The chemistry of
sulphonic acids, esters and their derivatives

The chemistry of sulphonic acids, esters and their derivatives
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$-SO_3H$

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sulphonic acids, esters and their derivatives

Edited by

SAUL PATAI

and

ZVI RAPPOPORT

The Hebrew University, Jerusalem

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To
Zvi, Carmel and Ephraim,
the dependable communicators

Contributing authors

K. K. Andersen — Department of Chemistry, University of New Hampshire, Durham, NH 03824, USA

M. R. F. Ashworth — Fachrichtung 15.3, Organische und Instrumentelle Analytik, Universität des Saarlandes, 6600 Saarbrücken, Germany

H. Basch — Department of Chemistry, Bar-Ilan University, Ramat Gan 52100, Israel

A. R. Bassindale — POCRG, Department of Chemistry, The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK

G. A. Benson — School of Science, Regional Technical College, Ballinode, Sligo, Ireland

T. W. Bentley — Department of Chemistry, University College of Swansea, Singleton Park, Swansea, SA2 8PP, Wales, UK

A. J. Buglass — Anglia Higher Education College, East Road, Cambridge, CBI IPT, UK

Q.-Y. Chen — Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

S. Fornarini — Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi di Roma 'La Sapienza', Piazzale Aldo Moro 5, I-00185 Rome, Italy

H. Fujihara — Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

N. Furukawa — Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

W. M. Horspool — Department of Chemistry, University of Dundee, Dundee, DDI 4HN, Scotland, UK

J. Hoyle — Department of Chemistry-Soils, Nova Scotia Agricul-

tural College, P.O. Box 550, Truro, Nova Scotia, Canada B2N 5E3

T. Hoz — Department of Chemistry, Bar-Ilan University, Ramat Gan 52100, Israel

W.-Y. Huang — Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

J. Iley — POCRG, Department of Chemistry, The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK

A. Kalir — Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

H. H. Kalir — Department of Neurology, Mount Sinai School of Medicine, The Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY 10029–6574, USA

M. Kańska — Department of Chemistry, University of Warsaw, Warsaw, Poland

J. F. King — Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

J. F. Liebman — Department of Chemistry and Biochemistry, The University of Maryland, Baltimore County Campus, Baltimore, Maryland 21228, USA

J. B. Peel — Department of Chemistry and Research Centre for Electron Spectroscopy, La Trobe University, Bundoora, Victoria 3083, Australia

R. Rathore — Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

J. Simonet — Laboratoire d'Electrochimie organique, CNRS, Université de Rennes 1, France

W. J. Spillane — Department of Chemistry, University College, Galway, Ireland

K. Tanaka — Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606, Japan

J. G. Tillett — Department of Chemistry and Biological Chemistry, University of Essex, Wivenhoe Park, Colchester, Essex, CO4 3SQ, UK

D. M. Vofsi — The Weizmann Institute of Science, Rehovot 76100, Israel

M. Zieliński — Isotope Laboratory, Faculty of Chemistry, Jagiellonian University, 30-060 Kraków, Karasia 3, Poland

Foreword

This is the last volume in the sub-series on sulphur-containing functional groups in *The chemistry of functional groups* series. The other volumes were *The chemistry of the thiol group* (1974), with additional relevant chapters appearing also 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); *The chemistry of sulphinic acids, esters and their derivatives* (1990); *The chemistry of sulphenic acids and their derivatives* (1990). It is also intended, in the not too distant future, to publish a supplementary volume containing matter on more recent developments in the subject, as well as chapters which did not materialize for the other volumes.

Almost all the planned chapters could be included in the present volume, with the exception of a chapter on structural chemistry.

The authors' literature search in most cases included publications up to the end of 1989.

We will be indebted to readers who will bring to our attention mistakes or omissions in this or any other volume of *The chemistry of the functional groups* series.

Jerusalem
Autumn 1990

SAUL PATAI
ZVI RAPPOPORT

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 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 and 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
Alk	alkyl
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_3)
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital

i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
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 or Ts	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, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

General and theoretical

HAROLD BASCH and TOVA HOZ

Department of Chemistry, Bar-Ilan University, Ramat Gan 52100, Israel

I. INTRODUCTION

This chapter is concerned with a quantum chemical description of sulphonic acids and their derivatives. The characteristic feature of this class of compounds is the four coordination of the central sulphur atom, including the sulphonyl fragment $> SO_2$, where one of the other coordinating ligands is usually an acidic (—OH) or acid derivative group. We have taken the definition of acid derivatives here in a broad sense. Therefore, some of the material in this chapter is relevant to, and refers to, the previous volume in this series on sulphones[1].

The sulphur–oxygen linkage in the $> SO_2$ fragment is usually written S=O with a formal double bond. This is how we will write it here to indicate a terminal bond to oxygen, and to differentiate it from the pure S—O single bond in S—OR type linkages. Along with two singly-bonded groups or atoms X,Y in $XYSO_2$, this adds up to a formal valence or oxidation state of + 6 for the central sulphur atom and poses the interesting question of the nature of the sulphur atom hypervalency in this class of compounds. A resolution of this question, or, at least, insight into its nature, is important for an understanding of many of the properties of sulphonic acids and their derivatives.

There are not many general reviews of the sulphonic acids as a separate class, either experimentally[2] or theoretically, and they are usually included in general discussions of sulphones[1,3]. However, in contrast to the dearth of work on simple sulphinic acids and

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their derivatives[4], there is a noticeable body of published work relevant to the subject matter of this chapter and with which we can compare corresponding results, both theoretical and experimental.

As in the previous study of sulphinic acids and their derivatives[4], this chapter explores the simpler sulphonyl compounds using extended basis set *ab initio* molecular orbital theory methods wih post-Hartree–Fock correlation effects. The systems studied are of the form XSO_2Y, where X = H, CH_3, F, Cl, OH, NH_2 and SH, and Y = H, OH, F, Cl, NH_2, CH_3, SH and OCH_3, only in single substitution combinations (i.e. X = H with Y = any or X = any with Y = OH), except for $X = Y = CH_3$ which is included, and a few other types. Besides extensive tabulation of numerical values for a variety of properties, this systematic study at a uniformly high level of theory on a well-defined set of simple compounds of a given class should provide insight and understanding into the underlying electronic structure factors that produce these properties. Presumably, the main conclusions reached here will also be applicable to larger systems, at least on a local or regional molecular level in the bigger system. These ideas should also stimulate theoretical interest in the larger, more experimentally interesting systems.

