvate via cysteinesulphinic and β-sulphinopyruvic acids[103, 104]. This major metabolic pathway has also been indicated by the extensive incorporation of the isotopic carbon-14 from dietary DL-[β-^{14}C]cystine into alanine, aspartic acid, glutamic acid, and into the acetyl group of α-acetamido-γ-phenylbutyric acid, found in urine. DL-cystine is nearly as effective a source of acetyl groups as DL-[γ-^{14}C] valine, which is bioconverted to 3-carbon acids, propionate and pyruvate. Some rather poor conversion of [^{14}C]cystine into [^{14}C]-serine was also found. Practically no incorporation of [^{14}C]cystine and [^{35}S]cystine into methionine was found. [β-^{14}C] of cystine did not incorporate into methyl groups of choline and methionine. Neither was DL-[γ-^{14}C]valine a precursor of methyl groups.

22. Syntheses, biomedical studies and applications of ^{125}I-labelled peptide hormones

a. Syntheses of ^{125}I labelled neurohypophyscal hormones. The iodinated neurohypophyscal hormones (NHH)[105], [3-Iodo-Tyr]oxytocin, MIOT; [3,5-diiodo-Tyr]oxytocin, DIOT; [3-iodo-Tyr, Lys]vasopressin, MILVP; [3,5-diiodo-Tyr]vasopressin, DILVP; [3-iodo-Tyr, Arg]vasopressin, MIAVP, and [3,5-diiodo, Tyr, Arg]vasopressin, DIAVP, were synthesized by direct mild iodination of the hormones (30–90 mg scale) using I_2 in $CHCl_3$–MeOH–H_2O at pH 8, thus avoiding reactions with disulphide and tyrosyl–peptide bonds. Some of the above iodo derivatives of NHH, DIOT, DILVP and DIAVP were deiodo-tritiated with carrier-free tritium in MeOH–EtOAc–AcOH in the presence of 5% Pd/$CaCO_3$ yielding [^{3}H]OT (25.31 and 25 Ci/mmol), [^{3}H]LVP (26 and 23 Ci/mmol) and [^{3}H]AVP (17 Ci/mmol), respectively, and used to determine NHH receptor sites in kidney and uterine membranes.

b. ^{125}I-labelled antibodies to polypeptide hormones. The problem of the production of antibodies to vasopressin from porcine blood has been investigated[106] using [^{125}I] [8-arginine]-vasopressin[107] produced according to Greenwood and coworkers[107]. The kinetics and mechanism of binding insulin to specific sites ('receptors') on the cell membranes of mice mammary glands was studied with crystalline porcine Zn–insuline

iodinated with [^{125}I][108]. ^{125}I($t_{1/2}$ = 60 d, K, noβ^+, γ0.035, e$^-$)-labelled antibodies to polypeptide hormones, of high specific radioactivities, permitting one to detect 90 pg of human growth hormone/ml or 100 pg of bovine insulin/ml, have also been prepared[109]. 1–2 mCi of ^{125}I and 25 μg of chloramine-T were used in single preparations, applied in immunoradiometric assays and in various immunological reactions carried out *in vivo* and *in vitro*.

c. ^{125}I-arginine vasopressin and oxytocin syntheses and medical studies. ^{125}I iodo AVP prepared from synthetic AVP[110, 111] has been used for radioimmunoassay of arginine vasopressin in *Rhesus* monkey plasma[112]. [8-Arginine]-vasopressin (AVP) labelled with ^{125}I on the tyrosyl residue has been used in the determination of this antidiuretic hormone in daily urinary excretion of women (34 ng) and men (70 ng). Extremely high values of AVP were observed in the urine of subjects with bronchogenic tumours[113]. ^{125}I-labelled oxytocin[111] has been used to investigate[114] the role of oxitocin in endocrine changes associated with labor, to determine the plasma concentrations of oxytocin during pregnancy and parturition and to disclose whether it is of foetal or maternal origin.

The limit of radioimmunoassay detection of oxytocin was 2.5 pg/ml of plasma. Practical proposals for arginine-vasopressin radioimmunoassay with the use of ^{125}I-AVP[115], protected from damage by ε-aminocaproic acid(EACA)[116], were given by Moulin and coworkers[117].

d. Syntheses and radioimmunoassay studies with ^{125}I-insulin and other insulin associated peptides. The methodology of preparation of ^{125}I-insulin for radioimmunoassay and for receptor assay has been carefully re-examined by Schneider and coworkers[118] and it has been shown that the distribution of iodine atoms depends only on the average iodine number. The same quality, stability and distribution of ^{125}I was found whether the radioiodoinsulin was prepared by fast (15 s) iodination with chloramine T or by stepwise addition of the oxidizing agent[118]. Improvements in the ^{125}I-labelled insulin and glucagon syntheses[119] and their quality control[120] were proposed by Ziegler and coworkers[119, 120]. ^{125}I-labelled NSILA [a group of low-molecular-weight, *ca* 6000, non-suppressible insulin-like substances extracted from human serum by chromatography and designated NSILA-S, NSILA-I and -II] has been used for quantitative determination of NSILA in human serum[121].

'C-peptide' (molecular weight about 3000) has no or negligible biological activity and radioimmunoassay is the only analytical tool for its determination. Thus, ^{125}I-Tyr-C-peptide has been used in a method of separation of proinsulin, insulin and intermediates from C-peptide, using antibodies against pork insulin coupled to sepharose. As little as 2 ml of serum suffices to isolate proinsulin and to determine human C-peptide[122]. The cross-reactivity of porcine and human proinsulin, the single-chain precursor of insulin[123], with different insulin antisera in the ^{125}I-insulin radioimmunoassay has been investigated by Starr and coworkers[124]. In the course of studies on specific binding sites for ^{125}I-labelled insulin in purified nuclei isolated from rat liver, it has been found that ^{125}I-labelled glucagon, which binds 5- to 10-fold more strongly to liver plasma membranes than insulin itself, does not bind to liver nuclei[125]. It has been suggested that insulin also enters the cell and direct interactions of insulin with intramolecular structures *in vivo*, besides the well-established binding to receptors on the plasma membrane, constitute a second intracellular path of insulin action regulating the intracellular metabolism of glucose and other intracellular events.

^{14}C-labelling permitted one to identify *N*-alkaline phosphatase, the enzyme[126] which catalyzes the hydrolysis of the monoesters of orthophosphoric acid but not of thiophosphoric acid. This suggests that the enzyme interacts directly with P–O or P–S bonds, differing in that respect from other alkaline phosphatases which catalyse with similar efficiencies the esters of type **149** and **150**.

(149) (150)

R = *p*-$NO_2C_6H_4$–, –$(CH_2)_2NH_2$,

$H_2NCHCOOH$
|
CH_2

Using [^{3}H] labelled dexamethasone cytosol, it has been noted[127, 127a] that the rat liver glucocorticoid–receptor complex (binding to DNA–cellulose) can be activated by three procedures: heating, gel filtration and dilution. The heat-activated steroid receptor complex loses its capacity to bind to DNA–cellulose with time, while activation by gel filtration or by dilutions maintains the DNA–cellulose binding capacity. This has been interpreted as indicating that filtration and dilution remove the low-molecular inhibitor while heat treatment changes the chemical equilibrium between inhibitor and acceptor[128a].

The ^{125}I-radioimmunoassays, the radioreceptor assays and the bioassays have indicated that insulin, proinsulin and glucagon from obese rats are indistinguishable from insulin, proinsulin and glucagon from lean rats[128b]. It has been concluded therefore that metabolic abnormalities observed in obesity are not caused by the alterations in the biological properties of pancreas insulin or glucagon. The observation that insulin from lean rats was slightly less potent (*ca* 70%) than standard rat insulin in some bioprocesses might be caused by different extraction or estimation procedures[128b].

III. EXCHANGE STUDIES WITH LABELLED SULPHENIC ACID DERIVATIVES

A. ^{36}Cl Isotope Exchange Studies with Sulphenyl Chlorides

1. *Heterogeneous ^{36}Cl exchange between organosulphenyl chlorides and Ag^{36}Cl*

The rate of the reaction between halogenated organosulphenyl chlorides of the type $Cl_{3-n}F_n$ CSCl and silver pseudohalides, AgCN, AgOCN, AgSCN and AgSeCN, yielding quantitatively the corresponding halogenated methanesulphenyl pseudohalides (equation 62) depends on the number of fluorine atoms in the methyl group. Replacement of the chlorine atoms in the perchloroderivative ($n=0$) with fluorine atoms ($n=3$) increases strongly the reactivity of the S–Cl bond [129, 130], suggesting that the more electronegative fluorine increases the degree of polarization of the S–Cl bond and weakens its covalent character. The above conclusion has been confirmed by studying the heterogeneous isotope exchange[131] (equation 63) between solid silver chloride and the liquid sulphenyl chlorides **151**–**162**.

$$R^1R^2R^3CSCl + AgX = R^1R^2R^3CSX + AgCl \tag{62}$$

$$-S-Cl + Ag^{36}Cl \rightleftharpoons -S-{}^{36}Cl + AgCl \tag{63}$$

F_3CSCl (**151**) $F_2ClCSCl$ (**152**) $(CF_3)_2ClCSCl$ (**153**) $(CF_3S)FClCSCl$ (**154**) FCl_2CSCl (**155**)

$(CF_3S)Cl_2CSCl$ (**156**) O=C(F)SCl (**157**) O=C(Cl)SCl (**158**) $(CF_3S)Cl_2CSCl$ (**159**)

Cl_3CSCl (**160**) S=CFCl (**161**) $FCl_2CS–CN$. (**162**)

The exchange experiments were carried out at 30°C, the molar ratio AgCl/sulphenyl chloride was 1:3 and the Ag[^{36}Cl] amounts were 0.5–3 g. The ^{36}Cl exchange was followed by measuring the increase in the radioactivity of the initially unlabelled sulphenyl chloride. At predetermined reaction times, the AgCl was filtered, a sample of the sulphenyl chloride was decomposed with Na_2O_2, treated with HNO_3, the chloride was precipitated with $AgNO_3$ and its radio-activity determined. With **152–156** and **158–160** the measured radioactivities were multiplied by the number of chlorine atoms in the organic chloride since it has been established that the compound **162** practically does not exchange its two chlorine atoms under the conditions chosen in this study (after 30 h at 30 °C no exchange was found). The reproducibility of the results was ±2%. In the case of compound **161** the exchange was negligible (3% after 10 h at 30 °C). The experimental results were presented in the form of time dependences of the ratios S_t/S_∞, where S_t is the radioactivity of the organic phase at time t and S_∞ is the radioactivity of the solid samples at infinity (in practice at $t = 10$–30 h). These results correspond to very fast exchange in the case of ions in the solution and a crystalline salt of these ions (e.g. in the system comprising a solution of $PbCrO_4$ and solid $PbCrO_4$)[132], but proceeds at measurable rates for ^{36}Cl exchange between a liquid sulphenyl chloride and the surface of the solid AgCl. The rates are comparable with the heterogeneous ^{18}O exchange between gaseous oxygen and metal oxides (e.g. γ-Al_2O_3) at higher temperatures[133]. The ^{36}Cl exchange data were used to classify the organic sulphenyl halides **151–160** according to the reactivity of their S–Cl bond. The highest $(S_t/S_\infty)_{t=1\ h}$ value was obtained in the case of the compound **151**, the smallest with the compound **160**. The (S_t/S_∞) ratio corresponding to $t = 1$ h was used as the 'reactivity index' and was taken equal to 100 for **151**. This reactivity index was correlated with the sum Σx_i of the Pauling electronegativity coefficients of the R^1, R^2 and R^3 atoms or groups. Values 4.0, 3.0, 3.2 and 2.7 were taken for F, Cl, CF_3 and CF_3S, respectively[134]. The results are presented in Table 1. The reactivity of the carbonyl compounds **157** and **158** (not included in Table 1) also increases upon replacement of Cl by F, being about 33 for the former and 13 for the latter. This study permitted one to classify the sulphenyl halides according to their reactivity and to establish a correlation between reactivity and the cumulative electronegativity of the substituents influencing the polar character of the S–Cl bond. The reaction has been studied only at 30 °C, and the temperature dependence was not investigated.

TABLE 1

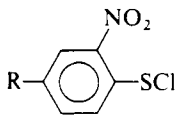
Compound	R^1	R^2	R^3	Reactivity index[a]	Σx_i
151	F	F	F	100	12.0
152	F	F	Cl	85	11.0
153	CF_3	CF_3	Cl	75	9.4
154	CF_3S	F	Cl	75	9.7
155	F	Cl	Cl	67.5	10.0
156	CF_3S	CF_3S	Cl	37.5	8.4
159	CF_3S	Cl	Cl	7.5	8.7
160	Cl	Cl	Cl	7.5	9.0

[a] Explanations and definitions are given in the text.

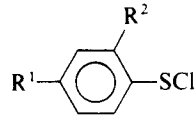
2. Homogeneous ^{36}Cl isotopic exchange of benzenesulphenyl chlorides and Li[^{36}Cl]

Two groups (A and B) showed sharply differing reactivities[135] in the homogeneous exchange between Li[^{36}Cl] and ArSCl, dissolved in CH_3COOH at 20 °C. Compounds

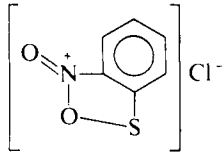
163–165 (Group A) which contain a nitro group in the *ortho* position, exchange their S–Cl chlorine unmeasurably fast with the chlorine of the Li[^{36}Cl]. On the other hand, compounds **166–170** (Group B), even those possessing the electron-withdrawing NO_2 groups in the *para* position, do not exchange the S–Cl chlorine during 24 h at 20 °C. The above findings are interpreted as showing that there is a strong interaction between the oxygen atom of the *o*-nitro group and the sulphur atom, and the ionic pair **171** is formed or the sulphurane structure **172**, which also accelerates the exchange of the chlorine bound to sulphur.[135]



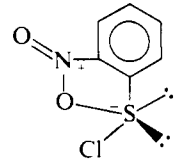
(**163**) R = NO_2
(**164**) R = H
(**165**) R = CH_3
'Group A'



(**166**) $R^1 = R^2 = H$
(**167**) $R^1 = CH_3$, $R^2 = H$
(**168**) $R^1 = Cl$, $R^2 = H$
(**169**) $R^1 = NO_2$, $R^2 = H$
(**170**) $R^1 = NO_2$, $R^2 = Cl$
'Group B'



(**171**)



(**172**)

B. ^{35}S Isotopic Exchange Study Between Sulphite and Alkyl Thiosulphates

A detailed kinetic isotope exchange study between sulphite and alkyl thiosulphates has been carried out[136, 137]. Alkyl thiosulphates can be considered as belonging to the class of sulphenyl compounds, defined as polarized compounds $RS^{\delta+}-X^{\delta-}$, undergoing nucleophilic displacements at the sulphur atom of the type

$$R\text{–}S^{\delta+}\text{–}X^{\delta-} + Y^- \longrightarrow R\text{–}S\text{–}Y + X^-$$

where S is the divalent sulphur atom and Y is the nucleophilic reagent (CN^-, SO_3^{2-}, SCN^-, etc.). The exchange reactions (equation 64)

$$R\text{–}S\text{–}SO_3^- + {}^{35}SO_3^{2-} \rightleftharpoons R\text{–}S\text{–}{}^{35}SO_3^- + SO_3^{2-} \qquad (64)$$

where R = Me, Et, benzyl, All, ethanedi, carboxymethyl, *i*-Pr and *t*-Bu, proceed at room temperature at rates which are conveniently followed. The sulphite labelled with radioactive $^{35}S(T_{1/2} = 88$ days, $E_{max\,\beta-} = 0.167$ MeV) has been prepared by reducing $Ba^{35}SO_4$ with red phosphorus[138]. The $^{35}SO_2$ was absorbed in 2N NaOH solution, where no appreciable oxidation of S^{IV} takes place. The weak β radioactivity of the sulphur-35 was measured using a Geiger–Müeller counter with a thin mica window. The reproducibility of radioactivity determinations was of the order of $\pm 3\%$.

The reaction is approximately first order in each of the reactants. In the expression $R = k[S]^n[AT]^m$, where [S] is the concentration of sodium sulphite and [AT] is the concentration of sodium carboxymethyl thiosulphate, $n = 1.09 \pm 0.06$ and $m = 1.06 \pm 0.09$ were found. The rate of exchange, R, depends strongly on the hydrogen ion concentration. Below pH 3 and above pH 9 alkyl thiosulphates are unstable. In the investigated pH range the value $R \times 10^7$ for carboxymethyl thiosulphate exchange increases from 0.17 (pH = 4.1) to 11.1 (pH = 8.4) under the conditions 50 °C, $I = 0.38$, $[S] = [AT] = 5 \times 10^{-3}$ mol dm^{-3}. Addition of sodium chloride to the reaction medium accelerates the exchange process, as shown in Table 2 (rows 1–3).

TABLE 2. Effect of NaCl concentration on the rate of exchange between sulphite and sodium ethyl thiosulphate (25 °C, pH = 7.4, $[SO_3^{2-}] = [EtS-SO_3^-] = 3 \times 10^{-3}$ mol dm^{-3})[a]

1	0.034	0.055	0.072	0.100	0.140	0.177
2	0.037	0.058	0.075	0.103	0.143	0.180
3	4.13	5.25	5.92	6.93	8.18	8.97
4	1.937	2.112	2.159	2.216	2.257	2.217

[a] Row 1 presents concentration of $[Na^+]$. Row2 presents ionic strength of the solution, $I = \frac{1}{2}\Sigma C_i z_i^2$ mol dm^{-3}. Row 3 presents exchange rates $R \times 10^7$, calculated by the McKay equation

$$R = -\frac{1}{t}\frac{[S]\cdot[AT]}{[S]+[AT]}\ln(1-F)$$

where R is the exchange rate expressed in mol dm^{-3} s^{-1}, t is the time, F is the fraction of exchange, [S] and [AT] are the concentrations of the reagents. Row 4 presents exchange rates $R_0 \times 10^7$ extrapolated to zero ionic strength with the use of the approximate relation

$$\log(R_0) = \log(R) - 2A_t z_A z_B \sqrt{I}/(1+\sqrt{I})$$

where $A_t = 1.825 \times 10^6/(\varepsilon_t T)^{3/2}$, ε_t is the dielectric constant at the reaction temperature, T is the absolute temperature, z_A and z_B are charges of the reacting ions and I is the ionic strength[138a].

Row 4 of Table 2 shows exchange rates R_0 reduced to zero ionic strength[138a]. The mean value of R_0 calculated omitting the first experimental point equals $(2.191 \pm 0.056) \times 10^{-7}$ mol dm^{-3} s^{-1} while $\bar{k}_0$, calculated by the expression $\bar{k}_0 = \bar{R}_0/[S][AT]$, equals 2.39×10^{-2} dm^3 mol^{-1} s^{-1}.

The catalysis of the exchange by the salts of polyvalent cations has also been noted. The temperature dependence of the exchange rates was investigated in the 7–50 °C temperature range (pH = 7.3, $I = 0.104$, concentration of the reagents 3×10^{-3} mol dm^{-3} in the case of ethyl and allyl derivatives and 5×10^{-3} in all other cases)[136]. The entropies, enthalpies and free energies of the investigated exchanges are given in Table 3. The effect of substituting hydrogen atoms by methyl groups in the α position to the reaction centre has also been investigated. The relative rates $100\,k/k_{Me}$ of the sulphite exchange between $R-S-SO_3^-$ and $^{35}SO_3^{2-}$ measured at 25 °C, pH = 7.9 and ionic strength $I = 0.5$, for R = Me, Et, *i*-Pr and *t*-Bu, are as follows:

	Me	Et	*i*-Pr	*t*-Bu
$(100k/k_{Me})$	100	50	0.7	0.0006

where the last value (for *t*-Bu) was extrapolated from data obtained in the temperature range 60–90 °C.

These differences in reactivities have been attributed to the steric hindrance in the transition state analogously to the differences in bromide exchange rates in β-branched

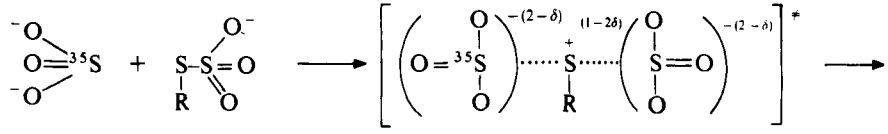
TABLE 3. Entropies, enthalpies and free energies of activation, calculated by the absolute rate theory expression: $k=(k_BT/h)e^{\Delta S^{\neq}/R}e^{-\Delta H^{\neq}/RT}$

Compound	$\Delta S^{\neq}$(e.u.)	$\Delta H^{\neq}$(kcal mol^{-1})	$\Delta F^{\neq}$ at 25 °C (kcal mol^{-1})
Thiosulphate	−32	13.8	23.3 [a]
1/2 Trithionate	−43	9.50	22.1
Ethyl thiosulphate	−32	9.74	19.27
Benzyl thiosulphate	−36	9.04	20.12
Allyl thiosulphate	−43	7.86	20.53
1/2 Ethane dithiosulphate	−37	8.43	19.56
Carboxymethyl thiosulphate	−41	8.73	21.23

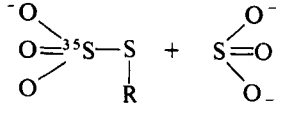
[a] $\Delta F^{\neq}=\Delta H^{\neq}-T\Delta S^{\neq}$, $T=298.16$ K. Relatively large variations in $\Delta S^{\neq}$ and $\Delta H^{\neq}$ mutually compensate each other, yielding rather small free-energy changes. $\Delta F^{\neq}$ values shown in column 4 are those given in Reference 136. Using $\Delta S^{\neq}$ and $\Delta H^{\neq}$ entries shown in columns 2 and 3 we obtain slightly different $\Delta F^{\neq}$ values; 23.34, 22.32, 19.28, 19.77, 20.68, 19.46 and 20.96 respectively. The discrepancies between values of $\Delta F^{\neq}$ of Fava and Pajaro given in column 4 and those listed in the footnote are negligible. In the original paper (ref. 136) the rate constrants: k × 10^2 dm^3.mole^{-1}.s^{-1} equal at 25 °C 0.005, 0.035, 5.9, 2.0, 0.55, 2.8 and 0.31 for the compounds listed in Table 3 are given also. The $\Delta F^{\neq}$ values calculated directly from the above rate constants with the use of the formula $k_0=(k_BT/h)e^{-\Delta F^{\neq}/RT}$, are equal 23.31 (compare with 23.3), 22.16, 19.12, 19.76_4, 20.53, 19.56_5 and 20.867 kcal/mole. They coincide in several cases exactly with values listed in column 4 above. Small differences are probably caused by calculational errors.

alkyl bromides, Et, Pr, *i*-Bu and neopentyl, where the relative rates are 100, 65, 3.3 and 0.0015, respectively[139]. The bimolecular character of the exchange reaction indicates that the transition state of the rate-determining step involves sulphite ion and alkyl thiosulphate. Sulphite is displaced from alkyl thiosulphate by free sulphite approaching the reaction centre (positively polarized sulphur) from the back side. However, in the encounter preceding the transition state formation, the negatively charged sulphite ion is approaching the negatively charged alkyl thiosulphate and the reaction is accelerated by the increase in the ionic strength of the solution (Table 2).

The large negative entropy of activation and asymmetric charge distribution in the alkyl thiosulphate suggest the structure **173** for the transition state as the most probable one (equation 65). This involves large steric crowding in the transition state, which carries a total electric charge of −3 units and thus causes strong structural orientation of the polar solvent in its vicinity.



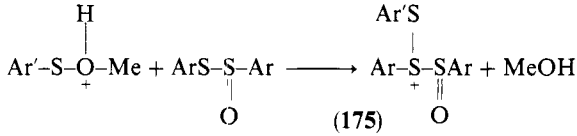
(173)

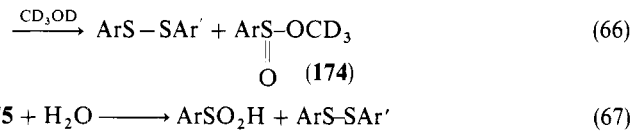


(65)

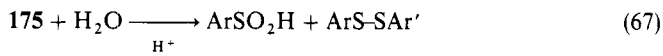
C. Exchange of the D_3-Methoxy Group Between Sulphenate Ester and Sulphinate

Ciuffarin and coworkers[140] investigated the chemistry of methyl toluene-*p*-sulphenates in acidic media by NMR spectroscopy and noted the exchange of the methoxy group between the sulphenate ester and sulphinate. Reaction 66 carried out in CD_3OD produced the methyl sulphinate **174**, with a fully deuteriated methyl group. In the absence of water the intermediate **175** reacts with methanol, yielding disulphide and sulphinate. In the presence of water, the very fast reactions (67) and (68) occur:

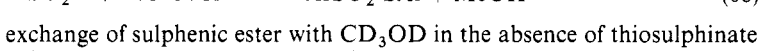




(66)



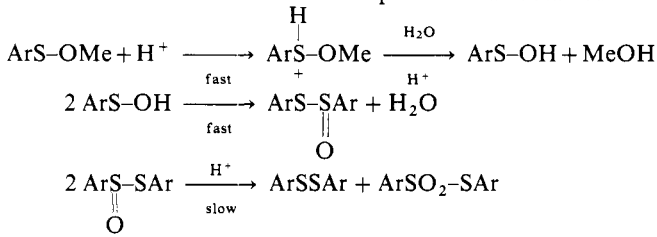
(67)



(68)

The methoxy exchange of sulphenic ester with CD_3OD in the absence of thiosulphinate proceeds very slowly. The sulphinate **174** exchanges methoxy group with methanol slowly, both in the presence and absence of thiosulphinate.

The sulphenate reaction rates could be studied by NMR only qualitatively. Methyl toluene-*p*-sulphenate is hydrolyzed rapidly in moist solvents (equation 69) and in some cases the reactions were over before the NMR spectrum was obtained.



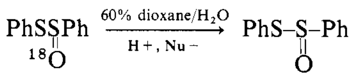
(69)

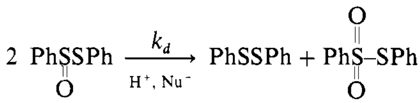
Like sulphenyl halides, protonated sulphenic esters are powerful electrophilic catalysts.

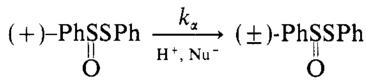
D. ^{18}O Exchange of Phenyl Benzenethiolsulphinate Catalysed by Acids and Nucleophiles

Most information concerning the reactivity of the sulphenic acid PhSOH is derived in an indirect manner[141], particularly by studying the acid and nucleophile catalysed oxygen-18 exchange[41] of PhS (^{18}O)SPh with aqueous dioxane followed by measuring at different reaction times the ^{18}O content of the thiolsulphinate samples using the Doering and Dorfman procedure[142, 143]. At low thiolsulphinate concentrations the rates of the acid and nucleophile catalysed disproportionations of PhS(O)SPh (equation 71) are significantly slower than that of reaction 70, and at short exchange times the first-order McKay plots of the ^{18}O exchange data hold well. Butyl sulphide, bromide and chloride ions were used as the nucleophilic catalysts, and perchloric acid as the acid catalyst. All experiments have been carried out[144] at ionic strength of 0.50 and at 39.6 °C. Values of first-order exchange rate constants, r_{exch} (s^{-1}), expressing the slopes of the plots of log

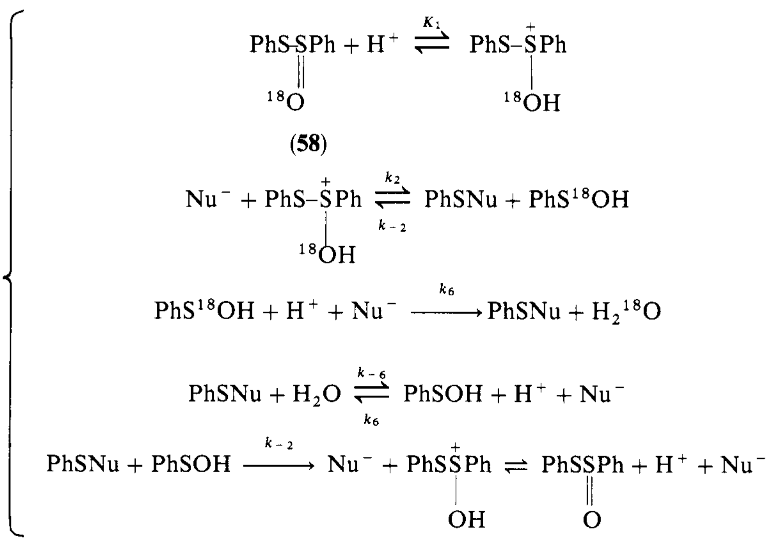
$[(P_t\text{-}P_\infty)/(P_o\text{-}P_\infty)]$ vs. time, where P_t is the atom% ^{18}O in the thiolsulphinate at time t, are tabulated in Table 4[41,145,146]. Column 6 displays the first-order rate constants k_α for the racemization of optically active PhS(O)SPh (equation 72); they are considerably larger than the exchange rates r_{exch} under the same experimental conditions.


(70)


(71)


(72)

There is a normal solvent isotope effect[144,12] ($k_{H_2O}/k_{D_2O} \cong 0.55$) similar to that found in isotopic studies with vinyl ethers ($k_{H_2O}/k_{D_2O} \cong 0.65$–$0.66$). The data presented in Table 4 have been rationalized by the mechanism shown in equations 73 and 74. Assuming


(73)

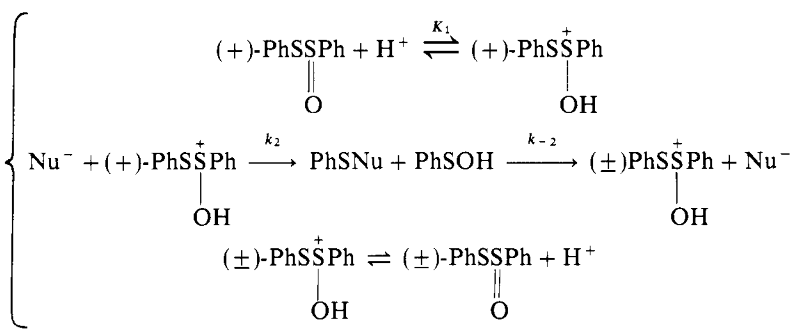

(74)

TABLE 4. First-order ^{18}O exchange rate constants r of phenyl benzene thiosulphinate-^{18}O in 60% dioxane/H_2O at 39.6 °C[a]

1	2	3	4	5	6	7
Bu_2S	0.050	1.0×10^{-2}	0.50	7.0×10^{-4}	240×10^{-4}	34
		1.0	0.10	1.5	47	31
		0.20	0.50	1.5	47	31
	0.025	0.20	0.10	0.63	9.4	15
	0.0125	0.20	0.10	0.83	9.4	11.3
Br^-	0.050	3.0	0.50	1.5	30	20
		1.0	0.50	0.60	10	17
Cl^-	0.050	10.0	0.40	1.0	3.2	3.2

[a] Column 1 gives the nucleophile. Concentrations in moles: phenyl benzenethiolsulphinate-^{18}O (column 2), nucleophile (column 3), $HClO_4$ (column 4). Column 5 gives the exchange rate constant r_{exch} in s^{-1}. Column 6 gives the rate constant k_α in s^{-1} of the racemization of (+)-**58**. Column 7 gives the value of k_α/r_{exch}.

steady-state concentrations of PhSNu and PhSOH, the loss of ^{18}O by **58** is given by equation 75:

$$k_{exch} = k_2 K_1 a_{H^+} [Nu^-] \left[\frac{1}{1 + \{k_2 K_1 k_{-2} [\mathbf{58}]/k_6 k_{-6} [H_2O]\}^{1/2}} \right] \tag{75}$$

and since $k_\alpha = k_2 K_1 a_{H^+} [Nu^-]$, k_α/k_{exch} simplifies to the expression given in equation 76:

$$k_\alpha/k_{exch} = 1 + \{k_2 K_1 k_{-2}/k_6 k_{-6} [H_2O]\}^{1/2} [\mathbf{58}]^{1/2} \tag{76}$$

Equation (76), expression 78 for the equilibrium constant K_{eq} in the reversible reaction 77 (assumed to be less than 10^{-6}) and the data presented in column 7 of Table 4 lead to the important conclusion that $k_{-2}/k_{-6} \geqslant 4 \times 10^5$. This implies that PhSOH is by many orders of magnitude more reactive than water as a nucleophile in reactions in which Bu_2S was used as catalyst (equations 79).

$$\underset{\underset{O}{\|}}{PhSSPh} + H_2O \overset{K_{eq}}{\rightleftharpoons} 2\ PhSOH \tag{77}$$

$$K_{eq} = \frac{[PhSOH]^2}{[\mathbf{58}][H_2O]} = \left(\frac{k_2 K_1}{k_6}\right)\left(\frac{k_{-6}}{k_{-2}}\right) \tag{78}$$

$$Bu_2\overset{+}{S}SPh + PhSOH \xrightarrow{k_{-2}} Bu_2S + PhS\overset{+}{\underset{\underset{OH}{|}}{S}}Ph$$

$$Bu_2\overset{+}{S}SPh + H_2O \xrightarrow{k_{-6}} Bu_2S + PhSOH + H^+ \tag{79}$$

The above conclusion which is valid also for other nucleophiles such as Br^-, Cl^-, etc., explains why thiolsulphinates and not sulphenic acids are the isolable products of the

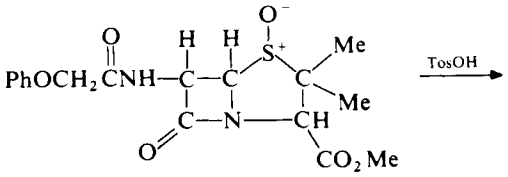
hydrolysis of the reactive sulphenyl derivatives. Note that the above quantitative considerations were possible since, under the experimental conditions used in this study of the ^{18}O exchange, there is 400–1600 times more water than the **[58]**-[^{18}O] compound.

IV. MECHANISTIC TRACER AND ISOTOPE EFFECT STUDIES WITH SULPHENIC ACID DERIVATIVES

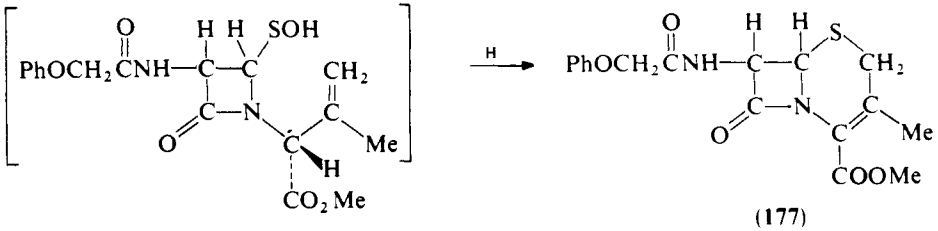
A. Deuterium Tracer Studies of the Open Sulphenic Acid Intermediate in the Rearrangement of the Cyclic Penicillin Sulphoxide Ester

In the rearrangement of the cyclic penicillin sulphoxide ester **176** to **177**, the formation of the highly reactive open sulphenic acid intermediate **178** has been postulated[147] (equation 80). Intermediate **178** has been postulated also in the thermal rearrangement of **176** to the thiazoline ring derivative **179** in the presence of trimethyl phosphite (equation 81) which reduces the sulphenic acid to a thiol, which in turn condenses with the amide side-chain[148]. The intermediacy of **178** in the thermal six-electron sigmatropic rearrangements of penicillin sulphoxides[149] has been substantially corroborated by deuterium experiments[150, 151]. Heating **176** in benzene containing an excess of deuterium oxide at 80 °C during 24 h gave **176**-D, deuterated in the β-methyl group with 100% stereospecific yield[152]. The product **176**-D had 45% d_0, 43% d_1, 11% d_2 and 1% d_3 isomers[150]. A similar experiment with phthalimidopenicillin α-sulphoxide[153] led to stereospecific deuteration of the α-methyl group only, yielding **180**-D, with the distribution of isotopic isomers being 0% d_0, 24% d_1, 52% d_2 and 24% d_3 [150]. In both experiments the recovered sulphoxides had the same stereochemistry as the starting sulphoxides, which resisted isomerization.

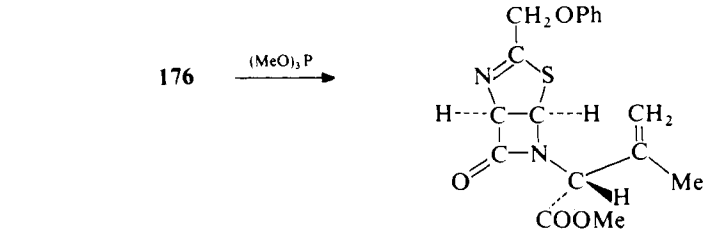
The deuterium exchange results have been interpreted as pointing to the existence of thermal equilibria (equation 82) between the sulphoxides **176** and the sulphenic acids **178** leading to the deuteration of the methyl group(s) of the sulphoxides **176**. The rearrangement in equation (82) is possible due to the overlap of symmetrical s electrons of the



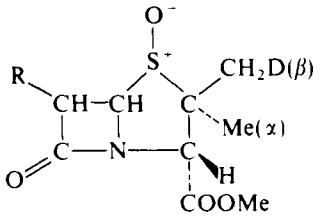
(**176**) (80)



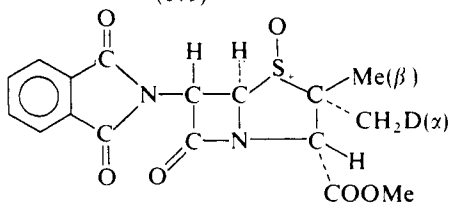
(**178**) (**177**)



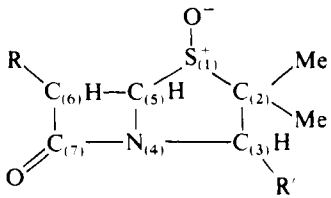
(81)



(176) – D



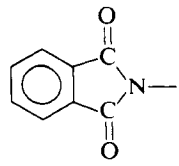
(180)- D



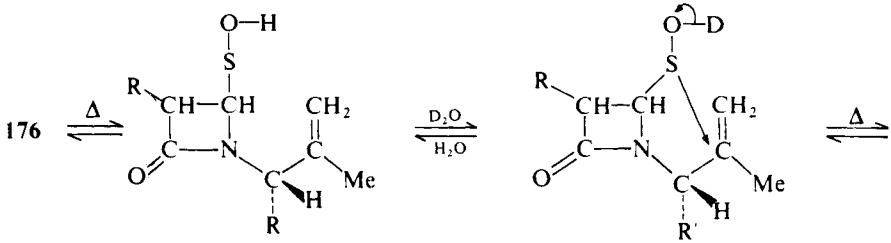
(181) R = $PhCH_2C(O)NH-$
R′ = $-COOCH_2CCl_3$

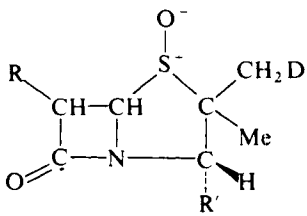
(176) R = $PhOCH_2C(O)-NH-$
R′ = – COOMe

(180)
R =



R′ = – COOMe





(176) – D

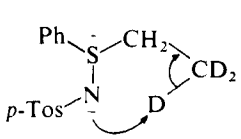
(82)

methyl hydrogens with the oxygen *p*-orbitals in the forward reaction and to the overlap of the π-orbitals of the carbon–carbon double bond with the deuterium atom in the reverse reaction leading to the deuteration of the methyl group *cis* to the sulphoxide. Owing to hydrogen bonding between the imido group in the side-chain R and the sulphenic acid group, the intermediate **178** has a restricted configuration and ring closure takes place on the face of the molecules **176**, **181**. In the case of **180**, the ring closure operates on the α side since in place of the –NH– group in the side-chain there is the strong electron-withdrawing phthalimido group which, by weakening the sulphur–$C_{(2)}$ bond, lowers the activation energy and accelerates the deuterium incorporation into the α-methyl group (α, due to steric effects).

Specific incorporation of one deuterium atom (60%) into the 2β-methyl group has also been found[151] when the (*R*)-sulphoxide **181** was heated in *t*-BuOD. This has been interpreted similarly by invoking the formation of intermediate **178**, which prefers to transfer its deuteron on the β face of the molecule in the recyclization step, with (*S*) sulphoxide formation[154].

B. Deuterium Tracer and Isotope Effect Study of the Decomposition of Ethyl(Phenyl)-*N*-*p*-tosyl sulphenamide (182)

Olefins are produced in 60–85% yield when N-sulphonylsulphilimines are heated at 100–130 °C during several hours under a stream of nitrogen[155]. Thus, **182** yielded ethylene and phenyl-*N*-*p*-tosyl sulphenamide **183**, which hydrolyses to *p*-tosylamide, thiophenol and diphenyl disulphide (equations 83 and 83a). The deuterium kinetic isotope effect, $(k_{H(s^{-1})}/k_{D(s^{-1})} = 1.05 \times 10^{-8}/0.356 \times 10^{-8}) = 3.034$, found in the first-order elimination reaction of **182** carried out at 80.3 °C in benzene (equation 83), indicated that the reaction proceeded according to a cyclic internal concerted mechanism represented by the transition state structure **183**. A ^{15}NMR study of the N–S bond of such compounds has been performed[155a, b].

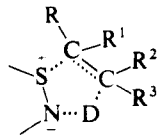


(182)

$$\longrightarrow \quad CH_2=CD_2 \quad + \quad PhS\overset{D}{\underset{|}{N}}Tos\text{-}p \qquad (83)$$

(183) 60% yield

$$\mathbf{183} \xrightarrow[-p\text{-}TosNH_2]{H_2O} [PhSOH] \longrightarrow PhSH + PhSSPh \qquad (83a)$$



(183)

C. Deuterium Study of the Thermal Rearrangement of Benzyl *p*-Toluenesulphenate to Benzyl *p*-Tolyl Sulphoxide

The thermal rearrangement (equation 84) of benzyl *p*-toluenesulphenate (**8**) to benzyl *p*-tolyl sulphoxide (**9**) taking place in benzene has been investigated in sealed tubes at

110–130 °C by observing the decrease in the methylene NMR signal of **8** (singlet at $\tau = 5.38$ in benzene) and the increase in the methylene signal of **9** (singlet at $\tau = 6.35$ in benzene). The reverse rearrangement 9→8 was found to be negligible during the period of measurements[22, 22a]. The first-order rate constants were $3.28 \pm 0.14 \times 10^{-5}\,s^{-1}$, 8.75 ±0.47 and 24.0±1.2 at 110, 120 and 130 °C, respectively, and gave the following activation parameters: $E_a = 30.5$ kcal mol^{-1}, $\log A = 12.9$, $\Delta H^{\neq} = 29.7$ kcal mol^{-1} and $\Delta S^{\neq} = -2$e.u.

$$\underset{\textbf{(8)}}{p\text{-TolSO}\overset{*}{\text{C}}\text{HDPh}} \rightleftharpoons \underset{\textbf{(9)}}{p\text{-Tol-}\overset{\overset{\text{O}}{\|}}{\text{S}}\text{-CHDPh}} \qquad (84)$$

Dissociation of **8** into a radical pair which either recombines to **8** or rearranges into **9** had to be rejected because the slightly negative entropy of activation suggests an intramolecular rearrangement, contrasting with the highly positive entropy of activation, $\Delta S^{\neq} = \pm 24.6$ e.u., found in the dissociation of **9** into the same radicals. The rearrangement of **8** and the racemization of **9** do not have a common radical pair or a common transition state. Rearrangement of **8** to **9** proceeds with predominant retention of configuration at carbon and does not induce asymmetry at the sulphur (base catalysed D/H exchange in benzyl methyl sulphoxide is also stereospecific [156]). In the case of benzyl *p*-tolyl sulphoxide the racemization proceeds through homolytic cleavage of the benzylic carbon–sulphur bond leading to racemization at both chiral centres simultaneously (equation 8a). This route is supported also by the value of the α-deuterium isotope effect of *ca* 5% per D atom observed [$k_H/k_D \approx 1.05 \pm 0.02$, where k_H and k_D are the rates with *p*-Tols(O)CH_2Ph and *p*-Tols(O)CHDPh, respectively], similar to the secondary deuterium isotope effect found in other homolytic bond dissociation reactions[157, 158]. The pyramidal inversion mechanism for the racemization of (**9**) is therefore rejected. A general suggestion has been made[22] that homolytic scission–recombination is the pathway of lowest energy when large, extremely stable resonance stabilized radicals are produced in the course of a decomposition and this may be also the main reason for fast racemization of **9**. However, such a radical pathway for the **8** to **9** rearrangement is energetically unfavourable and this involves a benzyl O→S shift of an intramolecular type. The decomposition side-products observed in reaction 84 arise probably from the subsequent decomposition of the sulphoxide **9**.

$$\underset{(R_C, R_S)}{p\text{-Tol-}\overset{\overset{\text{O}}{\|}}{\text{S}}\text{*-}\ \overset{*}{\text{C}}\text{HDPh}} \rightarrow \underset{\text{achiral}}{p\text{-TolSO}^{\cdot}} + \underset{\text{achiral}}{\text{PhCHD}} \rightarrow \underset{(R_C, R_S)}{p\text{-Tol-}\overset{\overset{\text{O}}{\|}}{\text{S}}\text{*-}\ \overset{*}{\text{C}}\text{HDPh}} \qquad (84a)$$

D. Deuterium Solvent Isotope Effect Study of the Thiolsulphinate (Sulphenic Anhydride)–Sulphinic Acid Reaction

Aryl thiolsulphinates (Ar = *p*-Tol) react with arylsulphinic acids in AcOH–H_2O–H_2SO_4 medium (equation 85) much faster than they undergo disproportionation to thiolsulphonate and disulphide[159] (equation 86). Reaction 85 is catalysed by alkyl sulphides, when it is first order in thiolsulphinate, first order in sulphide and zero order in sulphinic acid concentration. The constant k_s in the equation $k_{cat} = k_s(R_2S)$ varies

$$2\,ArSO_2H + PhS(=O)\text{-}SPh \longrightarrow 2\,ArS(=O)_2\text{-}SPh + H_2O \tag{85}$$

$$2\,ArS(=O)SAr \longrightarrow ArSSAr + ArS(=O)_2\text{-}SAr \tag{86}$$

tremendously with sulphide structure, being for instance 60,000-fold higher in tetrahydrothiophene than in thiodiacetic acid, $(HOOCH_2CH_2)S$. The negative value of the slope ($\rho^* = -2.0$) of the linear relation between k_s and $\Sigma\sigma$ for R in R_2S indicates that the electron density on the sulphide sulphur is significantly lower in the transition state than it is in the sulphide itself.