This survey attempts to correlate the observed trends in calculated geometric and electronic structural properties in terms of familiar chemical and physical indices and concepts. These latter are not directly observable properties but have long been used for their interpretive and predictive value. Atomic charges, electron pair repulsions, and bonding, non-bonding and anti-bonding orbital interactions are all part of the chemist's arsenal of conceptual weaponry used in trying to explain chemical structure and processes. However, these simple models are not always well-defined or unambiguous. They are also usually somewhat rigid, in the sense that they attempt to explain or correlate chemical and physical changes in terms of only an initial or final state within an inflexible reference framework. The attempt to fold a quantitative-level-of-theory description of such changes into simple models can be problematic. The approach taken here is pragmatic and selective. Each observed trend will be correlated using the simplest model or explanation that seems to give the correct qualitative results. The quantitative results themselves are independent of the chosen framework of interpretation, and are available for more comprehensive treatment.

The specific properties studied here include charge distributions, energies, geometric structures and conformations, dipole moments, isomerization energies, bond dissociation energies, proton affinities, electron affinities, ionization potentials and spin populations, as well as the general trends in these and other properties, such as hypervalency character, and their underlying electronic structure causes. The comparison of calculated with experimental property values affords an opportunity to evaluate the computational methods.

II. THEORETICAL METHODS AND RESULTS

Ab initio self-consistent field (SCF) calculations were carried out on all the parent XSO_2Y molecules described in the previous section, the radical and anion systems derived by removal of a hydrogen atom or proton, respectively, from the parent neutrals, a selected number of related cations, and sundry atoms and small fragment species needed to complete certain types of chemical thermodynamic energy calculations. The geometric structures of the neutral compounds (parents, radicals) and cations were SCF gradient optimized in the standard 6-31G* basis set[5]. The anion geometries were treated similarly using the 6-31 + G* basis. All calculations were carried out using the GAUSSIAN 82[6] and GAUSSIAN 86[7] sets of computer programs. The polarization d-type functions added to the first- and second-row atoms (denoted by the * in the basis set description) included only the five spherical harmonic components.

At each final optimized geometry the MP2 energy was calculated in the 6-31 + G* and

6-31G* bases, except for the anions for which the MP2 energies were calculated in the former basis set only. Excitations from the core electrons were not included in the MP2 treatment. The restricted Hartree–Fock (RHF) method was used for the closed-shell molecules (parents and anions) and the unrestricted Hartree–Fock (UHF) method was applied to the spin doublet open-shell species (radicals and cations). Both methods are variants of the SCF approximation. A fuller description and explanation of the basis set and methods has been given previously[8].

Altogether, 62 $>SO_2$ molecules were studied, not counting the atom and small fragment species needed to calculate certain thermodynamic quantities. The calculated results are presented in Tables 1–18 and Figures 1–60. Generally, the tables fall into the following categories.

(a) Energies and dipole moments for the parent neutral molecules (Table 1), radicals (Table 4), anions (Table 8), cations (Table 11) and small fragments (Table 17).

(b) Calculated optimum bond lengths and angles for the parent neutrals (Table 2), radicals (Table 5), anions (Table 9) and cations (Table 12).

(c) Mulliken atomic charges and central sulphur atom d-orbital occupancies for the parent neutrals (Table 3), radicals (Table 6), anions (Table 10) and cations (Table 13).

(d) Orbital spin populations in the neutral radical species (Table 7) and in the radical cations (Table 14).

(e) Ionization energies from the parent neutral molecules (Table 15). Electron affinities (radical → anion) are tabulated in Table 8.

(f) Bond energies for the homolytic (Table 18) and the heterolytic (Table 16) cleavage of an atom–H bond. The latter gives the proton affinities of the anions.

III. HYPERVALENCY AND d ORBITALS

Two properties that are characteristic of second-row atoms in the Periodic Table, compared to the corresponding valence isoelectronic first-row atoms, are hypervalency (increased coordination) and the relative importance of d-type orbitals to their molecular electronic structure description. Hypervalency in sulphur compounds is represented by trivalent, tetravalent and hexavalent sulphur where a central sulphur atom is bonded to more than two ligand atoms or groups, compared to the oxygen atom which is almost exclusively divalent. Sulphur-containing compounds are typically classified in this manner[9]. Here, we have not differentiated between coordination number, valency and oxidation state. This point will be addressed later.

The classical explanation for the increased coordination or valency of sulphur is its use of atomic d orbitals in molecules to form more hybrid orbitals for bonding than can be formed from just s- and p-type orbitals[10]. The dominant thinking on this subject today[11] is that d-type orbitals provide needed spatial flexibility[12] for bonding molecular orbitals that are formed even without the d orbitals (in theoretical descriptions or calculations, for example). The d orbitals in hypervalent sulphur are needed for quantitative accuracy and have not been found to be required for the qualitative electronic structure description[13].

The d orbitals used in the calculational work reviewed here are called polarization-type, because they are functionally located in the same region of space as the valence s- and p-type orbitals, in order to be effective in enhancing angular polarization around the atom. These d orbitals differ from spectroscopic (Rydberg) d-type orbitals, which in the free atom are naturally more diffuse. As the positive charge on an atom increases, the spectroscopic atomic d orbitals become less diffuse. In hypervalent or high formal oxidation state compounds, the polarization and spectroscopic d-type orbitals are therefore more similar in spatial extent and their importance is correspondingly increased. The central sulphur-atom d orbitals in hypervalent compounds can thereby serve a double role; both in local atomic polarization and as available, low energy, valence atomic orbitals for molecular

back-bonding. Low-valence sulphur compounds (sulphenes, S for example) do not need special spatial flexibility and their spectroscopic d orbitals are not sufficiently stabilized. Therefore, as the valency of the atom decreases, so should its d-orbital occupancy.

However, these are quantitative effects and, for the basic electronic structure description of hypervalent compounds, d-type orbitals are apparently not essential. Hypervalency or increased coordination must then be connected to the spatially larger size of the sulphur atom (compared to oxygen), with concomitant larger sulphur–ligand bond lengths, which can accommodate more coordinating atoms/groups in spite of their mutual electrostatic repulsion[14].

The classification of hypervalency is unambiguous with respect to ligands having only single bonds to a central sulphur atom (such as halogens or the —OR group). The pure sulphur–oxygen bond when oxygen is a terminal ligand is usually written covalently, S=O, indicating both σ and π bonding interactions, and formally counts as raising the valency of sulphur by 2. However, this bond can also be considered as a single covalent bond $S^+—O^-$ together with an ionic or zwitterionic interaction having little or no π bonding[11,15,16]. The latter structure has been found to be more appropriate for the analogous P=X (X = O, S and CH_2) bonds[17,18] in hypervalent phosphorus compounds. The $S^+—O^-$ structure is also an expression of the high polarizability of the S=O bond and explains the preferred centre of electrophilic attack at the S=O oxygen atom in sulphonyl compounds[11].

In theoretical treatments, Boys localization[19] of the occupied molecular orbitals (MOs) in the parent sulphonic acid (HSO_2OH) shows 4 electron pairs around each terminal oxygen atom ligand and 4 around sulphur, more consistent with the $S^+—O^-$ structure and indicating only tetravalency for the sulphur atom in HSO_2OH[20]. Thus, in contrast to the usual classification[9,16], the valency of the sulphur atom in SO_2 compounds could be 4 and the oxidation state, 6. This approach is in contrast to the apparent pentavalency of pure SO_2[12,21] by the same criterion which therefore puts bare SO_2 into a different category from the sulphonyl compounds. The short S=O bond distance (relative to S—OR), which is usually cited as evidence for the double-bonded structure, is not an unambiguous criterion here because the $S^+—O^-$ structure is also expected to have short bond lengths due to electrostatic effects, like all ionic bonds. Although degree of covalency is not a direct experimental observable, the charge distribution is, and this point impacts on the basic electronic structure description of sulphonyl compounds.

The major evidence suggests[14,22] that the S=O bond in sulphonyl compounds can best be described essentially as a combination of a normal (polarized) covalent σ bond and a very polarized π bond whose MO is mainly (perhaps 80–90% depending on other substituents and S=O distance[23]) localized on the oxygen atom. The extent of S→O charge transfer is moderated by the low-lying d orbitals on the central sulphur atom which enter the π MOs in the S=O bonds and thereby acquire additional electron occupancy[24]. The availability of the d orbitals and resistance to ionic character (or enhanced back-bonding to S) will increase from >S=O to SO_2. The latter-type compounds are therefore expected to be more covalent and have a higher sulphur d occupancy than the former[25].

IV. NEUTRAL PARENTS

The simplest sulphone is dihydrosulphone, H_2SO_2, or HSO_2H (**1**) as it is listed in the tables, and has been discussed previously[8,26]. Its data are reproduced here in Tables 1–3 for completeness. The numbers in parentheses refer to the sequential listing of structures in the tables. The 6-31G* optimized geometry of the simplest sulphonic acid, HSO_2OH (**3**), is shown in Figure 1. The STO-3G* structure has been calculated previously[27]. However, as will be shown in subsequent comparisons, the geometries calculated here using an

TABLE 1. Energies and dipole moments of neutral parent species

Molecule	6–31 G*[a] Energy (a.u.) RHF	6–31 G*[a] Energy (a.u.) MP2	6–31 G*[a] Dipole moment (*D*)	6–31 + G*[b] Energy (a.u.) RHF	6–31 + G*[b] Energy (a.u.) MP2	6–31 + G*[b] Dipole moment (*D*)
(1) HSO_2H	− 548.276711	− 548.765030	4.08	− 548.284668	− 548.782472	4.12
(2) HSO_2F	− 647.145616	− 647.817800	3.03	− 647.164796	− 647.841377	3.09
(3) HSO_2OH	− 623.159465	− 623.826403	3.48	− 623.168837	− 623.848190	3.54
(4) HSO_2Cl	−1007.180873	−1007.803320	3.01	−1007.189350	−1007.822762	3.11
(5) HSO_2NH_2(I)	− 603.332130	− 603.982389	3.66	− 603.341620	− 604.004444	3.76
HSO_2NH_2(II)	− 603.329096	− 603.965812	5.24	− 603.339161	− 604.001918	5.26
(6) HSO(NH)OH	− 603.285551	− 603.940202	2.07	− 603.295122	− 603.962228	2.07
(7) HSO_2SH	− 945.791927	− 946.402605	3.87	− 945.801038	− 946.423357	4.04
(8) HSO_2CH_3	− 587.334686	− 587.954118	4.69	− 587.342216	− 587.972340	4.88
(9) HSO_2OCH_3	− 662.186884	− 662.979970	4.63	− 662.196368	− 663.003171	4.72
(10) $CH_3SO_2CH_3$	− 626.388588	− 627.139780	5.11	− 626.395942	− 627.159572	5.32
(11) FSO_2OH	− 722.028195	− 722.866356	3.28	− 722.039056	− 722.892151	3.26
(12) $HOSO_2OH$(I)	− 698.031679	− 698.874289	3.88	− 698.042291	− 698.899700	3.85
$HOSO_2OH$(II)	− 698.034292	− 698.876679	3.48	− 698.044957	− 698.902164	3.47
(13) $ClSO_2OH$	−1082.053738	−1082.853885	3.26	−1082.068868	−1082.893338	3.30
(14) H_2NSO_2OH	− 678.204844	− 679.031800	3.06	− 678.215380	− 679.057279	3.11
(15) $HSSO_2OH$(I)	−1020.666337	−1021.455764	4.01	−1020.677182	−1021.481623	4.12
$HSSO_2OH$(II)	−1020.667798	−1021.457217	3.77	−1020.678747	−1021.483268	3.89
(16) CH_3SO_2OH	− 662.214834	− 663.012567	3.89	− 662.223787	− 663.035332	4.00

[a]Geometry SCF optimized with no symmetry or atom equivalence constraints.
[b]In the 6–31 G* basis optimized geometry.

TABLE 2. Calculated optimized bond lengths and angles of the neutral parent species[a]

Molecule	Bond lengths (Å)								Bond angles (deg)	
	H—S	X	X—S[b]	S=O	N—H	C—H[c]	O—H	S—O	O=S=O	X—S—Y[i]
(1) HSO_2H	1.328			1.426					123.0	99.5
(2) HSO_2F[d]	1.315	F	1.553	1.407					123.4	95.9
(3) HSO_2OH	1.318			1.421			0.955	1.579	122.5	98.9
				1.413						
(4) HSO_2Cl[d]	1.322	Cl	2.008	1.415					122.9	97.5
(5) HSO_2NH_2(I)[d,e]	1.320	N	1.638	1.424	1.001				122.6	101.2
HSO_2NH_2(II)[d,e]	1.325	N	1.619	1.422	0.998				123.4	104.7
(6) HSO(NH)OH	1.312	=N	1.487	1.434	1.002		0.955	1.600	—	—
(7) HSO_2SH[g]	1.324	S	2.056	1.425					123.0	101.7
				1.423						
(8) HSO_2CH_3[d]	1.330	C	1.767	1.431		1.082			121.4	101.2
(9) HSO_2OCH_3[h]	1.322			1.421		1.079		1.566	122.2	99.9
				1.414						
(10) $CH_3SO_2CH_3$[d]		C	1.774	1.437		1.082			120.0	104.2
(11) FSO_2OH		F	1.546	1.407			0.956	1.558	124.1	98.6
				1.400						
(12) $HOSO_2OH$(I)[f]				1.419			0.955	1.564	122.1	99.3
				1.406				1.579		
$HOSO_2OH$(II)[d,f]				1.411			0.955	1.573	123.7	101.7
(13) $ClSO_2OH$		Cl	1.999	1.414			0.957	1.568	123.2	100.8
				1.406						
(14) H_2NSO_2OH		N	1.626	1.425	1.000		0.955	1.581	121.3	100.7
				1.417	0.999					
(15) $HSSO_2OH$(I)	1.326	S	2.045	1.424			0.956	1.584	122.5	103.9
				1.414						
$HSSO_2OH$(II)	1.326	S	2.050	1.414			0.955	1.581	123.2	100.2
				1.420						
(16) CH_3SO_2OH		C	1.763	1.428		1.080	0.955	1.591	120.6	100.2
				1.420						