In the case of the benzyl sulphide catalysed reaction of *p*-tolyl *p*-toluenethiolsulphinate with *p*-toluenesulphinic acid in AcOD–0.56 M D_2O–0.10 M H_2SO_4, the solvent isotope effect is given by $k_s^{AcOH}/k_s^{AcOD} = 0.75$. In reaction 85 catalysed by sulphide, the nucleophile is converted in the rate-determining step to a sulphonium species (equations 87a–87e) and involves rate-determining nucleophilic attack of the sulphide on the sulphenyl sulphur (*not* the sulphinyl sulphur) of the sulphinyl-protonated form 87a of the thiol sulphinate. The ion $R_2\overset{+}{S}-SPh$, produced in the rate-determining step, reacts rapidly with sulphinic acid to yield thiolsulphonate. Sulphenic acid produced in reaction 87b yields the same product reacting according to equations 87d–87e.

$$PhS(=O)\text{-}SPh + H^+ \rightleftharpoons PH\overset{+}{S}(OH)\text{-}SPh \tag{87a}$$

$$R_2S + PhS\text{-}\overset{+}{S}(OH)Ph \xrightarrow[\text{determining}]{\text{rate}} R_2\overset{+}{S}\text{-}SPh + PhSOH \tag{87b}$$

$$R_2\overset{+}{S}\text{-}SPh + ArSO_2H \xrightarrow{\text{fast}} ArS(=O)_2\text{-}SPh + R_2S + H^+ \tag{87c}$$

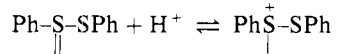
$$PhSOH + R_2S + H^+ \rightleftharpoons R_2\overset{+}{S}\text{-}SPh + H_2O \tag{87d}$$

$$PhSOH + ArSO_2H \longrightarrow ArS(=O)_2\text{-}SPh + H_2O \tag{87e}$$

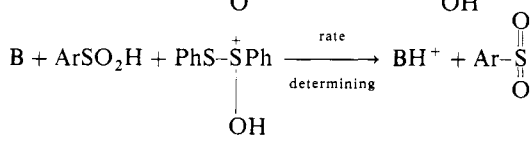
The value $k_{H_2O}/k_{D_2O} \approx 0.75$ in the benzyl sulphide catalysed reaction indicates that the rupture of the O–D bond does not take place in the rate-determining step, or that deuterium is slightly more covalently bound in the transition state. The catalysed rate of reaction 85 is probably slightly faster in the D_2O/AcOD mixture since deuterium, being closer to oxygen in $PhS(OD)\overset{+}{S}Ph$, stabilizes this cation better than hydrogen in the $PhS(OH)\overset{+}{S}Ph$ cation, so that the concentration of the $PhS(OD)\overset{+}{S}Ph$ species is larger.

$ArSO_2D$ is not involved in the rate-determining step of the sulphide-catalysed reaction. The equilibrium with D^+ in equation 87a is shifted more to the right than with H^+. The positive solvent isotope effect, $k_{D_2O}/k_{H_2O} > 1$, suggests its thermodynamic nature.

The thiolsulphinate–sulphinic acid reaction 85 is first order in both thiolsulphinate and sulphinic acid, and the rate constant depends linearly on $C_{H_2SO_4}$. The reaction of *p*-Tol SO_2H with *p*-tolyl *p*-toluenethiolsulphinate in AcOD–0.56 M D_2O–0.1 M H_2SO_4 is slower than in the corresponding undeuterated solvent, $k^{AcOH}/k^{AcOD} = 1.274 = 0.0093/0.0073$. In summary, the mechanism is represented as follows:

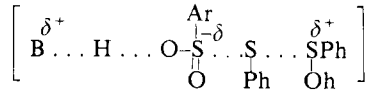


(87a)



(88)

In the transition-state structure **184**, proposed for reaction 88, the formation of the new S–S bond between the sulphinic acid and the sulphenyl sulphur is concerted with base-catalysed cleavage of the OH bond in the sulphinic acid. The breaking of the O–H bond should be slightly ahead of the formation of the SO_2–S bond. In the non-catalyzed reaction 85 with transition-state structure **184**, the value $k_{H_2O}/k_{D_2O} \cong 1.274$ can be interpreted within the same framework, since in the transition-state structure **184** the formation of the new SO_2–S bond is synchronized with the rupture of the D–OS bond in the course of the transfer of the hydrogen ion to base B. $ArSO_2D$ acid is involved in the formation of the transition-state structure **184**.

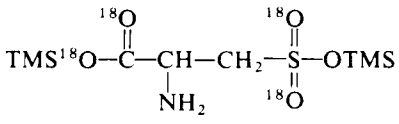


(**184**)

Finally, one should point out that further kinetic sulphur isotope effect studies of S–S bond ruptures and S–S bond formations are needed to serve as the ultimate test of the validity of equations 87 and 88, of the proposed transition states and of other suggestions concerning the not yet fully understood reactions of sulphenic acids, which appear as the highly reactive intermediates in the above schemes.

E. ^{18}O Studies of the Cyclic Carboxylic Sulphenic Acid Anhydride Intermediate in the Oxidation of Cystine to Cysteic Acid by Bromine

Mass spectrometric investigation[160] of the bis-trimethylsilyl derivative **185** of ^{18}O-labelled cysteic acid **186** (obtained by bromine oxidation of L-cystine **187** in $H_2{}^{18}O$ and mass spectrometric investigation of the dimethyl ester **188** of the ^{18}O-labelled cysteic acid (with ^{18}O removed from the carboxylic acid group) showed that **186** contains two ^{18}O atoms in the carboxylic acid group and two ^{18}O atoms in the sulphonate group. This result needed the postulate that the single ^{16}O atom in cysteic acid originates from a cyclic mixed carboxylic–sulphenic anhydride intermediate **189** formed during the oxidation (equation 89), and a cyclic mixed anhydride of sulphonic acid **190** which, upon hydrolysis, yields the final product **186**.



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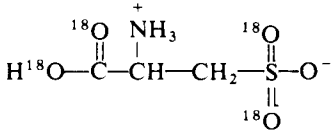
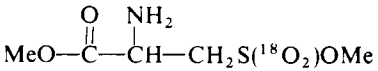


(186)



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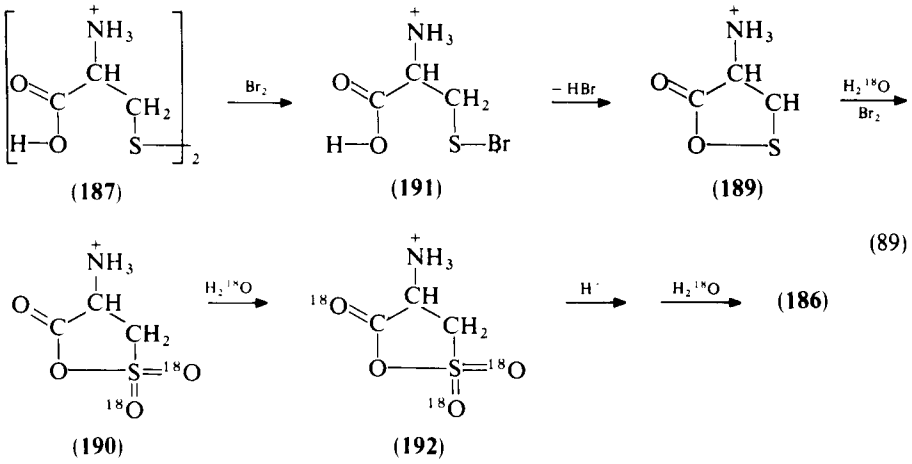
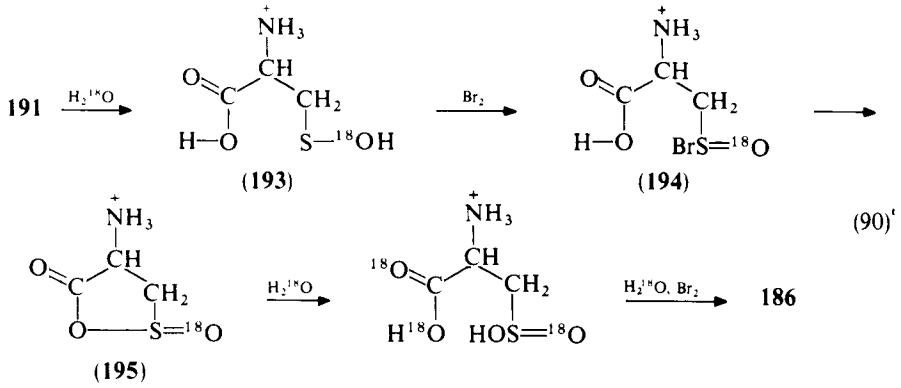


(187) (191) (189)

(89)

(190) (192) (186)

A second route (equation 90), involving formation of a sulphenic acid **193**, its oxidation by bromine to sulphinyl bromide **194** and formation of the cyclic structure **195** which, upon hydrolysis with $H_2{}^{18}O$ and subsequent oxidation by bromine, yields product **186** seems less probable, since the oxidation of cystine to cysteic acid by bromine is



(193) (194)

(90)

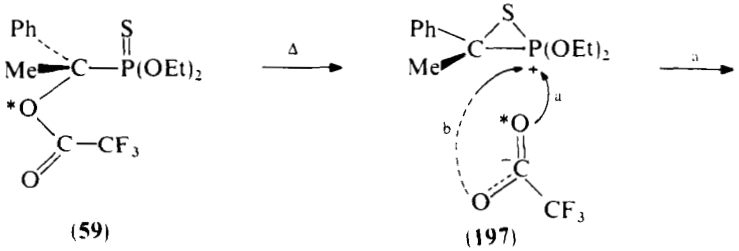
(195)

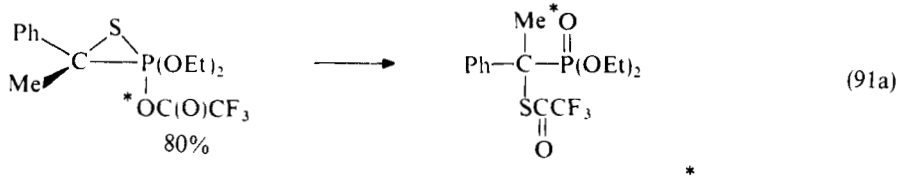
instantaneous and the rate of cyclization of **191** to a five-membered ring proceeds faster than its hydrolysis.

The existence of the mixed carboxylic–sulphinic anhydrides has been questioned by Kasperek[161]. Exchange of ^{18}O of water with carboxylic acid oxygens is expected to occur more probably with anhydrides than with open structures, due to the increased rate of ^{18}O exchange in the former[162]. Sulphates do not exchange their oxygens with water[163] and the synthesized ^{18}O-labelled cysteic acid **186** is of potential use to trace biosynthetic pathways leading to the production of naturally occurring sulphonic acids.

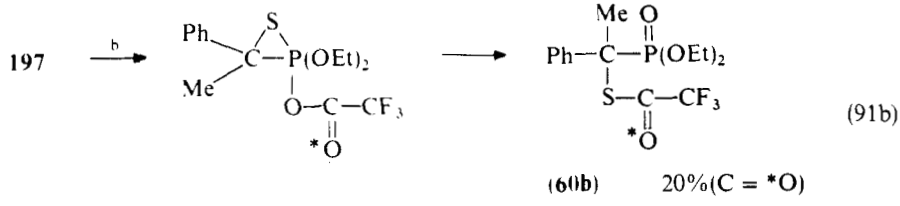
F. ^{17}O and ^{18}O Study of the Mechanism of the Rearrangement of α-Thiophosphoryl Trifluoroacetate

The position of oxygen-17 in the rearrangement of **59**-^{17}O into **60**-^{17}O was determined directly by ^{17}O NMR spectroscopy. The acetolysis of **59**-^{18}O was followed by ^{31}P NMR[42]. It has been found that 80% of the label locates in the phosphoryl group and 20% incorporates into the carbonyl group. These findings and complementary studies of **59**-^{18}O acetolysis in the presence of unlabelled thiol (**196**), PhC(Me) (SH) P(O) $(OEt)_2$ (which did not give incorporation into **60**), ruled out a concerted mechanism for the formation of the intermediate **197**, which predicts a complete incorporation of $\overset{*}{O}$ into the carbonyl group, and suggested this ion-pair (**197**) Δ mechanism as the most probable one (equation 91)[42, 164].





(91a)



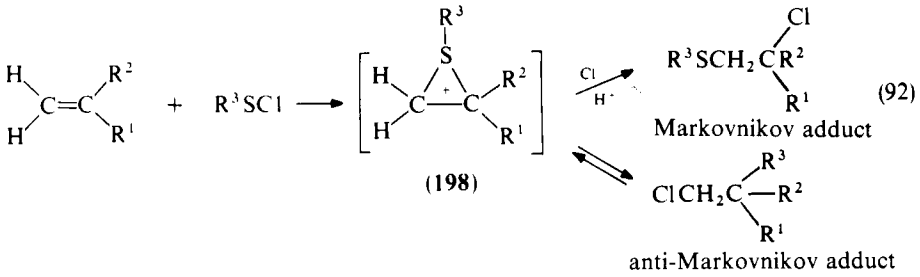
(91b)

The rearrangement of **197** into **60** is an intramolecular trifluoroacetyl group transfer process not involving the free thiol **196**. The trifluoroacetate oxygens are 'functionally' non-equivalent in the short-lived ion-pair intermediate, which does not attain the 'solvent separated' stage. The internal return of trifluoroacetate at phosphorus in route a is four times more probable than by route b, which requires rotation of the carboxylate group to bring the more distant unlabelled oxygen closer to the positive phosphorus[42, 164].

G. Deuterium and ^{14}C Tracer and Isotope Effect Studies of Sulphenyl Halide Additions to Olefins

1. General introduction

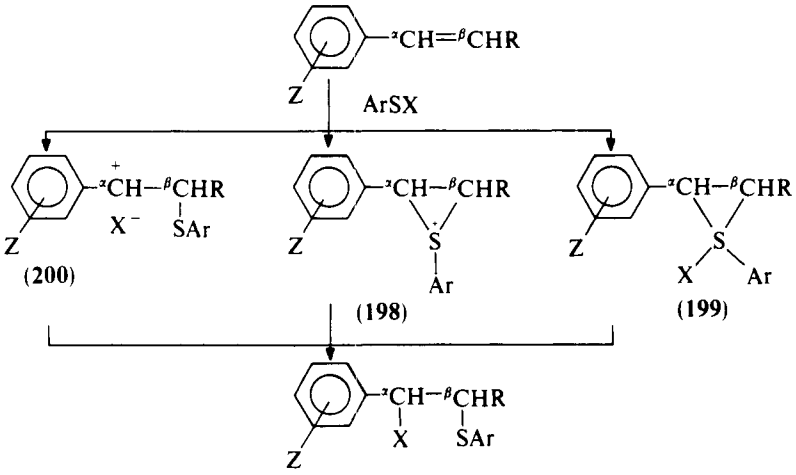
Earlier work concerning the electrophilic sulphenyl halide addition to olefins has been reviewed by Fahey[165], who outlined the general features of these reactions. The additions proceed according to Markovnikov's rule in the majority of reactions and the skeletal rearrangements are quite rare. The additions are first order in olefin and in the sulphenyl halide and their rates are faster in polar than in non-polar solvents. The electrophilic character of the additions has been established by obtaining negative ρ values. Besides the partial positive charge on C_α in the transition state, there is also a small positive charge on the sulphur in the activated complex of the rate-determining step[166a, 166b]. The mechanism (equation 92) probably involves an episulphonium bridged ion intermediate **198**.



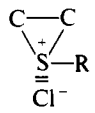
(92)

Crystalline thiiranium salts were isolated many years ago[167]. New, more refined reaction schemes have been proposed (equation 93)[182] to rationalize the accumulated new experimental data. Besides the polar bridged intermediate **198**, a second covalent σ-sulphurane intermediate **199** had to be invoked, as well as an open cation intermediate **200** to explain the non-stereospecific or preferential *cis* additions.

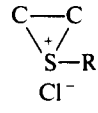
The scheme in equation 92 implies that halosulphides are formed by encounter of the negative Cl^- anion with the positive episulphonium ion in the second fast reaction step. Rates of reactions between charged species in solutions can be altered by changing the ionic force of the medium. These non-specific ionic interactions are sometimes overshadowed by specific 'complexing' interactions between the added electrolyte and the reacting ionic species, and the simple electrostatic theories do not predict correctly the rates at large concentrations of reacting ions. The positive salt effect in the addition of dinitrobenzenesulphenyl chloride (2,4-DNBSC) to styrene, caused by addition of LiCl and $NaClO_4$ to AcOH, was explained by electrostatic attractions of chlorine by Li^+ and Na^+ ions which facilitate the rupture of the sulphur-chlorine bond in the transition state[168]. The influence of $LiClO_4$ on the course of the addition of sulphenyl chlorides to olefins in AcOH[7] showed that products obtained in the presence of $LiClO_4$ differ from



(93)



(202) solvent separated ion pair

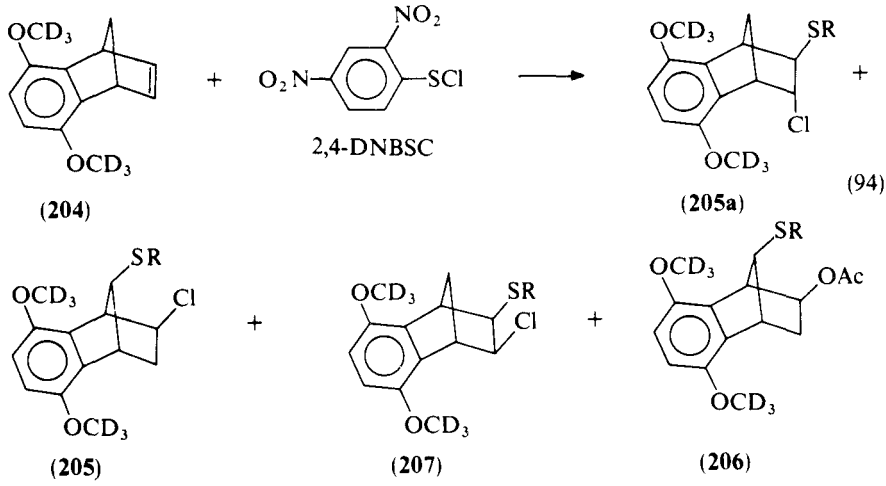


(203) tight ion pair

those obtained in the absence of inorganic salts. This evidence for the existence of charged polarized species in the reactions of sulphenyl halides with alkenes prompted the above authors[7] to admit that besides the free chlorine anions separated from the episulphonium ion **198**, and besides structure **199**, there are also 'tight ion pairs' (**203**) and 'solvent separated ion pairs' (**202**), which participate in the fast step leading to products. Addition of lithium perchlorate to the medium weakens the interactions between the chlorine anion and the cationic centre, and the probability of diffusion of free Cl^-, solvated Cl^- or a Li^+–Cl^- pair away from the reaction centre increases. The concentration of Cl^- near the reaction centre decreases also by the exchange of Cl^- anions with perchlorate anions. These processes increase the probability of reaction of acetate anions with the cationic organic centre and the production of acetoxy adducts in acetic acid medium. In a nitrile medium, thio amides are also produced from olefins[169].

2. *Addition of sulphenyl chlorides to deuterated olefins*

a. Addition of sulphenyl chlorides to dimethoxybenzonorbornadiene. The course of addition of sulphenyl chlorides, *o*-$NO_2C_6H_4SCl$ and 2,4$(NO_2)_2C_6H_3SCl$ (DNBSC), to dimethoxybenzonorbornadiene in AcOH[170] has been followed using the deuterated olefin **204**[171] to avoid the overlap of some ^1H NMR signals. Addition of 2,4-DNBSC to **204** in acetic acid (equation 94) gave the rearranged chloride **205** as the predominant product of reaction. In the presence of $LiClO_4$ the formation of the rearranged acetate **206** takes place mainly. 2,4-DNBSC and *o*-$NO_2C_6H_4SCl$ gave the same product distribution.



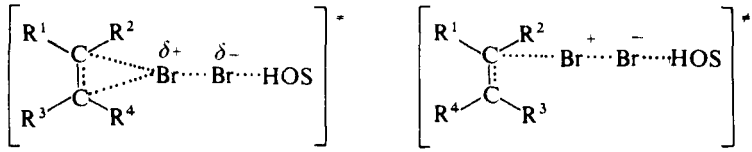
R = 2,4-DNBSC

Solvent CCl_4; **205a** (33%), **205** (15%), **207** (17%)
CH_3COOH: **205a** (5%), **205** (36%), **206** (9%)
$ArSCl/LiClO_4$:, **205** (26%), **206** (47%)
1:2

The observed effects have been used as 'unambiguous evidence' of the intermediacy of the ion pairs **202–203**, located between the extreme structures **198** and **199** in the reactions (equation 94). The transition state is characterized by a relatively large positive charge on the carbon atom, which leads to the rearranged norbornadiene product, and by the lack of complete dissociation of the sulphur–chloride bond as judged by the formation of rearranged chlorides.

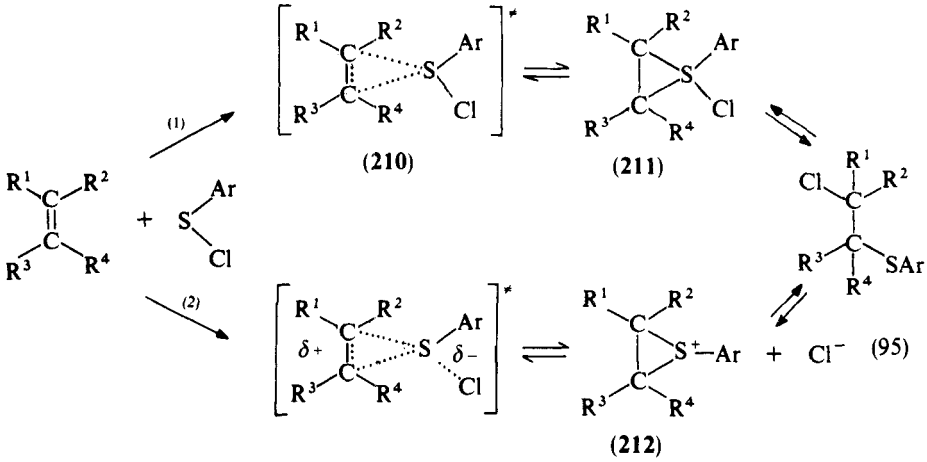
b. Deuterium kinetic solvent isotope effects in the additions of 4-chlorobenzenesulphenyl chloride to alkenes and alkynes. Deuterium kinetic solvent isotope effect (KSIE) investigation[172] of bromine and 4-chlorobenzenesulphenyl chloride addition reactions to alkenes and alkynes has been undertaken to obtain information about the role of the solvent in the rate-determining step of the reactions of non-polar or weakly polar reactants passing to products through a highly polar transition state. The solvation of non-polar substrates in these transformations can be neglected and the effect of solvent upon rates and isotope effects is entirely due to solvation of the transition state. The deuterium KSIE found in the bromination of pentene-1, *cis*-hexene-3, styrene pentyne-1, hexyne-3 and phenylacetylene was positive and almost identical ($k_H/k_D = 1.23 \pm 0.02$) for bromine additions to all compounds studied and in relatively good agreement with earlier, less precise data ($k_H/k_D = 1.40 \pm 0.2$) for the bromination of pentene-1 in CH_3OH/CH_3OD[173]. These KSIE of deuterium have been used as a strong indication of hydrogen bond formation (specific electrophilic solvation) between the solvent, HOS, and the leaving negative bromide anion, Br^-, in the rate-determining transition state (structures **208** and **209**).

Nucleophilic solvent participation, i.e. increase of the rate in aqueous EtOH relative to AcOH solvent, was found only in the case of bromination of alkylacetylenes. No correlation was found between nucleophilic solvent assistance in bromination of alkenes and alkynes and the $(k_H/k_D)_{KSIE}$ ratios.



(208) (209)

Deuterium kinetic solvent isotope effects, k_H/k_D, in the additions of 4-chlorobenzenesulphenyl chloride to alkenes and alkynes, in AcOH and AcOD and obeying normal second-order kinetics, depend on the structure of the unsaturated substrate and vary in the range 1.00–1.28 ($k_{H_{AcOH}}/k_{D_{AcOD}} = 1.16 \pm 0.01$ for pentene-1, 1.02 ± 0.01 for *cis*-hexene-3, 1.20 ± 0.01 for styrene, 1.25 ± 0.02 for pentyne-1, 1.00 ± 0.1 for hexyne-3 and 1.28 ± 0.01 for phenylacetylene). These variations of KSIE have been explained qualitatively by assuming that the reaction proceeds through two routes (equation 95). In the first route a non-ionized tetravalent sulphur intermediate **211** is formed, while in the second route an ionized thiiranium ion **212** (preceded by a transition state whose polarity depends on the structure of the given unsaturated compound) is developed. Small (or no) KSIE are found for rate-determining transition states in which the S–Cl bond is not significantly broken; larger KSIE are observed when the S–Cl bond is substantially polarized and broken in the transition state, as in the case of brominations.

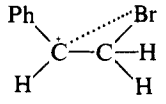


(210) (211) (212) (95)

Large and nearly constant KSIE, $k_H/k_D \cong 1.23$, for alkenes and alkynes are governed by electrophilic solvations with rather negligible nucleophilic solvation contributions. Solvent deuterium kinetic isotope effect determinations alone are insufficient to assess the relative contributions of the paths (1) and (2) in equation 95 to the overall reaction.

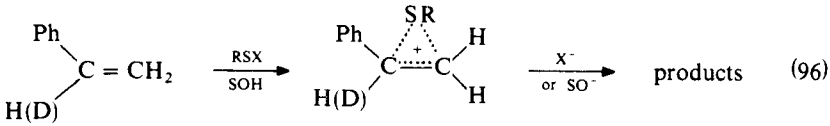
c. Secondary deuterium isotope effects in 2,4-dinitrobenzenesulphenyl halide additions to styrenes and trans 1-phenylpropene. Secondary deuterium isotope effects frequently used to study the reaction mechanisms and the structures of transition states[173–175] have also been utilized to elucidate the reaction path of polar electrophilic additions to olefins. Inverse isotope effects were found in additions of electrophilic bromine ($k_H/k_D = 0.91$) and of 2,4-dinitrobenzenesulphenyl chloride ($k_H/k_D = 0.87$) to *trans*-stilbene-d_2[176,177]. The

detailed comparative study of the mechanism of addition of chlorine, bromine and 2,4-dinitrobenzenesulphenyl halides as electrophiles to *trans*-1-phenylpropene, *p*-bromo-, *p*-chloro- and *p*-nitrostyrene by examining α-deuterium isotope effects has also been carried out[178]. Very small isotope effects, $k_H/k_D = 0.97–1.00$, have been found in nearly all bromine and chlorine additions to *p*-substituted styrenes, with the exception of *p*-nitrostyrene when k_H/k_D values were 0.96 ± 0.01 and 0.95 ± 0.01. This means that in all the above electrophilic additions, the deuterium labelled α-carbon retains its sp^2 hybridization in the transition state (sp^2 π bond changes to sp^2 carbenium ion). There are no force constant changes at the α-carbon. Only when *p*-nitro ($\sigma^+ = 0.78$) is the substituent does a small departure from sp^2 hybridization occur in the transition state **213**. The highly asymmetrical structure of the open carbonium ion **213** is also supported by the unique 1-acetoxy adduct formation in small yields and following the stereochemistry of chlorine additions[178].



(213)

Secondary α-deuterium kinetic isotope effects for polar electrophilic additions of 2,4-DNBS chloride and bromide to styrene, *p*-chloro-, *p*-bromo-, *p*-nitro-styrene and *trans*-1-phenylpropene were found to be 0.95 ± 0.01 and 0.94 ± 0.01, 0.95 and 0.95, 0.95 and 0.95, 0.97 and 0.96, 0.94 and 0.96, respectively. The k_H/k_D values are thus insensitive to substituent. Both DNBS chloride and bromide additions have, within experimental error, the same isotope effect in all investigated reactions. The magnitude of k_H/k_D values in sulphenyl halide additions and the insensitivity indicate that they are determined mainly by the sulphur atom and by the nearly symmetrical structure of the transition state in which the α-carbon considerably lost its sp^2 character and approaches the sp^3 character found in the sulphonium ion **214** bridged by the electrophile and thus stabilized. Partial formation of the new bonds at the α-carbon (significant bridging) results in the larger inverse deuterium effect (0.85). The k_H/k_D values, equal to 1–0.98, indicate that in the bromine and chlorine additions to styrene only weak bridging, if any, is taking place and there are no bonding changes at the deuterium-labelled carbon. It is suggested that in a less nucleophilic solvent the decreased solvation of the transition state might lead to more bridging and, consequently, to smaller values of k_H/k_D than found in this study.



(96)

(214)

3. The relations between carbon-14 kinetic isotope effects and mechanisms of addition of 2,4-DNBSC to substituted styrenes-1-^{14}C and -2-^{14}C

a. ^{14}C isotope effect addition studies in anhydrous acetic acid. Information on charge distributions and the structures of transition states in the additions of sulphenyl chlorides to alkenes is derived mainly from product distribution, stereochemistry and the effect of substituents on the rate of additions. Kinetic isotope effect studies permit one to test

hypotheses on transition states and to formulate correct concepts of reactivity. Deuterium kinetic solvent isotope effect studies give information about the degree of polarity of the transition state. Secondary α-deuterium kinetic isotope effect studies distinguish between carbenium ions and bridged episulphonium ions. Carbon-14 labelling of styrene at the α and β positions should also provide information about the structures of transition states. However, ^{14}C kinetic isotope effects in sulphenyl additions to styrene involve both bond-rupture and bond-formation processes, which depend on the substituents in different manners, and precise experimental determinations of ^{14}C KIE are needed.

The ^{14}C labelled styrenes used in this section have been obtained according to reaction schemes 97a and 97b[179-182]. $^{14}C_{\alpha}$ and $^{14}C_{\beta}$ carbon isotope effect studies[179-182] and kinetic data presented in Table 5 provide strong support to the suggestions concerning the structures of transition states postulated in double-bond addition reactions and even explain some previously rejected experimental data. The Hammett plot (log k/k_H vs σ^+) for all substituents is curved, but this may be interpreted as the result of superposition of two linear plots, the first with a large slope ($\rho = -4.62$ characteristic for bromination) which includes points corresponding to *p*-MeO and *p*-Me, and the second with a smaller slope ($\rho = -1.82$) fitting the *p*-Me, H, *p*-Cl and *m*-NO_2 points. The curved Hammett plot points to a change in mechanism and in the structure of the transition state from an open

$$\mathrm{Me^{14}COONa + MeCOCl \longrightarrow Me^{14}COCl + MeCOONa}$$

$$\mathrm{ZC_6H_5 + Me^{14}COCl \xrightarrow{AlCl_3} ZC_6H_4{}^{14}COMe \xrightarrow{LiAlH_4} ZC_6H_4{}^{14}CH(OH)Me}$$

$$\xrightarrow{SOCl_2} \mathrm{ZC_6H_4{}^{14}CHClMe} \xrightarrow[t\text{-BuOH, DMSO}]{t\text{-BuOK}} \mathrm{ZC_6H_4{}^{14}CH{=}CH_2} \qquad (97a)$$

$$\mathrm{{}^{14}CH_3COONa + CH_3COCl \longrightarrow {}^{14}CH_3COCl + MeCOONa}$$

$$\mathrm{ZC_6H_5 + {}^{14}CH_3COCl \xrightarrow{AlCl_3} ZC_6H_4CO{}^{14}CH_3 \xrightarrow{LiAlH_4}}$$

$$\mathrm{ZC_6H_4{-}CH(OH){}^{14}CH_3} \xrightarrow[t\text{-BuOH, DMSO}]{t\text{-BuOK}} \mathrm{ZC_6H_4CH{=}{}^{14}CH_2} \qquad (97b)$$

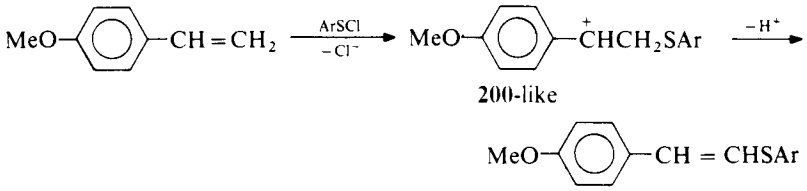
TABLE 5. Rate constants and carbon-14 kinetic isotope effects for the reaction of 2,4-dinitrobenzenesulphenyl chloride with various α- and β-labelled styrenes, carried out in anhydrous AcOH at 30.1 °C.

Substituent in styrene	$k(M^{-1}s^{-1})$	$(^{12}k/^{14}k_{\alpha})_{av}$	$(^{12}k/^{14}k_{\beta})_{av}$
p-MeO	0.31[a]		
p-Me	2.09×10^{-3}	1.004 ± 0.003	1.037 ± 0.004
H	7.11×10^{-4}	1.022 ± 0.004	1.032 ± 0.003
p-Cl	2.31×10^{-4}	1.027 ± 0.004	1.035 ± 0.004
m-NO_2	3.01×10^{-5}	—	—
p-NO_2	1.7×10^{-5}[b]	—	—

[a] Minimum value: the reaction is too fast for reliable measurements.

[b] Extrapolated from data at other temperatures.

carbonium ion-like transition state **200** with large positive charges at C_α for styrenes containing electron-donating groups (EDG), to bridged transition states **198** or **199** when there is less positive charge at C_α (smaller responsivness to EDG). The above considerations are supported by the $^{12}k_\alpha/^{14}k_\alpha$ ratios. The kinetic carbon-14 isotope effect is very small in the addition of 2,4-DNBSC to *p*-methylstyrene-1-^{14}C where the electron-donating *p*-Me stabilizes the large positive charge at C_α in a **200**-like structure. On the other hand, $^{12}k_\alpha/^{14}k_\alpha$ values of 1.022 and 1.027 are found for unsubstituted and *p*-Cl substituted styrenes, which have a partly bridged unsymmetrical transition state. The formation of **200** in the reaction of the *p*-MeO compound is also supported by the formation of the vinyl sulphide, obtained from the open carbenium ion by loss of an adjacent proton (equation 98). (The HCl produced is stabilized by complexing with the ether linkage, which prevents its reversible addition to the double bond.)



(98)

The ^{14}C isotope effects are larger for the β carbon than for the α carbon and do not change with substituents. They might be considered as characteristic for the conversion of a double bond to a single bond with simultaneous formation of the new C–S bond. Carbon kinetic isotope effects associated with breaking of the C–C bond are larger than the carbon isotope effects accompanying carbon–heteroatom bond rupture. Carbon and sulphur isotope effects in C–S and C=S bond formations and ruptures will be very helpful in further considerations. We must assume rather small but not negligible force constants for the new C–S bond developing in the bent transition state, since the $^{12}k/^{14}k_\beta$ values of 1.032–1.037 are smaller than KIE characteristic for single ^{14}C–^{12}C bond rupture.

The new C–S bond formed in a bent (or triangular) transition state does not balance completely the one breaking bond in the process of transformation of the C=C double bond into a single C–C bond. The lack of correlation between ring substituents and the $^{12}k/^{14}k_\beta$ values is rather obvious: There is no direct interaction of C_β with the aromatic ring as there is in the case of C_α which is connected to the ring. In the absence of special bonding interactions between the α carbon and the benzene ring the differences between the $^{12}k/^{14}k_\alpha$ and $^{12}k/^{14}k_\beta$ values should be governed mainly by the differences between the 'effective masses' of the C_α and C_β carbons. (Two vibrating hydrogen atoms are attached to the β carbon, one hydrogen atom and the benzene ring are attached to the α carbon. The secondary vibrational contributions to the KIE might cancel in going from the initial to the transition state for both the α and β carbons.) Both the $^{14}C_\alpha$ and $^{14}C_\beta$ isotope effects should be more or less similar for a symmetrical bridged transition state, while in the case of an asymmetrical bridged or linear transition state the $^{14}C_\alpha$ effect should be larger than the $^{14}C_\beta$ effect, being largest in the case of an open carbenium ion like **200** with the positive charge located at C_α.

The experimental data (Table 5) show that the $^{14}C_\alpha$ kinetic isotope effect is strongly dependent on ring substituents and is the smallest for the *p*-Me case, which according to pure mechanistic considerations should result in the largest KIE. This contradiction may be resolved by assuming that in the transition state a new bond develops between the ring and the C_α which is the strongest one when the positively, charged C_α is stabilized by the strong EDG (i.e. the *p*-Me) group.

There are no other ^{14}C kinetic isotope effect data which could be used for comparison, and the above discussion is to a large extent of a speculative and qualitative nature.

We will supplement the above discussion by carrying out brief calculations on ^{14}C KIE using the general relation 99[183-185]

$$^{12}k/^{14}k = (\mathrm{TIF})(\mathrm{TDF}) \tag{99}$$

where the temperature-independent factor (TIF) represents the ratio of the 'effective' masses of the heavy and light transition complexes along the reaction coordinate, and the temperature-dependent factor (TDF) is given by expression 100. In the function $G(u_i)$, introduced by Bigeleisen and Mayer[183a], we have $u_i = h\nu_i/k_B T$ and $\Delta u_i = (u_{1i} - u_{2i})$, where the subscript 1 refers to the fundamental frequency of the molecule containing ^{12}C, and u_{2i} to the same labelled with ^{14}C.

$$\mathrm{TDF} = \left[1 + \sum_{i=1}^{3n-6} G(u_i)\Delta u_i - \sum_{i=1}^{3n-6} G(u_i^{\neq})\Delta u_i^{\neq} \right] \tag{100}$$

We assume in these preliminary calculations that TIF is practically equal to unity and the ^{14}C kinetic isotope effect is determined by TDF (equation 100). To calculate TDF we should know all normal vibrations in the normal and labelled styrene molecules and transition states. We also assume that in the first approximation the ^{14}C effect is determined by the isotopic carbon skeletal vibrations in styrene and by isotopic skeletal vibrations in the transition state composed of the aliphatic side-chain and of sulphur. These model calculations lack subtlety, since secondary deuterium isotope effects indicate some changes in the carbon–hydrogen bond character dependent on the reaction coordinate while the neglected H–^{14}C bond contributions to the $\Sigma G(u_i)\Delta u_i$ and $\Sigma G(u_i^{\neq})\Delta u_i^{\neq}$ terms might not cancel completely. Taking the values 1620 cm^{-1} for $\omega(^{12}C=^{12}C)$, 1561 cm^{-1} for $\omega(^{14}C=^{12}C)$ in styrene, $\omega(^{12}C-^{12}C) = 993\ cm^{-1}$ and $\omega(^{14}C-^{12}C) = 956.83\ cm^{-1}$ for the fully developed single C–C bond in the transition state, we obtain at 30.1 °C the temperature-dependent factor

$$[1 + G(u_i)\Delta u_i - G(u_i^{\neq})\Delta u_i^{\neq}] = [1 + 0.1036 - 0.0509] = 1.0527$$

which is larger than the $k_{^{12}C}/k_{^{14}C} = 1.032$–$1.037$ values experimentally found for $^{14}C_{\beta}$.

In the second extreme model calculation we assume that the sulphur is vibrationally coupled with C_{β} and the covalent carbon–sulphur bond is fully developed in the transition state. Taking $\omega = 700\ cm^{-1}$ for the (^{12}C–^{32}S) vibration and the isotopic shift $\Delta\omega = 37.4\ cm^{-1}$ for the $\omega_{(^{12}C-^{32}S)} - \omega_{(^{14}C-^{32}S)}$ difference, we obtain a second term, $G(u^{\neq})\Delta u^{\neq} = 0.0419$, which lowers the TDF to 1.0108. The results of the above two model calculations indicate that partial formation of a carbon–sulphur bond takes place in the transition state. $^{34}S/^{32}S$ and $^{35}S/^{32}S$ kinetic isotope effect studies of these additions should provide additional data concerning the degree of carbon–sulphur bonding in the transition state.

b. ^{14}C kinetic isotope effects in the additions of 2,4-DNBSC to substituted styrenes in the presence of lithium perchlorate. $^{14}C_{\alpha}$ and $^{14}C_{\beta}$ isotope effects have also been investigated in AcOH medium in the presence of varying amounts of lithium perchlorate[186-188], when considerable amounts of the acetates $ZC_6H_4{}^{z}CH(OAc)^{\beta}CH_2SAr$ (**215**), besides the chlorosulphides $ZC_6H_4{}^{z}CHCl^{\beta}CH_2SAr$ (**216**) were formed. For *p*-chlorostyrene the percentage acetate changed from 3 to 36 to 48 to 61 and to 63 when the $LiClO_4/ArSCl$ ratio changed from O to 2 to 4 to 6 and to 8, but it appeared that both reaction paths are

TABLE 6. $^{14}C_\alpha$ and $^{14}C_\beta$ kinetic isotope effects in the additions of 2,4-DNBSC to substituted styrenes as a function of $LiClO_4$ concentration in AcOH medium (accuracy of values ± 0.005)

Substituent in styrene	$LiClO_4$/ArSCl ratio	$(^{12}k/^{14}k)_\alpha$	$(^{12}k/^{14}k)_\beta$
Cl	0	1.026	1.038
	2	1.035	1.036
	4	1.039	1.034
	8	1.044	1.034
H	0	1.022	1.032
	2	1.027	
	4	1.038	
	8	1.038[a]	
		1.044[b]	
Me	0	1.002	1.037
	4	1.004[a, b]	

[a] Chlorosulphide formation.
[b] Acetate formation.

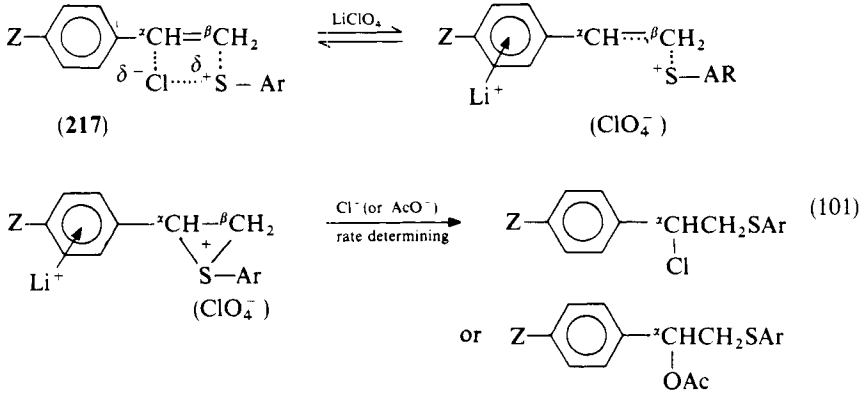
accompanied by almost identical $^{12}k_\alpha/^{14}k_\alpha$ and $^{12}k_\beta/^{14}k_\beta$ isotope effects. For instance, in the case of *p*-chlorostyrene, for a salt/ArSCl ratio of 4:1, $(^{12}k/^{14}k)_\beta$ is 1.034 for the acetate **215** and 1.036 for the normal chlorosulphide product **216**. The values of the isotope effects at different concentrations of lithium perchlorate are presented in Table 6. The $(^{12}k/^{14}k)_\beta$ values do not change with the salt concentration changes, while the $(^{12}k/^{14}k)_\alpha$ values increase in the case of *p*-chlorostyrene and styrene with increasing salt concentration, but there is practically no effect with *p*-methylstyrene, nor is it influenced by the addition of $LiClO_4$. These results indicate that $^{14}C_\alpha$ and $^{14}C_\beta$ kinetic isotope effects are decided in the common slow intermediate-forming step and do not depend on the nature of the nucleophile in the subsequent fast product-forming step. The $(^{12}k/^{14}k)_\alpha$ and $(^{12}k/^{14}k)_\beta$ ratios are practically the same both for acetate and for chloride formation. Independence of the $(^{12}k/^{14}k)_\beta$ ratio on the $LiClO_4$ concentration in the acetic acid solutions suggests that the bond changes at the β-C do not depend on the ionic situation in the medium, nor on the character of bonding changes at the α-C. The ^{14}C carbon isotope effect is governed only by the transformation of sp^2 to *partial* sp^3 hybridization at C_β with one partial C–S bond. The partial C–S bond formation and partial hybridization changes do not balance fully the process of transformation of the double $C_\alpha{=}C_\beta$ bond of styrene to the single bond of chlorosulphide or acetate which should result in at least 5–6% ^{14}C isotope effect at 30 °C.

The situation at the α-C is more complicated in the presence of lithium perchlorate. The negligible isotope effect, $^{12}k_\alpha/^{14}k_\alpha = 1.002 \pm 0.002$ (*p*-methylstyrene in pure AcOH), does not change in the presence of significant amounts of salt [$LiClO_4$/ArSCl = 4, $(^{12}k/^{14}k)_\alpha = 1.004 \pm 0.005$]. This means that the $^{14}C_\alpha$ isotope effect is governed by intramolecular effects in *p*-methylstyrene which do not depend on the ionic surrounding. The double bond rupture at C_α of styrene is completely balanced by the increased bonding of $\overset{+}{C}_\alpha$ with the benzene ring when the reaction proceeds by an open carbenium ion mechanism through intermediate **200**. The *p*-Me group stabilizes strongly the positive charge at $\overset{+}{C}_\alpha$ through EDG effects increasing the bond order of C_α with $C_{(1)}$ of the benzene ring. The positive charge at C_α is less stabilized by the unsubstituted and by the *p*-chloro substituted benzene ring. It is suggested that the addition proceeds in this case by a cyclic mechanism

through the intermediate **198**. The ratio $^{12}C_\alpha/^{14}C_\alpha$ increases from 1.022 to 1.044 with increasing salt/ArSCl ratio from 0 to 8.

The smaller $(^{12}C/^{14}C)_\alpha$ ratios compared to the $(^{12}C/^{14}C)_\beta$ ratios are caused by increasing C_α–$C_{(1)}$ bonding in the open transition state which balances partially the loss of one of the two bonds in C_α=C_β. Increase of the $^{12}C/^{14}C$ ratio with increasing $LiClO_4$ concentration implies that in the presence of salt the C_α is less bonded in the open **200**-like transition state than in the initial state. Interaction with the bulky ClO_4^- carrying a single negative charge cannot be responsible for changes of the mechanism of addition reaction. The small Li^+ carrying a positive charge may intervene by interacting with π electrons of the benzene ring and thus minimizing the interaction of the benzene ring with the positive charge at $\overset{+}{C}_\alpha$.