[a]From the 6–31 G* basis optimized geometries.
[b]X = C, N, F, S or Cl atom attached to central sulphur atom.
[c]Average value lengths.
[d]The two S=O bond lengths are equivalent, to the accuracy of the table.
[e]The two N—H bond lengths are equivalent, to the accuracy of the table.
[f]The two O—H bond lengths are equivalent, to the accuracy of the table.
[g]S—H bond length = 1.326 Å.
[h]O—C bond length = 1.432 Å.
[i]Y = H, C or O.

TABLE 3. Mulliken atomic charges and d-orbital occupancies on sulphur in the neutral parent species[a]

Molecule	Atomic charges								d-Orbital occupancy[e]
	S	H(—S)	X[b]	H(—O)	H(—N)	H(—C)[d]	O(=S)	O(—S)	
(1) HSO_2H	+1.26	+0.05					−0.67		0.62
(2) HSO_2F	+1.60	+0.06	−0.43				−0.62		0.69
(3) HSO_2OH	+1.54	+0.05		+0.51			−0.68	−0.79	0.69
							−0.63		
(4) HSO_2Cl	+1.31	+0.09	−0.17				−0.62		0.64
(5) HSO_2NH_2(I)[c]	+1.48	+0.05	−1.01		+0.42		−0.68		0.67
HSO_2NH_2(II)[c]	+1.48	+0.03	−1.00		+0.42		−0.68		0.68
(6) HSO(NH)OH	+1.40	+0.08	−0.87	+0.50	+0.39		−0.70	−0.81	0.62
(7) HSO_2SH	+1.24	+0.07[e]	−0.13				−0.66		0.62
		+0.14							
(8) HSO_2CH_3	+1.38	+0.03	−0.75			+0.24	−0.69		0.61
(9) HSO_2OCH_3	+1.55	+0.04	−0.19[h]			+0.21	−0.68	−0.70	0.69
							−0.64		
(10) $CH_3SO_2CH_3$[f]	+1.54		−0.75			+0.23	−0.71		0.60
(11) FSO_2OH	+1.85		−0.41	+0.52			−0.63	−0.75	0.75
							−0.59		
(12) $HOSO_2OH$(I)	+1.80			+0.52			−0.68	−0.79	0.64
				+0.51			−0.61	−0.76	
$HOSO_2OH$(II)[g]	+1.81			+0.51			−0.64	−0.78	0.75
							−0.64	−0.78	
(13) $ClSO_2OH$	+1.62		−0.14	+0.52			−0.64	−0.76	0.71
							−0.60		
(14) H_2NSO_2OH	+1.77		−0.99	+0.51	+0.42		−0.69	−0.79	0.72
					+0.43		−0.66		
(15) $HSSO_2OH$(I)	+1.54	+0.13	−0.09	+0.52			−0.68	−0.79	0.68
							−0.63		
$HSSO_2OH$(II)	+1.53	+0.14	−0.11	+0.51			−0.63	−0.78	0.68
							−0.67		
(16) CH_3SO_2OH	+1.69		−0.75[h]	+0.51		+0.24	−0.70	−0.82	0.67
							−0.66		

[a]From 6–31 G* basis SCF optimized wave functions.
[b]X = C, N, F, S or Cl atom attached to central sulphur atom. See Table 2.
[c]The two H(N) values are equal, to the accuracy of the Table.
[d]Averaged.
[e]Central sulphur atom.
[f]The two X values are equal, to the accuracy of the table.
[g]The two H(O) values are equal, to the accuracy of the table.
[h]Carbon atom.

extended valence basis set with d-type polarization functions on all the atoms (except hydrogen) are in excellent uniform agreement with experiment. The sulphurous acid isomer, $OS(OH)_2$, has been experimentally estimated to be more stable than sulphonic acid by ~ 4.4 kcal mol^{-1} (free energy of tautomerization)[28]. The analogous situation was encountered previously when HSO_2H (**1**) was calculated to be more stable than sulphinic acid (HSOOH)[8]. Presumably, alkyl substitution will preferentially stabilize the sulphonic acid form relative to the sulphoxide.

Hargittai[29] has reviewed structural correlations in the simple sulphonyl compounds, with emphasis on the experimentally observed S=O bond length and O=S=O bond angle. We can extend this comparison of trends using the calculated geometric structural parameters (Table 2) and add the S—H bond length and H—S—X bond angle in a study of the homologous series, HSO_2X, with X = H (**1**), OH (**3**, Figure 1), F (**2**, Figure 2), Cl (**4**, Figure 3), NH_2 (**5**-I, Figure 4 and **5**-II, Figure 5), SH (**7**, Figure 7), CH_3 (**8**, Figure 8) and OCH_3 (**9**, Figure 9). It can be seen from Table 2 that for the S=O bond length and O=S=O angle, the variations here are very small and agree closely with the narrow range of experimental values observed for these geometric parameters in similar compounds[29].

Not surprisingly, however, closer inspection of Table 2 reveals a significant correlation between the nature of the substituent X and increasing values of the S=O distance, decreasing O=S=O angle, increasing H—S—X angle and increasing S—H bond length in the order; X = F, Cl, OH, OCH_3, NH_2, SH, H and CH_3. This series should represent the decreasing order of polarization of the S—X bond towards X. Thus, the more electronegative the substituent X in XSO_2H, the shorter is the H—S bond and the smaller is the H—S—X bond angle.

Using the language of the Valence Shell Electron Pair Repulsion Theory[30] (VSEPR), this last trend could correlate with decreased electron-pair repulsion between the S—X and S—H bonding electrons. The more polarized S—X is towards X, the less the repulsion

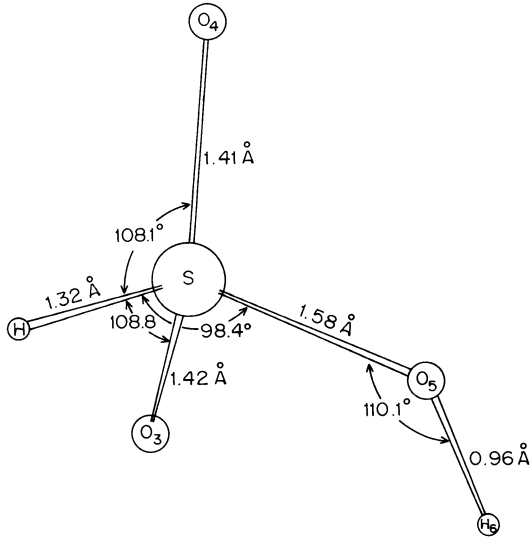


FIGURE 1. HSO_2OH, structure **3**, dihedral angles: $O_4SHO_3 = 135.2°$, $O_5SHO_3 = -111.9°$, $H_6O_5SO_3 = -1.6°$

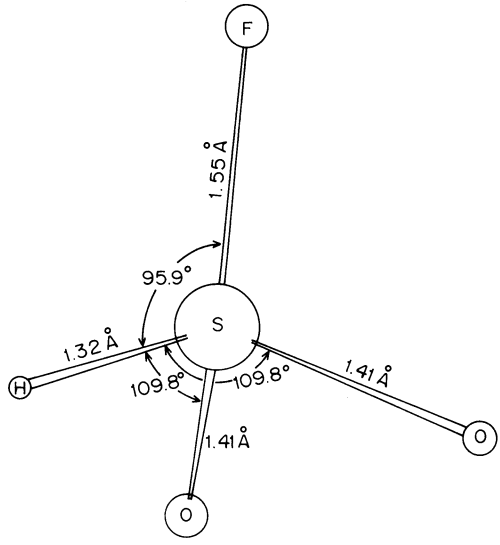


FIGURE 2. HSO_2F, structure **2**, dihedral angles: OSHO = 138.6°; FSHO = − 110.7°

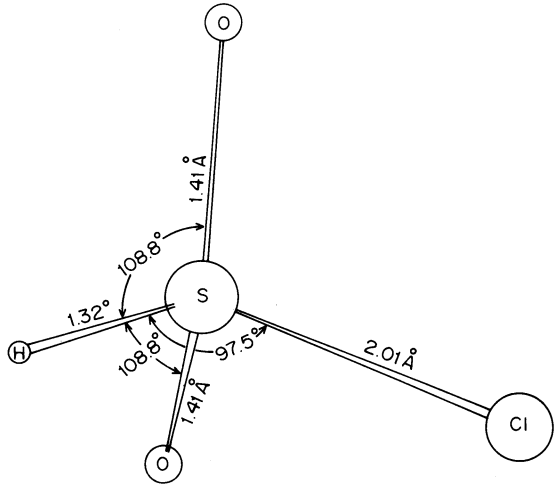


FIGURE 3. HSO_2Cl structure **4**, dihedral angles: OSHO = 136.2°, ClSHO = − 111.9°

between the S—X and S—H bonding electron pairs, since the σ(S—H) MO will be more polarized towards the sulphur atom as the latter's atomic charge increases[21]. The decrease in O=S=O bond angle with increased H—S—X angle is natural within the VSEPR model[21,30]. The shortening of the S=O bond with increased electronegativity of X possibly indicates an enhancement of the π bond structure representation of S=O at the

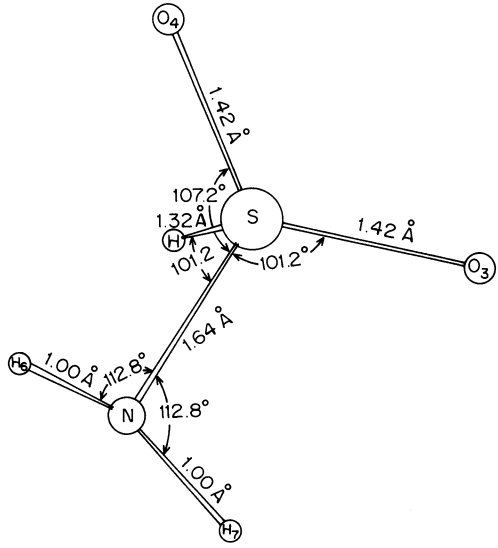


FIGURE 4. HSO_2NH_2, structure **5**-I, dihedral angles: $O_4SH_2O_3 = 226.6°$, $NSH_2O_3 = 113.3°$, $H_6NSO_3 = -2.2°$, $H_7NSO_3 = 227.4°$

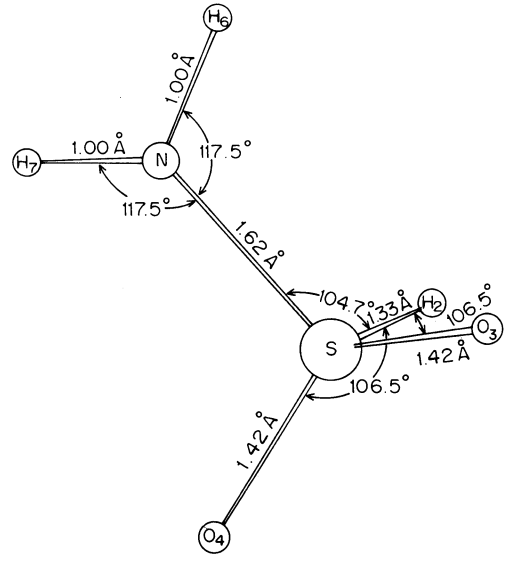


FIGURE 5. HSO_2NH_2 II, structure **5**-II, dihedral angles: $O_4SH_2O_3 = 226.6°$, $NSH_2O_3 = 113.3°$, $H_6NSH_2 = 74.8°$, $H_7NSH_2 = -74.8°$

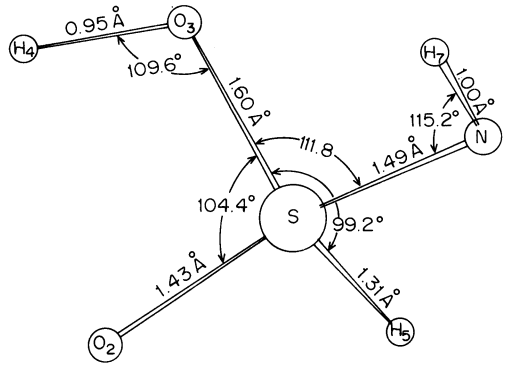


FIGURE 6. $HSO(NH)OH$, structure **6**, dihedral angles: $H_4O_3SO_2 = -10.0°$, $H_5SO_3H_4 = 104.2°$, $NSO_3H_4 = -148.0°$, $H_7NSO_3 = 78.4°$