It is also possible that the transition state in the absence of $LiClO_4$ is represented by the four-centre model **217**, and the effect in the presence of the salt is caused by the benzene–Li^+ interactions mentioned above and also by interactions of Li^+ with chlorine associated with the α–C. The latter interaction may even change the transition state from **217**-like to being linear, but with less bonding at C_α–$C_{(1)}$ due to the interactions of Li^+ with the π electrons of benzene. As an alternative explanation of the increase in $^{14}C_\alpha$ KIE with increasing $LiClO_4$ concentration, a reversible formation of the cyclic intermediate (equation 101) followed by rate-determining ring opening by AcO^- or Cl^- leading to increased ^{14}C KIE has been invoked[187]. Again ^{34}S and ^{35}S kinetic isotope effect data would be extremely helpful in rationalizing the data. Supplementary studies of sulphenyl chloride additions to styrenes labelled at the $C_{(1)}$ ring atom, which would be sensitive to bonding changes between $C_{(1)}$ and ^2C, would be highly desirable. Earlier sulphur isotope effect studies are reviewed by Fry[190] and by Zieliński[12].



4. Concluding remarks

Hydrogen and especially heavy atom kinetic isotope effect studies[189–192] offer the opportunity to investigate the transition state chemistry of sulphenic acid derivatives. The experimental results reviewed in this chapter point to the complexity of the research problem and to the necessity of using a multiplicity of labelling techniques. Sulphur, oxygen and chlorine isotope effect studies should also be used in the process of resolving the mechanisms of sulphenic acid reactions, in order to test the numerous views and suggestions accumulated in the course of the very active studies with sulphenic acid derivatives. Further isotope effect studies will undoubtedly stimulate theoretical inquiries

aimed at the investigation of the motion of atoms in molecular complexes on the route to transition state structures in reactions involving sulphenic acid derivatives.

V. ACKNOWLEDGEMENTS

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **15**

Directing and activating effects of chalcogen substituents*

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*For definitions of various terms, symbols and abbreviations used in this chapter, see the Glossary (Appendix I).

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I. STRUCTURAL EFFECTS

A. Introduction

In this work we consider structural effects of substituents of the type –SZ in which sulfur is dicoordinate. For purposes of comparison we have also considered other dicoordinate chalcogen substituents, MZ, where M is O, Se or Te and other sulfur substituents with coordination numbers 3, 4 and 6.

In earlier volumes of this series we have remarked[1,2] that there are three methods available for the quantitative description of structural effects:

1. Quantum chemical calculations.
2. Molecular mechanics.
3. Correlation analysis (also known as linear free-energy relationships)[3–6].

Although quantum chemical calculations have the strongest theoretical basis, all of the methods are empirical. As correlation analysis is the easiest and the least expensive method, it is the only one we shall consider.

It is of the greatest importance to note at this point that the quantitative description of substituent effects given below is not only based on that in Reference 2 and often refers to it, but frequently quotes from it as well. The reasons for doing this are as follows:

1. The descriptions of electrical effects, steric effects and intermolecular forces given in Reference 2 represent *in our opinion* the state of the art. We have therefore reworded or modified them only when the changes resulted in a text which is clearer and easier to understand, or when new results could be incorporated.

2. We envisioned the present work as a continuation and extension of the methodology developed in Reference 2 to a very different type of substituent. It is impossible to carry out this extension without continual reference to the methodology used. Unless this material were made available directly to the reader of this volume it would be necessary to alternate almost continually between the new material reported here and the basis for its interpretation in Reference 2. As it is, we have repeatedly referred to tables and text in that work. To further do so would place an intolerable burden on the reader who, in turning back and forth from this work to that, might well feel as though he or she were attending a tennis match.

3. This approach makes the comparison of the electrical, steric and intermolecular force effects of chalcogen groups with those of doubly bonded groups much more facile. In

our opinion this improves the understanding of substituent effects for both types of group. It also furthers the readers' understanding of the application of the methods described.

4. The Glossary (Appendix I) of Reference 2 has also been included in this work in order to assist the reader with unfamiliar terms and parameter definitions. New definitions have been added where necessary. Our objective is again to make this as self-contained and easy to use as possible.

What is particularly new and novel in this work is not the methodology used but rather the parameter values which have been estimated for many chalcogen groups, especially those of Se and Te, and those which are sulfenic acid derivatives or analogs of them. Also new are the methods used to estimate them and the generalizations drawn from comparisons among them and with other types of groups.

Those sections which are largely based on Reference 2 and often quote from it are designated by the superscript 2 after the title of the section.

B. Structure–Property Quantitative Relationships (SPQR)[2]

1. The nature of SPQR

Those properties which do not involve a permanent change in bonding or intermolecular forces are physical properties. Some examples are IR, NMR, UV, visible and Mossbauer spectra, as well as molecular geometry which includes bond lengths, bond angles and dihedral angles, and dipole moment. Those properties which involve a difference between inter- or intramolecular forces in initial and final states are chemical properties. Examples are equilibrium constants for partition, hydrogen bonding, charge transfer complex formation and conformational equilibria; chromatographic quantities such as R_M, R_F, retention rates and capacity factors; and melting and boiling points. Those properties which involve the forming and/or breaking of chemical bonds are chemical reactivities. Those which involve biological substrates which range from pure enzymes to live multicellular organisms are bioactivities. It follows that structure–property quantitative relationships (SPQR) are of four kinds:

1. Quantitative structure–reactivity relationships (QSRR) which model chemical reactivities.
2. Quantitative structure–chemical property relationships (QSCR) which describe chemical properties.
3. Quantitative structure–physical property relationships (QSPR).
4. Quantitative structure–activity relationships (QSAR) which model bioactivities.

2. The function of SPQR

SPQR can be used to predict values of a property for some structural change. QSAR, for example, have been used to design medicinal drugs and pesticides. They are also employed in the prediction of toxicity and other environmental properties. SPQR can store experimental results in a convenient compact format. They are useful in the determination of reaction mechanism. Finally, they are vital to our understanding of how and why a change in structure results in a change in properties.

A substituent exerts three types of structural effects: electrical effects, steric effects and intermolecular force interactions. Electrical effects and in some cases steric effects as well can account for structural effects on most chemical reactivities in solution and on many chemical and physical properties. Gas-phase reactivities as well as physical and chemical properties generally require an additional polarizability term. All of the factors are usually needed to account for structural effects on bioactivity.

II. ELECTRICAL EFFECTS

A. Introduction[2]

The complete range of substituent effects can be represented by the triparametric equation[7]

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + h \quad (1)$$

where σ_{IX} is the localized (field and/or inductive) electrical effect parameter and is identical to the σ_I constant[8]; σ_{dX} is the intrinsic delocalized electrical effect parameter and characterizes the delocalized effect when the electronic demand in the system studied is zero; σ_{eX} describes the sensitivity of the substituent delocalized electrical effect to electronic demand; L, D and R are the coefficients of the electrical effect parameters σ_I, σ_d and σ_e, while h is the intercept of the line; Q_X is the experimental value of the quantity measured for the data set member bearing the X substituent.

Table 1 reports values of σ_I, σ_d and σ_e for MZ groups where Z is O, S, Se and Te. Values of these parameters are also given for tri- and tetracoordinate sulfur and selenium groups for purposes of comparison. The electronic demand is given by the ratio

$$\eta = R/D \quad (2)$$

TABLE 1. Values of σ_I, σ_d and σ_e[a]

Substituent	σ_I	σ_d	σ_d
	Chalcogen Substituents		
Oxa			
OH	0.35E	−0.57E	−0.044E
$OCCl_3$	0.47E	−0.33E	0.017E
OCF_3	0.51E	−0.30E	0.014
OCN	0.62E	−0.31E	0.014E
OMe	0.30	−0.55	−0.064
OC≡CH	0.44E	−0.41E	−0.046E
$OCH{=}CH_2$	0.35E	−0.49E	−0.085E
OAc	0.38	−0.24E	−0.005E
OEt	0.28	−0.55	−0.070
OCO_2Et	0.44E	−0.30E	0.001E
OPr	0.28	−0.55E	−0.067E
OPr-*i*	0.27	−0.55E	−0.067E
OBu	0.28	−0.55E	−0.067E
$OC_6H_4NO_2$-4	0.41E	−0.42E	−0.027E
OPh	0.40	−0.51	−0.083
OBz	0.43	−0.28	−0.025
OCH_2Ph	0.32E	−0.54E	−0.074E
ONH_2	0.38E	−0.80E	−0.17E
ONHMe	0.36E	−0.80E	−0.20E
$ONMe_2$	0.38E	−0.79E	−0.22E
ONHAc	0.43E	−0.59E	−0.089E
OOH	0.46E	−0.69E	−0.093E
OOMe	0.44E	−0.69E	−0.11E
OOAc	0.49E	−0.51E	−0.024E
OOPh	0.48E	−0.64E	−0.096E
OSH	0.43E	−0.62E	−0.10E
OSMe	0.44E	−0.60E	−0.11E
OSPh	0.45E	−0.58E	−0.12E

TABLE 1. (*continued*)

Substituent	σ_I	σ_d	σ_d
OSO_2Me	0.55	−0.23E	−0.065
OF	0.55E	−0.59E	−0.019E
OCl	0.52E	−0.50E	−0.021E
OBr	0.52E	−0.50E	−0.023E
OI	0.49E	−0.48E	−0.039E
Thia			
	Dicoordinate		
SH	0.27	−0.40E	−0.098E
$SCCl_3$	0.44E	−0.18E	−0.046E
SCF_3	0.45	−0.15E	−0.040E
SCN	0.56	−0.15E	−0.040E
SMe	0.30	−0.38	−0.13
SC≡CH	0.40E	−0.26E	−0.13E
$SCH{=}CH_2$	0.32E	−0.34E	−0.17E
SAc	0.39	−0.08E	−0.057E
SEt	0.26	−0.39E	−0.12E
SCO_2Et	0.44E	−0.15E	−0.063E
SPr-*i*	0.26	−0.23E	−0.12E
$SC_6H_4NO_2$-4	0.35	−0.27E	−0.09E
SPh	0.31	−0.34	−0.17
S-*c*-Hex	0.32	−0.39E	−0.13E
SBz	0.41E	−0.13E	−0.077E
SCH_2Ph	0.26	−0.39E	−0.14E
SNH_2[b]	0.35E	−0.64E	−0.23E
SNHMe[b]	0.33E	−0.65E	−0.26E
$SNMe_2$	0.35E	−0.63E	−0.28E
SNHAc[b]	0.40E	−0.44E	−0.15E
SOH[b]	0.43E	−0.54E	−0.16E
SOMe[b]	0.41E	−0.54E	−0.17E
SOAc[b]	0.44E	−0.35E	−0.087E
SOPh[b]	0.45E	−0.49E	−0.16E
SSH[b]	0.39E	−0.47E	−0.17E
SSMe[b]	0.41E	−0.45E	−0.17E
SSPh[b]	0.41E	−0.43E	−0.18E
SF[b]	0.52E	−0.44E	−0.082E
SCl[b]	0.49E	−0.35E	−0.085E
SBr[b]	0.49E	−0.35E	−0.086E
SI[b]	0.45E	−0.33E	−0.10E
	Tricoordinate		
SOMe	0.54E	−0.09	−0.10E
SOEt	0.54E	−0.09E	−0.082E
SOPh	0.51	−0.13E	−0.082E
	Tetracoordinate		
SO_2NH_2	0.44E	0.23E	−0.082E
SO_2CF_3	0.71	0.29	−0.056
SO_2Me	0.59	0.13	−0.052
SO_2Et	0.59	0.13E	−0.052E
SO_2Pr	0.57	0.13E	−0.052E
SO_2Pr-*i*	0.57	0.13E	−0.052E
SO_2Ph	0.56	0.08	−0.082

TABLE 1. (*continued*)

Substituent	σ_1	σ_d	σ_d
	Hexacoordinate		
SF_5	0.59	0.04E	−0.040E
Selena			
SeH	0.30E	−0.41E	−0.096E
$SeCCl_3$	0.44E	−0.18E	−0.044E
$SeCF_3$	0.45E	−0.16E	−0.038E
SeCN	0.56	−0.16E	−0.038E
SeMe	0.28E	−0.40E	−0.14E
SeC≡CH	0.40E	−0.27E	−0.11E
$SeCH{=}CH_2$	0.32E	−0.35E	−0.15E
SeAc	0.37E	−0.08E	−0.055E
SeEt	0.27E	−0.40E	−0.060E
$SeCO_2Et$	0.41E	−0.16E	−0.60E
SePh	0.26	−0.35E	−0.15E
SeBz	0.41E	−0.14E	−0.075E
$SeCH_2Ph$	0.28E	−0.39E	−0.14E
$SeNH_2$	0.35E	−0.65E	−0.23E
SeNHMe	0.33E	−0.66E	−0.26E
$SeNMe_2$	0.35E	−0.64E	−0.28E
SeNHAc	0.40E	−0.44E	−0.15E
SeOH	0.43E	−0.54E	−0.15E
SeOMe	0.41E	−0.55E	−0.17E
SeOAc	0.45E	−0.36E	−0.085E
SeOPh	0.45E	−0.50E	−0.16E
SeSH	0.39E	−0.47E	−0.16E
SeSMe	0.41E	−0.46E	−0.17E
SeSPh	0.41E	−0.43E	−0.18E
SeF	0.52E	−0.45E	−0.080E
SeCl	0.49E	−0.36E	−0.082E
SeBr	0.49E	−0.35E	−0.084E
SeI	0.45E	−0.33E	−0.10E
Tellura			
TeH	0.26E	−0.27E	−0.12E
$TeCCl_3$	0.42E	−0.12E	−0.072E
$TeCF_3$	0.44E	−0.095	−0.066E
TeCN	0.52E	−0.05E	−0.060E
TeMe	0.25E	−0.34E	−0.16E
TeC≡CH	0.39E	−0.20E	−0.13E
$TeCH{=}CH_2$	0.31E	−0.28E	−0.17E
TeAc	0.39E	−0.05E	−0.092E
TeEt	0.25E	−0.33E	−0.16E
$TeCO_2Et$	0.39E	−0.09E	−0.088E
TePh	0.31E	−0.30E	−0.18E
TeBz	0.39E	−0.07E	−0.10E
$TeCH_2$ Ph	0.27E	−0.33E	−0.16E
$TeNH_2$	0.33E	−0.58E	−0.26E
TeNHMe	0.32E	−0.59E	−0.28E
$TeNMe_2$	0.33E	−0.57E	−0.30E
TeNHAc	0.38E	−0.38E	−0.18E
TeOH	0.42E	−0.48E	−0.18E
TeOMe	0.39E	−0.48E	−0.19E

TABLE 1. (*continued*)

Substituent	σ_I	σ_d	σ_d
TeOAc	0.43E	−0.29E	−0.11E
TeOPh	0.44E	−0.43E	−0.18E
TeSH	0.38E	−0.41E	−0.19E
TeSMe	0.39E	−0.39E	−0.20E
TeSPh	0.40E	−0.36E	−0.21E
TeF	0.50E	−0.38E	−0.11E
TeCl	0.47E	−0.29E	−0.11E
TeBr	0.47E	−0.28E	−0.11E
TeI	0.44E	−0.27E	−0.13E
Other groups			
H	0	0	0
F	0.54	−0.48	0.041
Cl	0.47	−0.28	−0.011
Br	0.47	−0.27	−0.018
I	0.40	−0.20	−0.057
Me	−0.01	−0.14	−0.030
Et	−0.01	−0.12	−0.036
c-Pr	0.01	−0.17	−0.069
CF_3	0.40	0.13	−0.026
C≡CH	0.29	−0.02	−0.10
CH=CH_2	0.11	−0.08	−0.12
C_6F_5	0.31	0.08	−0.068
Ph	0.12	−0.12	−0.12
HCO	0.30E	0.27	−0.10
CO_2H	0.30	0.17	−0.051
Ac	0.30	0.25	−0.095
$CONH_2$	0.28	0.12	−0.055
CO_2Me	0.32	0.16	−0.070
CN	0.57	0.12	−0.055
NO_2	0.67	0.18	−0.077
$SiMe_3$	−0.11	−0.13	−0.046
NHAc	0.28	−0.35	−0.088
NHEt	0.17E	−0.66E	−0.15E
NMe_2	0.17E	−0.66	−0.24
PMe_2	0.10E	−0.50E	−0.27E
$POMe_2$	0.30	0.14	−0.036
$PO(OMe)_2$	0.36	0.24E	−0.033E

[a] Values labelled E are estimates, regarded as generally less reliable than unlabelled ones.
[b] Indicates substituents derived from sulfenic acid and its derivatives.

When η is held constant the LDR equation simplifies to the LD equation[8,9]

$$Q_X = L\sigma_{IX} + D\sigma_{DX} + h \tag{3}$$

The σ_D parameters are composite delocalized effect constants given by the equation

$$\sigma_{DX} = \eta\sigma_{eX} + \sigma_{dX} \tag{4}$$

Values of η for the common σ_D parameters are reported in Table 2 of Reference 2. If the approximate value of the electronic demand is known, then the data set can be correlated with the LD equation using σ_D values with the appropriate electronic demand.

An alternative diparametric relationship is the CR equation

$$Q_X = C\sigma_{ldX} + R\sigma_{eX} + h \tag{5}$$

where σ_{ld} is a composite parameter defined by the equation

$$\sigma_{ldX} = l\sigma_{lX} + d\sigma_{dX} \tag{6}$$

with a percent composition P_D that is given by

$$P_D = (d \cdot 100)/(l + d) \tag{7}$$

For any particular value of P_D the σ_{ldX} parameter can be written as

$$\sigma_{ldXk'} = \sigma_{lX} + [P_D/(100 - P_D)]\sigma_{dX} \tag{8}$$

The CR equation is useful for the determination of η in small data sets. Values of the σ_D and σ_{ld} parameters are reported in Table 4 of Reference 2. The CR equation was originally simply defined as an alternative diparametric relationship. It can however be derived from the LDR equation in the following manner. If P_D is equal to the constant k', we have from equation 8

$$\sigma_{ldX} = \sigma_{lX} + k'/(100 - k')\sigma_{dX} \tag{8a}$$

$$= \sigma_{lX} + k^*\sigma_{dX} \tag{8b}$$

where

$$k^* = k'/(100 - k') \tag{8c}$$

Substituting equation 8b in equation 5 gives

$$Q_X = C\sigma_{lX} + Ck^*\sigma_{dX} + R\sigma_{eX} + h \tag{8d}$$

which is equivalent to the LDR equation (equation 1) with $L = C$ and $D = Ck^*$.

If the electronic demand is held constant ($\eta = k$) the LDR equation becomes the diparametric LD equation, while if the composition P_D is held constant ($P_D = k'$) the LDR equation becomes the diparametric CR equation. If both η and P_D are held constant, the monoparametric Hammett equation is obtained:

$$Q_X = \rho\sigma_X + h \tag{9}$$

The composite Hammett σ_X is given by the relationship

$$\sigma_X = l\sigma_{lX} + d\sigma_{dX} + r\sigma_{eX} \tag{10}$$

where

$$\eta = r/d \tag{11}$$

Any monoparametric electrical-effect substituent constant has both the composition and the electronic demand fixed. The constant is therefore characterized by its values of P_D and η. We may write it as $\sigma_{k'/kX}$ where k' is the value of P_D and k that of η. Values of σ_D for which η is fixed are written as $\sigma_{Rk,X}$ while σ_{ld} values for which P_D is fixed have the form $\sigma_{ldk',X}$.

The $\sigma_{k'/kX}$ values are useful in describing the overall electrical effect of a group. They show its dependence on electrical-effect composition and electronic demand. They can be calculated from the relationship

$$\sigma_{k'/kX} = \sigma_{lX} + [P_D/(100 - P_D)](\sigma_{dX} + \eta\sigma_{eX}) \tag{12}$$

In the table for each group the horizontal rows show the variation of the electrical effect with change in substituent effect composition (P_D) at constant electronic demand (η). The

vertical columns show the variation of the group electrical effect with change in the electronic demand at constant substitution effect composition. Plotting the P_D and η values on the x and y Cartesian axes and the $\sigma_{k'}/_k$ values on the z axis generates a surface that characterizes the electrical effect of the substituent. Consider, for example, the $\sigma_{k'}/_{kX}$ constants for the vinyl group given in Table 5 of Reference 2. They show clearly that this group is an overall electron donor when P_D and η are large and that it is an overall electron acceptor when η is negative and/or P_D is small. By contrast, the table for the formyl group shows that it is an acceptor except for the very small region of η less than or equal to -4 and P_D greater than or equal to 70. Table 2 of this work reports $\sigma_{k'}/_k$ matrices for the SCF_3, SCN, SMe, SPh, SCl and SOH groups. It is convenient to characterize the overall effect of a group by the percent of the $\sigma_{k'}/_k$ values in the matrix which are acceptor, donor, or not significantly different from zero (P_{EA}, P_{ED} and P_0, respectively). These percents are given by the number of $\sigma_{k'}/_k$ values of each type multiplied by the factor 100/104, where 104 is the total number of values in the matrix.

TABLE 2. Values of $\sigma_{k'}/_k$ for some SX groups[a]

	SCF_3		σ_I, 0.45		σ_d, −0.15		σ_e, −0.04	
	10	20	30	40	50	60	70	80
−6	**0.46**	**0.47**	**0.49**	**0.51**	**0.54**	**0.59**	**0.66**	**0.81**
−5	**0.46**	**0.46**	**0.47**	**0.48**	**0.50**	**0.53**	**0.57**	**0.65**
−4	**0.45**	**0.45**	**0.45**	**0.46**	**0.46**	**0.47**	**0.47**	**0.49**
−3	**0.45**	**0.44**	**0.44**	**0.43**	**0.42**	**0.41**	**0.38**	**0.33**
−2	**0.44**	**0.43**	**0.42**	**0.40**	**0.38**	**0.35**	**0.29**	**0.17**
−1	**0.44**	**0.42**	**0.40**	**0.38**	**0.34**	**0.29**	**0.19**	0.01
0	**0.43**	**0.41**	**0.39**	**0.35**	**0.30**	**0.23**	**0.10**	−0.15
1	**0.43**	**0.40**	**0.37**	**0.32**	**0.26**	**0.17**	0.01	*−0.31*
2	**0.42**	**0.39**	**0.35**	**0.30**	**0.22**	**0.11**	−0.09	*−0.47*
3	**0.42**	**0.38**	**0.33**	**0.27**	**0.18**	0.05	*−0.18*	*−0.63*
4	**0.42**	**0.37**	**0.32**	**0.24**	**0.14**	−0.02	*−0.27*	*−0.79*
5	**0.41**	**0.36**	**0.30**	**0.22**	**0.10**	*−0.08*	*−0.38*	*−0.95*
6	**0.41**	**0.35**	**0.28**	**0.19**	**0.06**	*−0.14*	*−0.46*	*−1.11*

	SCN		σ_I, 0.56		σ_d, −0.15		σ_e, −0.04	
	10	20	30	40	50	60	70	80
−6	**0.57**	**0.58**	**0.60**	**0.62**	**0.65**	**0.70**	**0.77**	**0.92**
−5	**0.57**	**0.57**	**0.58**	**0.59**	**0.61**	**0.64**	**0.68**	**0.76**
−4	**0.56**	**0.56**	**0.56**	**0.57**	**0.57**	**0.58**	**0.58**	**0.60**
−3	**0.56**	**0.55**	**0.55**	**0.54**	**0.53**	**0.52**	**0.49**	**0.44**
−2	**0.55**	**0.54**	**0.53**	**0.51**	**0.49**	**0.46**	**0.40**	**0.28**
−1	**0.55**	**0.53**	**0.51**	**0.49**	**0.45**	**0.40**	**0.30**	**0.12**
0	**0.54**	**0.52**	**0.50**	**0.46**	**0.41**	**0.34**	**0.21**	−0.04
1	**0.54**	**0.51**	**0.48**	**0.43**	**0.37**	**0.28**	**0.12**	−0.20
2	**0.53**	**0.50**	**0.46**	**0.41**	**0.33**	**0.22**	0.02	*−0.36*
3	**0.53**	**0.49**	**0.44**	**0.38**	**0.29**	**0.16**	*−0.07*	*−0.52*
4	**0.53**	**0.48**	**0.43**	**0.35**	**0.25**	**0.10**	*−0.16*	*−0.68*
5	**0.52**	**0.47**	**0.41**	**0.33**	**0.21**	0.04	*−0.26*	*−0.84*
6	**0.52**	**0.46**	**0.39**	**0.30**	**0.17**	−0.03	*−0.35*	*−1.00*

(*continued*)

TABLE 2. (*continued*)

	MeS		σ_I, 0.30		σ_d, −0.38		σ_e, −0.13	
	10	20	30	40	50	60	70	80
−6	**0.34**	**0.40**	**0.47**	**0.57**	**0.70**	**0.90**	**1.23**	**1.90**
−5	**0.33**	**0.37**	**0.42**	**0.48**	**0.57**	**0.71**	**0.94**	**1.38**
−4	**0.32**	**0.34**	**0.36**	**0.39**	**0.44**	**0.51**	**0.63**	**0.86**
−3	**0.30**	**0.30**	**0.30**	**0.31**	**0.31**	**0.32**	**0.32**	**0.34**
−2	**0.29**	**0.27**	**0.25**	**0.22**	**0.18**	**0.12**	0.02	*0.18*
−1	**0.27**	**0.24**	**0.19**	**0.13**	0.05	*−0.08*	*−0.28*	*−0.70*
0	**0.26**	**0.21**	**0.14**	0.05	*−0.08*	*−0.27*	*−0.59*	*−1.22*
1	**0.24**	**0.17**	**0.08**	−0.04	*−0.21*	*−0.47*	*−0.89*	*−1.74*
2	**0.23**	**0.14**	0.03	*−0.13*	*−0.34*	*−0.66*	*−1.19*	*−2.26*
3	**0.21**	**0.11**	−0.03	*−0.21*	*−0.47*	*−0.86*	*−1.50*	*−2.78*
4	**0.20**	**0.08**	−0.09	*−0.30*	*−0.60*	*−1.05*	*−1.80*	*−3.30*
5	**0.19**	0.04	*−0.14*	*−0.39*	*−0.73*	*−1.25*	*−2.11*	*−3.82*
6	**0.17**	0.01	*−0.20*	*−0.47*	*−0.86*	*−1.44*	*−2.41*	*−4.34*

	SPh		σ_I, 0.31		σ_d, −0.34		σ_e, −0.17	
	10	20	30	40	50	60	70	80
−6	**0.39**	**0.48**	**0.60**	**0.76**	**0.99**	**1.33**	**1.90**	**3.03**
−5	**0.37**	**0.44**	**0.53**	**0.65**	**0.82**	**1.08**	**1.51**	**2.35**
−4	**0.35**	**0.40**	**0.45**	**0.54**	**0.65**	**0.82**	**1.10**	**1.67**
−3	**0.33**	**0.35**	**0.38**	**0.42**	**0.48**	**0.57**	**0.71**	**0.99**
−2	**0.31**	**0.31**	**0.31**	**0.31**	**0.31**	**0.31**	**0.31**	**0.31**
−1	**0.29**	**0.27**	**0.24**	**0.20**	**0.14**	**0.06**	*−0.09*	*−0.37*
0	**0.27**	**0.23**	**0.16**	**0.08**	−0.03	*−0.20*	*−0.48*	*−1.05*
1	**0.25**	**0.18**	**0.09**	−0.03	*−0.20*	*−0.46*	*−0.88*	*−1.73*
2	**0.23**	**0.14**	0.02	*−0.14*	*−0.37*	*−0.71*	*−1.28*	*−2.41*
3	**0.22**	**0.10**	−0.06	*−0.26*	*−0.54*	*−0.97*	*−1.67*	*−3.09*
4	**0.20**	**0.06**	−0.13	*−0.37*	*−0.71*	*−1.22*	*−2.07*	*−3.77*
5	**0.18**	0.01	*−0.20*	*−0.48*	*−0.88*	*−1.48*	*−2.47*	*−4.45*
6	**0.16**	−0.03	*−0.27*	*−0.60*	*−1.05*	*−1.73*	*−2.86*	*−5.13*

	SCl		σ_I, 0.49		σ_d, −0.35		σ_e, −0.085	
	10	20	30	40	50	60	70	80
−6	**0.51**	**0.53**	**0.56**	**0.60**	**0.65**	**0.73**	**0.86**	**1.13**
−5	**0.50**	**0.51**	**0.52**	**0.54**	**0.57**	**0.60**	**0.65**	**0.79**
−4	**0.49**	**0.49**	**0.49**	**0.48**	**0.48**	**0.48**	**0.47**	**0.45**
−3	**0.48**	**0.47**	**0.45**	**0.43**	**0.40**	**0.35**	**0.27**	**0.11**
−2	**0.47**	**0.45**	**0.41**	**0.37**	**0.31**	**0.22**	**0.07**	*−0.23*
−1	**0.46**	**0.42**	**0.38**	**0.31**	**0.23**	**0.09**	*−0.13*	*−0.57*
0	**0.45**	**0.40**	**0.34**	**0.26**	**0.14**	−0.04	*−0.33*	*−0.91*
1	**0.44**	**0.38**	**0.30**	**0.20**	**0.06**	*−0.16*	*−0.52*	*−1.25*
2	**0.43**	**0.36**	**0.27**	**0.14**	−0.03	*−0.29*	*−0.72*	*−1.59*
3	**0.42**	**0.34**	**0.23**	**0.09**	*−0.12*	*−0.42*	*−0.92*	*−1.93*
4	**0.41**	**0.32**	**0.19**	−0.03	*−0.20*	*−0.55*	*−1.12*	*−2.27*
5	**0.40**	**0.30**	**0.16**	−0.03	*−0.29*	*−0.67*	*−1.32*	*−2.61*
6	**0.39**	**0.28**	**0.12**	*−0.08*	*−0.37*	*−0.80*	*−1.52*	*−2.95*

TABLE 2. (*continued*)

	SOH		σ_i, 0.43		σ_d, −0.54		σ_e, −0.16	
	10	20	30	40	50	60	70	80
−6	**0.48**	**0.54**	**0.61**	**0.71**	**0.85**	**1.06**	**1.41**	**2.11**
−5	**0.46**	**0.50**	**0.54**	**0.60**	**0.69**	**0.82**	**1.04**	**1.47**
−4	**0.44**	**0.46**	**0.47**	**0.50**	**0.53**	**0.58**	**0.66**	**0.83**
−3	**0.42**	**0.42**	**0.40**	**0.39**	**0.37**	**0.34**	**0.29**	**0.19**
−2	**0.41**	**0.38**	**0.34**	**0.28**	**0.21**	**0.10**	*−0.08*	*−0.45*
−1	**0.39**	**0.34**	**0.27**	**0.18**	0.05	*−0.14*	*−0.46*	*−1.09*
0	**0.37**	**0.30**	**0.20**	**0.07**	*−0.11*	*−0.28*	*−0.83*	*−1.73*
1	**0.35**	**0.26**	**0.13**	−0.04	*−0.27*	*−0.62*	*−1.20*	*−2.37*
2	**0.33**	**0.22**	**0.06**	*−0.14*	*−0.43*	*−0.86*	*−1.58*	*−3.01*
3	**0.32**	**0.18**	−0.01	*−0.25*	*−0.59*	*−1.10*	*−1.95*	*−3.65*
4	**0.30**	**0.14**	*−0.08*	*−0.36*	*−0.75*	*−1.34*	*−2.32*	*−4.29*
5	**0.28**	**0.10**	*−0.14*	*−0.46*	*−0.91*	*−1.58*	*−2.70*	*−4.93*
6	**0.26**	**0.06**	*−0.21*	*−0.57*	*−1.07*	*−1.82*	*−3.23*	*−5.57*

Values of P_{EA}, P_0 and P_{ED}.

X	$CH{=}CH_2$	E–CH=CHMe	CHO	$CONH_2$	SCF_3
P_{EA}	53.8	39.4	91.3	92.3	82.7
P_0	10.6	17.3	2.9	1.9	3.8
P_{ED}	35.6	43.3	5.8	5.8	13.5
X	SCN	SMe	SPh	SCl	SOH
P_{EA}	86.5	53.8	58.7	69.2	57.7
P_0	3.8	7.7	4.8	3.8	2.9
P_{ED}	9.6	38.5	36.5	26.9	39.4

[a] Values in boldface indicates that the group behaves as an electron acceptor, values in italics indicate that it acts as an electron donor, values in ordinary typeface indicate that the group exerts no significant electrical effect.

The σ_m constants used for substituents in the *meta* position on a benzene ring have P_D values in the range 25 to 31. For the σ_p constants, P_D is usually in the range 45 to 55. Values of σ_m and σ_p, σ_p^0, σ_p^+ and σ_p^- are given in Table 6 of Reference 2.

B. The Dependence of the Electrical Effect on Electronic Demand[2]

Substituents are usually classified as electron donors or electron acceptors depending on their ability to stabilize an electron-poor or an electron-rich active site. A body of evidence now available shows, however, that some groups generally thought to be strong acceptors can, when directly bonded to cationic carbon, stabilize the positive charge[9] while other groups usually considered to be electron donors can stabilize anionic carbon. Such electron-acceptor groups include nitro, cyano, acetyl and carbomethoxy. Electron-donor groups of this type include phenyl, vinyl, ethynyl and acetylamino. Values of $\sigma_{Rk,X}$ and $\sigma_{50/k}$ for a number of groups that are reported in Table 7 of Reference 2 support this conclusion. Values of η used range from +6 to −6. We regard groups as overall electron

donors when $\sigma_{X,50/k} < -0.05$, and as electron acceptors when $\sigma_{X,50/k} > 0.05$. Groups for which the statement

$$-0.05 \leqq \sigma_{X,50/k} \leqq 0.05$$

holds are considered to have no significant electrical effects.

C. The Dependence of Electronic Demand Sensitivity on Substituent Type[2]

If the delocalized effect of every substituent had the same sensitivity to electronic demand, only two parameters would be required for the characterization of substituent electrical effects. We now know that this is not the case. The sensitivity to electronic demand depends at least in part on the mode of electron delocalization. Substituents can be classified into categories based on the type of molecular orbitals involved in delocalization. These categories are:

1. X_n groups. The first atom of the substituent (this is the atom bonded to the skeletal group) has a full nonbonding orbital. Examples are, Cl, F, OMe, NH_2, SMe.
2. X_π groups. The first atom of the substituent is involved in a π orbital. Examples are $CH{=}CH_2$, Ac, $-C{\equiv}CH$, $-C{\equiv}N$, Ph.
3. X_h groups. The delocalized electrons are in σ orbitals on the first atom of the substituent. Examples are Me, CF_3, CH_2Cl, $CHBr_2$. The delocalized effect in this case involves hyperconjugation.
4. X_e groups. An empty orbital on the first atom is involved in delocalization. The best known example is $SiMe_3$.
5. $X_{\pi(pd)}$. Groups in which the first atom of the group is involved in a pdπ bond. Examples are SOMe, SO_2CF_3, $PO(OEt)_2$.
6. $X_{n,\pi}$ groups. In these groups the first atom of the substituent involves both a full nonbonding orbital and a π orbital. Such groups include N=CPh, N=NPh, N=O and SOMe.

The range of σ_e observed for each of these types of substituent for which it is available is shown in Table 2. X_n groups have a very wide range of sensitivity to electronic demand. It is a function of the electronegativity of the first atom in the group[9], and of the number and type of fragments attached to it. X_n in this sense is an atom or group of atoms of the type MZ_n where n may have integer values of 0, 1, 2 or 3,

$$\sigma_e = a_M\chi_M + a_1 n_Z + a_0 \tag{13}$$

where χ_M is the Allred–Rochow electronegativity value of the atom M[11].

The X_π groups have a smaller range of substituent electronic demand than that observed for the X_n groups. The X_h groups exhibit an even smaller range. Apparently the order is

$$X_n > X_\pi > X_h \sim X_{\pi(pd)}$$

There are not enough groups of the X_e and $X_{n,\pi}$ types for which values of σ_e are available to permit any conclusions to be drawn.

D. Electrical Effect Substituent Constant Values for Chalcogen Groups.

Sulfenyl acids are characterized by the functional group SOH. Groups of the type SOR, where R is alkyl or aryl, may be thought of as sulfenyl esters, while those of the type SNR^1R^2, where R is H, alkyl or aryl, are considered to be sulfenyl amides. The SHal groups are sulfenyl halides, the acyl halides of sulfenic acids. SSR groups, where R is alkyl or aryl, are thioesters of sulfenic acids. Groups of the type $SOC(O)Z$ and $SOSO_2Z$, where Z is any substituent, are equivalent to mixed anhydrides and $SNHC(O)Z$ or $SNHSO_2Z$ are mixed imides. Very little experimental work is available on the measurement of

chemical reactivities or physical properties of compounds bearing these groups. Values of σ_I and σ_R^0 based on F^{19} chemical shifts have been reported for SCl, SOMe and $SNMe_2$[12]. The lack of experimental results for these substituents makes it necessary to estimate values of the electrical-effect constants. We have reported that relationships analogous to equation 13 can be used to calculate σ substituent constants for MZ_n groups. All types of groups may be included in the relationship for the calculation of σ_I,

$$\sigma_{I,MZn} = a_M\chi_M + a_{1I}n_Z + a_{0I} \tag{14}$$

For σ_d values for which the equation is

$$\sigma_{dMZn} = a_{Xd}\chi_M + a_{Id}n_Z + a_{0d} \tag{15}$$

and for σ_e values for which equation 13 is used, the method applies only to those groups which belong to the same delocalized effect category. For MZ^1Z^2 groups the general equation has the form

$$\sigma_{MZ^1Z^2} = a_M\chi_M + a_1n_{Z^1} + a_2n_{Z^2} + a_0 \tag{16}$$

while for $MZ^1Z^2Z^3$ groups it has the form

$$\sigma_{MZ^1Z^2Z^3} = a_M\chi_M + a_1n_{Z^1} + a_2n_{Z^2} + a_3n_{Z^3} + a_0 \tag{17}$$

We have shown elsewhere that the coefficients a_1, a_2 and a_3 are a function of the electrical effects of Z. Thus we may write

$$a_i = L\sigma_{IZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_{i,0} \tag{18}$$

Substituting equation 18 in the general form of equations 13–15 yields

$$\sigma_{MZ} = a_M\chi_M + (L\sigma_{IZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_{i,0})n_Z + a_0 \tag{19}$$

For dicoordinate chalcogen groups where $n_Z = 1$ we have

$$\sigma_{MZ} = a_M\chi_M + L\sigma_{IZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_{i,0} + a_0 \tag{20}$$

$$= a_M\chi_M + L\sigma_{IZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_0' \tag{21}$$

Correlation of σ_{IMZ}, σ_{dMZ} and σ_{eMZ} with equation 21 (M = O, S and Se) gave

$$\sigma_{IMZ} = 0.0311(\pm 0.0136)\chi_M + 0.462(\pm 0.0312)\sigma_{IZ} + 0.193(\pm 0.0389) \tag{22}$$

$100R^2 = 91.42$, $F = 117.2$, $s_{est} = 0.0339$, $s^0 = 0.312$, $n = 25$,

$$\sigma_{dMZ} = -0.146(\pm 0.0177)\chi_M + 0.266(\pm 0.0603)\sigma_{IZ} + 0.534(\pm 0.0898)\sigma_{dZ} + 0.0222(\pm 0.0527) \tag{23}$$

$100R^2 = 93.58$ $F = 82.54$, $s_{est} = 0.0418$, $s^0 = 0.282$, $n = 21$,

$$\sigma_{eMZ} = 0.0598(\pm 0.00445)\chi_M + 0.123(\pm 0.0159)\sigma_{IZ} + 0.145(\pm 0.0240)\sigma_{dZ} + 0.447(\pm 0.0613)\sigma_{eZ} - 0.243(\pm 0.0135) \tag{24}$$

$100R^2 = 96.87$; $F = 146.8$, $s_{est} = 0.0112$, $s^0 = 0.199$, $P_D = 54.1$, $= 3.08$, $n = 24$.

The values of σ_I, σ_d and σ_e for sulfenic acid substituents were calculated from equations 22–24. The remaining values are from our compilation, as are the values for tricoordinate, tetracoordinate and hexacoordinate chalcogen substituents.

1. The variation of substituent effect with M

The values of σ_{IMZ} are in the order O > S = Se > Te. For σ_d the sequence is reversed with Te > S = Se > O. For σ_e the sequence is again O > S = Se > Te. The equality of SZ

and SeZ substituent constants is due to the lack of significant difference in the Allred–Rochow electronegativities, which are 2.44 for S and 2.48 for Se. These groups are all medium to strong localized electrical effect acceptors and delocalized effect donors. They are expected to be capable of stabilizing both positively and negatively charged active sites.

2. The variation of substituent effect with the number of O atoms bonded to M.

On introducing an oxygen atom into an SZ substituent to obtain a sulfinyl derivative, σ_l increases to a considerable extent, as does σ_d, while σ_e shows a small increase.

If we assume that equation 16 applies to S(O)Z groups and substitute equation 18 into it, we obtain

$$\sigma_{S(O)Z} = a_M\chi_M + Lc_{lZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_{1o} + L\sigma_{lo} + D\sigma_{do} + R\sigma_{eo} + a_{2O} + a_o \tag{25}$$

As σ_{lO}, σ_{dO} and σ_{eO} are all constant we obtain

$$\sigma_{S(O)Z} = a_M\chi_M + L\sigma_{lZ} + D\sigma_{dZ} + R\sigma_{eZ} + a_0^* \tag{26}$$

which differs from equation 21 only in the intercept. Then,

$$\sigma_{S(O)Z} = \sigma_{SZ} + (a_0^* - a_0') \tag{27}$$

$$= \sigma_{SZ} + a_0^0 \tag{27a}$$

Similarly, we can obtain for sulfinyl derivatives, $O_{S(O)2Z}$, the equation

$$\sigma_{lSO2Z} = \sigma_{lSZ} + a_0^{02} \tag{28}$$

Equation 28 should not apply to σ_d and σ_e constants. SO_2Z groups are of the $X_{\pi,pd}$ type and cannot be treated as equivalent to X_h groups for the delocalized effect.

Unfortunately, the data are very limited. We can draw no conclusion from the values available other than that the second oxygen atom introduced has a much smaller effect than does the first.

E. The Description of Electrical Effects by Correlation Analysis[2]

Table 1 of this chapter and Tables 4, 6 and 7 of Reference 2 provide substituent constants for use with all of the possible types of electrical-effect equations, including the monoparametric Hammett equation, the diparametric LD and CR equations and the triparametric LDR equation. The choice of which of these relationships to use depends on the nature of the problem studied. Four cases which must be considered are:

1. Approximate values of both P_D and η are available. Consider the rate constants for the solvolysis of a set of 4-substituted phenyl-1,1′-cyclopentyl-1′-trifluoroacetates in 90% aqueous acetone at 25 °C. There is a large body of data available for the solvolysis of similar systems such as cumyl chlorides. The rate constants are generally well correlated by the Hammett equation using the σ_p^+ constants for which P_D is 50 and $\eta = 2$. The simple Hammett equation should provide a good model for this data set using the σ_p^+ constants.

2. η is known; P_D is not. Consider the pK_a values of the E-4-substituted 3-butenoic acids in 80% aqueous methylcellosolve at 25 °C. Generally, a system in which a substituted π-bonded skeletal group, such as an aromatic ring or double bond, is separated from an active site by one or more methylene groups is best modelled by the LD equation using the σ_R^0 constants, for which $\eta = -0.4$. The value of P_D can vary from 40 to 50 in these systems. The data should be correlated with the LD equation using σ_R^0 as the σ_D

parameter. The value of P_D is then calculated from the values of L and D obtained using the equation

$$P_D = D \cdot 100/(L + D) \tag{29}$$

3. P_D is known, while η is not. Consider the pK_a values of 4-substituted naphthylammonium ions in 50% aqueous ethanol at 25 °C. For similar reactions P_D is about 50. The η value should be in the range -1 to -2.5. The data set can be correlated with the CR equation using the $\sigma_{Id,50}$ and σ_e constants; η can then be calculated from the regression equation using equation 2 and the fact that $CK^* = D$.

4. Both η and P_D are unknown. Consider, for example, the rate constants for the reaction of 1-substituted-1-aza-1,3-butadiene with acrylonitrile in ethylene glycol at 100 °C. If the number of data points available is sufficient (at least ten are required for reliable results) the LDR equation is the correlation equation of choice; otherwise the set may be correlated first with the LD equation using in turn the $\sigma_{R,2}$, $\sigma_{R,-1}$, σ_d, $\sigma_{R,1}$ and $\sigma_{R,2}$ constants as σ_D. An approximate value of η is determined by the σ_D constant that gives the best fit. The value of P_D can be calculated from equation 7 using the L and D values obtained from the best regression equation in place of l and d. The alternative is a series of correlations with the CR equation using $\sigma_{Id,k'}$ values with $k' = 30$, 40, 50 and 60. The best regression equation obtained will give an approximate value of P_D (it is equal to k') and a value of η can be calculated from equation 2.

These examples illustrate the use of the LDR, LD, CR and Hammett equations in the quantitative description of electrical effects. They should aid in the choice of an equation for a particular problem.

The tables of $\sigma_{k'/k}$ values (Table 5 in Reference 2) are useful in choosing the members of a data set when the η and P_D values for the property to be measured are known.

III. STERIC EFFECTS

A. Introduction[2]

When a substituent and an active site are in proximity to each other (usually situated on adjacent atoms of a skeletal group) steric effects are often observed. They result from repulsions between occupied valence shell orbitals on atoms which are not bonded to each other and they may be intermolecular or intramolecular. Steric effects always result in an increase in the energy of the species involved. Their effect on a measured property however may be either incremental or decremental. For example, in the case of chemical reactivity the incremental or decremental nature of the steric effect depends on whether it is greater in the reactant than in the product or transition state or whether the reverse is the case. Steric effects can be manifested in several ways. Intramolecular steric effects include:

1. Relief of steric strain. Repulsions are greater in the reactant than in the product or transition state resulting in an incremental effect on an equilibrium or rate constant relative to a reference substrate free of steric effects.

2. Steric inhibition of resonance. When a planar π-bonded substituent or active site attached to a π-bonded skeletal group undergoes a rotation out of the plane of the skeletal group due to the steric effect exerted by an adjacent substituent or active site, the delocalized electrical effect of the first substituent or active site is reduced.