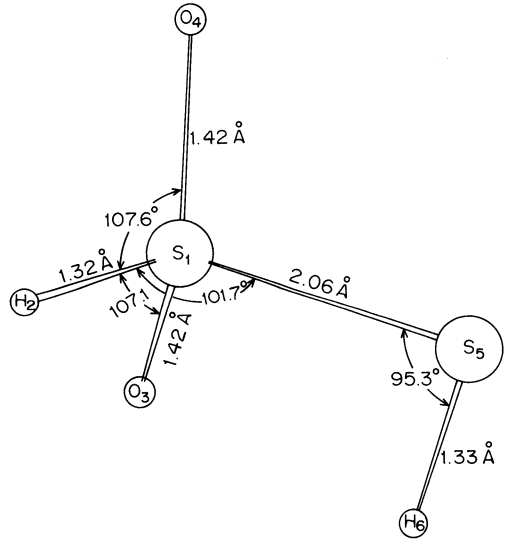


FIGURE 7. HSO_2SH, structure 7, dihedral angles: $O_4S_1H_2O_3 = 134.1°$, $S_5S_1H_2O_3 = -114.5°$, $H_6S_5S_1O_3 = -29.6°$

expense of the ionic structure $S^+—O^-$, because of the increased atomic charge on the central sulphur atom. The calculated Mulliken atomic charge on the O (=S) atom (Table 3) decreases erratically with the increased electronegativity of X, which clouds the correlation of the S=O bond length and O=S=O angle based on purely electrostatic considerations.

In molecular orbital terms the behaviour of the geometric parameters with substituent X may be explained as follows. The more polarized the σ(S—X) bond is towards X, the

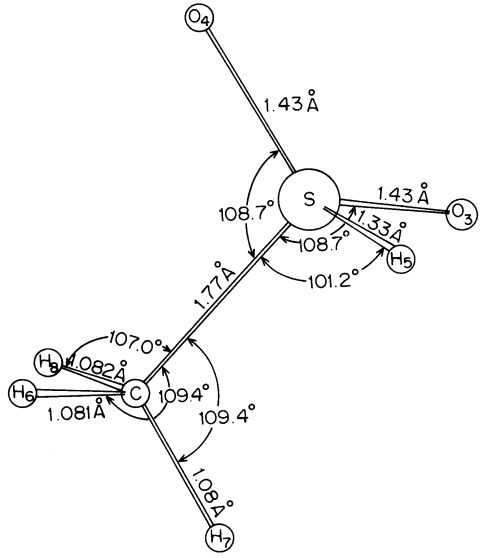


FIGURE 8. CH_3SO_2H, structure **8**, dihedral angles: $O_4SCO_3 = 134.0°$, $H_5SCO_3 = -113.0°$, $H_6CSO_3 = 174.1°$, $H_7CSO_3 = 51.9°$, $H_8CSO_3 = -67.0°$

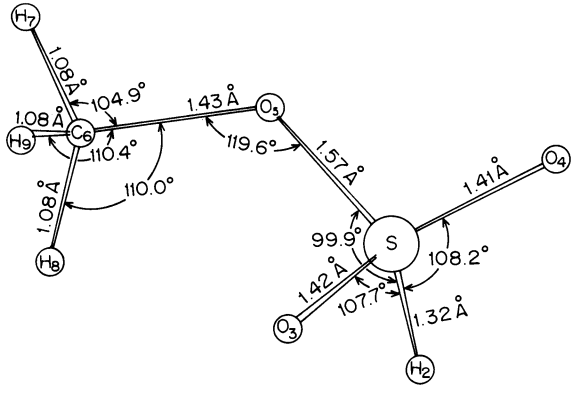
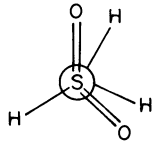


FIGURE 9. HSO_2OCH_3, structure **9**, dihedral angles: $O_4SH_2O_3 = 134.0°$, $O_5SH_2O_3 = -114.2°$, $CO_5SO_3 = -27.2°$, $H_7CO_5S = 180.0°$, $H_8CO_5S = 60.5°$, $H_9CO_5S = -61.5°$

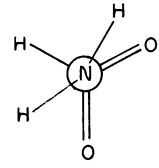
more the corresponding σ^*(S—X) bond is concentrated closer to the central sulphur atom and is available for a stabilizing interaction with the S—H and S=O bonding orbitals, which will lead to shorter S—H and S=O bond lengths. Ideally, in simple MO terms, the behaviour of the O=S=O and H—S—X angles with substituent X should be discussed in terms of the change in energy with bond angles of the major S—X and S—Y (Y = H,O)

bonding MOs as a function of X. This approach is complicated and the VSEPR model is usually preferred. These points need further study.

For hydrogen sulphonamide, HSO_2NH_2 (**5**), two stable conformations (**5-I**, Figure 4 and **5-II**, Figure 5) were found in the calculations. Both are listed in Tables 1–3. Viewed along the S—N bond, the more stable rotamer, **5**-I, by 1.6 kcal mol^{-1} (MP2/6-31 + G*), has the pair of N—H and S=O bonds almost perfectly eclipsed. Therefore, in projection, the nitrogen atom lone pair of electrons is maximally aligned with the S—H bond (rotamer **a**). The latter is a repulsive interaction, while the former is stabilizing due to intramolecular O···H interactions. The hydrogen-bond distances here for the close-contact O,H pairs are both 2.51 Å, which is similar to intermolecular hydrogen-bonded distances found recently for water–sulphinic acid and similar-type complexes[8]. This intramolecular form of hydrogen bonding in the sulphinic acids will be noted more generally later. Rotamer **b** (**5**-II), which is related to **a** approximately by a rotation of 180° about the S—N bond, has the staggered conformation, which reduces the nitrogen atom lone pair (S—H) bond pair repulsion but weakens the attractive O···H interaction. In fact, Dorie and Gouesnard[31] have found for N-alkyl substituted sulfonamides at low temperature in condensed phase that confomer **b** is favoured. Thus the possibility of internal O···H interaction must be a contributing factor in confomer stability in these types of compound. The higher dipole moment of **5**-II (Table 1) will also favour its stability in polar solutions.



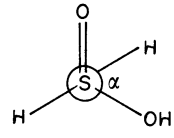
(**a**)



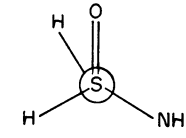
(**b**)

The various possible conformations of hydrogen sulfonamide have previously been studied by Elguero and coworkers[32], who carried out a RHF/6-31G* geometry optimization on **5**-I but only RHF/STO-3G* level optimization for the other confomers. They found a 2.5 kcal mol^{-1} energy difference between **5**-I and **5**-II in the 6-31G* basis. A complete MP2/6-31G* geometry optimization of the two rotamers gives a 2.1 kcal mol^{-1} energy difference favouring I[33].

Elguero and coworkers[32] have also calculated the geometry of the imido isomer **6** (Figure 6). In agreement with them, we find the lowest energy confomer as shown in **c** and **d**. Looking down the S—N bond in **c**, N—H is located between the S=O and S—OH bonds with dihedral angle $\alpha = 78.4°$. Viewed down the S—O(—H) line in **d**, the O—H bond has a 9.9° dihedral angle with the S=O bond. In the latter case significant O···H interaction is achieved ($O_2 \cdots H_4$ distance of 2.34 Å) at the expense of the lone pairs of electrons on the oxygen atom approximately eclipsing the S—H and S—N bonds. The $O_2 \cdots H_7$ interaction in **c** is weaker with an interatomic distance of 2.88 Å. The double bond character of the S=N bond, which places a lone pair of electrons in the H—N=S plane,



(**c**)



(**d**)

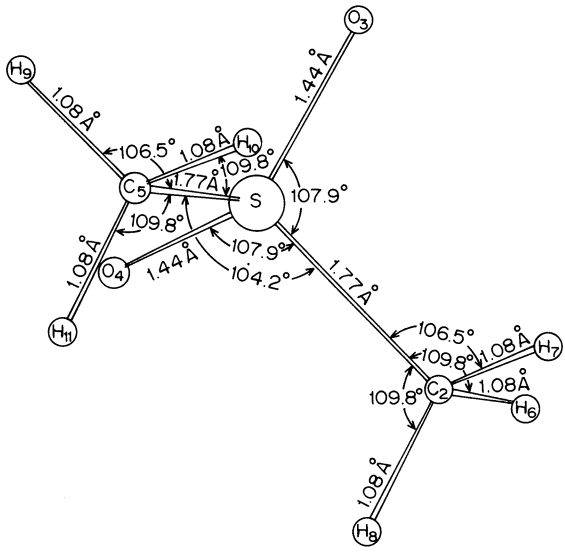
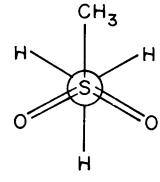


FIGURE 10. $CH_3SO_2CH_3$, structure **10**, dihedral angles: $O_4SC_2O_3 = 131.0°$, $C_5SC_2O_3 = -114.5°$, $H_6C_2SO_3 = 53.2°$, $H_7C_2SO_3 = -65.5°$, $H_8C_2SO_3 = 175.7°$, $H_9C_5SO_3 = 65.4°$, $H_{10}C_5SO_3 = -53.3°$, $H_{11}C_5SO_3 = 184.1°$

is clear from the significant reduction in this bond length relative to **5** (Table 2). The MP2/6-31G + G* calculated isomerization energy (**5**-II → **6**) is + 26.5 kcal mol^{-1}.

Dimethyl sulphone **10** (Figure 10) is well studied experimentally[29,34] and discussed theoretically[35]. The optimized geometric parameters in Table 2 are in very good agreement with the corresponding electron diffraction values for the S=O bond length (exp. value 1.435 Å, calc. value 1.437 Å), the S—C bond length (exp. value 1.771 Å, calc. value 1.774 Å), the O=S=O angle (exp. value 119.7°, calc. value 120.0°) and the C—S—C angle (exp. value 102.6°, calc value 104.2°). This comparison gives confidence to the calculated structural values presented here. The projection form of $CH_3SO_2CH_3$ viewed along the S—C bond (rotamer **e**) is completely staggered and this conformation is also adopted by HSO_2CH_3 (**8**, Figure 8) and CH_3SO_2OH (**16**, Figure 18). Hargittai and Hargittai[34] have discussed the sulphur–carbon bond in sulphonyl compounds in detail. HSO_2CH_3 and HSO_2F were also studied by Boyd and Szabo[35].



(**e**)

The $HOSO_2OH$ molecule **12** or, as it is more commonly written, H_2SO_4, sulphuric acid, has been much studied[27,36–40]. Experimentally[36,37], a single conformation (**12**-II, Figure 13) has been identified with the following observed (calculated) structural parameters:

d(S=O) = 1.42 Å (1.41 Å), d(S—O = 1.57 Å (1.57 Å), d(O—H) = 0.97 Å (0.96 Å), < O=S=O = 123.3° (123.7°), < O—S—O = 101.3° (101.7°), < O—S=O = 106.4° and 108.6° (106.5° and 108.2°) and < S—O—H = 108.5° (110.4°). The agreement is very good, being worst for the S—O—H angle which is experimentally the most uncertain (± 1.5°)[36]. The symmetry is very close to C_2 where the observed (calculated) dihedral angles of

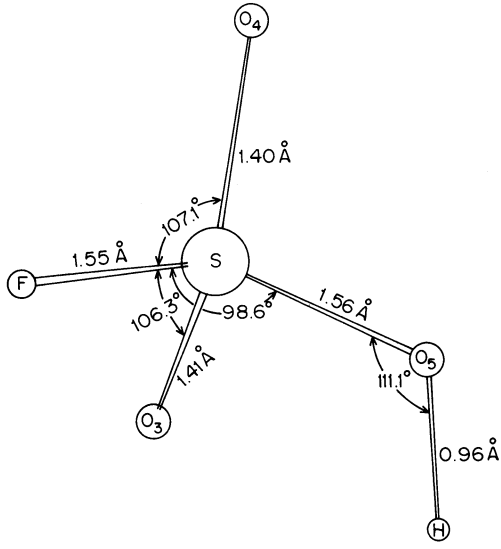


FIGURE 11. FSO_2OH, structure **11**, dihedral angles: $O_4SFO_3 = 134.5°$, $O_5SFO_3 = -113.2°$, $HO_5SO_3 = 22.4°$

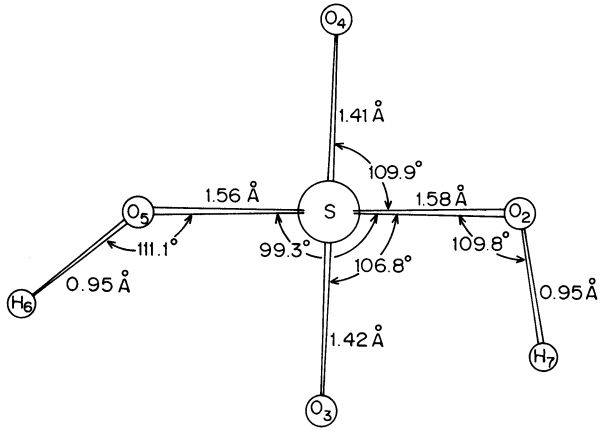


FIGURE 12. $HOSO_2OH$ I, structure **12** – I, dihedral angles: $O_4SO_2O_3 = 134.4°$, $O_5SO_2O_3 = -113.9°$, $H_6O_5SO_3 = -33.5°$, $H_7O_2SO_3 = -27.3°$

interest are $H_6—O_5—S=O_4 = 20.8°$ (24.8°) and $H_6—O_5—S=O_2 = -90.9°$ (−87.3°). This places each hydrogen atom 2.43 Å from a different (O(=S) atom (Figure 13). The 6-31 + G* basis calculated dipole moment is 3.47 *D* while the experimental value is 2.72 *D*[36]. This discrepancy is larger than expected for a polarized double-zeta basis calculation[41].