3. Steric effect on conformational preference. Steric effects may determine the position of the conformational equilibria extant in a substrate. If only one conformation is active in determining the measured property, this results in a steric effect.

Intermolecular steric effects include:

1. Steric sheilding of the active site. As the size of an adjacent substituent increases, the region of space available to an attacking reagent is decreased.

2. Steric inhibition of solvation. The substituent can decrease the access of solvent molecules to the active site.

B. Intramolecular Force Proximity Effects[2]

When a substituent and an active site are adjacent to each other, intramolecular forces can occur. These are not true steric effects. They do not result from repulsions between occupied orbitals on nonbonded atoms. They have nevertheless traditionally been described in the literature as steric effects. They are more properly referred to as intramolecular force proximity effects, or, more simply, imf proximity effects. The most clearcut examples involve the formation of 'strong' intramolecular hydrogen bonds. Alternatively there is intramolecular active site solvation. This process can change the energy of the reactant relative to that of the product or transition state.

C. Steric Effect Properties[2]

Steric effects are characterized by a number of properties. If they are to be successfully parameterized it is necessary to take these properties into account. Thus:

1. The observed steric effect may be composite. Components of several different types contribute to the observed effect.
2. Steric effects are vector rather than scalar properties. They depend on both magnitude and direction.
3. Steric effects obey the principle of minimal steric interaction (MSI). This principle states that a nonsymmetric substituent will prefer that conformation which minimizes steric repulsions.
4. The major part of the steric effect of a polyatomic substituent may be exerted at any point along the main chain of the substituent. Where it occurs depends on the steric requirements of the phenomenon being studied.

D. Steric Effect Parameterization[2]

1. Symmetric groups

For many years there has been general agreement that the best measure of atomic size is the van der Waals radius. The distance between the nuclei of two nonbonded atoms in contact is equal to the sum of their van der Waals radii. The van der Waals radii of monatomic groups can be used directly as a measure of the steric effect[13]. It is more convenient however to define a steric parameter based on van der Waals radii[14-16] for which the value for hydrogen is zero. Thus, the steric parameter υ is defined as

$$\upsilon_X = r_{VX} - r_{VH} = r_{VX} - 1.20 \tag{30}$$

for the monatomic substituents H, F, Cl, Br and I. For groups of the type $X = M(lp)_nH_{3-n}$ we may assume that $r_{VX} = r_{VM}$. The values for OH, SH, SeH, NH_2, PH_2 and AsH_2 are easily obtained. Values of υ for tetrahedral groups of the type MZ_3 can be calculated from the length of the MZ bond and r_{VZ}. This type of group is described by three radii: the minimum and maximum radii perpendicular to the group axis and the radius parallel to the group axis. The most useful is the minimum perpendicular radius. In this way υ values are easily calculated for CH_3, CF_3, CCl_3, CMe_3, $SiMe_3$ and other tetrahedral MZ_3 groups. For cylindrically symmetric groups, –C≡C–Z– and –C≡N, the minimal perpendicular radius and the parallel radius can be calculated. In this manner υ parameters

have been obtained for a number of groups whose steric effect is independent of conformation or is nearly so.

2. Nonsymmetric groups

For a remaining nonsymmetric groups $MZ_2^1Z^2$ and $MZ^1Z^2Z^3$, υ values can be calculated from experimental measurements of rate or equilibrium constants using the regression equation resulting from the correlation of sterically dependent data sets in which all of the substituents in the set have conformationally independent steric effects. The correlation equation is

$$Q_X = S\upsilon_X + h \tag{31}$$

3. Planar π-bonded groups

The steric effect of a planar π-bonded group varies from a minimum value which is equal to the half-thickness of the group, to a maximum value in the plane of the group perpendicular to the group axis. The minimum value is given by υ_{ef}, the maximum value by υ_{mn}. Note that although υ_{mn} is a measure of the maximum steric effect exerted by the planar π-bonded group, it is at the same time the maximum radius in the plane of the group. For a nonsymmetric group this is υ_{mn}. The υ value derived from the larger of the two radii in the plane of the group is designated υ_{mx}. Values of υ_{ef} and υ_{mn} for planar π-bonded groups are reported in Table 3.

TABLE 3. Steric parameters[a]

		Chalcogen			
MZ	υ_{ef}	n_1	n_2	n_3	n_b
Oxa					
OH	0.32	−0.84	0	0	−0.89
$OCCl_3$		1	3.39	0	2.13
OCF_3	1.03E	1	2.46	0	1.82
OCN	*0.40*	1	0.91	0	1.91
OMe	0.36	1	0	0	1
OC≡CH	*0.58*	1	1	0	2
$OCH{=}CH_2$	*0.57*	1	1	0	2
OAc	*0.50*	1	1	0	2
OEt	*0.48*	1	1	0	2
OCO_2Et	*0.50*	1	0.87	1	3.87
OPr	0.56	1	1	1	3
OPr-*i*	0.75	1	2	0	2
OBu	0.58	1	1	1	4
$OC_6H_4NO_2$-4	*0.57*	1	1	1	4
OPh	*0.57*	1	1	1	4
OCH_2Ph	0.55E	1	1	1	5
ONH_2	0.36E				
ONHMe	0.53E				
$ONMe_2$	0.89E				
ONHAc	0.69E				
OOH	0.35E				
OOMe	0.47E				

(*continued*)

TABLE 3. (*continued*)

	Chalcogen				
MZ	υ_{ef}	n_1	n_2	n_3	n_b
OOAc	0.69E				
OOPh	0.60E				
OSH	0.46E				
OSMe	0.55E				
OSPh	0.70E				
OF	0.46E				
OCl	0.44E				
OBr	0.48E				
OI	0.52E				
Thia					
			Dicoordinate		
SH	0.60	0.33	0	0	0
$SCCl_3$		1.07	3.39	0	2.20
SCF_3	1.36	1.07	2.45	0	1.89
SCN	1.21	1.07	0.91	0	1.98
SMe	0.64	1.07	0	0	1.07
SC≡CH	1.04E	1.07	1	0	2.07
$SCH{=}CH_2$	0.85E	1.07	1	0	2.07
SAc	0.93E	1.07	1	0	2.07
SEt	0.94	1.07	1	0	2.07
SCO_2Et	0.72E	1.07	0.87	1	3.94
SPr-*i*	1.19	1.07	2	0	2.07
$SC_6H_4NO_2$-4	1.00	1.07	1	1	5.94
SPh	1.00	1.07	1	1	4.07
S-C-Hex	1.21	1.07	2	2	4.07
SCH_2Ph	1.00	1.07	1	1	5.07
SNH_2	0.67E				
SNHMe	0.84E				
$SNMe_2$	1.19E				
SNHAc	0.99E				
SOH	0.66E				
SOMe	0.78E				
SOAc	0.99E				
SOPh	0.91E				
SSH	0.76E				
SSMe	0.86E				
SSPh	1.00E				
SF	0.76E				
SCl	0.74E				
SBr	0.79E				
SI	0.82E				
			Tricoordinate		
S(O)Me	0.66E	1.97	0	0	1.07
S(O)Et	1.10E	1.97	1	0	2.07
S(O)Ph	1.10E	1.97	1	1	4.07
			Tetracoordinate		
SO_2CF_3		2.94	2.45	0	1.89
SO_2Me	1.13	2.94	0	0	1.07

TABLE 3. (*continued*)

		Chalcogen			
MZ	υ_{ef}	n_1	n_2	n_3	n_b
SO_2Et		2.94	1	0	2.07
SO_2Ph		2.94	1	1	4.07
SO_2NH_2	1.03E	2.94	0	0	0.97
			Hexacoordinate		
SF_5	1.37	4.40	0	0	0.88
Selena					
SeH	0.70	0.75	0	0	0.75
$SeCCl_3$		1.30	3.39	0	2.43
$SeCF_3$	1.48E	1.30	2.46	0	2.12
SeCN	1.24E	1.30	0.91	0	2.21
SeMe	0.74E	1.30	1	1	1.30
SeC≡CH	1.19E	1.30	1	0	2.30
$SeCH{=}CH_2$	0.96E	1.30	1	0	2.30
SeAc	1.09E	1.30	1	0	2.30
SeEt	0.80E	1.30	1	0	2.30
$SeCO_2Et$	0.83E	1.30	1	0	4.17
$SeC_6H_4NO_2$-4	1.03E	1.30	1	1	6.17
SePh	1.03E	1.30	1	1	4.30
$SeCH_2Ph$	0.97E	1.30	1	1	5.30
$SeNH_2$	0.78E				
SeNHMe	0.94E				
$SeNMe_2$	1.30E				
SeNHAc	1.10E				
SeOH	0.77E				
SeOMe	0.89E				
SeOAc	1.10E				
SeOPh	1.02E				
SeSH	0.87E				
SeSMe	0.97E				
SeSPh	1.11E				
SeF	0.87E				
SeCl	0.85E				
SeBr	0.90E				
SeI	0.93E				
Tellura					
TeH	0.86E				
$TeCCl_3$					
$TeCF_3$					
TeMe	0.90e				
TeC≡CH	1.37E				
$TeCH{=}CH_2$	1.13E				
TeAc	1.21E				
TeEt	1.12E				
$TeCO_2Et$	1.00E				
$TeC_6H_4NO_2$-4	1.14E				
TePh	1.14E				
$TeCH_2Ph$	1.14E				
$TeNH_2$	0.95E				

(*continued*)

TABLE 3. (*continued*)

	Chalcogen				
MZ	υ_{ef}	n_1	n_2	n_3	n_b
TeNHMe	1.12E				
$TeNMe_2$	1.48E				
TeNHAc	1.27				
TeOH	0.94E				
TeOMe	1.06E				
TeOAc	1.27				
TeOPh	1.19E				
TeSH	1.05E				
TeSMe	1.14E				
TeSPh	1.29E				
TeF	1.05E				
TeCl	1.02E				
TeBr	1.07E				
TeI	1.11E				
			Other Groups		
H	0	−2.17	0	0	−2.17
F	0.27	−1.04	0	0	−1.04
Cl	0.55	0.12	0	0	0.12
Br	0.65	0.54	0	0	0.54
I	0.78	1.08	0	0	1.08
Me	0.52	0	0	0	0
Et	0.56	1	0	0	1
c-Pr	0.64	1	0	0	1
CF_3	0.90	2.45	0	0	0.82
C≡CH	0.58	1	0	0	1
CH=CH₂	0.57	1	0	0	1
C_6F_5	0.57	1	1	1	3.82
Ph	0.57	1	1	1	3
HCO	0.50	0.87	0	0	0.87
CO_2H	0.50	0.87	0	0	0.87
Ac	0.50	1	0	0	1
$CONH_2$	0.50	0.91	0	0	0.91
CO_2Me	0.50	0.87	1	0	1.87
CN	0.40	0.91	0	0	0.91
NO_2	0.35	0.87	0	0	0.87
$SiMe_3$	1.40	3.21	0	0	1.08
NHAc	0.50	1	1	0	2
NHEt	0.59	1	1	0	2
NMe_2	0.52	2	0	0	1
PMe_2	0.84	2.16	0	0	1.08
$POMe_2$	0.84	3.10	0	0	1.08
$PO(OMe)_2$	1.04	2.83	2	0	1.94

[a] Groups in italics are planar π-bonded. For these groups υ_{ef} represents the half-thickness. υ_{mx} and υ_{mn} lie in the plane of these groups.
Values labelled E are estimates. They were generally obtained from the equation

$$\upsilon_{MZ} = 1.09\upsilon_M + 1.19\Delta\upsilon - 0.0089$$

where $\upsilon_M = r_{VM} - 1.20$ and $\Delta\upsilon = \upsilon_{CH2Z} - \upsilon_{Me} = \upsilon_{CH2Z} - 0.52$
The value of r_{VM} for Te of 2.06 Å is from our results (M. Charton, *Abstracts*, Int. Symp. Strain and Steric Effects in Organic Chemistry, Bangor, U.K., 1985, p. 27).

When a planar π-bonded substituent is bonded to a planar π-bonded skeletal group G or an active site Y, the dihedral angle θ formed by X_π with G or Y will vary with the size of G or Y. Both σ_d and the electronic demand will be a function of θ. Then, both the delocalized effect of X_π and its steric effect will be a function of the dihedral angle θ.[17]

Consider a typical χ_π group of the type MZ^1Z^2 (Figure 1 of Reference 2). Z^1 may or may not be identical to Z^2. Examples of these groups are the acetyl group in which Z^1 is O and Z^2 is Me; and the nitro group in which $Z^1 = Z^2 = O$. When Z^1 and Z^2 are different, the MSI principle shows that the smaller of the two Z groups will determine the steric effect of MZ^1Z^2. This is the group designated as Z^1. The steric effect of the MZ^1Z^2 group must lie between its υ_{mx} and υ_{mn} values. The geometry of a typical system in which MZ^1Z^2 is bonded to a planar π-bonded skeletal group, G_π, which in turn is bonded to an active site that is in close proximity to MZ^1Z^2, is shown in Figure 2 of Reference 2. In general, the dependence of a property Q on the dihedral angle θ is best represented by the relationship

$$Q_\theta = Q_0 \times \cos^2\theta \tag{32}$$

where Q_θ is the value of the property when the dihedral angle is equal to θ and Q_0 when it is equal to zero. Then, from the geometry in Figures 1 and 2 of Reference 2 and equation 32 we have

$$\sigma_{dX\theta} = \cos^2\theta \times \sigma_{dX0} \tag{33}$$

$$\sigma_{eX\theta} = \cos^2\theta \times \sigma_{eX0} \tag{34}$$

$$\upsilon_X = d \times \cos\theta + r_{VZ} - 1.20 \tag{35}$$

or

$$\cos\theta = (\upsilon_X - r_{Z^1} + 1.20)/d \tag{36}$$

It is not possible at the present time to assign values of θ *a priori*. The inclusion of X_π values in a data set in which steric effects occur can be done only by an iteration method[18]. In the first step the correlation is carried out with all X_π groups excluded from the data set. The LDRS equation

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + S\upsilon_X + h \tag{37}$$

can be used as the correlation equation. The iteration is carried out by correlation of the data set including the value of an X_π group and varying θ by increments, usually of 5° or 10°. For each value of θ the corresponding values of υ, σ_d and σ_e are used. The proper value of θ is assumed to be that which gives the best fit of the data to the correlation equation. For the best fit $100R^2$ and F are maximal, while s_{est} and s^0 are minimal. It is also necessary that the coefficients of the best equation show no significant difference from those obtained excluding the X_π group.

Values of υ are reported for chalcogen groups in Table 3. The υ parameters of substituents are strongly dependent on the van der Waals radius of the first atom in the main chain of the substituent. This is the atom bonded to the skeletal group G in an XGY system or to the active site Y in an XY system. The magnitude of υ for dicoordinate chalcogen groups MZ varies with the chalcogen atom M in the sequence $O < S < Se < Te$. Thus though SZ and SeZ have essentially the same values for their electrical-effect parameters, there is a small but significant difference in their υ values. CH_2Z groups have υ values which lie between those of OZ and SZ.

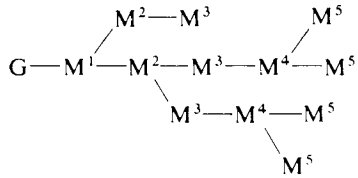
E. Branching Parameters[2]

A major disadvantage of monoparametric treatments of the steric effect is that nonsymmetric substituents exhibit a variable steric effect which depends on the steric

demand of the system studied. If the steric requirements of the system studied resemble those of the reference system used to determine the steric parameters for the nonsymmetric groups, then there is little or no problem. This is often not the case, however. There are two methods for dealing with this problem. One of these involves the definition of a number of different sets of steric parameters for nonsymmetric groups. The set chosen for a particular problem is that in which the steric demand in the reference system most closely matches that in the data set to be modelled. It is frequently difficult to determine *a priori* which set of steric parameters to choose. This approach results in many steric parameter sets and is a major cause of confusion. The other approach is the use of a multiparametric model. A suitable topological model of this type is the simple branching (SB) equation.[15,19,20]

$$Q_X = {}^S\sum_{i=1}^{m} a_i n_i + a_0 = \sum_{i=1}^{m} a_i n_i + a_0 \tag{38}$$

where n_i is the total number of branches on the ith atoms of the substituent X, a_i is its coefficient and a_0 is the intercept. Consider, for example, the substituent **1** which is shown bonded to a skeletal group G. Hydrogen atoms are not considered as branches, therefore **1** is shown as a hydrogen-suppressed structure; n_i is equal to the number of M atoms labelled $i+1$. Then for **1** the n_i values are: $n_1 = 2$; $n_2 = 3$; $n_3 = 2$; $n_4 = 4$.



(1)

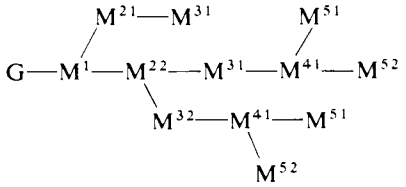
In this very simple model the effect of branching is assumed to be the same for all branches. This assumption is at best a crude approximation. Frequently, the first branch on an atom exerts little or no steric effect while the effect of the third branch is large. Consider the series, CH_3, CH_2Me, $CHMe_2$ and CMe_3 for which the υ values are 0.52, 0.56, 0.76 and 1.24. Thus, the first, second and third branches increase the size of the methyl group by factors of 1.08, 1.46 and 2.38, respectively. This is the result of the MSI principle. The effect of the first branch can be minimized by a suitable conformation of the substituent in which the branch is rotated away from the active site. Such a rotation becomes much more difficult to achieve on introduction of a second branch and impossible on the introduction of a third.

When all of the atoms M are not identical, a second approximation often made is that the effect of all second- or third-period elements acting as either skeletal or branch atoms is about the same. This approximation is also crude. Nevertheless, the simple branching equation can often give a reasonable description of steric effects.[19–22]

The expanded branching (XB) equation, which takes into account the effect of the order of branching, gives a much improved description of steric effects. It has the form[1,2,21–23]

$$Q_X = \sum_{i=1}^{m}\sum_{j=1}^{3} a_{ij} n_{ij} + a_{00} \tag{39}$$

where n_{ij} is the total number of jth branching atoms bonded to the ith atoms in the substituent and a_{ij} is its coefficient. We may consider the same example as before. This time, however, it is numbered to indicate the order of branching (**2**); n_{ij} is equal to the



(2)

number of atoms bearing the label $i+1, j$. Then for **2** the n_{ij} values are: $n_{11}=n_{12}=1$; $n_{21}=2$; $n_{22}=1$; $n_{31}=n_{41}=n_{42}=2$; all other $n_{ij}=0$.

Although the XB equation is a far better model of steric effects than is the SB equation, it requires many more independent variables. It is therefore useful only when the data set to be studied is very large. The variation in atomic size can be accounted for when applying the branching method. Values of n_i or n_{ij} can be multiplied by an appropriate factor for this purpose. In Table 3, n_i values of this type are reported.

When the SB equation is applied to planar π-bonded groups, it is assumed on the basis of the MSI principle that the half-thickness of the group determines its steric effect. An evaluation of the branchimg parameters for the phenyl group gave $n_1=n_2=n_3=1$. It is assumed that the values for doubly bonded groups containing the fragments C=C, C=N, C=O and N=N are comparable.

It is useful to have a parameter which represents group length. A crude but useful length parameter is n_b, which is defined as the number of bonds in the group skeleton. The group skeleton is the longest chain of atoms in the group; n_b is given by

$$n_b = i_{max} - 1 \tag{40}$$

where i_{max} is the highest value of i for any atom in the group. Thus, the value of n_b for **1** or **2** is 4.

IV. INTERMOLECULAR FORCES

A. Introduction[2]

Many chemical properties including melting and boiling points, solubility, chromatographic quantities such as R_M and R_F values, retention times, as well as capacity factors and equilibrium constants for hydrogen bonding or charge transfer complex formation are a function of the difference in intermolecular forces (imf) between an initial state, 1, and a final state 2. Thus,

$$Q_X = f[(\text{imf}_X)_2 - (\text{imf}_X)_1] = f[\Delta\text{imf}_X] \tag{41}$$

Many types of biological activities are also well represented by equation 41. In order to model these quantities it is necessary to determine what imfs are involved and parameterize them. Intermolecular forces and their parameterization are reported in Table 4. The parameters not described previously are: the polarizability parameter α, the hydrogen bonding parameters n_H and n_n, the ionic parameter i, and the charge transfer parameters n_D and n_A.

B. Intermolecular Force Parameters[2]

The polarizability parameter is defined by the relationship

$$\alpha_X = (MR_X - MR_H)/100 \tag{42}$$

$$= MR_X/100 - 0.0103 \tag{43}$$

TABLE 4. Intermolecular forces[a]

Interaction (abbreviation)	Parametrization
Dipole–dipole [Keesom] (dd)	σ_l, σ_d, σ_e
Dipole–induced dipole [Debye] (di)	σ_l, σ_d, σ_e, α
Induced dipole–induced dipole [London] (ii)	α
Hydrogen bonding (hb)	σ_l, σ_d, σ_e, n_H, n_n
Charge transfer (ct)	σ_l, σ_d, σ_e, n_A, n_D
Ion-dipole (Id)	σ_l, σ_d, σ_e, i
Ion-induced dipole (Ii)	i, α

[a] Parameters are described and their sources given in Section IV. ii interactions are also called dispersion forces. dd, di and ii interactions are frequently referred to collectively as van der Waals forces.

where MR_X and MR_H are the molar refractivities of X and H, respectively[23–26]. Although there are many other polarizability parameters they are all linear functions of α. There is no reason for preferring any one of them over any other. The requirements for a polarizability parameter are that values are either readily available or easily estimated for all common substituents, and that they are so scaled that when they are used in a correlation equation the coefficient of the polarizability parameter obtained from the regression analysis will be comparable in magnitude to the coefficients of the other parameters.

The n_H parameter is defined as the number of NH and/or OH bonds in the substituent and n_n is defined as the number of lone pairs on O and/or N atoms. These parameters may be thought of as a measure of the probability that the substituent will act as a hydrogen-bond electron acceptor (n_H) or electron donor (n_n)[23–26].

The ionic parameter i takes the value 1 for ionic substituents and the value 0 for nonionic substituents.

The charge transfer parameter n_D takes the value 1 when the substituent can act as a charge transfer donor or the value 0 when it cannot. The n_A parameter takes the value 1 when the substituent can act as a charge transfer acceptor or the value 0 when it cannot. Values of the imf parameters are given in Table 5. The α values of the MZ groups as a function of M are in the sequence O < S < Se < Te. The α values of CH_2Z groups lie between those of the OZ and those of the SZ groups. Values of n_n are 0 for MZ groups

TABLE 5. Intermolecular force parameters[a]

X	α	n_H	n_n	i	n_A	n_D
Oxa						
			Chalcogen			
OH	0.018	1	2	1/0	0	1
$OCCl_3$	0.213	0	2	0	0	1
OCF_3	0.068	0	2	0	0	1
OCN	0.073	0	3	0	0	1
OCH_3	0.068	0	2	0	0	1
OC≡CH	0.107	0	2	0	0	1
$OCH{=}CH_2$	0.122	0	2	0	0	1
OAc	0.114	0	4	0	0	1
OEt	0.114	0	2	0	0	1
OCO_2Et	0.186	0	6	0	0	1
OPr	0.160	0	2	0	0	1

TABLE 5. (*continued*)

X	α	n_H	n_n	i	n_A	n_D
OPr-*i*	0.160	0	2	0	0	1
OBu	0.206	0	2	0	0	1
$OC_6H_4NO_2$-4	0.227	0	6	0	1	1
OPh	0.267	0	2	0	0	1
OBz	0.293	0	4	0	1	1
OCH_2Ph	0.312	0	2	0	0	1
ONH_2	0.064	2	3	0	0	1
ONHMe	0.115	1	3	0	0	1
$ONMe_2$	0.165	0	3	0	0	1
ONHAc	0.159	1	5	0	0	1
OOH	0.040	1	4	0	0	1
OOMe	0.040	0	4	0	0	1
OOAc	0.136	0	6	0	0	0
OOPh	0.289	0	4	0	0	1
OSH	0.104	0	2	0	0	1
OSMe	0.150	0	2	0	0	1
OSPh	0.355	0	2	0	0	1
OSO_2Me	0.145	0	6	0	0	1
OF	0.019	0	2	0	0	1
OCl	0.079	0	2	0	0	1
OBr	0.099	0	2	0	0	1
OI	0.149	0	2	0	0	1
Thia						
			Dicoordinate			
SH	0.082	0	0	0	0	1
$SCCl_3$	0.273	0	0	0	0	1
SCF_3	0.128	0	0	0	0	1
SCN	0.124	0	0	0	0	1
SMe	0.128	0	0	0	0	1
SC≡CH	0.167	0	0	0	0	1
$SCH=CH_2$	0.182	0	0	0	0	1
SAc	0.174	0	2	0	0	1
SEt	0.175	0	0	0	0	1
SCO_2Et	0.246	0	4	0	0	1
SPr	0.221	0	0	0	0	1
SPr-*i*	0.222	0	0	0	0	1
$SC_6H_4NO_2$-4	0.387	0	0	0	1	1
SPh	0.333	0	0	0	0	1
S-*c*-Hex	0.339	0	0	0	0	1
SCH_2Ph	0.372	0	0	0	0	1
SNH_2	0.126	2	1	0	0	1
SNHMe	0.175	1	1	0	0	1
$SNMe_2$	0.227	0	1	0	0	1
SNHAc	0.221	1	3	0	0	1
SOH	0.100	1	2	1	0	1
SOMe	0.150	0	2	0	0	1
SOAc	0.196	0	4	0	0	1
SOPh	0.349	0	2	0	0	1
SSH	0.164	0	0		0	1
SSMe	0.210	0	0	0	0	1
SSPh	0.415	0	0	0	0	1
SF	0.081	0	0	0	0	1

(*continued*)

TABLE 5. (*continued*)

X	α	n_H	n_n	i	n_A	n_D
SCl	0.137	0	0	0	0	1
SBr	0.161	0	0	0	0	1
SI	0.211	0	0	0	0	1
			Tricoordinate			
SOMe	0.127	0	2	0	0	1
SOEt	0.174	0	2	0	0	1
SOPh	0.320	0	2	0	0	1
			Tetracoordinate			
SO_2CF_3	0.118	0	4	0	0	1
SO_2Me	0.125	0	4	0	0	1
SO_2Et	0.172	0	4	0	0	1
SO_2Pr	0.218	0	4	0	0	1
SO_2Ph	0.322	0	4	0	0	1
SO_2NH_2	0.113	2	5	0	0	1
			Hexacoordinate			
SF_5	0.089	0	0	0	0	0
Selena						
SeH	0.124	0	0	0	0	1
$SeCCl_3$	0.305	0	0	0	0	1
$SeCF_3$	0.153	0	0	0	0	1
SeCN	0.158	0	0	0	0	1
SeMe	0.160	0	0	0	0	1
SeC≡CH	0.199	0	0	0	0	1
$SeCH{=}CH_2$	0.214	0	0	0	0	1
SeAc	0.224	0	2	0	0	1
SeEt	0.207	0	0	0	0	1
$SeC_6H_4NO_2$-4	0.419	0	4	0	1	1
SePh	0.362	0	0	0	0	1
$SeCH_2Ph$	0.404	0	0	0	0	1
$SeNH_2$	0.158	2	1	0	0	1
SeNHMe	0.207	1	1	0	0	1
$SeNMe_2$	0.254	0	1	0	0	1
SeNHAc	0.253	1	3	0	0	1
SeOH	0.132	1	2	1	0	1
SeOMe	0.182	0	2	0	0	1
SeOAc	0.228	0	4	0	0	1
SeOPh	0.381	0	2	0	0	1
SeSH	0.196	0	0	0	0	1
SeSMe	0.242	0	0	0	0	1
SeSPh	0.447	0	0	0	0	1
SeF	0.113	0	0	0	0	1
SeCl	0.169	0	0	0	0	1
SeBr	0.193	0	0	0	0	1
Tellura						
TeH	0.175	0	0	0	0	1
$TeCCl_3$	0.356	0	0	0	0	1
$TeCF_3$	0.205	0	0	0	0	1
TeCN	0.218	0	0	0	0	1

TABLE 5. (*continued*)

X	α	n_H	n_n	i	n_A	n_D
TeMe	0.211	0	0	0	0	1
TeC≡CH	0.250	0	0	0	0	1
TeCH=CH_2	0.265	0	0	0	0	1
TeEt	0.258	0	0	0	0	1
TeC$_6$H$_4$NO$_2$-4	0.470	0	0	0	0	1
TePh	0.408	0	0	0	0	1
TeCH$_2$	0.455	0	0	0	0	1
TeNH$_2$	0.209	2	1	0	0	1
TeNHMe	0.258	1	1	0	0	1
TeNMe$_2$	0.305	0	1	0	0	1
TeNHAc	0.304	1	3	0	0	1
TeOH	0.183	1	2	1	0	1
TeOMe	0.236	0	2	0	0	1
TeOAc	0.279	0	4	0	0	1
TeOPh	0.432	0	2	0	0	1
TeSH	0.247	0	0	0	0	1
TeSMe	0.293	0	0	0	0	1
TeSPh	0.498	0	0	0	0	1
TeF	0.164	0	0	0	0	1
TeCl	0.220	0	0	0	0	1
TeBr	0.244	0	0	0	0	1
			Other Groups			
H	0	0	0	0	0	0
F	−0.001	0	0	0	0	0
Cl	0.050	0	0	0	0	0
Br	0.079	0	0	0	0	0
I	0.129	0	0	0	0	0
Me	0.046	0	0	0	0	0
Et	0.093	0	0	0	0	0
c-Pr	0.125	0	0	0	0	0
CF_3	0.040	0	0	0	0	0
C≡CH	0.085	0	0	0	0	1
CH=CH_2	0.100	0	0	0	0	1
C_6F_5	0.230	0	0	0	0	1
Ph	0.243	0	0	0	0	1
HCO	0.059	0	2	0	1	0
CO_2H	0.059	1	4	1	1	0
Ac	0.102	0	2	0	1	0
$CONH_2$	0.088	2	3	0	1	0
CO_2Me	0.118	0	4	0	1	0
CN	0.053	0	0	0	1	0
NO_2	0.063	0	4	0	1	0
$SiMe_3$	0.239	0	0	0	1	0
NHAc	0.139	1	3	0	0	1
NHEt	0.140	1	1	1/0	0	1
NMe_2	0.145	0	1	1/0	0	1
PMe_2	0.202	0	0	0	0	1
$OPMe_2$	0.189	0	2	0	0	1
$OP(OMe)_2$	0.208	0	6	0	0	1

[a] When the value of i given is in the form 1/0, i equals 1 if the substituent is bonded to sp^3-hybridized carbon; otherwise it is equal to zero.

with M other than O unless Z has lone pairs on O and/or N. All of the dicoordinate chalcogen groups will be charge transfer donors by virtue of the lone pairs on the chalcogen atom and will therefore have n_D values of 1.

Chemical properties and many biological activities are well modelled by the intermolecular force (IMF) equation

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + A\alpha_X + H_1 n_{HX} + H_2 n_{nX} + Ii_X + C_1 n_{DX} + C_2 n_{AX} + S\upsilon_X + B^0 \quad (44)$$

In an alternative form of the IMF equation the steric effect term $S\upsilon_X$ is replaced by the simple branching (SB) equation.

V. DIRECTING AND ACTIVATING EFFECTS OF CHALCOGEN GROUPS

A. Introduction[2]

Although the terms *directing* and *activating* are often used by organic chemists to describe properties of functional groups, they are ill-defined. We define directing effects as those structural effects which determine orientation or regioselectivity in chemical reactivity, a preference for a particular tautomer, a configurational preference or a conformational preference. When a substituent causes a preference for one product, tautomer, configuration or conformation over another, we consider this to be a directing effect. Activation has often been used to mean that a group makes possible a reaction which does not otherwise occur. We prefer to define an activating effect as a substituent effect which increases the magnitude of a rate or equilibrium constant.

B. Activating Effects[2]

We have restricted our discussion of substituent effects on chemical reactivity to systems in which the substituent X is directly bonded to the active site Y (XY systems). These systems provide the strongest test of a model as they exhibit a wide range of electronic demand, generally from -6 to 6. By contrast, systems in which X and Y are bonded to a phenylene skeletal group (typical XGY systems) have a much narrower range of electronic demand, generally from -3 to 3.

In our discussion of the electrical effects of thia substituents we shall use a reference set which contains typical groups of each type. Included in this reference set are all of the sulfenic acid derivative substituents; SOH, SOMe, SOAc, SOPh, SNH_2, SNHMe, $SNMe_2$, SNHAc, SSH, SSMe, SSPh, SF, SCl, SBr and SI.

The overall electrical effect of a group in a particular data set of interest, as was noted above, can be determined easily from a table of its $\sigma_{k'/k}$ constants by using the η and P_D values that have been determined for the data set. The $\sigma_{k'/k}$ value required is that for which the η and P_D values most closely match those of the data set. As the value of ρ in the Hammett equation

$$Q_X = \rho\sigma_{k'/k,X} + h \quad (45)$$

is equal to that of L in the LDR equation, values of Q_X can be estimated from the values of L and h obtained with the LDR equation and the value of $\sigma_{k'/k,X}$.

1. *Substituent effects at cationic carbon*

Data sets of interest include the ionization potentials of substituted methyl radicals (set 72) and of substituted benzenes (set 18), and the rates of hydration of $XCH{=}CH_2$ and $XCMe{=}CH_2$ (sets 109 and 110, respectively). Gas-phase elimination reactions of

1-substituted 1-chloroethanes (set 11.1) and 2-substituted 2-acetoxypropanes (set 14) were also examined[26,27]. The $\sigma_{k'/k,X}$ values for the members of the sulfenic acid derivative reference set are given in Table 6, as are the η, P_D, L and h values of the data sets. All of the sulfenic acid derivative (SAD) groups should act as donor groups when attached to cationic carbon. The sulfenyl halide groups are the weakest donors of the SAD substituents. It seems then that the SAD groups should increase the rates for hydration and gas-phase elimination. They may be expected to decrease the ionization potentials of the substituted methyl radicals and of the substituted benzenes. The SMe, SCH_2Ph, SPh, $SCH{=}CH_2$, and to a somewhat lesser extent the SC≡CH groups are also effective electron donors when bonded to cationic carbon. The SCF_3, SCN and SC(O)Z groups are electron acceptors or show almost no electrical effect in all sets but 11.1 for which the P_D values are very large.

2. *Substituent effects at radical carbon*

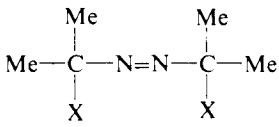
Radical reactions may involve the attack of either nucleophilic or electrophilic radicals. It follows then that their η values may be either positive (electrophilic) or negative (nucleophilic). Relative rates of addition of methyl radicals and of polystyryl radicals to

TABLE 6. $\sigma_{k'/k}$ values for sulfenic acid derivative groups linked to cationic carbon[a]

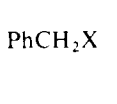
Set	72	18	109	110	11.1	14
η	2.98	2.64	1.62	0.961	3.69	3.20
P_D	63.1	53.7	57.4	62.2	71.9	46.4
L	1.13	1.19	−21.1	−13.7	−3.10	−2.52
h	8.76	9.31	−4.985	−1.161	−2.10	0.542
X			$\sigma_{k'/k,X}$			
SNH_2	−1.65	−0.98	−1.30	−0.96	−3.29	−0.98
SNHMe	−1.82	−1.10	−1.43	−1.04	−3.61	−1.10
$SNMe_2$	−1.86	−1.12	−1.44	−1.02	−3.73	−1.12
SNHAc	−0.94	−0.49	−0.71	−0.49	−2.02	−0.49
SOH	−1.10	−0.59	−0.86	−0.62	−2.32	−0.59
SOMe	−1.17	−0.64	−0.91	−0.66	−2.43	−0.64
SOAc	−0.48	−0.17	−0.35	−0.22	−1.19	−0.17
SOPh	−1.01	−0.52	−0.77	−0.53	−2.18	−0.52
SSH	−1.08	−0.59	−0.83	−0.57	−2.29	−0.59
SSMe	−1.03	−0.55	−0.78	−0.52	−2.22	−0.55
SSPh	−1.05	−0.56	−0.78	−0.51	−2.27	−0.56
SF	−0.51	−0.17	−0.39	−0.26	−1.27	−0.17
SCl	−0.42	−0.12	−0.29	−0.16	−1.12	−0.12
SBr	−0.42	−0.12	−0.29	−0.16	−1.13	−0.12
SI	−0.50	−0.18	−0.35	−0.20	−1.25	−0.18
SH	−0.77	−0.42	−0.62	−0.48	−1.58	−0.42
SCF_3	0.05	0.18	0.11	0.17	−0.27	0.18
SCN	0.16	0.29	0.22	0.28	−0.16	−0.29
SMe	−0.86	−0.47	−0.66	−0.47	−1.80	−0.47
SC≡CH	−0.58	−0.25	−0.38	−0.19	−1.42	−0.25
SAc	0.01	0.14	0.10	0.18	−0.33	0.14
SCO_2Et	−0.07	0.10	0.03	0.12	−0.50	0.10
SPh	−0.95	−0.54	−0.71	−0.46	−2.07	−0.54
SBz	−0.13	0.05	−0.02	0.10	−0.61	0.05
SCH_2Ph	−0.96	−0.55	−0.75	−0.54	−1.95	−0.55

[a]Set numbers refer to Table 6 of Reference 7 unless otherwise noted. Sets 11 and 14 are from Reference 26.

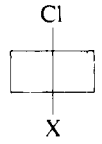
substituted ethylenes (sets 84 and S174), relative rates of thermal decomposition of 2,5-disubstituted 2,5-dimethyl-3,4-diaza-3-hexenes (**3**) (set 266), relative rates for the reaction of 1′-substituted toluenes (**4**) with bromine atoms (set S89) and rates of thermal cleavage of the 1,4 bond in 4-substituted 1-chloro-[2,2,0]-bicyclohexanes (**5**) were the sets studied. The $\sigma_{k'/k,X}$ values for SAD and other dicoordinate sulfur groups together with the η, P_D, L and h values for the data sets are given in Table 7. The three data sets involving the attack of nucleophilic radicals (sets 84, S174 and 266) should all show incrementation of the rate constants by all of the dicoordinate sulfur groups we have examined. For the sets involving electrophilic radical attack (sets S89 and 179) the SAD groups and the SMe, SCH_2Ph, SPh, $SCH{=}CH_2$ and SC=CH groups all seem to have an activating effect as



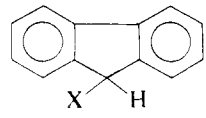
(**3**)



(**4**)



(**5**)



(**6**)

TABLE 7. $\sigma_{k'/k}$ values for sulfenic acid derivative groups linked to radical carbon[a]

Set	84	S174	266	S89	179
η	−4.32	−6.92	−6.77	2.62	−0.872
P_D	69.1	46.8	57.3	51.9	59.5
L	1.18	2.70	5.22	−3.14	5.23
h	1.492	−0.192	2.24	−0.306	0.407
X			$\sigma_{k'/k}$		
SNH_2	1.00	1.09	1.46	−0.98	−0.96
SNHMe	1.24	1.24	1.70	−1.10	−1.04
$SNMe_2$	1.49	1.40	1.93	−1.12	−1.02
SNHAc	0.77	0.86	1.09	−0.49	−0.49
SOH	0.66	0.85	1.06	−0.59	−0.62
SOMe	0.74	0.89	1.13	−0.64	−0.66
SOAc	0.44	0.61	0.70	−0.17	−0.22
SOPh	0.80	0.92	1.16	−0.52	−0.53
SSH	0.88	0.94	1.22	−0.59	−0.57
SSMe	0.95	0.98	1.27	−0.5	−0.52
SSPh	1.09	1.06	1.39	−0.56	−0.51
SF	0.26	0.57	0.60	−0.17	−0.26
SCl	0.47	0.65	0.73	−0.12	−0.16
SBr	0.48	0.66	0.74	−0.12	−0.16
SI	0.61	0.72	0.86	−0.18	−0.20
SH	0.25	0.46	0.55	−0.42	−0.48
SCF_3	0.47	0.54	0.59	0.18	0.17
SCN	0.58	0.65	0.70	0.29	0.28
SMe	0.63	0.70	0.90	−0.47	−0.47
SC≡CH	1.01	0.92	1.18	−0.25	−0.19
SAc	0.74	0.65	0.78	0.14	0.18
SCO_2Et	0.68	0.67	0.78	0.10	0.12
SPh	1.10	0.99	1.33	−0.54	−0.46
SBz	0.83	0.74	0.91	0.05	0.10
SCH_2Ph	0.66	0.71	0.94	−0.55	−0.54

[a]Set numbers refer to Table 6 of Reference 7. $\sigma_{k'/k}$ values for sets S174 and 266 are for $k = -6$.

they should increase the reaction rate by acting as electron donors. The SCF_3, SCN and SCOZ groups act as electron acceptors.

3. Substituent effects at anionic carbon

The data sets examined include the pK_a values in Me_2SO of XCH_2Z with $Z = NO_2$, SO_2Me and Bz, and of 9-substituted fluorenes, **6** (sets P97, S170, P172, and S173); the gas-phase proton affinities of substituted methanes (set S23); and the rates of elimination of 1-substituted-2-phenoxyethanes with ethoxide in ethanol (set 216). Values of the $\sigma_{k'/k,X}$ values for SAD groups together with the η, P_D, L and h values for the data sets are reported in Table 8. For the reactions studied, all of the dicoordinate thia groups act as electron acceptors, increasing methylene acidity and the rate of elimination.

4. Other XY systems

Values of η, P_D, L and h are given in Table 9 for rate constants for the thermal dissociation of 2-substituted dibenzocyclo[2.2.2]octanes[28], **7** (set 319), and for the

TABLE 8. $\sigma_{k'/k}$ values for sulfenic acid derivative groups linked to anionic carbon[a]

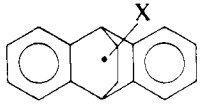
Set	P97	S170	P172	S173	S23	216
η	−3.10	−2.70	−2.70	−1.81	−5.45	−2.62
P_D	45.2	50.9	39.1	45.9	49.4	67.2
L	−11.7	−20.6	−18.3	−18.7	−45.4	8.20
h	16.55	29.5	24.4	21.4	415	−9.67
X			$\sigma_{k'/k}$			
SNH_2	0.40	0.40	0.38	0.17	0.86	0.47
SNHMe	0.46	0.46	0.42	0.20	0.98	0.64
$SNMe_2$	0.56	0.56	0.49	0.28	1.12	0.84
SNHAc	0.41	0.41	0.41	0.26	0.71	0.42
SOH	0.37	0.37	0.39	0.21	0.69	0.29
SOMe	0.38	0.38	0.39	0.21	0.72	0.34
SOAc	0.35	0.35	0.38	0.26	0.53	0.23
SOPh	0.44	0.44	0.44	0.28	0.76	0.43
SSH	0.43	0.43	0.42	0.26	0.77	0.48
SSMe	0.47	0.47	0.45	0.30	0.81	0.55
SSPh	0.52	0.52	0.48	0.34	0.88	0.67
SF	0.33	0.33	0.39	0.24	0.49	0.07
SCl	0.40	0.40	0.43	0.31	0.57	0.27
SBr	0.40	0.40	0.43	0.31	0.57	0.28
SI	0.42	0.42	0.43	0.32	0.62	0.38
SH	0.16	0.16	0.20	0.07	0.36	0.02
SCF_3	0.42	0.42	0.43	0.38	0.50	0.38
SCN	0.53	0.53	0.54	0.49	0.61	0.49
SMe	0.31	0.31	0.31	0.18	0.57	0.32
SC≡CH	0.53	0.53	0.49	0.40	0.79	0.70
SAc	0.48	0.48	0.45	0.42	0.60	0.60
SCO_2Et	0.48	0.48	0.47	0.42	0.61	0.53
SPh	0.48	0.48	0.42	0.31	0.82	0.71
SBz	0.51	0.51	0.48	0.43	0.67	0.65
SCH_2Ph	0.29	0.29	0.28	0.15	0.57	0.33

[a]Set numbers refer to Table 6 of Reference 7.

TABLE 9. $\sigma_{k'/k}$ values for sulfenic acid derivative groups linked to other XY systems[a]

Set	P319	210	349	350	T3
η	−11.8	−0.272	−0.864	−1.08	1.20
P_D	74.7	60.7	79.5b	36.5	67.5
L	0.573	6.23	1.21[b]	4.89	−1.45
h	−0.102	1.36	1.078	−0.479	12.16
X			$\sigma_{k'/k}$		
SNH_2	2.08	−0.61	−1.29	0.08	−1.68
SNHMe	2.46	−0.65	−1.23	0.07	−1.79
$SNMe_2$	2.80	−0.60	−1.05	0.12	−1.77
SNHAc	1.47	−0.26	−0.76	0.21	−0.97
SOH	1.41	−0.38	−1.09	0.18	−1.20
SOMe	1.53	−0.40	−1.07	0.16	−1.24
SOAc	0.84	−0.09	−0.61	0.26	−0.58
SOPh	1.55	−0.29	−0.87	0.23	−1.06
SSH	1.67	−0.32	−0.81	0.19	−1.10
SSMe	1.74	−0.27	−0.71	0.22	−1.03
SSPh	1.93	−0.24	−0.59	0.24	−1.01
SF	0.64	−0.14	−0.91	0.28	−0.70
SCl	0.86	−0.04	−0.57	0.31	−0.52
SBr	0.88	−0.04	−0.57	0.31	−0.53
SI	1.08	−0.05	−0.47	0.30	−0.55
SH	0.71	−0.33	−0.94	0.07	−0.89
SCF_3	0.66	0.23	0.00	0.38	0.01
SCN	0.77	0.34	0.12	0.49	0.12
SMe	1.23	−0.27	−0.70	0.13	−0.89
SC≡CH	1.61	0.01	−0.12	0.31	−0.51
SAc	1.00	0.27	0.30	0.37	0.07
SCO_2Et	0.97	0.22	0.09	0.38	−0.06
SPh	1.90	−0.20	−0.37	0.20	0.88
SBz	1.19	−0.22	−0.20	0.37	0.07
SCH_2Ph	1.31	−0.33	−0.74	0.09	−0.97

[a] Set numbers are from Table 6 of Reference 7.
[b] Values of $\sigma_{k'/k}$ for set 319 are for $\eta = -6$. As σ_1 and σ_d are highly collinear in Set 349, the values of P_D and L are uncertain.



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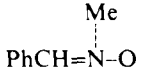

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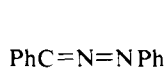


(9)

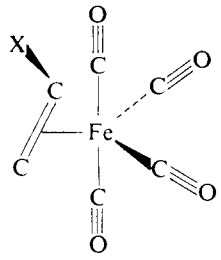
addition of diazomethane[29], of *C*-phenyl-*N*-methylnitrone[30] (**8**) and of diphenylnitrilimine[31] (**9**) to substituted ethylenes (sets 201, 349 and 350, respectively).

Rate constants for the thermal decomposition of iron tetracarbonyl substitited ethylene complexes[32], **10**, to give iron tetracarbonyl and substituted ethylenes were correlated with the LDRT equation[2],

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + T\tau + h \tag{46}$$

The temperature parameter τ is defined as

$$\tau = 1000/(t + 273.15) \tag{47}$$



(10)

where t is the temperature in degrees Celsius. This modification of the LDR equation is useful for the combination of rate data obtained at various temperatures into a single data set. Values of η, P_D, L and h for this set (set T3) are given in Table 9.

The SAD groups function as donors in sets 201, 349 and T3, together with the alkylthio and acylthio groups. The SCF_3, SCN and SC(O)Z groups are either acting as acceptors or have a very small electrical effect. All of the groups studied act as donors in sets P319 and 350.

5. XY_{Het} systems

We have shown that XY systems in which the substituent X is bonded to an element other than carbon can also be described by the LDR equation[33,34]. Values of P_D, η, L, h and the $\sigma_{k'/k}$ values for the SAD groups are reported in Table 10 for several reactions and properties of this type. They include pK_a values in water of XOH and XNH_3^+ and ionization potentials of XI and X_3P. All of the dicoordinate thia substituents have an acid strengthening effect on the pK_a values of XOH and XNH_3^+.

All but the SCF_3, SCN and SC(O)Z groups decrease the ionization potentials of XI and X_3P.

The range of reaction type covered in the 26 XY and XY_{Het} data sets discussed is very large. The electronic demand varies from -11.8 to 5.44. Clearly the validity of the LDR equation as a general model of electrical effects is supported by its ability to describe this wide spectrum of reactivity using the same three substituent constants in all cases.

C. Directing Effects of Sulfenic Acid Derivative Groups[2]

It is useful to classify directing effects in three categories:

1. Those involving a choice between structural isomers.
2. Those involving a choice between configurations.
3. Those involving a choice between conformational isomers.

1. Structural isomerism

Substituents are known to determine regioselectivity in a very wide range of reactions, including electrophilic, homolytic and nucleophilic aromatic substitutions; eliminations, addition to carbon–carbon double bonds, homolytic hydrogen abstraction and cycloadditions of various types. We will again, for purposes of comparison, consider the examples previously described[1,2]

TABLE 10. $\sigma_{k'/k}$ values for sulfenic acid derivative groups linked to elements other than carbon

Set	352	354	502	503
η	−4.56	−4.39	3.39	5.44
P_D	27.7	25.1	52.6	40.0
L	−20.0	−24.9	1.27	3.88
h	15.56	10.59	10.17	10.33
X			$\sigma_{k'/k}$	
SNH_2	0.57	0.47	−0.98	−0.84
SNHMe	0.61	0.50	−1.10	−0.97
$SNMe_2$	0.68	0.56	−1.12	−1.00
SNHAc	0.53	0.47	−0.49	−0.39
SOH	0.54	0.47	−0.59	−0.46
SOMe	0.54	0.47	−0.64	−0.52
SOAc	0.48	0.44	−0.17	−0.08
SOPh	0.58	−0.51	−0.52	−0.41
SSH	0.55	0.48	−0.59	−0.49
SSMe	0.58	0.51	−0.55	−0.46
SSPh	0.61	0.53	−0.56	−0.48
SF	0.51	0.47	−0.17	−0.05
SCl	0.52	0.49	−0.12	−0.03
SBr	0.52	0.49	−0.12	−0.03
SI	0.52	0.48	−0.18	−0.10
SH	0.31	0.27	−0.42	−0.32
SCF_3	0.47	0.45	0.18	0.22
SCN	0.58	0.56	0.29	0.33
SMe	0.42	0.36	−0.47	−0.39
SC≡CH	0.57	0.51	−0.25	−0.21
SAc	0.48	0.45	0.14	0.15
SCO_2Et	0.51	0.48	0.10	0.13
SPh	0.53	0.45	−0.54	−0.48
SBz	0.52	0.49	0.05	0.07
SCH_2Ph	0.39	0.33	−0.55	−0.47

In a kinetically controlled reaction the partial rate constant for the formation of the ith product is given by the relationship

$$k_i = f_i k / n_i \tag{48}$$

where k_i is the partial rate constant, f_i is the fraction of the total product which is i, k is the overall rate constant and n_i is the number of equivalent reaction sites at which attack of the reagent leads to the formation of the ith product. Applying the LDR equation gives

$$\log k_{i,X} = L_i \sigma_{IX} + D_i \sigma_{dX} + R_i \sigma_{eX} + h_i \tag{49}$$

Orientation (regioselectivity) is often expressed as the ratio of the fraction of the ith product to that of the jth product,

$$\phi_{ij} = f_i / f_j \tag{50}$$

From equation 48

$$f_i = k_i n_i / k \tag{51}$$

$$f_j = k_j n_j / k \tag{52}$$

$$\phi_{ij} = k_i n_i / k_j n_j \tag{53}$$

and

$$\log\phi_{ij}=\log k_i-\log k_j+\log(n_i/n_j) \tag{54}$$

$$=L_i\sigma_{1X}+D_j\sigma_{dX}+R_i\sigma_{eX}+h_i$$

$$-(L_j\sigma_{1X}+D_j\sigma_{dX}+R_j\sigma_{eX}+h_j)+\log(n_i/n_j) \tag{55}$$

where

$$L_{ij}=L_i-L_j,\ D_{ij}=D_i-D_j,\ R_{ij}=R_i-R_j \text{ and } h_{ij}=h_i-h_j \tag{56}$$

As $100\,f_i$ equals P_i, where P_i is the percent of the ith component in the product,

$$\phi=P_i/P_j \tag{57}$$

Orientation is therefore a function of the difference in substituent effects between the reaction which leads to the ith product and that which leads to the jth product. Usually the composition of the electrical effect differs in the two reactions. Thus, although the ratio ϕ can be quantitatively described by the LDR equation or some relationship derived from it, no mechanistic conclusion can be drawn from the resulting regression equation. Correlation of rate constants by the LDR equation will give L and D values of the same sign if there is a single rate-determining step. Different signs of L and D are diagnostic for a rate determined by more than one process. This may involve two competing rate-determining steps, or a combination, or a rate-determining step with an equilibrium. It is not at all unusual for a correlation of ϕ_{ij} values which are also a combination of two rate constants to have L and D values of different signs.

We consider the same three cases studied previously[2]:

a. Partial rate factors for the reaction of substituted benzenes with cyano radicals[35] in equimolar PhH–PhX at 15–20 °C were correlated with the LDRS equation in the case of f_o and with the LDR equation for the f_m and f_p values[36] to give

$$\log f_{oX}=-0.46\sigma_{1X}-0.463\sigma_{dX}-3.31\sigma_{eX}-0.116\upsilon_X+0.264 \tag{58}$$

$$\log f_m=-0.340\sigma_{1X}-0.0194\sigma_{dX}-0.00959\sigma_{eX}+0.0342 \tag{59}$$

$$\log f_{pX}=-0.366\sigma_{1X}-0.675\sigma_{dX}-3.08\sigma_{eX}-0.0193 \tag{60}$$

Then

$$\log(f_of_p)_X=-0.100\sigma_{1X}+0.212\sigma_{dX}-0.116\upsilon_X+0.0457 \tag{61}$$

$$\log(f_o/f_m)=-0.12\sigma_{1X}-0.444\sigma_{dX}-3.32\sigma_{eX}-0.116\upsilon_X-0.0078 \tag{62}$$

$$\log(f_m/f_p)_X=0.656\sigma_{dX}-3.07\sigma_{eX}+0.0535 \tag{63}$$

Thus, *ortho* versus *para* substitution is dependent on σ_1, σ_d and υ. *Meta* versus *para* is a function of σ_d and σ_e, and *ortho* versus *meta* depends on all four independent variables.

b. Selectivities for hydrogen abstraction from 1-substituted butanes by Cl[37]. The selectivity at position n relative to that at position 4 is given by S_4^n where

$$S_4^n=f_n/f_4 \tag{64}$$

Applying the LDR equation gives[38]

$$\log S_4^1=-1.57\sigma_{1X}-1.91\sigma_{dX}-4.98\sigma_{eX}-0.0671 \tag{65}$$

and

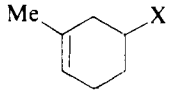
$$\log S_4^2=-0.456\sigma_{1X}+0.677\sigma_{dX}+4.20\sigma_{eX}+0.684 \tag{66}$$

c. Cycloaddition reactions. Isoprene reacts with substituted ethylene dienophiles to give rise to two products: 5- and 4-substituted-1-methyl cyclohexanes, **11** and **12**,

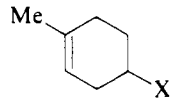
respectively[39]. The ratio $\phi = P_{11}/P_{12}$ when correlated with the LDR equation gives

$$\log \phi_X = 0.557\sigma_{1X} - 0.656\sigma_{dX} - 3.39\sigma_{eX} - 0.00906 \quad (67)$$

As ϕ equals 1 when X is H, this data point was included in the data set. As all of the dicoordinate sulfur groups have negative values of σ_d and almost all have negative σ_e values, they should all increase log ϕ and thereby favor the formation of **11** over **12**.



(**11**)

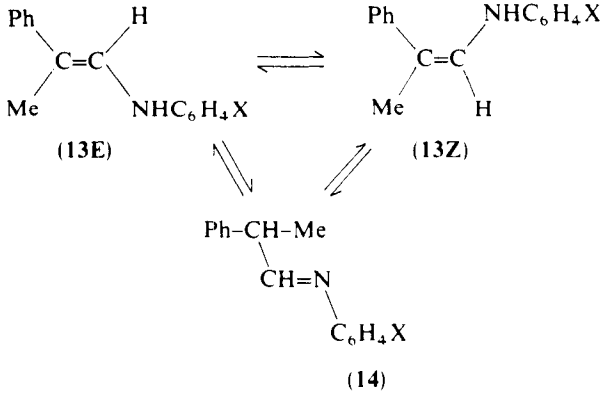


(**12**)

Tautomerism is defined as an equilibrium between structural isomers. It is therefore a prime example of directing effects. We consider here two examples of prototropic tautomerism. Values of K for the enamine equilibrium shown below have been determined[40]. The equilibrium constants for enamine–amine tautomerism are given by the relationships

$$K_{Ze/i} = P_{13Z}/P_{14} \quad (68)$$

$$K_{Ee/i} = P_{13E}/P_{14} \quad (69)$$



(**13E**) (**13Z**)

(**14**)

where *e* and *i* designate the enamine and imine, respectively. For 3-substituted compounds

$$\log K_{Ze/i,X} = 0.521\sigma_{1X} + 0.157\sigma_{dX} + 0.104\sigma_{eX} + 0.270 \quad (70)$$

$$\log K_{Ee/i,X} = 0.419\sigma_{1X} + 0.138\sigma_{dX} - 0.378\sigma_{dX} - 0.975 \quad (71)$$

while for 4-substituted compounds

$$\log K_{Ze/i,X} = 1.19\sigma_{1X} + 2.05\sigma_{dX} - 0.844\sigma_{eX} + 0.266 \quad (72)$$

$$\log K_{Ee/i,X} = 0.893\sigma_{1X} + 1.71\sigma_{dX} - 0.617\sigma_{eX} + 1.011 \quad (73)$$

The concentration of both *cis* and *trans* enamines should be favored over the imine by SAD groups.

We now consider the preference for *trans*-enamine versus that for *cis*-enamine. The quantity of interest is P_{12Ze}/P_{12Ee}. For the 3-substituted compounds

$$\log(P_{Ze}/P_{Ee}) = \log[(K_{Ze/i})/(K_{Ee/i})] \tag{74}$$

$$= \log K_{Ze/i} - \log K_{Ee/i} \tag{75}$$

$$= 0.102\sigma_{1X} + 0.019\sigma_{dX} + 0.482\sigma_{eX} - 0.705 \tag{76}$$

Similarly for the 4-substituted compounds

$$\log K_{Ze/i} - \log K_{Ee/i} = 0.297\sigma_{1X} + 0.340\sigma_{dX} - 0.227\sigma_{eX} - 0.745 \tag{77}$$

Thus, when X = H the *trans*-enamine is preferred.

For the SAD groups in the 3-position the *trans*-enamine should continue to be preferred as the substituent effect is very small. For these groups in the 4-position this will also be the case.

Another tautomeric example involves the equilibrium[41] between 1-substituted 3-methyl-1-butenes, **15**, and 1-substituted 3-methyl-2-butenes, **16**.

$$XCH{=}CHCHMe_2 \rightleftharpoons XCH_2{-}CH{=}CMe_2$$

(15) **(16)**

ΔG values for this reaction are described by the equation

$$\Delta G_X = -3.04\sigma_{dX} - 4.05\upsilon_X + 3.11 \tag{78}$$

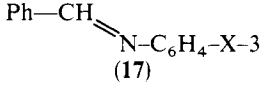
Steric effects are predominant. The σ_d values of dicoordinate sulfur groups are all negative, which should increase ΔG, while the larger the group the smaller will be the ΔG value. In Table 11 values of ΔG calculated from equation 78 for SAD groups and for some other SZ groups are reported.

2. *Configurational isomerism*

Correlation of rate constants for the thermal relaxation of photoisomerized 3′-substituted *N*-benzylideneanilines[42], **17**, with the LDR equation gave

$$\log k_{1X} = 1.596\sigma_{1X} + 0.5422\sigma_{dX} + 2.54\sigma_{eX} + 0.217 \tag{79}$$

with $P_D = 25.4$ and $\eta = 4.69$. All of the SAD groups except the sulfenyl halides will decrease $\log k_{1,X}$,



(17)

TABLE 11. Predicted values of ΔG_X for SAD groups calculated from equation 78

X	SNH_2	SNHMe	$SNMe_2$	SNHAc	SOH
ΔG_X	2.34	1.68	0.21	0.44	2.08
X	SOMe	SOAc	SOPh	SSH	SSMe
ΔG_X	1.59	0.16	0.49	1.46	1.00
X	SSPh	SF	SCl	SBr	SI
ΔG_X	0.43	1.32	1.18	0.97	0.79
X	SMe	SPh	SC≡CH	SCF_3	SCN
ΔG_H	1.67	0.09	−0.31	−1.94	−1.33

3. Conformational isomerism

Values of ΔG for the rotational barriers in 4-substituted acetophenones and benzaldehydes in a mixture of $CHCl_2F$ and $CHClF_2$ have been determined[43]. Also studied were ΔG values for protonated acetophenones in $SO_2ClF + HSO_3F$–SbF_5. Correlation with the LDR equation gave for the benzaldehydes

$$\Delta G = -5.31\sigma_{1X} - 12.0\sigma_{dX} - 25.4\sigma_{eX} + 31.5 \tag{80}$$
$$P_D = 69.4,\ \eta = 2.11$$

for the acetophenones

$$\Delta G = -5.54\sigma_{1X} - 11.6\sigma_{dX} - 22.8\sigma_{eX} + 22.4 \tag{81}$$
$$P_D = 67.6,\ \eta = 1.97$$

and for the protonated acetophenones

$$\Delta G = -19.4\sigma_{1X} - 35.4\sigma_{dX} - 47.4\sigma_{eX} + 60.1 \tag{82}$$
$$P_D = 64.6,\ \eta = 1.34$$

All of the dicoordinate sulfur groups increase ΔG for the benzaldehydes and acetophenones. All but SCF_3, SCN and SC(O)Z increase it for the protonated acetophenones.

D. Substituent Effects on Chemical Properties

We now consider some applications of the IMF equation to chemical properties. Haky and Young[44] have reported capacity factors k' for high-performance liquid chromatography (HPLC) of substituted benzenes. Correlation of $\log k'$ with the IMF equation gave (set C1)[45]

$$\log k'_X = -0.750\sigma_{1X} - 0.477\sigma_{dX} + 2.77\sigma_{eX} + 4.80\alpha_X - 0.489n_{HX} - 0.134n_{nX} + 0.949 \tag{83}$$

Using different experimental conditions Sader and Carr[46] have also determined capacity factors for the HPLC of substituted benzenes. Correlation of their data with the IMF equation gave (set C28)[45]

$$\log k'_X = -0.405\sigma_{1X} - 0.397\sigma_{dX} + 1.77\alpha_X - 0.402n_{HX} - 0.695i_X - 0.341 \tag{84}$$

A parameter often used in modeling bioactivities is π_X, which is defined by the relationship

$$\pi_X = \log P_{XGY} - \log P_{HGY} \tag{85}$$

where P is the partition coefficient between 1-octanol and water. Hansch and Leo[47] have reported a set of preferred π_X values. Correlation of these values with the IMF equation gave (set PI51)[45]

$$\pi_X = -0.569\sigma_{dX} + 5.77\sigma_{eX} + 9.01\alpha_X - 0.222n_{HX} - 0.421n_{nX} + 0.161 \tag{86}$$

Finally Taylor and coworkers[48] have reported $\log P$ values for 2-substituted pyridines. Correlation of these values with the IMF equation gave (set LP11)[45]

$$\log P_X = -0.238\sigma_{1X} - 0.763\sigma_{dX} + 2.53\sigma_{eX} + 6.58\alpha_X - 0.274n_{HX} - 0.160n_{nX} + 0.240\upsilon_X + 0.732 \tag{87}$$

Calculated values of $\log k'_X$, π_X and $\log P_X$ for SAD groups and for some other SZ groups of interest are reported in Table 12.

TABLE 12. Values of log k', π and log P calculated for SZ groups

Z	log k'	log k'	π	log P
NH_2	−0.15	−0.81	−0.53	0.84
NHMe	0.51	−0.31	−0.04	1.41
NMe_2	1.13	0.17	0.53	2.04
NHAc	0.61	−0.34	0.05	0.53
OH	0.16	−1.22	−0.62	0.86
OMe	0.88	−0.03	0.00	1.47
OAc	0.95	−0.03	−0.06	1.56
OPh	1.81	0.29	1.82	2.79
SH	1.20	−0.02	0.93	1.83
SMe	1.39	0.04	1.33	2.14
SPh	2.34	0.40	3.11	3.48
F	0.93	−0.23	0.67	1.45
Cl	1.17	−0.16	1.10	1.75
Br	1.28	−0.12	1.31	0.91
I	1.50	−0.02	1.67	2.21
CF_3	1.19	−0.24	1.17	1.81
CN	0.95	−0.29	0.71	1.56
Me	1.16	−0.09	0.78	1.62
C≡CH	1.21	−0.10	1.06	1.85
Ph	2.01	0.26	2.37	2.92
Set	Cl	C28	PI51	LP11
Substrate	PhX	PhX	PhX	2-XC_6H_4N

VI. CONCLUSIONS

Sulfenic acid derivative groups, alkylthio groups, arylthio and vinylthio groups, and ethynylthio groups are all capable of acting as electron donors when bonded to an electronically deficient active site. They are also all capable of acting as electron acceptors when bonded to an electron-rich active site. This is very different from the behavior of alkoxy groups, which act as electron donors over most of their electrical-effect surface. The difference is largely accounted for by the larger values of σ_e, the sensitivity to electronic demand. The ratio $\sigma_{eSX}/\sigma_{eOX}$ for most groups is about 2. Dicoordinate selenium substituents are predicted to behave very much like the dicoordinate sulfur substituents. Dicoordinate tellurium groups should behave somewhat like their sulfur analogs.

The steric effect of MZ groups as a function of M should increase in the order O < S < Se < Te as would be expected. The intermolecular force polarizability parameter will follow the same sequence. The charge transfer donor parameter will take the value 1 for all dicoordinate chalcogen groups.

We believe that these predictions are probably reasonable, but we must again emphasize the need for experimental work in this area. It is vital to be able to test our predictions by comparison with experimental results. We strongly urge experimentalists to measure chemical reactivities and properties which will enable us to determine the validity of our picture of chalcogen substituent effects.

VII. APPENDIX I. GLOSSARY

General

X A variable substituent.

Y An active site. The atom or group of atoms at which a measurable phenomenon occurs.

G	A skeletal group to which X and Y may be attached.
Parameter	An independent variable.
Pure parameter	A parameter which represents a single effect.
Composite parameter	A parameter which represents two or more effects.
Monoparametric equation	A relationship in which the structural effect on a property or reactivity is represented by a single generally composite parameter.
Diparametric equation	A relationship in which the structural effect on reactivity or properties is represented by two parameters. In the case of electrical effects either both parameters are composite or one is and the other is not. Examples are the LD and CR equations. Other examples are the Taft, Ehrenson and Brownlee DSP (Dual Substituent Parameter), Yukawa–Tsuno YT, and the Swain, Unger, Rosenquist and Swain SURS equations. The DSP equation is a special case of the LD equation with the intercept set equal to zero. It is inconvenient to use and has no advantage. The F and R parameters of the SURS equation, though intended to be pure localized and delocalized electrical effect parameters, are in fact composite making interpretation of the results more difficult. Our results concerning the nature of the σ_R^0 parameters throw some doubt on the interpretation of the results obtained from correlation with the YT equation. We prefer the use of the LDR, LD, CR and Hammett equations for which the interpretation of the results is clear and unambiguous.
Triparametric equation	The structural effect is represented by three parameters. They may all be composite parameters, they may all be pure parameters or they may be a combination of pure and composite parameters.
LDR equation	A triparametric equation which models electrical effects of substituents.

Electrical Effect Parametrization

σ_I	The localized electrical effect parameter. It is identical to σ_I. Though other localized effect parameters such as σ_I^q and σ_F have been proposed, there is generally no advantage in their use. The σ^* parameter is also sometimes used as a localized electrical-effect parameter. This is acceptable only if the values used are for CH_2X. In general it is best to avoid using this parameter.
σ_d	The intrinsic delocalized (resonance) electrical-effect parameter. It represents the delocalized effect in a system with zero electronic demand.
σ_e	The electronic demand sensitivity parameter. It adjusts the delocalized effect of a group to meet the electronic demand of the system.
σ_D	A composite delocalized effect parameter which is a function of σ_d and σ_e. Examples of σ_D constants are σ_R^+ and σ_R^- constants. The $\sigma_{R,k}$ constants, where k designates the value of the electronic demand η, are also examples of σ_D constants.

σ_R A composite delocalized electrical-effect parameter of the σ_D type with η equal to 0.380. It is derived from benzoic acid pK_a values.

σ_R^0 A composite delocalized electrical-effect parameter of the σ_D type with η equal to -0.376. It is derived from phenylacetic acid pK_a values.

σ_R^+ A composite delocalized electrical-effect parameter of the σ_D type with η equal to 2.04. It is derived from solvolysis of cumyl chlorides.

σ_R^+ A composite delocalized electrical-effect parameter of the σ_D type with η equal to 3.31. It is derived from ionization potentials of the lowest-energy π orbital in substituted benzenes.

σ_R^- A composite delocalized electrical-effect parameter of the σ_D type with η equal to -1.40. It is derived from anilium ion pK_a values.

σ_R^- A composite delocalized electrical-effect parameter of the σ_D type with η equal to -2.98. It is derived from substituted nitrile pK_a values.

σ_{Id} A composite parameter which is a function of σ_I and σ_d. Its composition is designated by k', the value of P_D.

σ A composite parameter which is a function of σ_I, σ_d and σ_e. Examples are σ_p^0, σ_p^+ and σ_m. Alternatively these constants may be written in the form $\sigma_{k'/k}$ where k designates the value of η and k' that of P_D.

P_{EA} The percent of the $\sigma_{k'/k}$ values in the matrices of Table 2 that exhibit an electron acceptor electrical effect.

P_{ED} The percent of the $\sigma_{k'/k}$ values in the matrices of Table 2 that exhibit an electron donor electrical effect.

P_0 The percent of the $\sigma_{k'/k}$ values in the matrices of Table 2 that exhibit no significant electrical effect.

η The electronic demand of a system. It is equal to the ratio R/D where R and D are the coefficients of σ_e and σ_d, respectively. They are obtained from the correlation of a data set with the LDR equation. It is a descriptor of the nature of the electrical effect in a given system.

P_D The percent delocalized effect. It too is a descriptor of the electrical effect exerted by a substituent in a given system.

Steric Effect Parametrization

r_V The van der Waals radius. The distance between the nuclei of two nonbonded atoms in contact is equal to the sum of their van der Waals radii.

υ A steric parameter. For groups whose steric effect is at most minimally dependent on conformation it represents the steric effect due to the first atom of the longest chain in the group and the branches attached to that atom. The only alternative monoparametric method for describing steric effects is that of Taft which uses the E_S parameter. This was originally developed only for alkyl and substituted alkyl groups and for hydrogen. Hansch and Kutter have estimated E_S values for other groups from the υ

values using a method which in many cases disregards the MSI principle. It is best to avoid their use.

Simple branching (SB) equation — A topological method for describing steric effects by using as parameters n_i, the number of atoms other than H that are bonded to the ith atoms of the substituent.

Expanded branching (XB) equation — A topological method for describing steric effects which takes into account the order of branching by using as parameters n_{ij}, the number of jth branching atoms bonded to the ith atoms of the substitutent.

n_b — The number of bonds in the longest chain of a substituent. It is a steric parameter which serves as a measure of the length of a group along the group axis.

MSI principle — The principle of minimal steric interaction which states that the preferred conformation of a group is that which results in the smallest possible steric effect.

Intermolecular Force Parameterization

α — A polarizability parameter defined as the difference between the group molar refractivities for the group X and for H divided by 100. Many other polarizability parameters such as the van der Waals volume, the group molar volume and the parachor can be used in its place. All of these polarizability parameters are very highly linear in each other.

n_H — A hydrogen-bonding parameter which represents the lone-pair acceptor (proton donor) capability of a group. It is defined as the number of OH and/or NH bonds in the group.

n_n — A hydrogen-bonding parameter which represents the lone-pair donor (proton acceptor) capability of the group. It is defined as the number of lone pairs on O and/or N atoms in the group.

A parameter which represents ion-dipole and ion-induced dipole interactions. It is defined as 1 for ionic groups and 0 for nonionic groups.

n_D — A charge transfer donor parameter which takes the values 1 when the substituent can act as a charge transfer donor and 0 when it cannot.

n_A — A charge transfer acceptor parameter which takes the values 1 when the substituent can act as a charge transfer acceptor and 0 when it cannot.

IMF equation — A multiparametric equation which models phenomena that are a function of the difference in intermolecular forces between an initial and a final state.

Statistics

Correlation equation — An equation with which a data set is correlated by simple (one parameter) or multiple (two or more parameters) linear regression analysis.

Regression equation — The equation obtained by the correlation of a data set with a correlation equation.

n — The number of data points in a data set.

Degrees of freedom (DF)	Defined as n minus the number of parameters N_p plus 1 [DF $= n-(N_p+1)$].
F statistic	A statistic which is used as a measure of the goodness of fit of a data set to a correlation equation. The larger the value of F the better the fit. Confidence levels can be assigned by comparing the F value calculated with the values in an F table for the N_p and DF values of the data set.
$100R^2$	A statistic which represents the percent of the variance of the data accounted for by the regression equation. It is a measure of the goodness of fit.
s_{est}	The standard error of the estimate. It is a measure of the error to be expected in predicting a value of the dependent variable from the appropriate parameter values.
s^0	Defined as the ratio of s_{est} to the root mean square of the data. It is a measure of the goodness of fit. The smaller the value of s^0 the better the fit.
Other	
SAD	Sulfenic acid derivative

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **16**

Biochemistry and metabolic pathways of sulfenic acids and their derivatives

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. INTRODUCTION

Sulfenic acids have been proposed as key intermediates in a number of biochemical reactions including metabolic pathways. However, the number of examples is rather limited; despite numerous attempts to find evidence for the formation of sulfenic acids in biological transformations, only a few examples have been presented that are based on conclusive evidence. This results not only from the high reactivity of sulfenic acids, but also from the high reactivity of some of the reaction products.

Biologically, the most important reaction of thiols is their oxidation to disulfides and higher sulfur oxides. In all these conversions sulfenic acids might be involved. The formation of protein disulfides (**3**) from protein thiols (**1**) could well involve the intermediacy of protein sulfenic acids (**2**) as expressed in equations 1 and 2. Beside the formation of a disulfide, the reaction considered to be most characteristic of sulfenic acids is dehydration to thiosulfinates (**4**) (equation 3). These compounds are thermally labile and have a tendency to disproportionate to thiosulfonate (**5**) and the corresponding disulfide (equation 4). Both equations 1 and 2 and equations 3 and 4 result in the formation of disulfides so often observed for protein thiols.

$$\underset{(1)}{\text{P–SH}} \xrightarrow{[O]} \underset{(2)}{\text{P–SOH}} \tag{1}$$

$$\text{P–SOH} + \text{P–SH} \longrightarrow \underset{(3)}{\text{P–SS–P}} + \text{H}_2\text{O} \tag{2}$$

$$2\ \text{P–SOH} \longrightarrow \underset{(4)}{\text{P–S(O)S–P}} + \text{H}_2\text{O} \tag{3}$$

$$2\ \text{P–S(O)S–P} \longrightarrow \underset{(5)}{\text{P–S(O}_2\text{)S–P}} + \text{P–SS–P} \tag{4}$$

P = protein

An interesting question is the biochemical importance of the formation of sulfenic acids. In Section II it is mentioned that the oxidation of a protein thiol to a protein sulfenic acid has been considered necessary for a certain enzymatic activity, whereas in other cases deactivation of the enzyme results. In Section III evidence is examined invoking the

intermediacy of sulfenic acid in order to rationalize the incorporation of inorganic selenium into organic molecules and thus into living systems. Moreover, their intermediacy in the biotransformation pathway and possible detoxification of xenobiotics has been discussed. And finally in Section IV evidence is presented that the antineoplastic activity of aromatic thiols might well be related to their metabolic activation giving sulfenic acids.

In this chapter we wish to discuss the biochemistry and metabolic pathways of the reactions given in equations 1–4. The role of sulfenic acids in these equations is still rather speculative. Nevertheless, evidence is accumulating that they might play a crucial—but hitherto neglected—role as intermediates in metabolic pathways. We feel that a comprehensive overview on this subject is timely. This chapter presents the first extensive review of this topic[1,2].

II. PROTEIN SULFENIC ACIDS AND THEIR DERIVATIVES

The side-chains of cysteinyl residues in proteins either exist in the free sulfhydryl form or are linked covalently to another cysteinyl side-chain through a disulfide bond. These disulfide bonds in native proteins are formed by the oxidation of specific pairs of cysteinyl residues that are brought into close proximity by the spontaneous folding of newly synthesized polypeptide chains. In specific proteins, viz. cysteine proteinases, thiol proteinases or sulfhydryl proteases, a free sulfhydryl group is present in the catalytically active site. Results from a number of investigations suggest that the sulfhydryl groups in these proteins are converted to sulfenic acids or other sulfenyl derivatives, and *not* to disulfide bonds, when they react with mild oxidants under nondenaturing conditons[2].

These sulfenic acids have been suggested to be intermediates but have been considered to be too unstable to accumulate to any extent. This consideration is based on the fact that sulfenic acids in small molecules readily react as either a nucleophile or an electrophile. However, certain protein cysteinyl side-chains are unique in that they are situated in a groove or a cleft of the enzyme. For this reason they are sterically restricted from forming intra- or intermolecular disulfides and, upon mild oxidation, form unusually stable protein sulfenic acids.

A. Identification

Since sulfenic acids are unstable and do not possess distinguishing spectroscopic features that can be used for their identification in intact proteins, the existence of protein sulfenic acids rests on indirect evidence. Frequently used test reactions to distinguish sulfenic acids (**2**) from sulfhydryls (**1**) involve 5,5′-dithiobis-2-nitrobenzoic acid (DTNB, Ellman's reagent) often with the addition of urea, 4,4′-bis(dimethylamino) thiobenzophenone (TMK, thio-Michler's ketone), sodium *p*-chloromercuribenzoate (*p*-CMB) or sodium *p*-hydroxymercuribenzoate (*p*-HMB, **6**), low molecular weight thiols (RSH) like cysteine, dithiothreitol (DTT) and β-mercaptoethanol or sodium arsenite (**7**). Moreover, protein sulfenic acids (**2**), unlike the higher oxidation products sulfinic and sulfonic acids, can be reduced to the corresponding thiols (**1**) by the addition of sulfhydryl compounds (RSH) as depicted in equations 5 and 6.

DTNB, *p*-CMB and *p*-HMB react with protein sulfhydryl groups. However, it was shown that *p*-HMB (**6**) reacts to some extent also with sulfenic acids (equation 7)[3]. Reaction of the thiol anion product of the DTNB reaction with sulfenic acid may also lead to anomalous results.

Sodium arsenite (**7**) is capable of reducing only sulfenic acids (equation 8), but not disulfide bonds[3]. TMK (thio-Michler's ketone) reacts specifically with sulfenyl derivatives[4].

$$\underset{\textbf{(2)}}{\text{P–SOH}} + \text{RSH} \longrightarrow \text{P–SSR} + \text{H}_2\text{O} \quad (5)$$

$$\text{P–SSR} + \text{RSH} \longrightarrow \underset{\textbf{(1)}}{\text{P–SH}} + \text{RSSR} \quad (6)$$

$$\underset{\textbf{(6)}}{\text{P–SOH} + \text{HOHgC}_6\text{H}_4\text{COO}^-} \longrightarrow \text{P–SOHgC}_6\text{H}_4\text{COO}^- + \text{H}_2\text{O} \quad \text{or P–SHgC}_6\text{H}_4\text{COO}^- + \text{H}_2\text{O}_2 \quad (7)$$

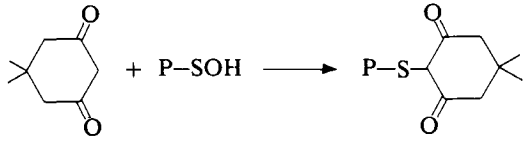
$$\underset{\textbf{(7)}}{\text{P–SOH} + \text{AsO}_2^- + \text{OH}^-} \longrightarrow \text{P–SH} + \text{AsO}_4^{3-} + \text{H}^+ \quad (8)$$

The specific conversion of Cys-149 in glyceraldehyde 3-phosphate dehydrogenase (GAPDH) to a sulfenic acid (**8**) (see the next section) converts the enzyme from a dehydrogenase to an acyl phosphatase as illustrated in equations 9 and 10[2, 5–7]. Thus, monitoring this activity has proved useful for the identification of sulfenic acids in this particular protein. The acyl phosphatase activity of GAPDH, mediated by the sulfenate ester **9**, disappears when the sulfenic acid is reduced or otherwise modified.

$$\underset{\textbf{(8)}}{\text{GAPDH–SOH} + \text{RC(O)OPO}_3\text{H}^-} \longrightarrow \underset{\textbf{(9)}}{\text{GAPDH–SOC(O)R}} + \text{H}_2\text{PO}_4^- \quad (9)$$

$$\text{GAPDH–SOC(O)R} + \text{H}_2\text{O} \longrightarrow \text{GAPDH–SOH} + \text{RC(O)O}^- + \text{H}^+ \quad (10)$$

Protein sulfenic acids react in two ways with a variety of nucleophiles[2]. Thiols like dithiothreitol and β-mercaptoethanol, thiosulfate, thiourea, azide, phenyl- and isopropylhydrazine and ascorbate *reduce* the sulfenic acid at the active site of GAPDH. Dimedone, olefins, semicarbazide, benzylamine and tetrahydrophthalimide, on the other hand, *react* irreversibly with the GAPDH sulfenic acid to form a derivative; see e.g. equation 11 [dimedone (**10**) inactivation of GAPDH].



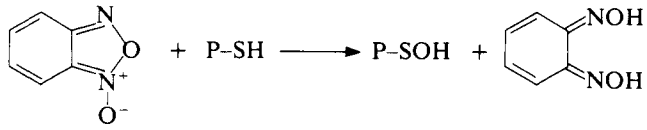
(11)

(10)

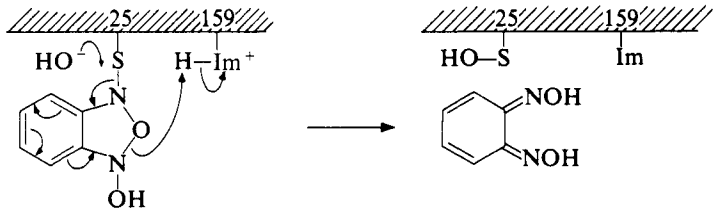
Peroxide-inactivated papain (P–SOH, see the next section) is repaired by the addition of cysteine or cyanide. After the addition of benzylamine, however, an irreparable enzyme is formed by formation of a sulfenamide derivative ($\text{P–SNHCH}_2\text{Ph}$) of the enzyme. Benzylamine has no effect on active GAPDH, but inhibits irreversibly the acyl phosphatase activity of the inactivated enzyme[2].

It was shown that benzofuroxan (**11**) reacts with the active site thiol group of actinidin, papain, ficin and bromelain. Hence it was concluded that this reagent is a suitable probe for investigating the catalytic site of cysteine proteinases[8–10]. Whereas reaction of

benzofuroxan with low-molecular-weight thiols, e.g. 2-mercaptoethanol, produces disulfides and *o*-benzoquinone dioxime (**12**), disulfide formation in the enzymes mentioned is prevented by steric factors and consequently the protein sulfhydryls are oxidized to sulfenic acids (equation 12). For papain, the mechanism for oxidation of Cys-25 by benzofuroxan was proposed to involve the imidazole of His-159 as a catalyst forming a S^-/ImH^+ ion-pair (equation 13). Little attention has been paid, however, to the experimental proof for the occurrence of the proposed protein sulfenic acid.



(**11**) (**12**) (12)



(13)

B. Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH) and Papain

1. Occurrence of sulfenic acids

Two characteristic examples of proteins having cysteinyl side-chains in the catalytically active site that are sterically restricted from forming disulfides are discussed here.

Studies on the catalytically active sulfhydryl groups of papain and GAPDH in particular have illustrated that specific protein sulfhydryl groups are oxidized to stable sulfenic acids[2]. Papain catalyzes the hydrolysis of peptide bonds and the hydrolysis of synthetic amides and esters, while GAPDH catalyzes the oxidative phosphorylation of 3-phosphoglyceraldehyde (equations 14 and 15). Both papain's Cys-25 and GAPDH's Cys-149 participate directly in catalysis, forming an enzyme thiol ester intermediate (**13**).

The elucidation of the three-dimensional structure of papain has revealed that the side-chain of Cys-25, the single sulfhydryl group in the enzyme, is located in a groove on the surface of the enzyme[11].

$$\begin{array}{l} \text{GAPDH–SH} + \text{RCHO} \longrightarrow \text{GAPDH–SC(O)R} + \text{H}^+ \\ \quad\vert \qquad\qquad\qquad\quad \vert \\ \text{NAD}^+ \qquad\qquad\quad \text{NADH} \\ \qquad\qquad\qquad\quad (\mathbf{13}) \end{array} \tag{14}$$

$$\begin{array}{l} \text{GAPDH–SC(O)R} + \text{H}_2\text{PO}_4^- \longrightarrow \text{GAPDH–SH} + \text{RC(O)OPO}_3\text{H}^- \\ \quad\vert \qquad\qquad\qquad\quad \vert \\ \text{NADH} \qquad\qquad\quad \text{NADH} \end{array} \tag{15}$$

The catalytically active sulfhydryl group of GAPDH reacts stoichiometrically with *o*-iodosobenzoate[5, 6, 12] or hydrogen peroxide[2] (equation 16) forming a sulfenic acid at Cys-149. By this reaction the enzyme loses its dehydrogenase activity, which can be restored by the addition of thiols as depicted in equations 5 and 6.

$$\text{GAPDH–SH} + \text{H}_2\text{O}_2 \longrightarrow \text{GAPDH–SOH} + \text{H}_2\text{O} \tag{16}$$

Upon irradiation of dilute aqueous solutions of papain[3, 13–15] or GAPDH[16] oxidation of the active site sulfhydryl groups to enzyme sulfenic acids occurs by hydrogen peroxide (equation 16) generated by the γ-irradiation of water (equation 17). Loss of enzyme activity is accompanied by a parallel loss of sulfhydryl groups. Enzyme activity was largely restored by post-irradiation treatment with thiols or sodium arsenite. Some nonrepairable, inactive enzyme is formed by the action of hydroxyl radicals (HO$^\bullet$) that were also formed upon γ-radiolysis (equations 18 and 19). It should be noted here that hydroxyl radicals not only destruct the protein sulfenic acid, but are also prone to react with the aromatic amino acid residues of tyrosine, tryptophan, phenylalanine and histidine[15].

$$\text{H}_2\text{O} \rightsquigarrow \text{e}_{\text{aq}}^- + \text{H}^\bullet + \text{HO}^\bullet + \text{H}_2 + \text{H}_2\text{O}_2 \tag{17}$$

$$\text{P–SH} + \text{HO}^\bullet \longrightarrow \text{P–S}^\bullet + \text{H}_2\text{O} \tag{18}$$

$$\text{P–S}^\bullet + \text{O}_2 \longrightarrow \text{P–SO}_2^\bullet \longrightarrow \text{P–SO}_2\text{H} + \text{P–SO}_3\text{H} \tag{19}$$

2. Sulfenic acids as catalytically active species

The conversion of GAPDH's dehydrogenase activity into acyl phosphatase activity is associated with the specific conversion of Cys-149 into a sulfenic acid moiety (equations 9 and 10). From studies with benzylamine evidence was presented that the sulfenic acid form of GAPDH also possesses a limited amine oxidase activity[2, 17, 18]. It was proposed that the sulfenic acid functions as an oxidizing agent or electron acceptor, being reduced to a sulfhydryl group concomitantly with oxidation of the amine substrate **14**, via the sulfenamide derivative **15**, to the imine **16** which then hydrolyzes to ammonia and benzaldehyde in the case of benzylamine (equations 20–22). This oxidative deamination of primary amines is known to be catalyzed by copper-containing nonflavin amine oxidases. However, in a later report it was shown that benzylamine oxidase contains pyridoxal phosphate as the prosthetic group, since there was no catalytic production of ammonia or hydrogen peroxide from benzylamine during the catalytic action of benzylamine oxidase under anaerobic conditions[19].

$$\underset{\text{Im}}{\text{GAPDH–SOH}} + \text{H}_2\text{NCH}_2\text{R} \longrightarrow \underset{\text{Im}}{\text{GAPDH–SNHCH}_2\text{R}} \tag{20}$$

(14) **(15)**

$$\begin{array}{l} \text{GAPDH–SNHCH}_2\text{R} \longrightarrow \text{GAPDH–S}^- + \text{HN=CHR} \\ \quad\vert \qquad\qquad\qquad\quad \vert \\ \quad\text{Im} \qquad\qquad\quad \text{ImH}^+ \end{array} \tag{21}$$

(16)

$$\text{HN=CHR} + \text{H}_2\text{O} \longrightarrow \text{NH}_3 + \text{RCHO} \tag{22}$$

3. Intramolecular disulfide formation

A stable sulfenyl thiosulfate derivative of Cys-149 (**17**) is formed when GAPDH is inactivated with tetrathionate (equation 23)[20]. Subsequent heat treatment causes the formation of an intramolecular disulfide bond, a structural moiety that is rarely formed in this class of proteins for reasons discussed above. It was proposed that, via a conformational change, Cys-153 is able to displace thiosulfate from the sulfenyl thiosulfate derivative of Cys-149 giving rise to an intramolecular disulfide bond (**18**) (equation 24)[2]. The formation of the disulfide bond irreversibly inactivates the enzyme, i.e. the enzyme cannot be reactivated by the addition of thiols.

$$\text{GAPDH–SH} + \text{S}_4\text{O}_6^{2-} \longrightarrow \text{GAPDH–SS}_2\text{O}_3^- + \text{S}_2\text{O}_3^{2-} + \text{H}^+ \tag{23}$$

(17)

$$\text{GAPDH}\begin{array}{l}\diagup\ \text{S}_{149}\text{S}_2\text{O}_3^- \\ \diagdown\ \text{S}_{153}\text{H}\end{array} \xrightarrow{\text{heat}} \text{GAPDH}\begin{array}{l}\diagup\ \text{S} \\ \diagdown\ \text{S}\end{array} + \text{S}_2\text{O}_3^{2-} + \text{H}^+ \tag{24}$$

(18)

Recently, it was shown that chemical modification of GAPDH's Cys-153 fully inactivates the phosphatase activity of the oxidized enzyme[21]. An acyl transfer between Cys-153 and the sulfenic acid derivative of Cys-149 in the mechanism of the phosphatase reaction was proposed. The substrate for the GAPDH phosphatase, 1,3-diphosphoglycerate is produced by 3-phosphoglycerate kinase. GAPDH and 3-phosphoglycerate kinase form a common enzyme–1,3-diphosphoglycerate–enzyme complex. Thus, it was speculated that Cys-153 might mediate the substrate transfer between the two enzymes to the GAPDH active site and that inhibitors of the phosphatase activity of GAPDH interfere with Cys-153.

C. Flavoenzymes

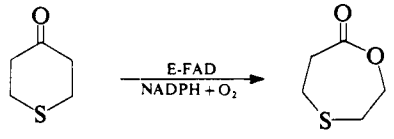
1. Occurrence of sulfenic acids

Binding studies of 6-thiocyanatoflavins (flavin-6-SCN) and 6-mercaptoflavins (flavin-6-SH) to a series of flavoproteins, i.e. riboflavin-binding protein, apoflavodoxin, apo-lactate oxidase, apo-Old Yellow Enzyme and apo-D-amino acid oxidase to form reconstituted enzymes, indicated the presence of a thiol group in the flavin binding sites of these proteins. After titration of 6-mercaptoflavin mononucleotide (FMN-6-SH) Old Yellow Enzyme, riboflavin-binding protein or flavodoxin with *m*-chloroperbenzoate, the primary oxidation product is a stable flavin-6-sulfenate (flavin-6-SOH)[22,23]. This product is

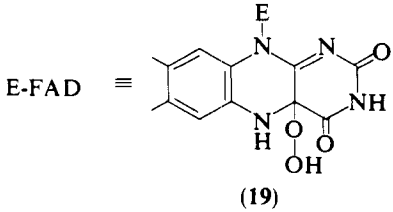
rapidly and quantitatively reconverted to the 6-mercaptoflavin mononucleotide enzyme (FMN-6-SH) upon addition of excess dithiothreitol according to equations 5 and 6. It was shown that the other flavoproteins stabilize the two-electron-oxidized mercaptoflavin as the S-oxide.

2. Sulfenic acid-mediated cross-linking

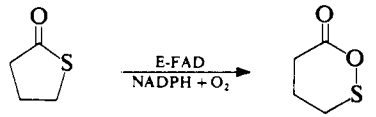
Cyclohexanone oxygenase is a flavin adenine dinucleotide (FAD)-linked monooxygenase able to carry out oxygen insertion–ring expansion reactions on cyclic ketones, equivalent to the peracid-mediated Baeyer–Villiger oxygenation as illustrated in equation 25[24]. The enzyme-bound FAD 4a-hydroperoxide **19** is the proposed oxygen-transfer reagent (definition 26). Oxygenation of cyclic thiol esters or thiolactones (**20**), ethylene monothiocarbonate or acyl sulfoxides by this enzyme produces a ring-expanded mixed sulfenic–carboxylic anhydride (**21**) as depicted in equation 27. It was proposed that this reactive anhydride, being an acylating agent, is opened by a sulfhydryl group of the enzyme thus generating an enzyme-bound electrophilic sulfenic acid intermediate (**22**). The sulfenic acid is subsequently attacked by a second sulfhydryl group to produce an intramolecularly cross-linked enzyme (**23**) as depicted in equation 28.



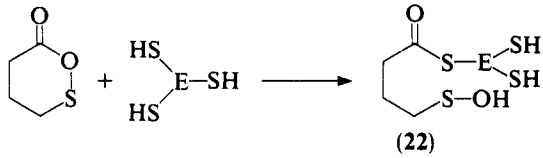
(25)



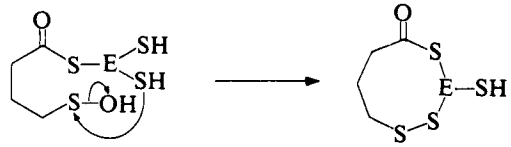
(19) (26)



(20) (21) (27)



(22)



(23) (28)

An example of such an irreversible enzyme inactivation was suggested to be the autodestruction of steroid cytochrome P-450 hydroxylase by the diuretic steroid 7-thioacetyl spironolactone[25].

D. Sulfurtransferases

The enzyme rhodanese, a thiosulfate sulfurtransferase, provides the sulfur that is part of the prosthetic group of iron–sulfur proteins. The sulfur atom that is transferred during catalysis is bound in a persulfide (P–SSH) linkage to Cys-247 at the active site[26, 27]. The active site sulfhydryl group is very sensitive to oxidation. Upon oxidation, the enzyme is inactivated due to a conformational change. It has been suggested that rhodanese oxidation by, e.g., hydrogen peroxide is at least a two-stage process. The first stage was supposed to involve the formation of a (reducible) sulfenic acid at Cys-247 which subsequently is attacked by a nucleophilic second sulfhydryl group of the enzyme to form a disulfide bond which would disturb the conformation of the protein, as in the case of GAPDH (equation 24) and cyclohexanone oxygenase (equation 28). Formation of the Cys-247-sulfinic or sulfonic acid upon further oxidation of the sulfenic acid derivative was also not excluded as a cause for the conformational change observed, since oxidation products were detected that could not be reduced.

E. Remote Sulfenic Acids

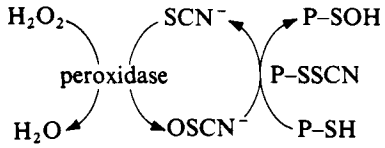
Formation of protein sulfenic acids does not always affect the activity. There are two examples of proteins of which sulfhydryls not important for the activity of the protein were reported to be converted into sulfenic acids, i.e. human transcortin[28] and the flavoprotein *p*-hydroxybenzoate hydroxylase[29]. The corticosteroid binding globulin, human transcortin, contains an accessible cysteine sulfhydryl group in the cortisol binding site which is, however, not essential for cortisol binding. It was suggested that this group is present in native transcortin, free or bound to cortisol, as a sulfenic acid moiety. Heat or acid inactivation of transcortin has been reported to result in aggregation and disulfide bridge formation which occur concomitantly with a modification of the secondary structure. As suggested for rhodanese and cyclohexanone oxygenase, the sulfenic acid could act as an electrophile for intramolecular nucleophilic attack by a second sulfhydryl group in transcortin, analogous to equations 24 and 28, forming the disulfide which causes the conformational change observed.

Highly purified *p*-hydroxybenzoate hydroxylase showed microheterogeneity, which was shown to be due to the (partial) oxidation of Cys-116 during isolation and purification. However, Cys-116 is not part of the active site of the enzyme since oxidation of Cys-116 did not affect the catalytic properties of the enzyme. Not only the sulfenic acid, but also formation of the sulfinic and sulfonic acid derivatives of the enzyme have been invoked. The sulfenic acid moiety of the inactive enzyme fraction could be reduced to the sulfhydryl group by treatment with dithiothreitol (equations 5 and 6).

F. Sulfenic Acids and Peroxidases

Milk and saliva possess antimicrobial activity. This activity has been ascribed to the lactoperoxidase–peroxide–thiocyanate system (equation 29) by which bacterial sulfhydryls are oxidized and by which inhibition of *E. coli* respiration occurs[30–34]. Lactoperoxidase catalyzes the oxidation of thiocyanate (SCN^-) producing hypothiocyanite ($OSCN^-$), which oxidizes bacterial sulfhydryls to yield sulfenyl thiocyanate (P–SSCN, **24**) and sulfenic acid (P–SOH) derivatives (equations 29 and 30). There was a direct

correlation between sulfhydryl oxidation and antimicrobial action. The growth inhibition could be restored by the addition of dithiothreitol (equations 31 and 32). In addition, thiocyanate is an antithyroid substance and the oxidation of thiocyanate is catalyzed by thyroid peroxidase. Thus, in a similar way thiocyanate may express its antithyroid activity by oxidation of protein sulfhydryls.



(29)

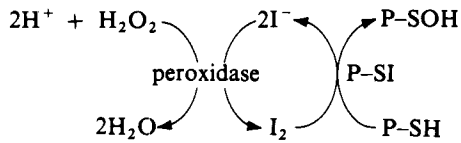
$$\text{P–SSCN} + \text{H}_2\text{O} \longrightarrow \text{P–SOH} + \text{SCN}^- + \text{H}^+ \quad (30)$$

(24)

$$\text{P–SSCN} + \text{RSH} \longrightarrow \text{P–SSR} + \text{SCN}^- + \text{H}^+ \quad (31)$$

$$\text{P–SSR} + \text{RSH} \longrightarrow \text{P–SH} + \text{RSSR} \quad (32)$$

Oxidation of protein sulfhydryls by the lactoperoxidase–hydrogen peroxide–thiocyanate system is analogous to oxidation by the lactoperoxidase–hydrogen peroxide–iodide system (equation 33), which leads to the formation of stable sulfenic acids in the case of, e.g., bovine serum albumin (BSA) and β-lactoglobulin. The enzyme could be replaced by myeloperoxidase or horseradish peroxidase. The sulfhydryls of bovine serum albumin and β-lactoglobulin are located in clefts within the proteins and are not accessible to bulky reagents; their sulfenyl derivatives are thus sterically restrained from forming inter- or intramolecular disulfide bonds.



(33)

Some plants, i.e. varieties of *Phaseolus vulgaris*, are sensitive to ozone exposure, which causes inhibition of plasma membrane ATPase activity and induces a change in membrane permeability[35]. It was suggested that this damage was effected by oxidation to sulfenic acids or disulfides of plasma membrane sulfhydryl groups. Thus, ozone-induced ATPase inhibition was completely reversed by post-exposure addition of sulfhydryl compounds, viz. dithioerythreitol. Unfortunately, no attempt was made, however, to distinguish between formation of the disulfide or the sulfenic acid.

G. Derivatives of Sulfenic Acids

1. Sulfenyl iodides (P–SI)

There is evidence for the formation of derivatives of protein sulfhydryl groups at the sulfenic acid oxidation state. The sulfhydryl group of the tobacco mosaic virus coat

protein is converted to a sulfenyl iodide when the protein is treated with triiodide[36]. Moreover, stable sulfenyl iodide derivatives of β-lactoglobulin and ovalbumin have been characterized[37–40]. The active site sulfhydryl group of creatine kinase is oxidized to a sulfenyl iodide by iodine which subsequently is hydrolyzed to form a sulfenic acid as shown in equations 34 and 35[41]. A similar hydrolysis of sulfenyl iodide derivatives formed by iodine oxidation of bovine serum albumin and β-lactoglobulin has been reported by Thomas and Aune[32].

$$\text{P–SH} + \text{I}_2 \longrightarrow \text{P–SI} + \text{HI} \tag{34}$$

$$\text{P–SI} + \text{H}_2\text{O} \longrightarrow \text{P–SOH} + \text{HI} \tag{35}$$

2. Other sulfenyl derivatives (P-SX)

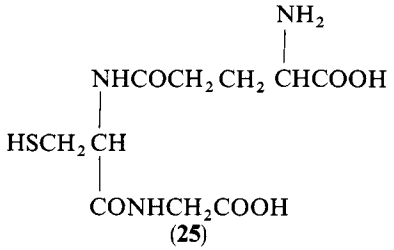
As stated above, a stable sulfenyl thiosulfate ($\text{P–SS}_2\text{O}_3^-$) derivative of GAPDH (**17**) is formed when the enzyme is inactivated with tetrathionate[20]. Tetrathionate reacts with Cys-149 to form a sulfenyl thiosulfate derivative (equation 23). The addition of simple thiols, e.g. cysteine, β-mercaptoethanol, dithiothreitol, to the inactivated enzyme releases thiosulfate and restores enzyme activity. The formation of sulfenyl thiocyanate (P–SSCN) derivatives of bovine serum albumin and β-lactoglobulin has also been reported[30, 31].

III. PEPTIDE SULFENIC ACIDS AND THEIR DERIVATIVES

So far we have discussed sulfur-containing macromolecules that, via oxidative pathways, yield sulfenic acids. Sulfur-containing peptides deserve attention as a separate class of compounds that are able to yield sulfenic acids.

A. Glutathione

Glutathione (GSH) is an endogenous tripeptide having structure **25** (see equation 36). Its sulfhydryl group is prone to be converted to sulfenic acid, although sulfenic acids of **25** have not been observed so far. This must be undoubtedly due to the high reactivity of this functionality. The sulfenic acid of **25** can be postulated as a reactive intermediate in the formation of GSSG (**26**), the disulfide of **25**, in a similar way as described above for proteins. Many mammalian tissues contain two enzymes capable of forming **26** from **25** in the presence of hydroperoxides. These two enzymes are glutathione peroxidase and glutathione S-transferase.



(**25**) = GSH (36)

Glutathione peroxidase has four subunits, each of which contains one atom of selenium. The mechanism by which this enzyme catalyzes the formation of **26** probably

involves the interaction of the anion of selenocysteine (P–Se^-) with the peroxide as presented in equations 37–40[42]. It is noteworthy that the intermediacy of P–SeOH has been invoked. The overall reaction is given in equation 40.

$$\text{P–Se}^- + \text{ROOH} \longrightarrow \text{P–SeOH} + \text{ROH} \tag{37}$$

$$\text{P–SeOH} + \text{GSH} \longrightarrow \text{P–SeSG} + \text{H}_2\text{O} \tag{38}$$

$$\text{P–SeSG} + \text{GSH} \longrightarrow \underset{\textbf{(26)}}{\text{GSSG}} + \text{P–Se}^- \tag{39}$$

$$\underset{\textbf{(25)}}{\text{ROOH}} + 2\text{GSH} \longrightarrow \underset{\textbf{(26)}}{\text{GSSG}} + \text{ROH} + \text{H}_2\text{O} \tag{40}$$

Of more relevance to the topic discussed here is the class of glutathione S-transferases. This is a group of proteins catalyzing the conjugation of **25** with a wide variety of hydrophobic substrates containing an electrophilic atom (C, O, S, N)[43]. Nucleophilic attack by GS^- on organic hydroperoxides results in the formation of the sulfenic acid of **25**, which reacts nonenzymically with **25** to produce **26**[44].

1. Reaction with nitriles and nitroso derivatives

When organic nitrate esters are acted upon by GSH transferases, **26** is being formed. Keen and coworkers[45] demonstrated that the unstable sulfenyl nitrite **27** was formed as an intermediate, which subsequently reacted with another molecule of **25** to produce the observed **26** (equations 41 and 42).

$$\text{RCH}_2\text{ONO}_2 + \text{GSH} \longrightarrow \underset{\textbf{(27)}}{\text{RCH}_2\text{OH} + \text{GSNO}_2} \tag{41}$$

$$\underset{\textbf{(27)}}{\text{GSNO}_2} + \underset{\textbf{(25)}}{\text{GSH}} \longrightarrow \underset{\textbf{(26)}}{\text{GSSG}} + \text{HNO}_2 \tag{42}$$

Glutathione readily reacts with several nitrosoarene compounds. Nitrosoarenes are the ultimate toxic species formed from arylamines. They are prone to react with tissue sulfhydryls and are responsible in this way for a variety of cytotoxic effects. The underlying mechanisms of the reaction of nitrosoarenes with sulfhydryl compounds have been studied by several groups[46, 47]. A reversible addition of the sulfhydryl compound to the nitroso group to form a so-called semimercaptal-like intermediate **28** has been accepted as the primary reaction step. Reaction of **28** with thiols yielded invariably a sulfenamide **29** and presumably the unstable sulfenic acid corresponding to the thiol. The sulfenamide **29** is thought to be hydrolyzed to aniline (**30**) rather than thiolytically cleaved (equation 43).

$$\text{ArNO} + \text{RSH} \longrightarrow \underset{\textbf{(28)}}{\text{ArN(OH)SR}} \xrightarrow[-\text{[RSOH]}]{\text{RSH}} \underset{\textbf{(29)}}{\text{ArNHSR}} \xrightarrow[-\text{[RSOH]}]{\text{H}_2\text{O}} \underset{\textbf{(30)}}{\text{ArNH}_2} \tag{43}$$

2. Incorporation of selenium

The formation of a sulfenic acid derivative of glutathione enables the incorporation of inorganic selenium into organic molecules and thus into living systems. The reaction of selenite (**31**) with the thiol groups in molecules like glutathione, but also cysteine or coenzyme A to form bis(alkylthio)selenides (**34**), is believed to be one of the principal pathways by which inorganic selenium is initially incorporated into living systems[48,49]. The first stage has been shown to be a reversible reaction of the thiol with selenious acid that leads to the formation of the thioselenic acid **32**. The second stage involves reaction with another thiol molecule to yield the intermediate **33**. The path by which **33** is converted to **34** has not yet been established with certainty. The intermediacy of a sulfenic acid has been invoked by the authors (equations 44–47). The overall reaction is presented in equation 48.

$$\underset{}{RSH} + \underset{(31)}{H_2SeO_3} \longrightarrow \underset{(32)}{RSSeO_2H} + H_2O \tag{44}$$

$$RSH + RSSeO_2H \longrightarrow \underset{(33)}{RSSe(O)SR} + H_2O \tag{45}$$

$$RSH + RSSe(O)SR \longrightarrow RSOH + \underset{(34)}{RSSeSR} \tag{46}$$

$$RSH + RSOH \longrightarrow RSSR + H_2O \tag{47}$$

$$4RSH + H_2SeO_3 \longrightarrow RSSeSR + RSSR + 3H_2O \tag{48}$$

3. Conjugation

The intermediacy of sulfenic acids derived from glutathione has recently been illustrated in the biotransformation pathways of hexachloro-1,3-butadiene (**35**) in rats[50]. Following administration of **35** to male rats, the principal route of excretion was biliary, the major metabolite, **36**, being a direct conjugate between **25** and **35** (Scheme 49). Evidence was obtained to show that the biliary metabolites of **35** are reabsorbed from the intestine and excreted via the kidneys. A urinary sulfenic acid derivative of **35**, metabolite **38**, has been identified, the formation of which has been rationalized as follows. The primary conjugate **36** is degraded to the corresponding cysteine conjugate **37**. This metabolite is supposedly oxidized to the sulfoxide and subsequently cleaved by the renal cytosolic enzyme β-lyase to give **38**, which caused localized kidney damage (scheme 49). This is the first evidence presented for this type of cleavage to occur *in vivo*. We are inclined to propose that the formation of sulfenic acid derivatives in the biodegradation of glutathione adducts is a pathway that is generally occurring.

$$Cl_2C{=}CCl{-}CCl{=}CCl_2 + GSH \longrightarrow GS{-}CCl{=}CCl{-}CCl{=}CCl_2 \quad (49)$$

(35) (25) (36)

↓ reabsorbed from intestine

kidney

↓ transpeptidase

$$HOS{-}CCl{=}CCl{-}CCl{=}CCl_2 \xleftarrow[\beta\text{-lyase}]{\text{S-oxidation}} HOOCCHCH_2SCCl{=}CCl{-}CCl{=}CCl_2$$

(38) (37)

B. *N*-γ-L-Glutamyl S-Substituted L-Cysteine Derivatives

A crucial role in the above-discussed formation of sulfenic acid derivatives from glutathione conjugates plays the C–S lyase enzyme. The C–S lyase induced β-elimination reaction is characteristic for another class of cysteine derivatives, i.e. S-substituted γ-glutamyl cysteine compounds which have been isolated from plants and mushrooms during the last decades[51]. One of these is γ-glutamylmarasmine (**39**). This dipeptide has been synthesized[52] subsequent to its isolation[53] from the Basidiomyceteous mushrooms *Marasmius alliaceus*, *M. scorodonius* and *M. prasiosmus*, which are known for their garlic-like odor[54]. γ-Glutamylmarasmine (**39**) is degraded first to marasmine (**40**) by the action of a transpeptidase. Marasmine (**40**) is then cleaved by a C–S lyase to give ammonia, pyruvic acid and an unstable sulfur compound, probably methylthiomethanesulfenic acid (**41**), which again decomposes, probably via the sulfinic ester (**42**) to give various odorous sulfur compounds (scheme 50).

$$H_2NCHCH_2CH_2CONHCHCH_2S(O)CH_2SCH_3 \xrightarrow{\text{transpeptidase}} {}^{+}H_3NCHCH_2S(O)CH_2SCH_3 \quad (50)$$

(39) (40)

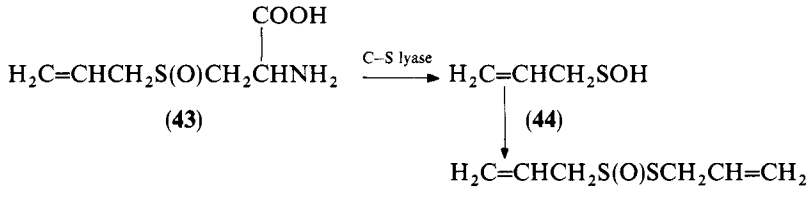
↓ C–S lyase

$$H_3CSCH_2SSCH_2SCH_3 + H_3CSCH_2SO_2SCH_2SCH_3 \leftarrow [H_3CSCH_2SS(O)CH_2SCH_3] \leftarrow [HOSCH_2SCH_3]$$

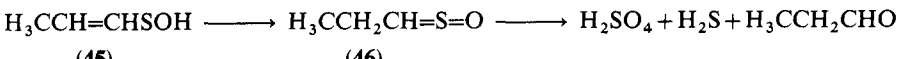
(42) (41)

Noteworthy examples of the C–S lyase induced β-elimination reaction are the conversion of several sulfur compounds in garlic and onions into sulfenic acid intermediates[55–57]. Most notably, in garlic the C–S lyase acts on alliin (**43**) to yield **44**. In onions the lacrimatory precursor **45** is formed, which rearranges to yield **46** (equations 51

and 52). In **45** the SOH group is attached to a double bond by which its instability increases. Consequently **46** is being formed, which undergoes hydrolysis giving propionaldehyde, sulfuric acid and hydrogen sulfide.



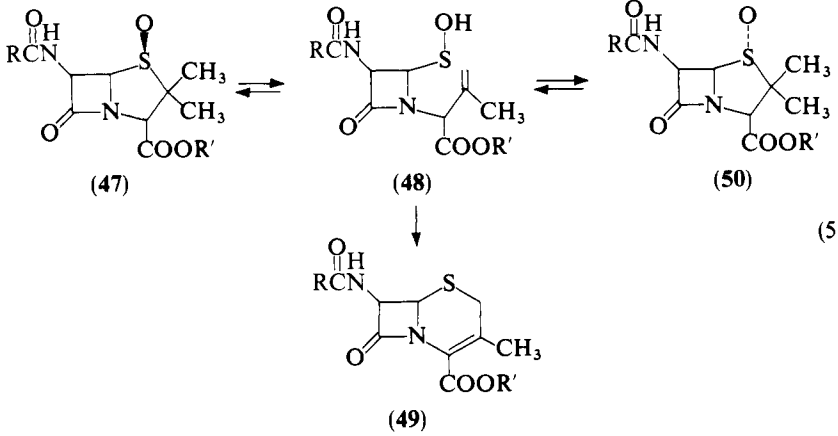
(43) (44) (51)



(45) (46) (52)

C. Penicillin Sulfoxides

The elimination mechanism involved in the formation of sulfenic acids from the above-described cysteine derivatives also plays a role in the metabolism of another class of sulfur-containing peptides, i.e. the penicillin S-oxides (**47**). Much of the *chemistry* of the penicillin sulfoxides is related to the relatively stable 2-oxazetidine-4-sulfenic acid **48**, which is in equilibrium with the two epimeric sulfoxides[58] (**47**) and (**50**). This sulfenic acid can be converted amongst other things into the corresponding cephalosporins **49**[59] (equation 53).



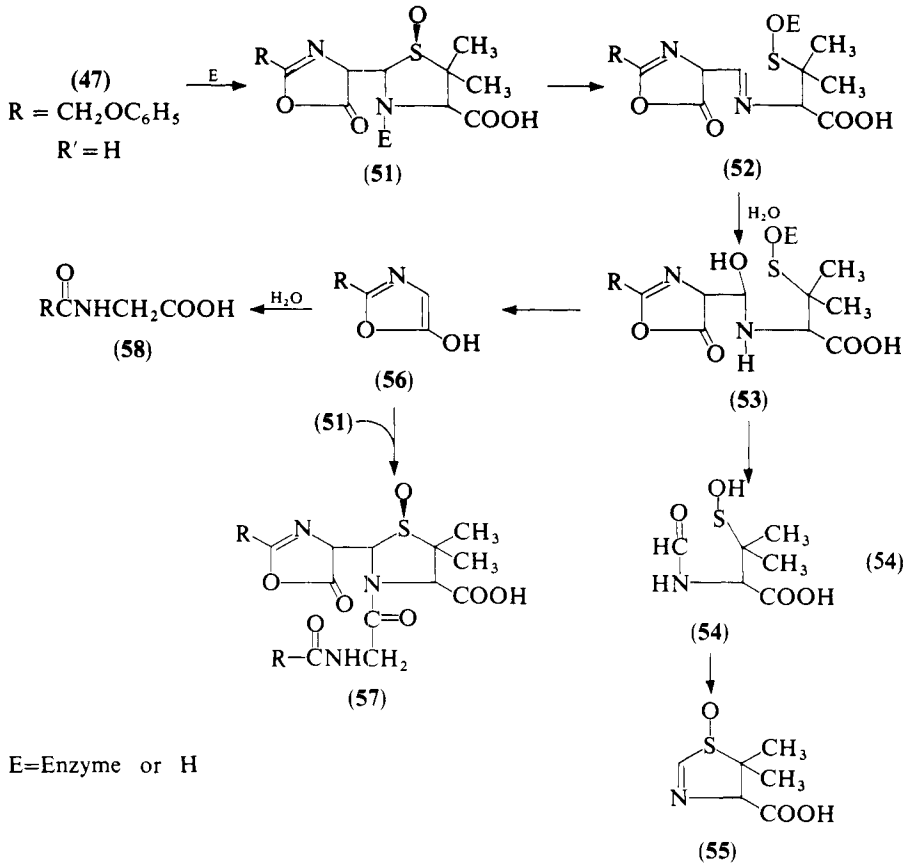
(47) (48) (50) (53)

(49)

In the *biotransformation* of penicillin sulfoxides some derivatives of sulfenic acid are also involved. In most cases studied the β-lactam ring is affected now before the C–S lyase exerts its function. During the transformation of the penicillin β-sulfoxide **51** by various bacteria, e.g. *Bacillus megaterium* and *Streptomyces venezuelae*, the intermediacy of sulfenic acids **52**, **53** and **54** has been invoked (equation 54)[60].

The first step in this scheme is the intramolecular ring opening of the β-lactam ring of **47** to give **51**. Subsequent β-elimination involving the thiazolidine ring results in the formation of the sulfenic acid intermediate **52**. The intermediacy of **52** as well as of the other sulfenic acid **53** has been postulated in the framework of a rationale for the

formation of **57** which was isolated and characterized. The metabolic degradation of penicillin V follows an analogous pathway as depicted in equation 54.

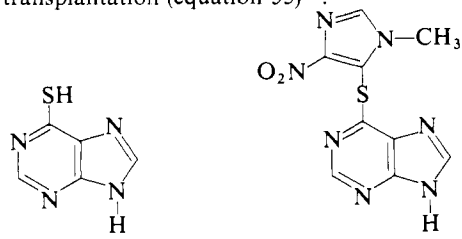


(54)

IV. SULFENIC ACIDS FROM EXOGENOUS COMPOUNDS

A. 6-Thiopurines

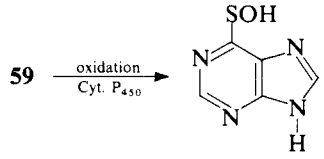
6-Thiopurine (**59**) is an antineoplastic agent that is used for the treatment of leukemias[61]. The drug is also immunosuppressive and is used, as the prodrug azathioprine (**60**), for organ transplantation (equation 55)[62].



(55)

(59) (60)

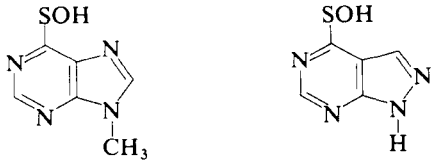
Hepatic microsomal cytochrome P-450 activates **59** to a reactive metabolite capable of binding to microsomal proteins via a mixed disulfide bond. This reaction was shown[63] to be dependent on both oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH). The proposed mechanism of this activation involves oxidation of **59** to purine-6-sulfenic acid (**61**), which then reacts with protein thiols (equation 56). This reaction of **61** with thiols from liver proteins may explain the hepatotoxic effects associated with the use of **59.**



(56)

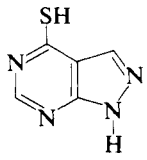
(**61**)

The biological consequences of oxidative, metabolic conversion of thiols like **59** to sulfenic acids may vary markedly depending on the stability of the particular sulfenic acid generated. The stability of **61** and of the sulfenic acids derived from the two structurally related compounds, 9-methyl-6-thiopurine (**62**) and 4-mercapto-1*H*-pyrrazolo-[3,4*d*]pyrimidine (**63**) (equation 57), possess a pH-dependent stability profile. The stability of **62** was greater than that of **61** throughout the pH range tested, whereas **63** was markedly more stable than either **61** or **62** over the pH range 4.6–9.0. Furthermore, the NADPH-dependent oxidation of allothiopurinol (**64**) (equation 58) by hepatic microsomes *in vitro* did not lead to the generation of covalently bound material whereas, under identical incubation conditions, use of **59** resulted in significant binding. Thus, the steric and electronic characteristics of the adjacent aromatic ring play a dominant role in the relative stability and reactivity of these sulfenic acids.



(57)

(**62**) (**63**)



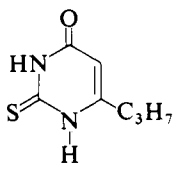
(58)

(**64**)

B. Thiocarbamides

Another class of compounds requiring metabolic activation for expression of their biological activity are thiourea derivatives (thiocarbamides). Their biotransformation has been studied in hepatic and pulmonary systems where microsomal mono-oxygenase

catalyzed oxygenation results in extensive covalent binding and toxic lesions[64]. Thiocarbamides share the property of suppressing thyroid function[65]. The mechanism of action involves inhibition of thyroid peroxidase, the enzyme responsible for synthesis of the thyroid hormones. Thiocarbamides such as propylthiouracil (**65**) and 1-methyl-2-mercapto-imidazole (**66**) are used therapeutically to treat hyperthyroidism[66]. The ready availability of lactoperoxidase has facilitated research on the mechanisms of thiocarbamide action, as lactoperoxidase is a faithful surrogate for thyroid peroxidase by many structural and catalytic criteria[67].



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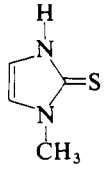

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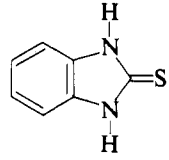
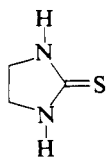
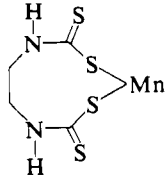


(67) (59)

Inhibition of lactoperoxidase by **66** and by model compounds based on **67** is characterized by distinctive changes in the visible spectrum of the haem prosthetic group of the enzyme. These changes occur at the same time as the time-dependent loss of enzymic activity and the kinetics are consistent with the suicide-mechanism based inactivation. This and other kinetic evidence suggest that a unique intermediate is involved in this lactoperoxidase inactivation. The sulfenic acid derivative of the inactivator studied is a likely intermediate due to its reactive electrophilic nature, which renders it capable of reacting with the haem prostetic group of lactoperoxidase.



(68)



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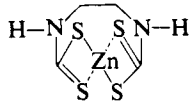
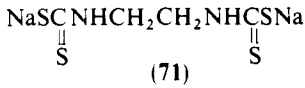
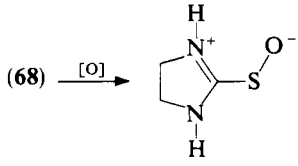


(70) (60)



(71)

Ethylene thiourea (**68**) is an important environmental contaminant derived from decomposition and metabolism of ethylene-bis-dithiocarbamate fungicides like Mabeb (**69**), Zimeb (**70**) and Nabam (**71**). Compound **68** has goitrogenic, teratogenic, carcinogenic and mutagenic properties[68–71]. It is metabolized in mice[72] by oxidation of the sulfur atom to form 2-imidazolin-2-yl sulfenate (**72**) (equation 61). The mutagenicities of **68** and **72** were compared in direct bacterial tests. In all test systems applied **72** was less mutagenic than **68**. At present, insufficient conclusive evidence is available to conclude whether **68** itself or any of its metabolites is responsible for the carcinogenic and goitrogenic effects. However, the results reported so far might indicate that the formation of **72** is actually a detoxifying step in the metabolism of **68**. Until chronic mammalian toxicity studies with **72** have been conducted this suggestion will remain speculative.



(68) [O] → (72) (61)

V. CONCLUDING REMARKS

The demonstration of sulfenic acids as intermediates in metabolic pathways, which has not received the attention it undoubtedly deserves, has been impeded by the instability of these compounds, by the occurrence of only minute quantities in biological material and often by the lack of proper analytical techniques. Evidence of their occurrence is often based solely on the isolation of subsequent products in the metabolic scheme, e.g. disulfides, or on the inhibition of catalytic processes in which the presence of a thiol function is a prerequisite.

Reagents capable of converting thiols into sulfenic acids are hydrogen peroxide with or without peroxidases, endogenous or exogenous ozone, cytochrome P450—a multiple function oxidase system capable of oxidizing particularly aromatic thiols—and flavoproteins which have in particular alkyl thiols or aralkyl thiols as substrates. It has been suggested that base (OH^-) catalyzed hydrolysis of a protein disulfide is best explained by the intermediacy of a sulfenic acid derivative, which would react further to produce the protein thiol and a sulfinic acid[73].

The sulfenic acids discussed in this chapter can be divided into two classes, i.e. sulfenic acids derived from (hetero) aromatic thiols or their masked derivatives and those derived from cysteine.

When a thiol of a protein cysteinyl residue is present in the catalytically active site, it can be converted to a sulfenic acid or a derivative. These functionalities render the protein unstable; the sulfenic acids are too unstable to accumulate to any extent. However, when the cysteinyl side-chain is situated in a sterically restricted domain of the protein, the sulfenic acid formed may be considerably stable.

Precautions should be taken to prevent the formation of sulfenic acid during the isolation and characterization of thiol-containing proteins. Oxidation of a thiol that is located in the active site influences the activity of the enzyme, whereas the oxidation of other thiol functions causes at least heterogeneity in the enzyme preparation.

Evidence is accumulating that sulfenic acids derived from peptide cysteinyl residues, cf. in glutathione, play a crucial role in metabolic processes. Nevertheless, their role remains rather speculative since due to their instability they have escaped isolation and rigid characterization. A C–S lyase-induced β-elimination is invoked to rationalize their formation.

Here, a warning seems to be justified as the occurrence of sulfenic acids may be the result of conditions employed during isolation and characterization. Sulfides are easily oxidized to sulfoxides, which may undergo a thermolytic β-elimination reaction to yield the corresponding sulfenic acid as an artefact. These required thermolytic conditions may also arise during GC/MS analysis. The reports on sulfenic acids derived from sulfoctidil must be considered in this light[74].

Because sulfenic acids derived from (hetero) aromatic thiols are reasonably stable, their role in metabolic processes has been established.

VI. ACKNOWLEDGMENT

We gratefully acknowledge Dr H. D. Berkeley for critical reading of the manuscript.

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The Chemistry of Sulphenic Acids and their Derivatives
Edited by Saul Patai

CHAPTER **17**

Sulfenimines

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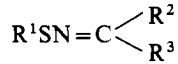
The Chemistry of Sulphenic Acids and their Derivatives
Edited by S. Patai

I. GENERAL ASPECTS

Sulfenimines **1**, R^1 = alkyl or aryl; R^2, R^3 = H, alkyl or aryl) represent a sub-class of sulfenamides with sp^2-hybridized nitrogen. According to their structure, they may be designated either as derivatives of sulfenamides (*N*-alkylidene sulfenamides), or of thiooximes (thiooxime ethers) or of imines (*N*-alkyl- or *N*-arylthio imines). The still scarce knowledge on sulfenimines is mainly due to the lack of general simple pathways for their preparation, and to the fact that most of the known methods suffer from severe structural limitations.

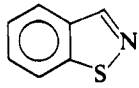


(1)

Most known sulfenimines are compounds of reasonable thermal stability, which can be isolated without major difficulties and stored indefinitely at least at low temperatures. For the majority of known sulfenimines the substituents R^1 on sulfur and/or R^2 or R^3 on carbon are aryl substituents. Parent thiooximes, $R_2C{=}NSH$, are only known in solution (see also Section III.F.1)[1].

Sulfenimine chemistry is included in several earlier reviews on sulfenamides[2-6].

Related compounds of the general type **1** containing the S–N=C skeleton but with substituents R^1, R^2 or R^3 other than alkyl, aryl or hydrogen are sometimes also addressed as sulfenimines but should be classified differently according to their specific structure and reactivity. The following compounds of this type are consequently not included in this article (representative references given): *N*-thio-carboximidic acid esters ($R^3 = OR^4$)[7-10], *N*-thio-carboximidothioic esters ($R^3 = SR^4$)[9,11], *N*-thio-carboximidoyl halides (R^3 = halogen)[9,12-15], *N*-thio-carbonimidic dichlorides ($R^2 = R^3 = Cl$)[14,17], *N*-thio-amidines ($R^3 = NR^4_2$)[9,18-20], *N*-thio-guanidines ($R^2 = R^3 = NR^4_2$)[21], *N*-thio-carbamidic acid chlorides ($R^2 = NR^4_2$, $R^3 = Cl$)[22,23], *N,N'*-thio-, dithio- or trithio-bis-imines ($R^1 = S_x{-}N{=}CR^4_2$; $x = 0$–2)[1,24-27], *N*-thio-cyanato-imines ($R^1 = CN$)[28], *N*-alkylidene sulfoxylic diamides ($R^1 = NR^4_2$)[29,30], or heterocycles such as benzisothiazoles (**2**)[31], 1,2,3-dithiazoles (**3**)[27] and 1,2,4- or 1,2,5-thiadiazoles (**4**), (**5**)[27].



(2)

(3)

(4)

(5)

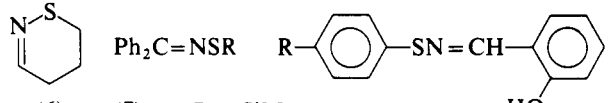
II. STRUCTURAL ASPECTS

A. Spectroscopic Characterization

Due to the paucity of general methods for the preparation of sulfenimines, systematic studies on spectroscopic characterization are rare.

1. UV spectra

Most of the sulfenimines investigated have aromatic substituents on sulfur or carbon in addition to the C=N chromophore. Amongst the few reported examples of only aliphatically substituted sulfenimines are cyclic derivatives of type **6**[32], revealing two maxima at 232 and 269 nm, respectively, in the UV spectrum. *S*-Trimethylsilyl benzophone thiooxime (**7a**), a precursor for generation of *S*-unsubstituted benzophenone thiooxime (**7b**)[33], similarly exhibits two maxima at 240 and 290 nm.



(**6**) (**7**) (**a**) R = $SiMe_3$ (**b**) R = H (**8**)

From studies with *p*-substituted aryl sulfenimines (**1**, R^1 = aryl) a transmission of electronic effects through the S–N bond has been assumed[34,35]. Electron-withdrawing substituents in *N*-benzylidene sulfenamides (**1**, R^2 or R^3 = aryl) shift the maximum to longer wavelengths[36,37].

2. IR spectra

The bands ascribed to the C=N stretching mode in those sulfenimines which have no group in conjugation with the imine carbon fall in the range of 1600–1620 cm^{-1}[31,32,36–38]. *N*-Aryl methylene (**1**, R^2 = aryl, R^3 = H)[36,37] or butenylidene sulfenimines (**1**, $R^2 = CH_3$, $R^3 = CH{=}CH_2$)[38] show a twinned peak between 1568 and 1610 cm^{-1}.

3. Mass spectra

Mass spectra of **6** and related cyclic sulfenimines indicate a relatively stable molecular ion (76–100% abundance)[32]. In a study of *ortho* effects on electron impact, stepwise ejection of SO_2 and N_2 from *N*-benzylidene-(*o*-nitrophenyl)sulfenamides (**1**, R^1 = *o*-nitrophenyl, R^2 = H, R^3 = Ph) caused by *ortho* interaction with the nitro group was reported[39].

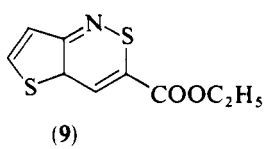
4. NMR spectra

Chemical shifts δ for N=C<u>H</u>-protons of *N*-alkylidene sulfenamides (**1**, R^2 = H, R^3 = alkyl or aryl) are in the range of 8.0 to 8.9 ppm[31,37,40] (in **6** and related cyclic compounds, *ca* 7.85 ppm[32]). Protons at α carbons appear in the range of 1.9–2.6 ppm (α to imine carbon: CH_3 1.87–2.3 ppm[32,37,38,41,42]; CH_2 2.0–2.6 ppm[32,41,42]) and 2.6–3.1 ppm (α to sulfur[28,32]), respectively.

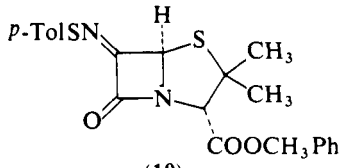
^{1}H-NMR shift values for sulfenimines (**8**) derived from salicylic aldehyde have been correlated with Hammett σ^+ constants. Electron-withdrawing groups R shift the imidoyl proton downfield ($-\rho$), the hydroxyl protons upfield ($+\rho$). From the substantial transmission of electronic effects, a conjugation between the two aryl groups by a mechanism involving both the p and d orbitals on sulfur has been concluded. The nitrogen lone pair is not directly conjugated with the aryl ring of the *N*-benzylidene group[35].

5. X-ray

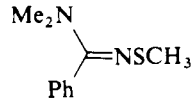
Only a few X-ray data on sulfenimines have been reported including a triaryl substituted sulfenimine (**1**) (R^1 = *p*-tolyl, $R^2 = R^3$ = phenyl)[43], the cyclic sulfenimine (**9**)[44], the penam derived sulfenimine (**10**)[45] and the sulfenamidine (**11**)[19].



(**9**)



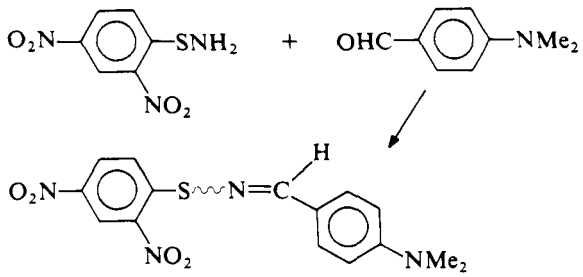
(**10**)



(**11**)

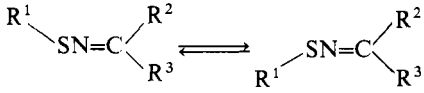
B. *Syn–Anti* Isomerism

The existence of *E*, *Z* isomers of sulfenimines was recognized early[46]: when *N*-unsubstituted sulfenamides, which are stabilized by electron-withdrawing groups, were condensed with *p*-dimethylaminobenzaldehyde (e.g. equation 1), a labile isomer was obtained on short heating of the reaction mixture, a stable product (presumably the *E* isomer) on prolonged heating.



(1)

Since this first observation *syn–anti* isomerism has frequently been reported[31,32,38,41,42]. The barrier to stereomutation (equation 2) of sulfenimines (thiooxime ethers) is much lower than the barriers of the corresponding oximes and oxime ethers, and has been studied extensively by variable-temperature NMR measurements[31,34,47–51]. Coalescence temperatures are in the range between −17 °C and +113 °C, and isomerization barriers of 56–85 kJ mol^{-1} (to be compared with > 165 kJ mol^{-1} for oximes) have been observed.



(2)

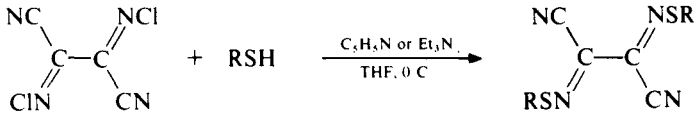
The data have been interpreted in favor of an inversion and against a torsional mechanism. Hyperconjugation of the nitrogen lone pair with substituents on the imine carbon and on nitrogen in a linear transition state adopted for the inversion process is considered to be responsible for the effects of substituents on the isomerization barrier[49].

III. FORMATION AND SYNTHESIS

The main pathways of formation are discussed in the order of increasing atomic number of the atom of X which is directly bonded to the sulfur atom of a starting material $(RS(O)_nX$ $(n = 0, 1)$. This order does not reflect relative importance for the synthesis of sulfenimines. Most of the considerable number of ways of formation suffer from strong structural limitations, and only few may be considered as rather general ones within these limitations.

A. From Thiols

Stable *N*-chloroimines and thiols react in the presence of bases (sodium carbonate, tertiary amines) with formation of *N*-sulfenylated imines. *N*-Arylsulfenylquinone imines (**23**) (see Section III.D.1 and equation 10 below)[52] and *N,N'*-diiminosuccinonitriles (**12**)[53,54] have been prepared by this method (equation 3).

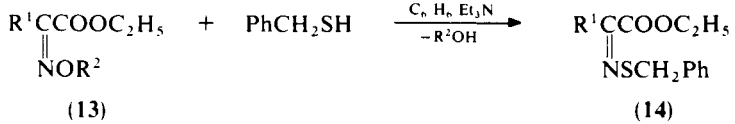


(3)

(**12**)

R = Et,*iso*-Pr, Ph, 4-ClC_6H_4, $PhCH_2$; 80–94%

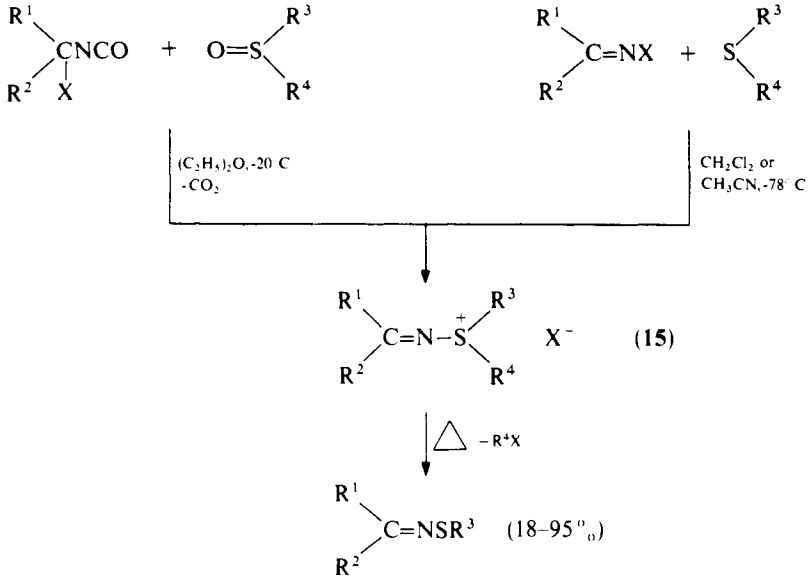
By a similar displacement, *O*-acyl oximes of α-ketoesters (**13**) ($R^1 = CH_3$, C_6H_5) and α-toluenethiol afforded 8–100% of the corresponding sulfenimines (**14**)[55] (equation 4).



(**13**) (**14**) (4)

B. From Sulfides or Sulfoxides

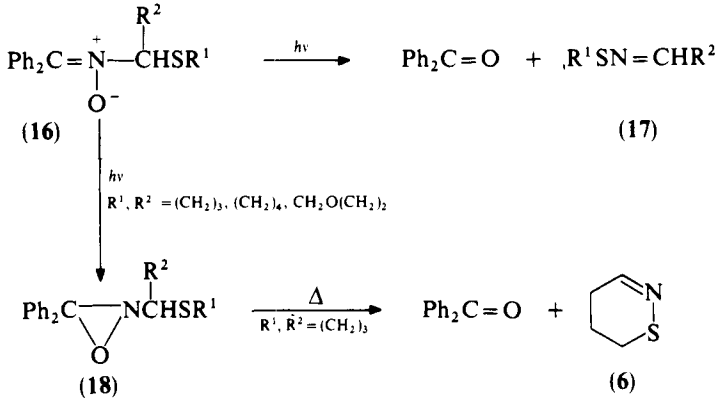
Condensation of sulfoxides with α-halogeno isocyanates at low temperatures (−20 °C) yielded 10–71% alkylidene aminosulfonium salts (**15**). Alternatively, these salts were formed by reaction of *N*-chloroimines with sulfides (45–94%)[28]. At higher temperatures (room temperature and above) sulfenimines are formed by nucleophilic displacement of R^4 through attack of X^- on carbon atoms α to sulfur (equation 5).



(5)

C. From α-Thionitrones

Irradiation of α-thionitrones (**16**) resulted in fragmentation with formation of benzophenone and *S*-alkyl thiooximes (**17**). Compounds with aliphatic substituents on the imine carbon not available by other methods could be obtained by this method[32]. Simple compounds of type **17** (e.g. with $R^1 = CH_3$, C_2H_5; $R^2 = H$, CH_3) could be observed spectroscopically in solution but formed polymers on further irradiation. In case of photolysis of 2-thiolanyl-, 2-thianyl- and 2-(1,4-oxathianyl-)nitrones, oxaziridines of type **18** were formed together with cyclic sulfenimines (e.g. **6**), which were obtained in high yields on heating of **18** (equation 6).

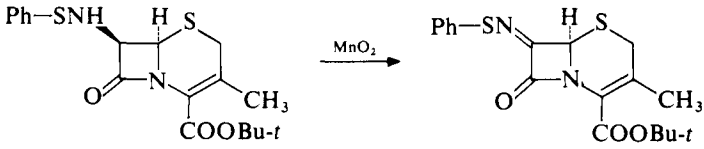


(6)

D. From Sulfenamides

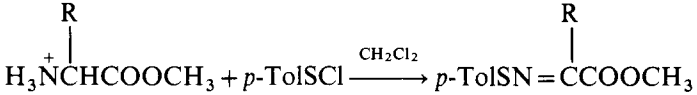
1. By oxidation

Arylsulfenamides derived from cephalosporin and penicillin derivatives (e.g. **19**) have been oxidized by active MnO_2 to give 68–86% of corresponding sulfenimines[56,57] (equation 7). Other oxidants, like *N*-chloro succinimide, trichloro isocyanuric acid or *t*-butyl hypochlorite, are less effective.



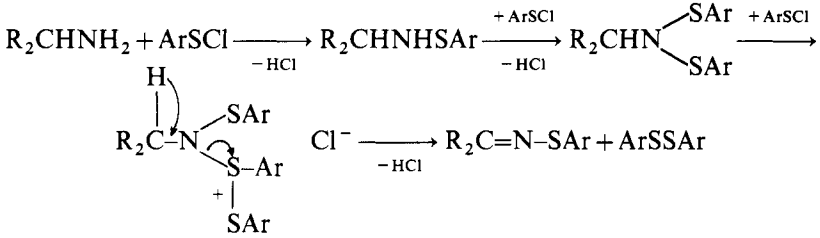
(19) (20) (7)

Sulfenimines of type **20** have also been obtained by reaction of 7β-NH_2-cephalosporins with an excess of arylsulfenyl chloride[45,56–58]. By the same reaction other amino compounds, in particular α-amino esters, could also be transformed to corresponding sulfenimines[2,59,60]. One or more acid scavengers such as pulverized molecular sieves, propylene oxide or anhydrous potassium carbonate are used to trap liberated hydrogen chloride[59]. The resulting *N*-arylthio-2-imino esters (**21**) (equation 8; 51–95% yield) are stable yellow-orange oils or low melting solids. Even free acids of 7-sulfenimino-β-lactams may be obtained in 27–95% yield (isolated as sodium salts) after silylation followed by reaction with arylsulfenyl chloride as described above[45].



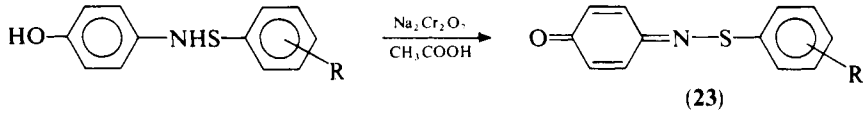
(21) (8)

The reaction is supposed to proceed via further sulfenylation of the intermediate sulfenamide, followed by additional sulfenylation on sulfur and fragmentation of an intermediate sulfonium ion (**22**) after deprotonation with formation of the sulfenimine and diaryl disulfide (equation 9; see also Section III.H).



(9)

N-Arylsulfenyl aminophenols have been oxidized with sodium dichromate to give *N*-sulfenyl quinone imines (**23**) (equation 10)[61–63].

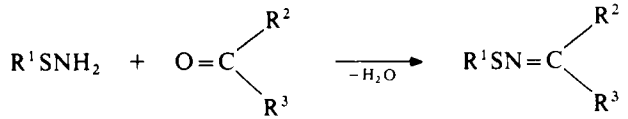


(23)

(10)

2. By reaction of N-unsubstituted sulfenamides with carbonyl compounds

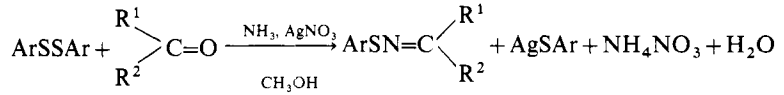
Condensation of *N*-unsubstituted sulfenamides (**24**) with aldehydes or ketones represents the earliest known synthesis of sulfenimines[64]. Though a variety of compounds (**24**) has become known, this pathway is limited to products where R^1 is either sterically crowded or strongly electron-withdrawing, because sulfenamides (**24**) with other Rs are unstable at room temperature, and therefore difficult to handle and practically unavailable by known preparative methods. Nevertheless quite a number of sulfenimines (**1**) have been obtained by applying this method[36,40,42,46,48,64-69] (equation 11).



(24) (1) (11)

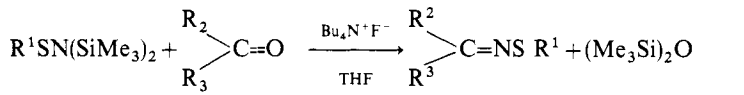
Stable sulfenamides (**24**) (e.g. R^1 = 4-nitrophenyl, 2-pyridyl) can be reacted with carbonyl compounds (including formaldehyde[48]) without catalyst by heating in benzene, toluene or xylene with azeotropic removal of water[48,69]. In other cases the reaction can be catalyzed either by bases (potassium carbonate[36], sodium hydroxide[68]) or acids (hydrogen chloride[31], sulfuric acid[40], ammonium chloride[31,46], pyridinium *p*-toluenesulfonate[42]).

Numerous arylsulfenimines have been prepared in one step from aryl disulfides, silver nitrate, ammonia, and an aldehyde or a ketone (see also Section III.G)[31]. This reaction proceeds via intermediate sulfenamides (**24**). The procedure works well with aldehydes, less well with ketones (in particular when sterically crowded), and fails with diaryl ketones or when starting with alkyl disulfides (equation 12).



(12)

Alternatively *N*,*N*-bis(trimethylsilyl)sulfenamides (**25**) [available by reactions of lithium bis(trimethylsilyl)amide with benzenesulfenyl chloride and dimethyl disulfide, respectively] have been used instead of **24**: condensation with ketones in THF by applying tetrabutylammonium fluoride as catalyst yielded 83–100% sulfenimines (**1**), including such with $R^1 = CH_3$, R^2 = alkyl or aryl and $R^3 = H$[70] (equation 13).

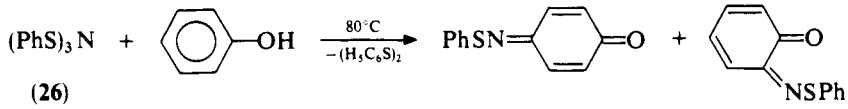


(13)

($R = C_6H_5$, CH_3)

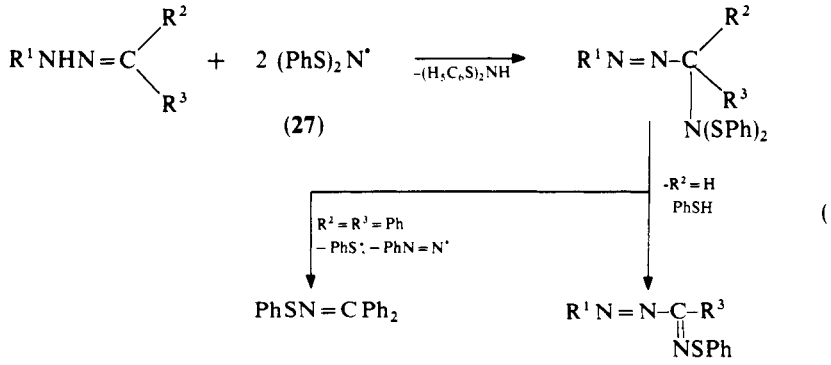
3. By reactions with tribenzenesulfenamide

The thermal decomposition of tribenzenesulfenamide (**26**) at temperatures over 70 °C is assumed to form the radical $(PhS)_2N^{\cdot}$ (**27**) by S–N bond scission; this attacks electron-rich molecules, such as phenols, anilines or hydrazones, resulting in the formation of sulfenimines[37,71,72]. Thus, a mixture of 1,2- and 1,4-benzoquinone monophenylthio-imines has been obtained by reaction with phenol (equation 14). Anilines similarly afforded quinone bisphenylthio-imines[71,72].



(14)

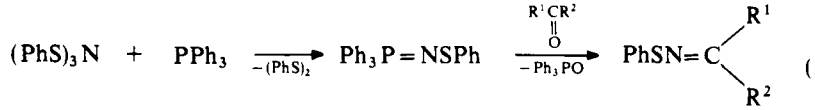
Hydrazones are attacked at the imine carbon, and finally afforded either (in case of reactions with benzophenone hydrazones[71]) sulfenimine (**1**) ($R^1 = R^2 = R^3 = Ph$) or (with aromatic or aliphatic aldehyde phenylhydrazones[37]) phenylazo-sulfenimines (**28**) (equation 15).



(15)

(28)

The reaction of triphenylphosphine with **26** results in the formation of *N*-(triphenylphosphoranylidene)-benzenesulfenamide (**29**), which is sensitive to oxygen and moisture and thus cannot be isolated but reacts with aromatic aldehydes or ethyl pyruvate, respectively, to give 21–89% of the corresponding *S*-phenyl-thiooximes[37] (equation 16).

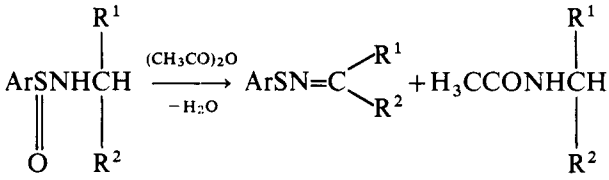


(16)

E. From Sulfinamides

The Pummerer reaction is a well-known reaction of sulfoxides resulting in a shift of the oxygen functionality to the α-carbon position. The first successful Pummerer reaction of

sulfinamides has been reported in the cephalosporin series[56,73]: 7β-cephalosporin derivatives were converted with sulfinyl chloride to the corresponding 7β-sulfinamido compounds. Pummerer reactions were effected by treatment of the sulfinamides with thionyl chloride in the presence of quinoline or triethylamine in 16–54% yield. In a later work, a number of *S*-arylsulfinamides have been treated with acetic anhydride at room temperature to give 10–58% yields of the sulfenimine together with 25–48% amide[74] (equation 17).

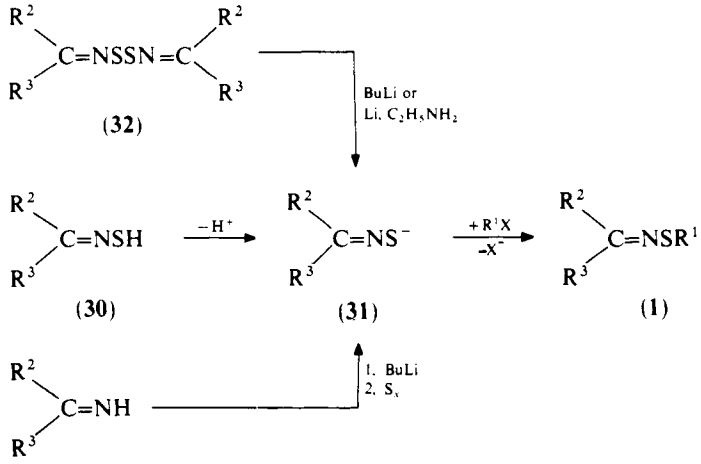


(17)

F. From Other Sulfenimines

1. *From parent thiooximes*

Parent thiooximes (**30**) became known just a few years ago[1,33,75]. Thiooxime anions (**31**) can be alkylated or arylated to give the corresponding sulfenimines (equation (18).

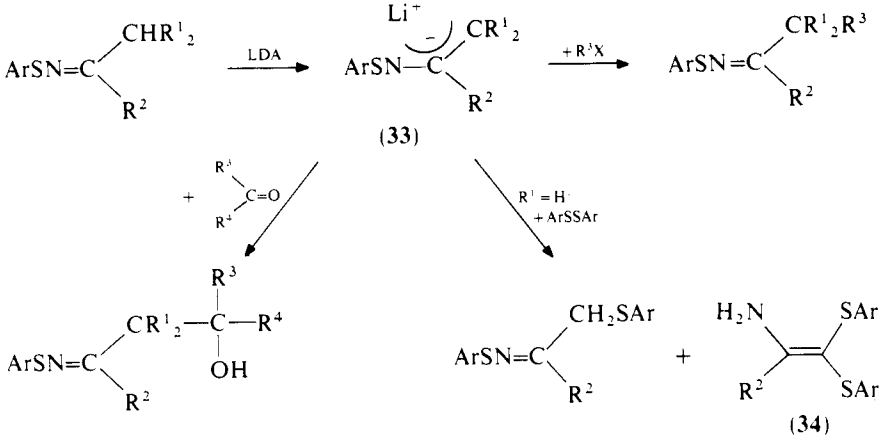


(18)

Solutions of **31** could be obtained from *N,N'*-dithio-bis-diaryl-methanimines (**32**) ($R^2 = R^3$ = aryl) through scission of the S–S bond either by reduction [with lithium/ethylamine or chromium(II)[1]] or by nucleophilic attack of butyllithium[75], and alkylated with methyl iodide[1] or arylated with 2,4-dinitro-fluorobenzene[75]. An improved pathway to **31** uses the reaction of imine anions with elemental sulfur[33]: starting with diphenylmethanimine, and quenching the solution with trimethylsilyl chloride, *S*-trimethylsilyl-benzophenone thiooxime (**1**) ($R^2 = R^3$ = Ph, $R^1 = Me_3Si$), a moderately stable precursor of parent thiooximes (**30**) and derived thiooximes (**1**), is formed in 95% yield.

2. From other sulfenimines (thiooxime ethers)

Sulfenamide enolate equivalents (**33**) obtained by treatment of sulfenimines with protons in α-position to the imine functionality with LDA[41] (see also Section IV) may be reacted with electrophiles, such as alkyl halides, carbonyl compounds and aryl disulfides[76], and thus transformed into new sulfenimines (equation 19).



(19)

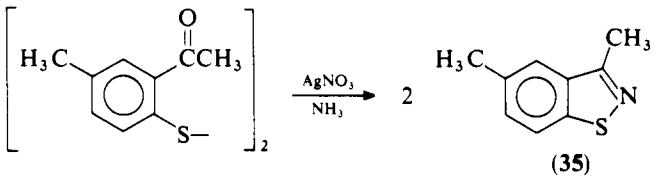
Regioselectivity is observed when α-protons are also present in R^2. As is known for the generation of other enolate equivalents, methyl groups are preferably deprotonated and alkylated by reactions with alkyl halides compared with other alkyl groups. The formation of **34** by reaction with diaryl disulfides was explained by bis-sulfenylation and scission of the S–N bond by attack of phenylthiolate on the intermediate sulfenamide.

G. From Disulfides

1. By metal-assisted reaction with amines in the presence of carbonyl compounds

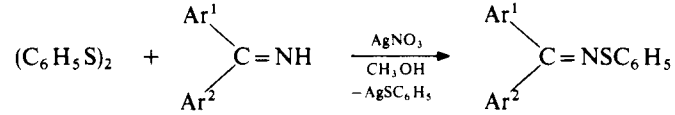
Silver-assisted reaction of amines with aliphatic and aromatic disulfides represents one of the most convenient syntheses of sulfenamides[6,77]. When this reaction is performed by applying an excess of ammonia in the presence of carbonyl compounds (such as aliphatic or aromatic aldehydes, acetone, 2-butanone, cyclohexanone, methyl *tert*-butyl ketone, acetophenone), condensation of the primary sulfenamide (**24**) formed intermediarily with the carbonyl compounds proceeds to give sulfenimines in good to excellent yields (see also Section III.D.2 and equation 8)[31,34,35,47,78–81]. Sterically hindered ketones gave only low yields, and reactions failed with camphor and with diaryl ketones.

The procedure may also be used for preparation of benzisothiazoles (**35**), representing cyclic sulfenimines, by an intramolecular reaction starting with *o*-acyl substituted diaryl disulfides[31] (equation 20).



(20)

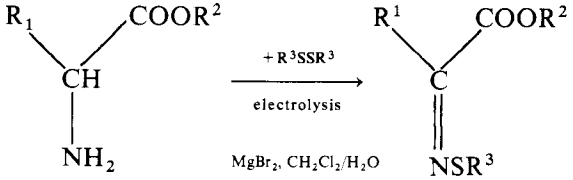
Sulfenimines derived from diaryl ketones could be prepared by reaction of the ketone with ammonia in toluene in the presence of titanium tetrachloride to give the corresponding imine, and silver assisted reaction (equation 21) of the imine with diphenyl disulfide[82]. Alternatively, diaryl ketimines were reacted with arylsulfenamides of type **24** (R^1 = 3-nitrophenyl, 3,4-dichlorophenyl) at 90 °C *in vacuo*, resulting in an imine exchange, or deprotonated with methyl lithium to the imine anion which was then sulfenylated by reaction with diphenyl disulfide[82].



(21)

2. *By $MgBr_2$-promoted electrolysis of α-aminoalkanoates and dialkyl or diaryl disulfides*

Electrolytic cross-coupling of α-aminoalkanoates, 6-aminopenicillins or 7-aminocephalosporins, respectively, and aliphatic or aromatic disulfides in the presence of magnesium bromide gave 55–93% of the corresponding sulfenimines (**36**)[83,84] (equation 22). Use of other magnesium salts or other bromides resulted in much lower yields. The reaction is assumed to proceed via the corresponding sulfenamides, which could be isolated in case of a penicillin derivative by interrupting the electrolysis. The latter are then converted to the sulfenimines under similar electrolysis conditions.

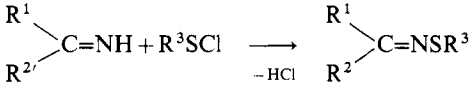


(22)

(**36**)

H. From Sulfenyl Chlorides

If imines are available as stable compounds on a preparative scale, they may be sulfenylated by reaction with sulfenyl chlorides to give sulfenimines (equation 23).



(23)

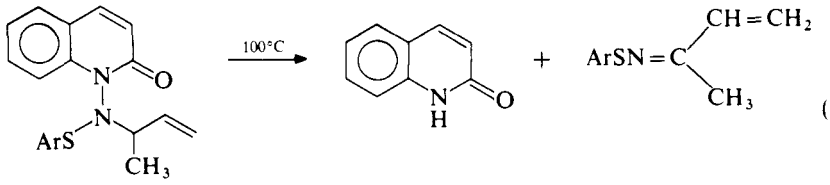
R^1, R^2 = aryl, CH_2Cl, CF_3; R^3 = aryl, CH_3, CCl_3, $C(CH_3)_3$, $C_6H_5CH_2$

Thus, sulfenimines with aryl or strongly electron-withdrawing groups on the imino carbon have been prepared[48,49,85]. This method has been frequently applied for preparation of *N*-thio-carboximidic acid derivatives[20,11,86].

On reaction with sulfenyl halides, amines form sulfenamides which may be further oxidized to the corresponding sulfenimines by an excess of sulfenyl halide (threefold molar amount; see also Section III.D.1 and equation 9)[45,56–60].

I. Miscellaneous Methods

Formation of sulfenimines has been occasionally observed in various transformations of sulfimides and aminosulfonium salts (the protonated forms of sulfimides), respectively. Thus, arylsulfen-(*N*-propenylidene-)amides (**38**) are formed by homolytic N–N fission on thermolysis of *N*-(3-propenyl-)sulfenamides of type **37**, which are obtained by addition of intermediate nitrenes to allyl aryl sulfides, followed by (2,3)-sigmatropic rearrangement of the formed sulfimides[38] (equation 24).

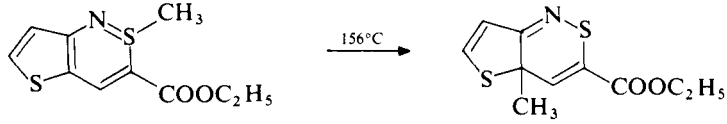


(24)

(**37**) (**38**)

In a related reaction, deprotonation and rearrangement of aminophenylpropargylsulfonium ions via (2,3)-sigmatropic shift of the propargyl group gives *N*-allenyl sulfenamides, followed by a hydrogen shift forming *N*-propenylidenearylsulfenamide[87].

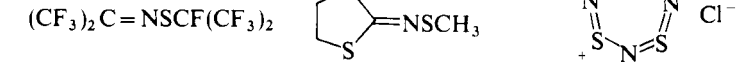
Cyclic sulfenimines, e.g. **39**, were formed by thermal 1,4-migration of *S*-methyl or aryl groups of cyclic sulfimides[44] (equation 25).



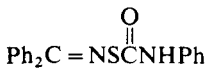
(25)

(**39**)

Sulfenimines with perfluorinated alkyl groups on sulfur or imine carbon, e.g. **40**, have been isolated in various reactions of perfluoroalkyl substituted imines[30,88,89]. The formation of **41** after a reaction of a 2-methylthio-2-(1,3-dithiolanium) salt with azide was explained by rearrangement of the intermediarily formed 2-azido-2-methylthio-1,3-dithiolane[90]. The reaction of thio-trithiazyl chloride (**42**) with benzophenone phenylhydrazones yielded *N*-diphenylmethylene arylsulfenamide[91], presumably via an intermediate thionitroso compound. *S*-(Phenylamino)carbonyl-thiooximes, e.g. **43**, have been obtained by thermal rearrangement of corresponding *O*-(arylamino)thiocarbonyl-oximes, formed by reaction of oxime anions with phenylisocyanate. Attack of *t*-BuONa on **43** results in scission of the S–C bond with formation of a thiooxime anion (**31**)[92,93] (see also Section III.F.1 and equation 18).



(**40**) (**41**) (**42**)



(**43**)

IV. REACTIVITY

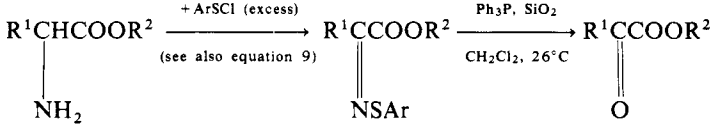
A. Thermal Stability

Most of the known sulfenimines have aryl substituents either on sulfur, or on the imine carbon atom, or on both, and are thermally stable. Sulfenimines with only aliphatic substituents are rare, but seem to be generally stable enough for isolation (e.g. compounds of type **6**[32]). Bulky groups in the imine part give rise to slow decomposition at room temperature[31].

B. S–N Bond Scission

Sulfenimines are considerably more resistant to hydrolysis than the corresponding imines[31]. Hydrolysis with acids (acetic acid, aqueous hydrochloric acid) or bases (sodium hydroxide in ethanol or aqueous ethanol) gave the corresponding carbonyl compounds and disulfides[42,94], respectively; in case of reactions with hydroxides, sulfinic acid by attack of hydroxide on the disulfide was also formed[94].

Hydrolysis of sulfenimines (**36**) derived from α-amino esters (see Section III.D.1 and III.G.2) by treatment with triphenylphosphine and silica gel in methylene chloride at room temperature afforded 45–92% α-keto esters[59]. The overall sequence (equation 26) represents a mild, neutral, two-step conversion of α-amino esters into α-keto esters.



(26)

(**36**)

Sulfenimines of type **10** or **20** derived from penicillins or cephalosporins (see Section III.D.1) form complexes with triphenyl phosphine which rearrange upon chromatography on silica gel to give the corresponding 7β-amino-7α-arylthio derivatives (see also Section IV.F.1 below)[45,58,95].

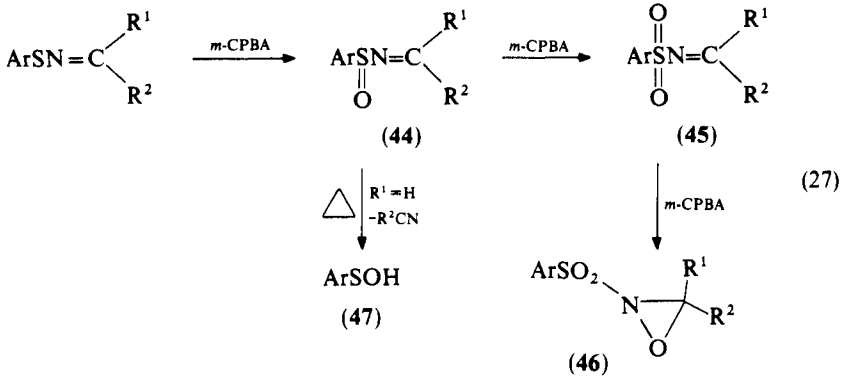
The S–N bond of sulfenimines is also ruptured by attack of butyllithium on sulfur, with formation of butyl sulfide and an imine anion[75].

C. Reduction

Reduction with borohydrides proceeds smoothly to give the corresponding sulfenamides in good yields[42,56,68]. Reductive acetylation with zinc/acetic anhydride[71] or Raney nickel/ethanol/acetic anhydride[32] results in S–N bond scission and formation of the corresponding amides.

D. Oxidation

Oxidation of sulfenimines with *m*-chloroperbenzoic acid (preferably by applying a two-phase oxidation system, e.g. in chloroform/aqueous sodium hydrogen-carbonate) affords the corresponding sulfinimines (**44**)[35,37,45,59,78,96,97] (equation 27). When two equivalents of peracid are applied, sulfonimines (*N*-sulfonylimines) **45** are formed[37], while with five equivalents, 2-arylsulfonyloxaziridines **46**, a new class of stable oxaziridine derivatives[97], are obtained.



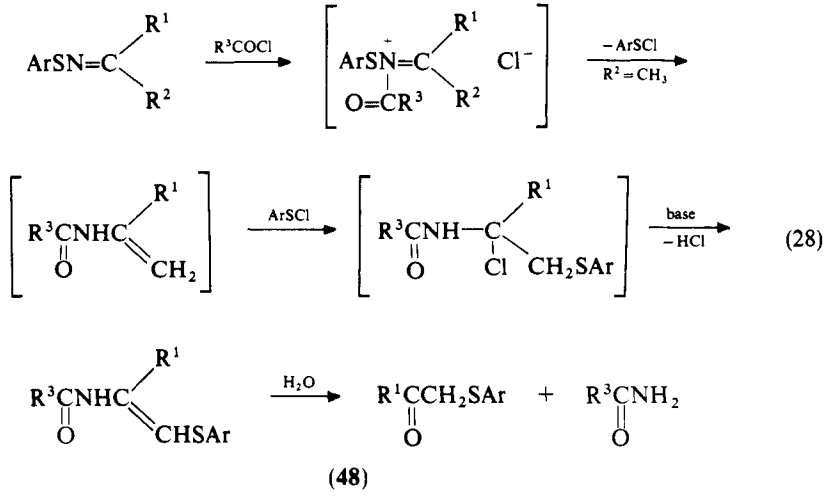
(27)

Thermally induced *cis*-elimination of nitriles from sulfinimines (**44**) afforded arenesulfenic acids (**47**)[78].

Chloramine-T oxidized sulfenimine (**41**) to the corresponding *S*-(*N*-tosyl)imide[90].

E. Alkylation and Acylation

Alkylation with trimethyloxonium hexachloroantimonate[28] or dimethyl sulfate[90] occurs on sulfur to give *N*-alkylidene aminosulfonium salts (**15**) (see also Section III.B and Reference 19). Acylation is assumed to proceed via attack on nitrogen[94], followed by rearrangement to give *β*-keto sulfides (**48**) after hydrolysis (equation 28).



(28)

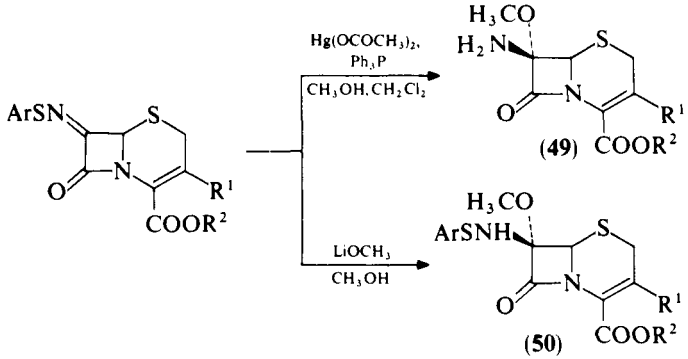
(**48**)

F. Additions to the C=N Bond

1. Addition of alcohols

Addition of methanol to the C=N bond of sulfenimines has been used for preparation of 7α-methoxycephalosporins **49** and **50**, and of corresponding penicillin

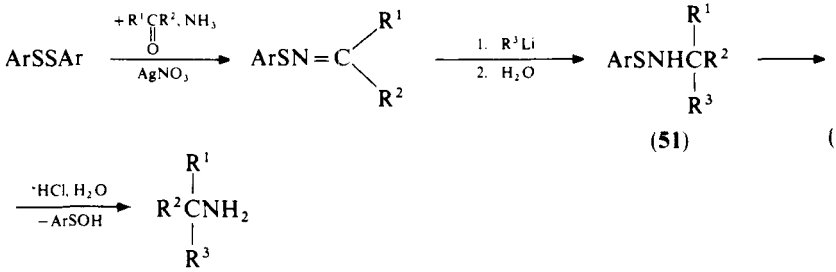
derivatives[45,56-58,73]. The addition to compounds of type **10** or **20** was either effected with methanol catalyzed by mercuric salt under the conditions of triphenylphosphine catalyzed sulfenyl transfer reactions (see also Section IV.B)[45,58], or by reaction with lithium methoxide or potassium *t*-butoxide in methanol[56,57,73] (equation 29).



(29)

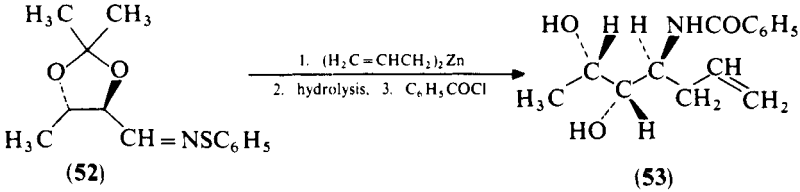
2. Addition of organometallics

While additions of organometallics to imine derivatives frequently proceed with low yields and/or undesirable side-reactions, reactions with sulfenimines which may be considered as 'masked' imine derivatives of ammonia are promising. Thus, addition of organolithiums (methyl, butyl and phenyl lithium), followed by hydrolysis, gave sulfenamides (**51**), which may be hydrolyzed by treatment with aqueous HCl[98] (equation 30). This sequence has been developed to a one-pot procedure. The overall sequence represents a synthesis of secondary or tertiary amines from ammonia via sulfenimines.



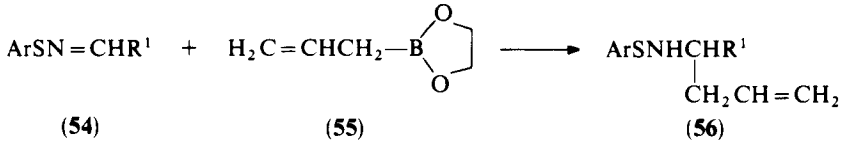
(30)

Analogous reactions of allylmagnesium bromide or diallylzinc with sulfenimine (**52**) derived from D-threonine resulted in a stereoselective addition to give addition products of type **53** after hydrolysis and benzoylation[79-81] (equation 31).



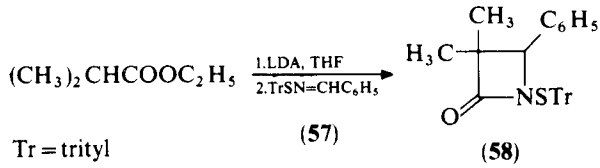
(31)

The addition of ethylene glycol allylboronate (**55**) to a series of arylsulfenaldimines (**54**) gave high yields (76–95%) of adducts (**56**)[99] (equation 32).



(**54**) (**55**) (**56**) (32)

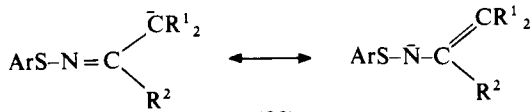
The known ester-imine route to β-lactams was successfully modified by reacting lithium enolates of esters with tritylsulfenimines, e.g. **57**, to give 70–87% β-lactams (**58**)[100] (equation 33).



Tr = trityl (**57**) (**58**) (33)

G. Sulfenimine Derived Enolate Equivalents

Treatment of sulfenimines (**1**) with R^2 or $R^3 = R^4_2CH$ with lithium diisopropylamide (LDA) in ether results in the formation of the corresponding anions, e.g. **33** (see also Section III.F.2 and equation 19), which can be considered as enolate equivalents, and react with a variety of electrophiles such as alkyl halides, carbonyl compounds or diaryl disulfides to afford high yields of new sulfenimine derivatives[41,42,76]. These may be hydrolyzed to the corresponding ketones, i.e. α-C-alkylated ketones, aldols or β-keto sulfides. In case of reaction with *N*-alkylidene tritylsulfenamides, alkylation at nitrogen instead at the α-carbon occurred at higher temperatures. Regioselective double alkylation of tritylsulfenimines was a key step in a synthesis of δ-coniceine[42].



(**33**)

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CHAPTER **18**

Mechanistic aspects of nucleophilic substitutions of sulfenic acid derivatives

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I. INTRODUCTION

The characteristic chemical behavior common to sulfenic acid derivatives arises from the divalent sulfur atom bonded to carbon (alkyl or aryl) and to a heteroatom. The heteroatom groups of these derivatives interchange with each other by a nucleophilic

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process, where the heteroatom group (X) typically leaves as an anion on attack of another anion also containing a heteroatom (Y^-) (equation 1).

$$RS\text{–}X + Y^- \longrightarrow RS\text{–}Y + X^- \tag{1}$$

$$X, Y = NR'_2, OH, OR', SR', S^+R'_2, S(O)R', S(O)_2R', SCN, \text{halogens}, CN$$

In the present chapter we will consider the mechanistic aspects of the nucleophilic substitution at the divalent sulfenyl sulfur. This reaction may be compared with well-known S_N1 and S_N2 reactions at saturated carbon. The substitution at sulfur can in principle also proceed through a process occurring by either a unimolecular or a bimolecular mechanism. The first S_N1-type process should involve a sulfenium ion as an intermediate (equation 2), while the S_N2-type process takes place in one step with synchronous (concerted) bond formation and cleavage (equation 3).

S_N-1-type Mechanism

$$RSX \xrightarrow{\text{slow}} RS^+ + X^- \xrightarrow{Y^-} RSY + X^- \tag{2}$$

S_N2-type Mechanism

$$RSX + Y^- \longrightarrow [Y\cdots S(R)\cdots X]^- \longrightarrow RSY + X^- \tag{3}$$

transition state

A third mechanism is possible for substitution at sulfur, since an adduct similar to the transition state for the S_N2-type process can in this case exist as a discrete intermediate of some stability (equation 4). The adduct can have a long enough lifetime ($> 10^{-12}$ s) to deserve to be considered an intermediate. This class of species contains a central atom bearing more formal valence electrons than an octet and is called a hypervalent compound. Several such hypervalent sulfur compounds are now known[1]. This mechanism may be referred to as an addition–elimination (A–E) mechanism.

Addition–Elimination Mechanism

$$RSX + Y^- \rightleftharpoons X\text{–}S(R)\text{–}Y \longrightarrow RSY + X^- \tag{4}$$

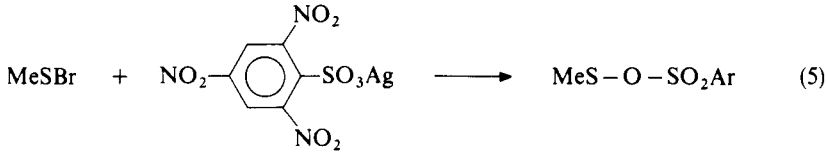
hypervalent
intermediate

We will discuss these mechanistic possibilities in the following sections. Attention will be focused particularly on two types of possible intermediate: a sulfenium ion for the S_N1-type process and a hypervalent sulfuranide anion for the addition–elimination mechanism. The central questions are whether an S_N1-type mechanism is operative or not and, in the case of a bimolecular process, whether it is concerted (S_N2) or stepwise? In previous reviews[2–4] nucleophilic substitution at divalent sulfur has been already discussed and the present chapter considers mainly recent advances in the mechanistic aspects of these processes.

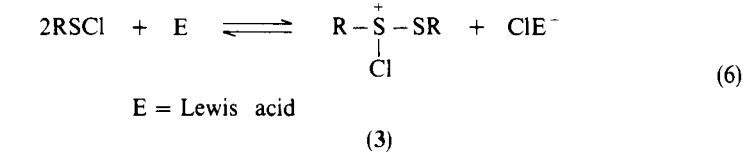
II. THE SULFENIUM ION INTERMEDIATE

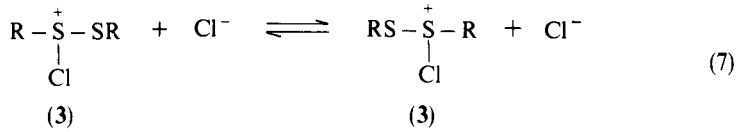
The unimolecular nucleophilic substitution (S_N1-type) at sulfenyl sulfur should involve a sulfenium ion (RS^+) as an intermediate, and indeed until the 1960s a number of nucleophilic substitutions at sulfenyl sulfur were formulated as involving such an intermediate. However, all the kinetic studies showed that the rates are dependent on the concentration of the nucleophiles and later the existence of this intermediate was doubted[2].

Sulfenyl halides are known to afford ionic species in strong acids[5] or by treatment with Lewis acids[6]. However, attempts to generate sulfenium ions by reaction of methanesulfenyl bromide with silver 2,4,6-trinitrobenzenesulfonate (**1**) resulted in formation of the sulfenic–sulfonic anhydride **2** (equation 5)[7]. The same reaction in acetonitrile afforded a conducting solution which was attributed at first to the formation of methanesulfenium ion, but was later more reasonably considered to be due to the adduct with the solvent $MeS{-}\overset{+}{N}{\equiv}C{-}Me$[7]. The potential sulfenium ion MeS^+ combines easily even with very weak nucleophiles present in the medium, suggesting the extremely unstable nature of MeS^+. It was claimed[8] that the treatment of benzenesulfenyl bromide with silver perchlorate in the nonnucleophilic solvent CH_2Cl_2 gave an adduct of the sulfenium ion with nitrogen, $PhSN_2^+$, though this result is also questioned.



Capozzi and coworkers[9] characterized carefully ionic species generated from methane and ethanesulfenyl chlorides in liquid sulfur dioxide in the presence of Lewis acids ($SbCl_5$, SbF_5, BCl_3, BF_3). The conductimetric and ^1H NMR behavior showed that the ionic species involved is an alkyl(alkylthio)chlorosulfonium ion (**3**) present in equilibrium (equation 6). Chloride exchange of **3** occurs under the reaction conditions (equation 7). This reaction is bimolecular, added chloride ion accelerating the exchange and the rate being greater with the weaker Lewis acid, and thus the unimolecular mechanism (equation 8) with transient formation of a sulfenium ion was excluded.





$$\underset{\text{(3)}}{R-\overset{+}{S}(Cl)-SR} \rightleftharpoons RSCl + RS^{+} \rightleftharpoons RS^{+} + RSCl \rightleftharpoons \underset{\text{(3)}}{RS-\overset{+}{S}(Cl)-R} \tag{8}$$

Treatment of an arenesulfenyl chloride or a diaryl disulfide with a strong Lewis acid such as $SbCl_5$ was found to result in formation of a highly colored ionic species formulated as an episulfonium ion (**4**) but not a sulfenium ion (equation 9)[10]. This ionic species may be formulated as degenerate thiasulfonium ion **5** which consists of three ions in a rapid equilibrium (equation 10). This cation is also readily generated from reaction of sulfenyl chloride with disulfide[11, 12].

$$ArSCl \text{ or } ArSSAr \xrightarrow{SbCl_5} \underset{\text{(4)}}{ArS(SAr)^{+}} \tag{9}$$

$$\underset{\text{(5)}}{\overset{+}{S}(ArS)(SAr)} \rightleftharpoons ArS-\overset{+}{S}(SAr)-SAr \rightleftharpoons SAr-\overset{+}{S}(SAr)-SAr \tag{10}$$

All the observations show that sulfenium ions are highly unstable, reactive species and can hardly exist as discrete intermediates for the substitution. No kinetic evidence shows unimolecularity of the nucleophilic substitution at a divalent sulfur.

III. BIMOLECULAR NUCLEOPHILIC SUBSTITUTION

A. Transition State Structure and Intermediacy of Hypervalent Species

Kinetic studies show that most of the nucleophilic substitution reactions at a sulfenyl sulfur are dependent on concentration of the nucleophile[2]. The reaction is believed to proceed through back-side attack on the central sulfur by the nucleophile[13]. Although stereochemical studies of dicoordinate sulfur are impossible, the nucleophilic substitution at sulfinyl sulfur usually occurs with inversion of configuration of the tricoordinate central sulfur[14].

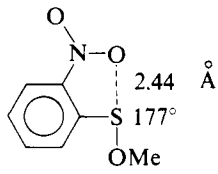
This mechanistic pathway for the sulfenyl derivatives was proposed from the observation that the rate profiles for the reaction of alkanesulfenyl derivatives RSX (equation 11) and the S_N2 reaction of RCH_2X (equation 12) were nearly identical[15]. However, these types of correlation regarding steric effects are very often observed for aliphatic compounds irrespective of mechanistic similarities, and cannot be diagnostic of mechanism[13].

$$Y^{-} + RSX \longrightarrow YSR + X^{-} \tag{11}$$

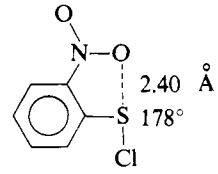
$$Y^{-} + RCH_2X \longrightarrow YCH_2R + X^{-} \tag{12}$$

One source of evidence for supporting the back-side attack mechanism comes from examination of crystal structures of relevant compounds involving dicoordinate sulfur

Y–S–Z. Nucleophilic atoms tend to approach approximately along the extension of one of the S–Y or S–Z bonds[16]. Attractive nonbonded interactions may be regarded as representing an incipient stage of chemical reactions. Intramolecular examples of such attractive nonbonded interactions involving dicoordinate sulfur are summarized in a review[17]. A typical example is methyl *o*-nitrobenzenesulfenate (**6**)[18]. One oxygen atom of the nitro group is essentially linearly aligned on the extension of the S–O bond and the nonbonded S · · · O bondlength is 2.44 Å. A similar interaction was also demonstrated for the sulfenyl chloride **7** in the vapor phase[19].

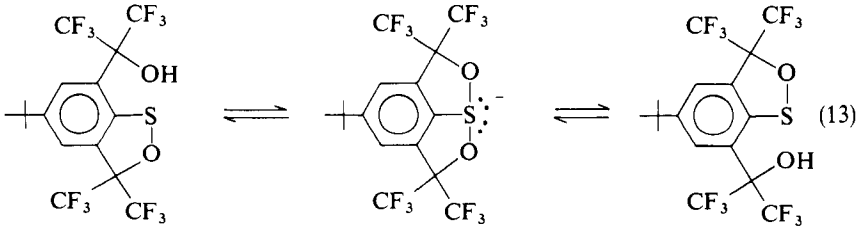


(**6**)



(**7**)

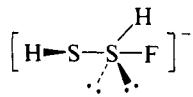
Various tricoordinate hypervalent sulfur species were isolated as salts[1]. All these stable sulfuranide anions have a cyclic structure. Dynamic NMR experiments show that the species **9** is in equilibrium with an open structure **8** (equation 13)[20]. The pK_a of **8** was evaluated to be 4.4 and the sulfuranide **9** was estimated to be about 7.5 kcal mol^{-1} more stable than the anion of **8**. The reaction 13 may be regarded as an intramolecular ester exchange of the sulfenate ester **8** and the hypervalent compound **9** is a discrete intermediate of this nucleophilic substitution.



(13)

(**8**) (**9**) (**8'**)

Theoretical studies also support the trigonal bipyramidal configuration of the sulfur center with the entering nucleophile and the leaving group in apical positions[21,22]. *Ab initio* MO calculations also suggest intermediacy of the hypervalent sulfur species. For example, a model intermediate **10** is about 6 kcal mol^{-1} more stable than the product [21].



(**10**)

In the following sections, we will examine previous results of kinetics of various nucleophilic substitutions at divalent sulfur to infer the transition state structure and intermediacy of the hypervalent species.

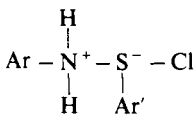
Intermediacy of hypervalent species was earlier discussed in terms of d-orbital participation. A more recent view of the hypervalent bonding shows, however, that the participation of d orbitals is not important in the formation of hypervalent bonds[1].

B. Sulfenyl Halides

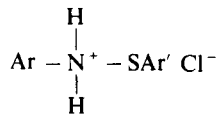
For the reaction of *p*-nitrobenzenesulfenyl chloride with aniline in benzene solution, formation of an intermediate was kinetically demonstrated (equation 14).[23,24]. The observed rates showed nonlinear dependence on concentration of $ArNH_2$ and followed equation 15 in accord with the reaction sequence of equation 14 involving an intermediate with the second molecule of amine serving as a base to facilitate the formation of product by removing a proton from the intermediate. With increase in $[ArNH_2]$ the rate-determining step changes from the second step to the first step. The problem remains, however, which structure should be assigned to this intermediate. It can be formulated either as the hypervalent addition intermediate **11** or alternatively as the ion pair **12**. Tetrabutylammonium perchlorate exerted a catalytic effect on this reaction, and this may be regarded as a special salt effect which prevents the ion pair **12** from returning to the reactants (to decrease k_{-1}) resulting in acceleration of the overall reaction. Alternatively, the perchlorate may operate as a base and may facilitate the formation of the products from intermediate **11** (to increase k_2). Since Ciuffarin and Guaraldi[25] observed that ammonium chloride can also accelerate a similar reaction of triphenylmethanesulfenyl chloride with butylamine, they preferred the latter possibility involving the addition intermediate **11**[23].

$$Ar'SCl + ArNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow[k_2]{ArNH_2} Ar'NHAr + ArNH_3Cl \qquad (14)$$

$$\text{rate} = k_1 k_2 [ArNH_2]^2 [Ar'SCl]/(k_{-1} + k_2 [ArNH_2]) \qquad (15)$$



(11)



(12)

Ciuffarin and coworkers[26,27] have also examined kinetically the element effect of leaving groups (X = Cl, Br, I, SCN) in the nucleophilic substitution of triphenylmethanesulfenyl derivatives **13** (equation 16). If the S–X bond breaking were important in this reaction, as would be the case for the synchronous S_N2-type mechanism (equation 3), the rates would be expected to correlate inversely with the bond strengths and to decrease with X in the order I > Br > SCN ≃ Cl. Bond strengths must be in the order S–Cl ≃ S–SCN > S–Br > S–I. However, the observed order of the rates, Cl > Br > I ≃ SCN, summarized in Table 1, is quite different from that expected. Since the substrates with weaker S–X bonds react more slowly, we cannot assume that appreciable S–X bond cleavage occurs in the transition state. The observed order of reactivity parallels the order of decreasing electronegativity of X. Thus it seems that the major effect of X is decreasing the electron density on the central sulfur and facilitating the nucleophilic attack leading to the intermediate without extensive bond breaking. These results conform well with the addition–elimination mechanism (equation 16) where attack of the nucleophile on the sulfenyl sulfur is rate determining.

$$\underset{\textbf{(13)}}{Ph_3CSX} + Nu \rightleftharpoons Nu-\overset{\overset{|}{CPh_3}}{\overset{-}{S}}-X \longrightarrow Ph_3CSNu + X^- \qquad (16)$$

$Nu = BuNH_2,\ OH^-$

TABLE 1. Relative rates of nucleophilic substitution of Ph_3CSX (equation 16)

		X				
Nucleophile	Solvent	I	SCN	Br	Cl	Ref.
$BuNH_2$	50% EtOH–PhH	1.0	2.2	191	400	26
$BuNH_2$	45% dioxane–H_2O	1.0	0.93	193	334	27
OH^-	45% dioxane–H_2O	1.0	0.29	5.83	7.77	27

For the reaction of *p*-nitrobenzenesulfenyl chloride with a series of anilines (equation 14), effects of pK_a of $ArNH_3^+$ on the rate of formation of the intermediate (k_1) were examined. The correlation of $\log k_1$ with pK_a gives the nucleophilic Brønsted coefficient $\beta_{Nu} = +1.25$ as a slope[24]. This result suggests extensive S–N bond formation in the transition state.

C. Sulfenate Esters

1. Hydrolysis

Nucleophilic substitutions of sulfenate esters usually occur at the sulfur atom. Only in special cases where the alkyl group can produce a stable carbocation and the sulfenate ion is a good leaving group (i.e. when the sulfenic acid is sufficiently strong) does the S_N1 reaction prevail[28]. Thus *p*-methoxybenzyl trichloromethanesulfenate **14** undergoes an S_N1 reaction with C–O bond cleavage in ethanol, while benzyl trichloromethanesulfenate, *p*-methoxybenzyl 2-nitrobenzenesulfenate and *p*-methoxybenzyl 2,4-dinitrobenzenesulfenate all undergo S–O bond cleavage involving nucleophilic attack at the sulfur atom (equation 17–19). Reaction 17 shows first-order kinetics without any catalysis by bases like acetate and lutidine, and its rate is greatly enhanced in polar solvents. By contrast, the latter reaction is second order depending on the concentration of base catalysts and faster in pure ethanol than in 80% aqueous ethanol.

$$\underset{\textbf{(14)}\ An = p\text{-}MeOC_6H_4}{AnCH_2OSCCl_3} \xrightarrow{\text{slow}} AnCH_2^+\ {}^-OSCCl_3 \xrightarrow{EtOH} AnCH_2OEt + \underset{\downarrow}{Cl_3CSOH} \rightarrow Cl_2C{=}S{=}O \qquad (17)$$

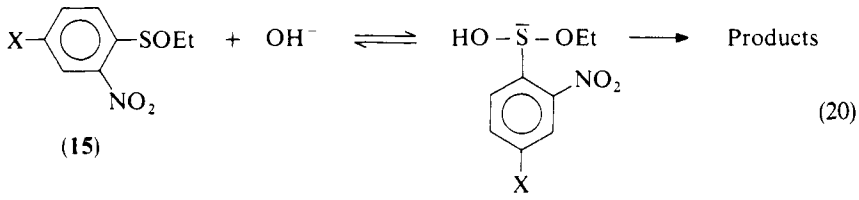
$$PhCH_2OSCCl_3 + EtOH \longrightarrow PhCH_2OH + Cl_3CSOEt \qquad (18)$$

$$AnCH_2OSAr + EtOH \longrightarrow AnCH_2OH + ArSOEt \qquad (19)$$

$Ar = 2\text{-}NO_2C_6H_4$ or $2,4\text{-}(NO_2)_2C_6H_3$

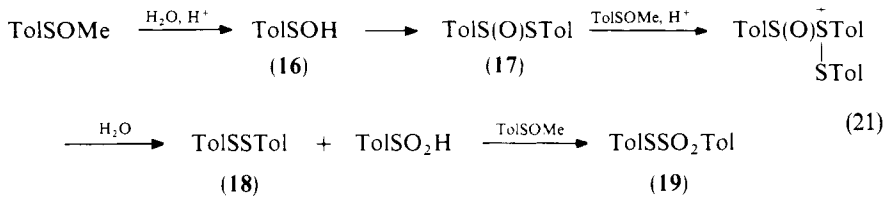
Base-catalyzed hydrolysis of various alkyl arenesulfenates was kinetically investigated in aqueous dioxane[29]. The rates for a series of alkyl 2-nitrobenzenesulfenates decrease with increase in steric effects of the alkyl groups with linear correlation to the Taft steric parameters E_s[30]. This implies that the differences in electronic effects of the alkyl groups have little or no influence on the relative reactivity and the reactivity is largely dependent on steric effects, which is consistent with a mechanism involving bimolecular attack of the nucleophile at the sulfur atom.

The rate for alkaline hydrolysis of ethyl 2-nitrobenzenesulfenate **15** is increased by both 4-methoxy and 4-chloro substituents, but is little affected by a 4-methyl or a 4-trifluoromethyl group (equation 20)[29]. These observations seem to conform with the addition–elimination mechanism with formation of hypervalent intermediate (equation 20). The hypervalent intermediate, and so the transition state of the rate-determining step, would be stabilized by the conjugative effect of an equatorial ligand. However, this same factor would also stabilize the transition state for the synchronous S_N2-type process.



(15) (20)

Hydrolysis of sulfenate esters takes place also in acidic media. The reaction of methyl *p*-toluenesulfenate in organic solvents containing a small amount of water (moist solvents) was found to occur in a manner shown in equation 21 involving both the disulfide **18** and the thiolsulfonate **19**[31]. The primary product, sulfenic acid **16**, is usually unstable and rapidly undergoes condensation to form the thiolsulfinate **17** which is considered to disproportionate easily to the disulfide and the thiolsulfonate. However, the disproportionation is actually slow in acid media, and hence the thiolsulfinate **17** is rather considered to react with a further molecule of the sulfenate as a nucleophile.



(16) (17) (18) (19) (21)

We have recently examined the kinetics of the acid-catalyzed hydrolysis of ethyl benzenesulfenate in wholly aqueous solution[32]. The product obtained in this case is the thiolsulfinate (equation 22). The hydrolysis rate is dependent on the concentration of the substrate and seems to follow equation 23. Hydrolysis is also accelerated by added nucleophiles such as Cl^-, Br^-, SCN^- and $(HOCH_2CH_2)_2S$ (equations 24 and 25). The substrate itself seems to act as a nucleophilic catalyst.

$$\mathrm{PhSOEt} + \mathrm{H_2O} \xrightarrow{\mathrm{H^+}} \mathrm{PhSOH} \xrightarrow{\mathrm{PhSOEt}} \mathrm{PhS(O)SPh} \tag{22}$$

$$\mathrm{rate} = k_2[\mathrm{H^+}][\mathrm{PhSOEt}] + k_3[\mathrm{H^+}][\mathrm{PHSOEt}]^2 \tag{23}$$

$$PhSOEt + H^+ \rightleftharpoons PhS\overset{+}{O}(H)Et \xrightarrow{H_2O} PhSOH + EtOH \quad (24)$$

$$PhS\overset{+}{O}(H)Et + Nu^- \longrightarrow PhSNu + EtOH \xrightarrow[\text{rapid}]{H_2O} PhSOH + Nu^- \quad (25)$$

Iodide ion induces the reduction of the sulfenate (equations 26–28). Since this reduction is first order in iodide, the first nucleophilic substitution (equation 26) must be rate determining[32]. Relative nucleophilic reactivities toward the protonated sulfenate are listed in Table 2 and can be compared with other related reactivities[33-38]. Both thiocyanate and sulfide are more effective nucleophiles than iodide ion. This reactivity pattern is quite different from those observed for nucleophilic reactions at saturated carbon[38] and peroxide oxygen[37], and is also different from that for the reaction at the divalent sulfur atom of thiolsulfinate[34], but closely similar to that observed for aminolysis of the thiolsulfonate[33]. The aminolysis of thiolsulfonate was assumed to occur by formation of an addition intermediate, and will be discussed in Section III.E.

$$PhS\overset{+}{O}(H)Et + I^- \longrightarrow PhSI + EtOH \quad (26)$$

$$PhSI + I^- \longrightarrow PhS^- + I_2 \quad (27)$$

$$PhS^- + PhSOEt \longrightarrow PhSSPh + EtO^- \quad (28)$$

TABLE 2. Relative reactivities of nucleophiles toward various electrophilic centers

Substrate	Solvent	Cl^-	Br^-	SCN^-	I^-	R_2S	Ref.
$PhS-\overset{+}{O}HEt$	H_2O	1.0	5.6	170	74	210[a]	32
			(1.0)	(31)	(13)	(38)	
$PhS-SO_2Ph$	60% dioxane		(1.0)	(19)	(3.0)		33
$PhS-\overset{+}{S}(OH)Ph$	60% dioxane	1.0	35	5.4×10^3	1.4×10^4	820[b]	34
			(1.0)	(150)	(400)		
$PhS(O)-SO_2Ph$	60% dioxane	1.0	5.4	14	83		36
$HO-\overset{+}{O}H_2$	H_2O	1.0	280	500	2.0×10^5	460[a]	37
CH_3-Br	H_2O	1.0	7.0	54	100		38

[a] $(HOCH_2CH_2)_2S$. [b] Bu_2S.

2. The Brønsted analysis of leaving ability and nucleophilicity

Ciuffarin and coworkers[27, 39, 40] have examined effects of basicity of a series of nucleophiles (amines and phenolate ions) and of a series of phenolate leaving groups in the reaction of aryl triphenylmethanesulfenates **20** (equation 29). Such studies in terms of the Brønsted correlation give information on the extent of bond formation and bond cleavage at the transition state.

$$\underset{\textbf{(20)}}{Ph_3CSOAr} + Nu^- \xrightarrow{k_2} Ph_3CSNu + ArO^- \quad (29)$$

From the rates of reaction of a given nucleophile with the sulfenate esters having a leaving group ArO^- of varying basicity, we can evaluate the leaving group Brønsted coefficient β_L as the slope of a plot of log k_2 *vs* pK_a of ArOH. On the other hand, from the reaction of a series of nucleophiles Nu^- with a selected sulfenate, the nucleophilic Brønsted coefficient β_{Nu} can be obtained by plotting log k_2 against the pK_a of NuH, the conjugate acids of nucleophiles. The coefficient β_L is considered to be a measure of the change in the effective charge on the oxygen atom of the phenoxy group of the substrate on going from the reactant Ph_3CS–OAr to the transition state, based on a scale where the charge on the oxygen of ArOH is taken as zero and that of ArO^- as -1 for acid dissociation (pK_a). Similarly, β_{Nu} may be a measure of the change in effective charge on the central atom of the nucleophile on going from the initial to the transition state, e.g. the change in effective charge on the nitrogen of $ArNH_2$ on going from the reactant to the transition state, based on a scale where the charge on the nitrogen of $ArNH_2$ is taken as zero and that of $ArNH_3^+$ as $+1$. Large values of β may correspond to large changes in effective charge and may suggest extensive cleavage of the S–OAr bond (β_L) and extensive formation of the new bond of S–Nu (β_{Nu}) in the transition state.

The results of Ciuffarin and coworkers[27,39,40] are summarized in Table 3. The Brønsted coefficient β_L values for the leaving groups are quite large and negative for nucleophiles including butylamine[27], pyridine[27] and hydroxide ion[39] ranging from -1.09 to -0.75. These large β_L values may suggest at first sight that there must be substantial bond cleavage of S–OAr in the transition state, opposing the conclusion obtained for sulfenyl halide derivatives from the element effect of leaving groups as discussed in Section III.B. These contradictory results may arise from differences in relative leaving abilities of the leaving group and the nucleophile from the intermediate. Magnitudes of the Brønsted coefficients for the reactions examined should be considered with great caution, since many factors affect the values and β_L can be greater than unity if the effective charge on the oxygen of RSOAr should happen to be significantly positive on a scale where that on the oxygen of ArOH is zero. The authors were inclined towards the addition–elimination mechanism, and considered that the Brønsted coefficient for the leaving groups might be related to the ability of X to facilitate the attack of the nucleophile. However, the step of the breakdown of the intermediate could be rate determining in the addition–elimination mechanism where the leaving group influences both formation of the S–Nu bond and cleavage of the S–X bond. This change in rate-determining step should depend on the relative leaving abilities of X^- and Nu^- from the addition (hypervalent) intermediate.

TABLE 3. The Brønsted coefficients for leaving groups and nucleophiles in nucleophilic substitutions of aryl triphenylmethanesulfenates **20**

Substrate[a]	Nucleophile	β_L	β_{Nu}	Ref.
Ph_3CSOAr	OH^-	-0.75		27, 39
	$BuNH_2$	-1.09		27
	Py	-1.06		27
$Ph_3CSOC_6H_4NO_2$-*p*	ArO^-		0.25	39
	RNH_2		0.58	40
	sec. cycl. amine		0.75	40
	PyR		0.84	40
	$ArNH_2$		1.5	40
p-$NO_2C_6H_4SCl$[b]	$ArNH_2$		1.25	24

[a] Reaction was carried out in 45% dioxane-H_2O solution.

[b] Reaction was carried out in benzene.

The Brønsted coefficients β_{Nu} for nucleophiles are largely dependent on the kind of nucleophiles. The β_{Nu} value for phenolate nucleophiles is small ($\beta_{Nu} = 0.25$)[40], suggesting a rather small extent of bond formation in the transition state. The authors described this reaction as a synchronous S_N2-type process.

With amine nucleophiles, β_{Nu} values are also different for different classes of amines changing from 0.58 (alkylamines) to 1.5 (anilines). Although the reason for this difference in β_{Nu} is not clear, the observations that β_{Nu} for $ArNH_2 > \beta_{Nu}$ for RNH_2 are often seen for substitutions at more polarizable centers like sp^3 or sp^2 carbon and sulfenyl sulfur, while in contrast similar values of β_{Nu} for $ArNH_2$ and RNH_2 are observed for reactions at nonpolarizable electrophilic centers such as $>C=O$ and $>SO_2$. Large differences in β_{Nu} may not necessarily mean large differences in the extent of S–N bond formation in the transition state for different classes of amines. It is noteworthy that nucleophilic reaction of anilines with sulfenyl chloride also gave the large value of $\beta_{Nu} = 1.25$ in benzene solution[24].

D. Disulfides

1. *Thiol–disulfide interchange*

Disulfide is a thio analogue of sulfenate ester and can be called thiosulfenate. Disulfides undergo various nucleophilic substitutions. Most extensively studied is the thiol–disulfide interchange, which may also be regarded as reduction of the disulfide and is important in biochemical processes such as disulfide-mediated redox reactions and changes in protein structures involving cystine disulfide bond cleavage[41-43].

This reaction proceeds through attack of the nucleophilic thiolate ($R_{Nu}S^-$) anion on the central thiol group (R_CS) with liberation of the leaving thiolate (R_LS^-). The leaving group of an unsymmetrical disulfide is usually the more acidic thiol; pK_a^L of $R_LSH < pK_a^C$ of R_CSH[44] (see equations 30–32).

$$R_{Nu}SH \rightleftharpoons R_{Nu}S^- + H^+ \tag{30}$$

$$R_{Nu}S^- + R_CS\text{–}SR_L \rightleftharpoons [R_{Nu}S\text{---}S\text{---}SR_L]^- \rightleftharpoons R_{Nu}S\text{–}SR_C + R_LS^- \tag{31}$$

$$R_LS^- + H^+ \rightleftharpoons R_LSH \tag{32}$$

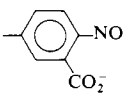
The effects of the structures of the three thiol functions on the rate and equilibrium have been extensively studied in terms of the Brønsted correlation[45-54]. The results are summarized in Table 4. Values of β_{Nu} for nucleophilic thiols are in the vicinity of 0.5, while those of the central thiol groups are roughly $\beta_C = -0.3 - -0.4$[46]. The sum of β_C and β_L was evaluated to be -1.0 from reactions of symmetrical disulfides[50,51]. The correlation of equation 33 was deduced from these results and on the basis of an assumption that $\beta_{Nu} = -\beta_L$ which comes from the symmetrical nature of this reaction[50].

$$\log k = 6.3 + 0.59pK_a^{Nu} - 0.40pK_c^C - 0.59pK_a^L \tag{33}$$

Hupe and Pohl[48] have recently measured rates and equilibrium constants for the thiol–disulfide interchange shown in equation 34. The equilibrium constants K_s are logarithmically plotted against ΔpK_a ($pK_a^C - pK_a^{Nu}$) including data for cystine and oxidized glutathione obtained by Whitesides[50]. The plot was fitted by a single straight line

TABLE 4. The Brønsted coefficients for thiol–disulfide interchange and related reactions

Disulfide[a]	Leaving group[a]	Nucleophile	β^b	Ref.
ESSE	ES^-	RS^-	0.49	45
		RS^-	0.41	50
		ArS^-	0.48	45
		RS^-, ArS^-	0.36	49
$HOCH_2CH_2SSE$	ES^-	RS^-	0.57	46
		ArS^-	0.59	46
$(HOCH_2CH_2S)_2$	$HOCH_2CH_2S^-$	ArS^-	0.68	48
GSSG	GS^-	RS^-	0.50	50
4-PySSPy-4	4-PyS^-	RS^-	0.34	53
$HOCH_2CH_2SSAr$	ArS^-	$HOCH_2CH_2S^-$	−0.29[c]	48
RSSE	ES^-	$MeOCOCH_2S^-$		
		$CF_3CH_2S^-$	−0.4–−0.3[d]	46
		$C_2F_5CH_2S^-$		
RSSR	RS^-	Dithiothreitol	−1.0[e]	50, 51
ESSE	ES^-	RNH_2	0.45	59
p-$NH_2C_6H_4SSAr$	ArS^-	CN^-	−0.77[c]	58
$ArSSC_6H_4COMe$-p	p-$MeOCOC_6H_4S^-$	CN^-	−0.66[d]	58
$ArSSC_6H_4NO_2$-p	p-$NO_2C_6H_4S^-$	OH^-	−0.74[d]	58
ESSE	ES^-	$R\bar{C}HNO_2$	0.95	60
ESSE	ES^-	$RCO\bar{C}HCOR$	0.49	60

[a] ESH = HS–  –NO_2 GSH = glutathione.

[b] β_{Nu} unless otherwise indicated. [c] β_L. [d] β_C. [e] $\beta_C + \beta_L$.

of slope $\beta_{eq} = 1.21$[48]. The slope greater than unity may imply that the effective charge on the sulfur in disulfide is slightly positive (+0.2) in accord with the more electron-withdrawing nature of the alkylthio group than of the hydrogen. The result is also consistent with the values given in equation 33 since $\beta_{eq} = \beta_{Nu} - \beta_L$.

$$ArS^- + (HOCH_2CH_2S)_2 \overset{K_x}{\rightleftharpoons} ArSSCH_2CH_2OH + HOCH_2CH_2S^- \qquad (34)$$

The Brønsted-type correlations of the rate constants for both the forward and reverse reactions of equation 34 gave $\beta_{Nu} = 0.68$ and $\beta_L = -0.29$ for a series of ArS^-, respectively[48]. These values deviate substantially from those given in equation 33 for the symmetrical reaction, and this probably reflects the Hammond postulate. That is, the difference in the pK_a values of the conjugate acids of nucleophilic and leaving thiolates makes the bondings to the central sulfur imbalanced in the transition state, i.e. the more strongly basic thiolate would form the stronger bond with the central sulfur in the transition state.

From these considerations, it may be concluded that the thiol–disulfide interchange may be described mechanistically as a simple S_N2 displacement reaction with a symmetrical transition state where there is a significant effective negative charge on all three sulfurs, but is concentrated mainly on the terminal positions[46,48,50]. Examination of the activation parameters for the reaction has also led to a similar conclusion[55].

This reaction is catalyzed by halogen acids but not by perchloric acid. Isotope exchange between benzenethiol and diphenyl disulfide is catalyzed by HCl, HBr and HI[56], relative

effects being $1:10^2:10^4$ (equation 35). This type of catalysis is often seen in nucleophilic reactions of sulfur compounds (we have already discussed acid- and nucleophile-catalyzed hydrolysis of sulfenate esters) and can be called 'concomitant electrophilic and nucleophilic catalysis'[57] (equation 36).

$$PhSSPh + PhS^*H \xrightarrow{HX} PhSS^*Ph + PhSH \tag{35}$$

$$PhSSPh + HX \rightleftharpoons PhS-\overset{+}{S}(H)Ph + X^- \xrightarrow{\text{rate determining}} PhSX + PhSH$$
$$PhSX \xrightarrow{PhS^*H} PhSS^*Ph \tag{36}$$

2. Reactions with other nucleophiles

In the base-catalyzed hydrolysis of unsymmetrical disulfides the more stable (less basic) thiolate ion is displaced[29] as is the case for thiol–disulfide interchange (equation 37). With 2,4-dinitrobenzenethiolate as a common leaving group, the rates of hydrolysis of diaryl disulfides decrease in the order *p*-Cl > *p*-NO_2 > *p*-Me > H, which is closely reminiscent of the order obtained for the sulfinate esters[29].

$$ArSSAr' + OH^- \longrightarrow ArSOH + Ar'S^- \tag{37}$$

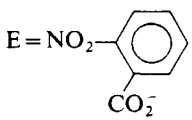
Variations in the leaving thiolates strongly affect the hydrolysis rates of disulfides. This sensitivity of the rate to changes in the leaving group is in marked contrast to the results obtained for the hydrolysis of aryl sulfenates (see Section III.C)[29]. This implies that extensive bond breaking is occurring in the transition state of the cleavage of the disulfide bond by hydroxide ion and seems to suggest the concerted S_N2-type mechanism for this reaction.

Effects of the central thiol group were examined with a series of aryl *p*-nitrophenyl disulfides (equation 38) and substituent effects corresponding to $\beta_C = -0.74$ were observed[58].

$$ArSSC_6H_4NO_2\text{-}p + OH^- \longrightarrow ArSOH + p\text{-}NO_2C_6H_4S^- \tag{38}$$

Primary and secondary amines react with Ellman's reagent, ESSE, to yield a sulfenamide in aqueous solution (equation 39). The reaction of primary amines is characterized by a Brønsted coefficient $\beta_{Nu} = 0.45$, consistent with only partial bond development between N and S occurring in the transition state[59].

$$ESSE + R_2NH \longrightarrow ESNR_2 + ESH \tag{39}$$



Tertiary amines were found to catalyze hydrolytic cleavage of the disulfide bond, β being 0.8, and the reaction catalyzed by trimethylamine shows a substantial solvent isotope effect $k_{H_2O}/k_{D_2O} = 1.72$, suggesting general-base-catalyzed attack of water[59].

Substituent effects on the reactions of cyanide ion with diaryl disulfides (equation 40) have been examined in detail in 60% aqueous *t*-butyl alcohol solution at pH 9.2[58]. Rates for symmetrically substituted disulfides showed a Hammett-type correlation with σ^0 constants, points for *m*-substituted substrates falling on a line of $\rho = 4.18$, while substituents capable of conjugative interaction deviated from the line. Electron-donating conjugative substituents (*p*-NH_2, *p*-MeO, *p*-F) deviate upward from the line and electron-withdrawing groups (*p*-NO_2, *p*-Ac) downward.

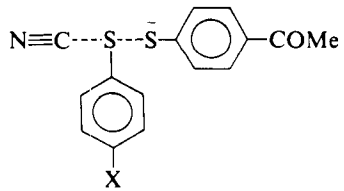
$$ArSSAr + CN^- \longrightarrow ArSCN + ArS^- \tag{40}$$

Rates were also measured for unsymmetrically substituted disulfides as shown in equations 41 and 42. The ρ values for the leaving and central groups are 1.97 (for reaction 41) and 1.70 (for reaction 42), respectively, and the deviations of the conjugative substituents arise solely from the central group. This was also confirmed by the reaction with hydroxide ion ($\rho = 1.89$ for reaction 38)[58].

$$p\text{-}NH_2C_6H_4SSAr + CN^- \longrightarrow p\text{-}NH_2C_6H_4SCN + ArS^- \tag{41}$$

$$ArSSC_6H_4COMe\text{-}p + CN^- \longrightarrow ArSCN + p\text{-}MeCOC_6H_4S^- \tag{42}$$

This behavior of substituent effects may be accommodated by the dual electronic nature of divalent sulfur which can act as both conjugative electron donor and acceptor. In the ground state of the disulfide the sulfur atom is an electron donor, but the central sulfur becomes an electron acceptor in the transition state. This seems to suggest that the bond breaking proceeds extensively in the transition state, which is product-like.



The reaction of stable carbanions with Ellman's reagent and other diaryl disulfides in aqueous solution and in dimethyl sulfoxide gives the corresponding sulfides and an arenethiolate anion[60] (equation 43). Kinetic studies on this reaction[60] show that electron-withdrawing substituents in the disulfide accelerate the reaction of 2,4-pentanedione carbanion in the same way as that of cyanide ion, the slope for the log–log plot of the rate constants being 1.1. The reaction of a series of 1,3-dicarbonyl carbanions with Ellman's reagent was characterized by the Brønsted coefficient $\beta_{Nu} = 0.49$, while similar reactions of nitroalkanes gave $\beta_{Nu} = 0.95$. Nitroalkane carbanions react 10^2–10^4 slower than 1,3-dicarbonyl or cyanocarbon carbanions of the same pK_a.The solvent effects on the reaction rates are much greater for nitroalkane carbanions as the solvent is changed from water to DMSO.

$$\rangle C^- + ArSSAr \longrightarrow \rangle C\text{–}SAr + ArS^- \tag{43}$$

The effects of disulfide and carbanion structure on the reactivity suggest a transition-state structure in which there is a significant amount of negative charge developed on both

the central and leaving sulfur with incomplete formation of the carbon–sulfur bond. These observations are consistent with a concerted S_N2 mechanism for the reaction. The nitroalkane anomalies observed are similar to those observed for proton transfer and may reflect a transition state in which the amount of negative charge on carbon is greater than in the ground-state carbanion[61,62].

E. Thiolsulfonates and Thiolsulfinates

Thiolsulfonates generally react in a manner shown in equation 44, and this reaction is classified as a nucleophilic substitution at sulfenyl sulfur. This is because the sulfinate ion (RSO_2^-) is a sufficiently good leaving group (pK_a of $RSO_2H \simeq 2$), though not as good as the sulfonate ion (RSO_3^-).

$$PhS\text{–}SO_2Ph + Nu^- \xrightarrow{k_{Nu}^S} PhSNu + PhSO_2^- \qquad (44)$$

(21)

Kice and coworkers[63] measured rates for reactions of a large number of nucleophiles with *S*-phenyl benzenethiosulfonate **21** (equation 44). The second-order rate constants k_{Nu}^S (some of them are given in Table 5) are plotted logarithmically against those obtained for the corresponding nucleophilic reactions of the disulfone **22** (equation 45)[64] in Figure 1[63].

$$PhSO_2\text{–}SO_2Ph + Nu^- \xrightarrow{k_{Nu}^{SO_2}} PhSO_2Nu + PhSO_2^- \qquad (45)$$

(22)

TABLE 5. Reactivity of nucleophiles toward *S*-phenyl benzenethiosulfonate **21** *vs* *S*-phenyl benzenethiosulfinate **23**[a]

Nucleophile	k_{Nu}^S for **21** (M^{-1}/s^{-1})	$k_s + k_{so}$ for **23** ($M^{-1}\,s^{-1}$)	$k_{Nu}^S/(k_s+k_{so})$	Remarks
OH^-	4.4×10^2	3.1×10^2	1.4	$k_s < k_{so}$
MeO^-	4.0×10^2	7.3×10^2	0.6	$k_s \ll k_{so}$
$CF_3CH_2O^-$	5×10^2	2.6×10^2	1.9	
HOO^-	1.8×10^3	1.9×10^3	1.0	
PhS^-	3.2×10^6	1.0×10^5	32	$k_s \gg k_{so}$
CN^-	7.8×10^3	1.9×10^2	41	$k_s \gg k_{so}$
SO_3^{2-}	7.8×10^3	4.1×10^2	19	
N_3^-	0.7	0.006	110	
Piperidine	27	0.047	570	$k_s > k_{so}$
Piperazine	3.0	0.0057	530	
Morpholine	0.33	0.00046	720	$k_s \gg k_{so}$
NH_2NH_2	0.9	0.0024	380	

[a] All data are for 25 °C in 60% aqueous dioxane solution except those for methoxide ion, which are in methanol[63, 67].

Although nitrogen nucleophiles show good linearity with a slope of 0.85, three anionic nucleophiles do deviate greatly from the correlation line, being from 10^5 to 10^6 times more reactive toward the sulfenyl compound than the sulfonyl derivative. These nucleophiles

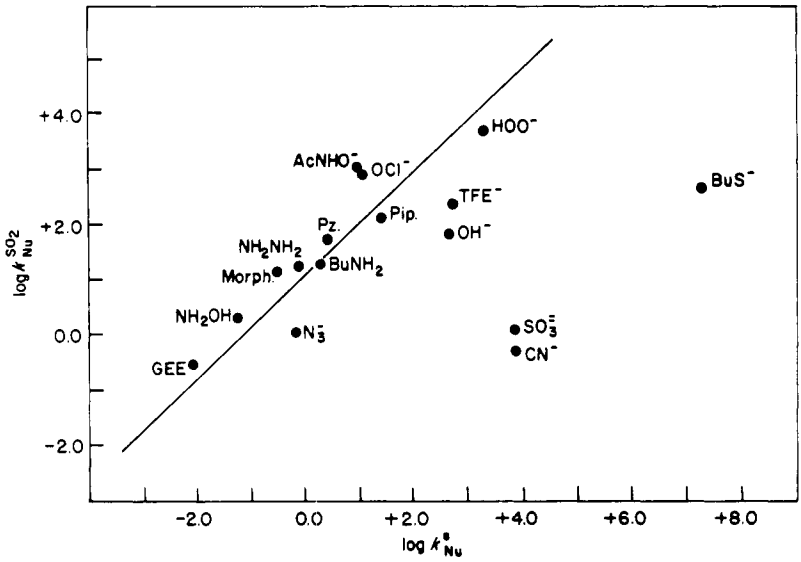


FIGURE 1. Plot of log k^{s}_{Nu} for reaction of nucleophiles with $PhSSO_2Ph$ *vs* log $k^{SO_2}_{Nu}$ for their reaction with $PhSO_2SO_2Ph$ in 60% aqueous dioxane at 25 °C. GEE, glycine ethyl ester; Morph., morpholine; Pz., piperazine; Pip., piperidine; TFE^-, $CF_3CH_2O^-$. Reproduced by permission of Academic Press from Kice, *Advances in Physical Organic Chemistry*, **17**, 155 (1980)

are classified as soft-base nucleophiles in terms of the hard and soft acids and bases (HSAB) concept proposed by Pearson and Songstad[65]. The divalent sulfur is a relatively soft electrophilic center and so the more reactive toward soft nucleophiles, while the sulfonyl sulfur is a hard electrophilic center. The sulfinyl sulfur was found to behave in between[66].

Reactions of thiolsulfinates with nucleophiles are often complicated by nucleophilic attacks occurring at both of the two electrophilic centers, namely at the sulfenyl and sulfinyl sulfur atoms (equation 46)[67]. Hard nucleophiles such as OH^- and MeO^- prefer to attack the sulfinyl sulfur which is the harder of the two, while most of other nucleophiles preferentially attack at the sulfenyl sulfur.

$$\underset{\textbf{(23)}}{PhS\text{–}S(O)Ph} + Nu^- \xrightarrow{k_s} PhSNu + PhSO^- \qquad (46a)$$

$$\underset{\textbf{(23)}}{PhS\text{–}S(O)Ph} + Nu^- \xrightarrow{k_{so}} PhS(O)Nu + PhS^- \qquad (46b)$$

The overall rate constants for **23** ($k_s + k_{so}$) were compared with those for the sulfonate **21** (k^{s}_{Nu} in equation 44) as summarized in Table 5[67]. Oxyanions react with **23** at a rate closely comparable to that of reaction with **21**, while soft nucleophiles like CN^-, SO_3^{2-} and PhS^- are less reactive toward **23** than they are toward **21** by a factor of 20–40. Amines are much less reactive toward **23** with the values of $k^{s}_{Nu}/(k_s + k_{so})$ being between 400 and 700. These variations in relative reactivities of nucleophiles toward **23** and **21** may be accommodated as follows[67].

Because of the better leaving ability of the sulfinate ion $PhSO_2^-$ as compared to the sulfenate ion $PhSO^-$, the reactivity of **21** would be greater than that of **23** if both of the substrates would react at the sulfenyl sulfur, as is the case for the soft nucleophiles. The

greater preference of oxyanions to react at the sulfinyl sulfur enhances the overall reactivity of **23** toward these nucleophiles and, as a result, the reactivity of **23** happens to become similar to that of **21** toward the oxyanion nucleophiles. Very large values of $k^{s}_{Nu}/(k_s + k_{so})$ observed for amines cannot easily be accommodated by this line of explanation. The products of the reactions of amines with **23** suggest that although attack at the sulfenyl sulfur is favored by the amine, the preference for attack at this site over the other sulfur is not as great as for the soft nucleophiles like CN^- and PhS^-. Hence, it is assumed that the reaction occurs with formation of an addition intermediate **24** (equation 47). The rate-determining step of this two-step reaction depends on the relative magnitudes of k_{-1} and k_2, i.e. the relative leaving ability of the nucleophile (amine) and X^- from the intermediate **24**. If the leaving ability of X^- is large enough to cause k_2 to become larger than k_{-1}, the rate-determining step is the formation of the intermediate, while the second step could be rate determining with a poor leaving group ($k_2 < k_{-1}$). Since the sulfinate is a relatively good leaving group, all the reactions of **21** may proceed with rate-determining attack of the nucleophiles ($k_2 > k_{-1}$). On the other hand, $PhSO^-$ should be a poorer leaving group than $PhSO_2^-$. In this case, k_2 would still probably be greater than k_{-1} for reactions of **23** with such nucleophiles as the oxyanions and cyanide ion, but for amines which are known in other substitutions to exhibit k_{-1} values 10^5 times larger than oxyanions of comparable basicity[68], k_2 could be much smaller than k_{-1}. In this case, k_s is given by k_1k_2/k_{-1} and should be much smaller than k_1. This could cause $k^{s}_{Nu}/(k_s + k_{so})$ to be exceptionally large.

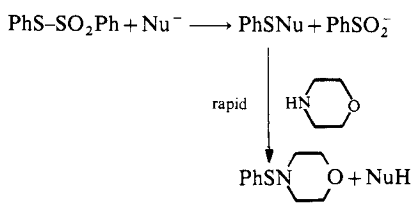
$$RNH_2 + PhS\text{–}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\overset{+}{N}H_2\text{–}\underset{\substack{|\\ Ph}}{\overset{-}{S}}\text{–}X \xrightarrow{k_2} PhS\overset{+}{N}H_2R + X^- \qquad (47)$$

$X = PhS(O)$ or $PhSO_2$ (**24**)

In acid solution thiolsulfinate may be protonated at the sulfinyl oxygen, when the reactions are initiated by attack of the nucleophile at the sulfenyl sulfur with departure of a neutral sulfenic acid (equation 48). With nucleophiles like halide ions, thiocyanate and dialkyl sulfides, the second step is reversible and racemization of optically active substrates can be observed[34], or ^{18}O isotope exchange can be measured by using a labelled substrate[35]. These reactions are first order in both nucleophile and proton. The rate-determining step is attack of the nucleophile on the protonated substrate. Relative reactivities of the nucleophiles obtained from the racemization[34] are given in Table 2.

Reaction of the thiolsulfonate **21** with morpholine to form the sulfenamide (equation 49) is catalyzed by halide ions and thiocyanate, and relative catalytic efficiencies[33] are also given in Table 2, in which nucleophilic reactivities are compared towards various electrophilic centers.

$$\underset{(\mathbf{23})}{PhS\text{–}S(O)Ph} + H^+ \rightleftharpoons PhS\text{–}\underset{\substack{|\\ OH}}{\overset{+}{S}}Ph \overset{Nu^-}{\rightleftharpoons} PhSNu + PhSOH \qquad (48)$$



(49)

Reactivities of halide ions toward the protonated **23** increase in the order $Cl^- < Br^- \ll I^-$ in a similar way to those toward the peroxide oxygen[37]. This is compatible with the reactivity toward the soft electrophilic center in terms of the HSAB theory[68]. Nucleophilic reactivities of several nucleophiles have been examined in their reaction towards the divalent sulfur in the trithionate ion and this divalent sulfur was classified as a soft electrophilic center[69,70] (equation 50). Variation in reactivities toward the sulfinyl sulfur[36] is smaller and similar to that observed for sp^3 carbon[38] as expected for a relatively hard (medium soft) electrophilic center.

$$^-O_3SS\text{–}SO_3^- + Nu^- \longrightarrow {}^-O_3SSNu + SO_3^{2-} \qquad (50)$$

$$Nu^- = RS^-,\ Ph_3P,\ CN^-,\ SO_3^-,\ S_2O_3^{2-}$$

The reactivity pattern toward the sulfenyl sulfur of **21**, where the leaving group is a sulfinate ion, is markedly different from that observed for protonated **23**: SCN^- is 6.3 times more reactive than I^-[33]. This peculiar change in the reactivity pattern found for two different sulfenyl sulfur atoms may be explained if attack of the nucleophiles on the sulfenyl sulfur involves an addition–elimination mechanism with an intermediate on the reaction coordinate (equations 51 and 52). In equation 52, neutral PhSOH will be a better leaving group than I^-, Br^- or SCN^-, so that $k_2 > k_{-1}$ in all cases, with the result that attack of the nucleophile on the protonated **23** will be rate determining, and the observed rate constants will be directly proportional to k_1. On the other hand, in the reactions of I^-, Br^- and SCN^- with **21** each of these anions should be a better leaving group than $PhSO_2^-$, so that $k_2 < k_{-1}$ in all cases. In this situation, step k_2, rather than attack of the nucleophile on **21**, will be rate determining and the observed rate constants will be presented by $k_1k_2/(k_{-1}+k_2)$. It would be reasonable to expect $k_2/(k_{-1}+k_2)$ to be considerably smaller for I^- than for the other two anions, because I^- would be the best leaving group of the three and thus k_{-1} for I^- would be much larger than that for either Br^- or SCN^-. A similar reactivity pattern of the nucleophilic catalysts was also observed for the acid-catalyzed hydrolysis of simple sulfenate esters[32] (see Section III.C).

$$Nu^- + \underset{\textbf{(21)}}{PhS\text{–}SO_2Ph} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Nu\text{–}\underset{\displaystyle Ph}{\underset{|}{\bar{S}}}\text{–}SO_2Ph \xrightarrow{k_2} PhSNu + PhSO_2^- \qquad (51)$$

$$Nu^- + \underset{\textbf{(23-H}^+\textbf{)}}{\underset{\displaystyle OH}{\underset{|}{PhS\text{–}\overset{+}{S}Ph}}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Nu\text{–}\underset{\displaystyle PhOH}{\underset{|\ |}{\bar{S}\text{–}\overset{+}{S}Ph}} \xrightarrow{k_2} PhSNu + PhSOH \qquad (52)$$

IV. SUMMARY

A general conclusion is that unimolecular substitution cannot occur at sulfenyl sulfur. However, most of the kinetic results reviewed in the preceding sections are not clear-cut in concluding whether the bimolecular mechanism is stepwise (addition–elimination or A–E mechanism) or not (S_N2-type mechanism). In many cases the results point to the A–E mechanism, but some other results suggest the synchronous S_N2-type mechanism. In an intramolecular transesterification of a sulfenate ester, a hypervalent intermediate was spectroscopically observed and the stepwise A–E mechanism was concluded[20].

The kinetic results reviewed are summarized in Table 6, including suggested mechanisms. Many of these studies are concerned with substituent effects on the reaction rates.

TABLE 6. Summary of mechanisms of nucleophilic substitutions at sulfenyl sulfur

No.	Substrate	Leaving group(L)	Nucleophile (Nu)	Mechanism[a]	Relative leaving ability	Ref.
1	ArCSCl	Cl^-	$ArNH_2$	$\underline{A}$–E	L > Nu	23, 24
2	Ph_3CSX	X^-	$BuNH_2$, OH^-	$\underline{A}$–E	L > Nu	26, 27
3	ArSOEt	EtO^-	OH^-	A–E/S_N2	L ~ Nu	29
4	Ph_3CSOAr	ArO^-	RNH_2, OH^-, ArO^-	A–E/S_N2	L ~ Nu	27, 39, 40
5	PhSO(H)Et	EtOH	X^-	A–E	L ~ Nu	32
6	$PhSSO_2Ph$	$PhSO_2^-$	RNH_2	$\underline{A}$–E	L > Nu	63
7	$PhSSO_2Ph$	$PhSO_2^-$	X^-	A–$\underline{E}$	L < Nu	33
8	PhSS(O)Ph	$PhSO^-$	OH^-, CN^-	$\underline{A}$–$\underline{E}$	L > Nu	67
9	PhSS(O)Ph	$PhSO^-$	RNH_2	A–$\underline{E}$	L < Nu	67
10	PhSS(OH)Ph	PhSOH	X^-	$\underline{A}$–$\underline{E}$/S_N2	L > Nu	34
11	RSSR	RS^-	RS^-, CN^-, $\geqslant C^-$	S_N2	L ~ Nu	45–51, 58–60

[a] Underlining in A–E indicates the suggested rate-determining step of the A–E mechanism.

Such analysis provides information on the electronic structure of the transition state but cannot be definitive in distinguishing the A–E mechanism from the S_N2 mechanism, since both of these mechanisms should proceed through a similar transition state. The difference between these is only in that there is an energy minimum on the reaction coordinate for the addition intermediate in the A–E mechanism but not in the S_N2 mechanism.

In the A–E mechanism, the rate-determining step depends on the relative leaving abilities of the leaving group L *vs* the nucleophile Nu from the intermediate: if the leaving ability of L is greater than that of Nu ($k_2 > k_{-1}$), the first (addition) step is rate determining, and *vice versa* (equation 53).

$$RS\text{–}L + Nu \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Nu\text{–}\underset{R}{\overset{|}{\underset{|}{S}}}\text{–}L \xrightarrow{k_2} RSNu + L \qquad (53)$$

If we cannot detect the intermediate (as is usually the case), the best way to demonstrate the A–E mechanism is to show that a change in the rate-determining step takes place by systematic variation of the substrate structure, nucleophiles or the reaction conditions. The change in the reaction rate with this systematic variation may show a break when the rate-determining step changes, namely when the sensitivities of the different transition states for the variations in the reaction system should be different from each other.

This criterion was used for the reaction of sulfenyl chloride with amine, where a curved dependence of the rates on amine concentration was observed (entry 1 of Table 6, see also Section III.B)[23,24]. However, a possibility of an ion-pair intermediate could not be excluded in this case.

In a symmetric reaction, the thiol–disulfide interchange (entry 11 of Table 6), the three thiolate groups were systematically changed to examine the effects of substituents on the reaction rate[45–51]. Although the variation extends widely from the situation where the leaving ability of L is greater than that of Nu, to the opposite situation, the substituent effects did not show any anomalies. Hence the synchronous S_N2-type mechanism was proposed for the reaction of disulfides. If the reaction were stepwise and a changeover of

the rate-determining step would occur with changing the substituents, the slope of the linear free-energy correlation would have changed.

On the other hand, when an anomalous order of leaving abilities or nucleophilicities was observed, the A–E mechanism was proposed (entries 2, 5 and 7 of Table 6) and was rationalized as follows: if the rate-determining step is addition of the nucleophile and does not involve departure of the leaving group, effects of the leaving group do not arise from the leaving ability but from other factors. If the elimination step is rate determining, the equilibrium nucleophilicity rather than the kinetic nucleophilicity is the controlling factor of the reactivity.

In conclusion, the A–E mechanism is not excluded by any experimental observations but rather often suggested as a reasonable mechanism. At least in some favorable cases, the hypervalent intermediate does exist, and theoretical considerations more generally support the intermediacy of such an intermediate for nucleophilic substitution at divalent and trivalent sulfur. However, to obtain experimental proof for the intermediate is extremely difficult, because the transition state for the A–E mechanism could be essentially the same as that for the S_N2-type mechanism.

V. REFERENCES

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