However, a second low-energy structure has also been found by the full 6-31G* basis

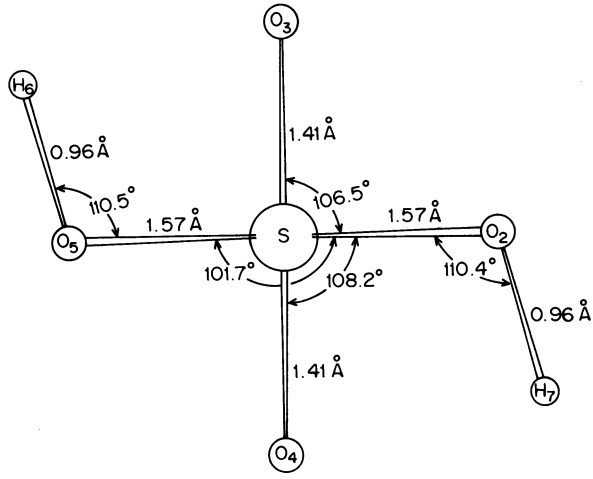


FIGURE 13. $HOSO_2OH$ II, structure **12**-II, dihedral angles: $O_4SO_2O_3 = 134.9°$, $O_5SO_2O_3 = -113.2°$, $H_6O_5SO_3 = +24.6°$, $H_7O_2SO_4 = +24.8°$

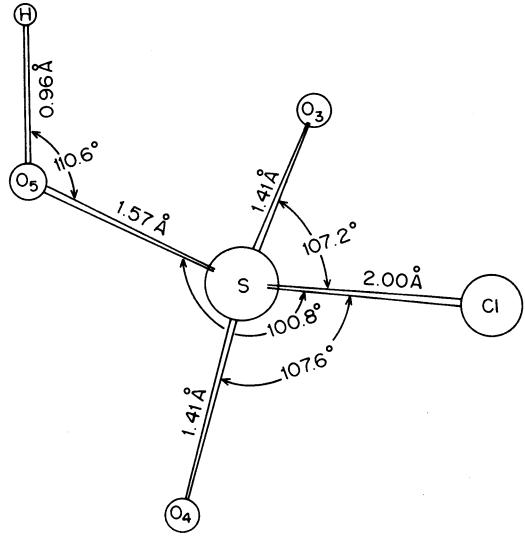


FIGURE 14. $ClSO_2OH$, structure **13**, dihedral angles: $O_4SClO_3 = 134.4°$, $O_5SClO_3 = -113.1$, $HO_5SO_3 = -20.9°$

SCF optimization (**12**-I, Figure 12) having close to C_2 symmetry. This confomer, with both hydrogen atoms located 2.46 ± 0.5 Å from the same O(=S) atom, is calculated (Table 1) to be (MP2/6-31 + G*) 1.5 kcal mol^{-1} above the C_2 structure in energy and to have a larger dipole moment (3.85 *D*). Lohr[42] also found only two stable rotamers for H_2SO_4 with an SCF energy difference of 1.4 kcal mol^{-1} in a smaller basis set and without geometry re-

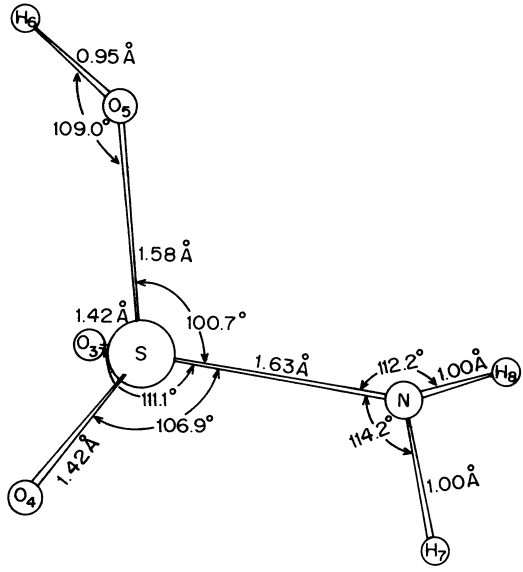


FIGURE 15. H_2NSO_2OH, structure **14**, dihedral angles: $O_4SNO_3 = 134.4°$, $O_5SNO_3 = -111.5°$, $H_6O_5SO_3 = 20.9°$, $H_7NSO_3 = 16.9°$, $H_8NSO_3 = 244.6°$

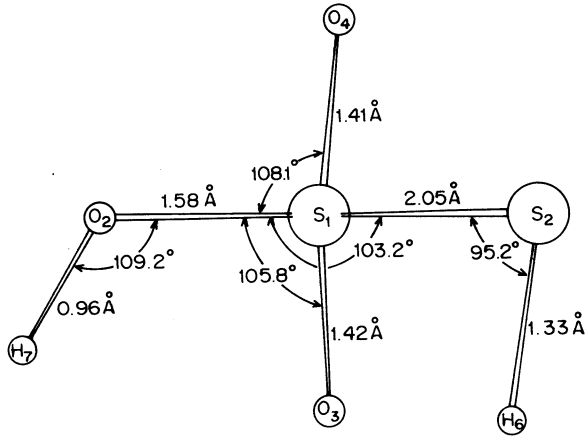


FIGURE 16. $HSSO_2OH$ I, structure **15**-I, dihedral angles: $O_4S_1O_2O_3 = 132.8°$, $S_2S_1O_2O_3 = -115.7°$, $H_6S_2S_1O_3 = -38.9°$, $H_7O_2S_1O_3 = -1.95°$

optimization for the higher-energy confomer. An energy difference of ~ 1.5 kcal mol^{-1} implies an about 8% concentration of the C_2 structure in equilibrium with the lower energy C_2 rotamer at room temperature. Perhaps the low concentration presence of the high-energy rotamer explains the unassigned weak transitions in the gas-phase microwave spectrum of H_2SO_4[36].

The analogous $HSSO_2OH$ system (**15**) also has two stable confomer structures (Figures

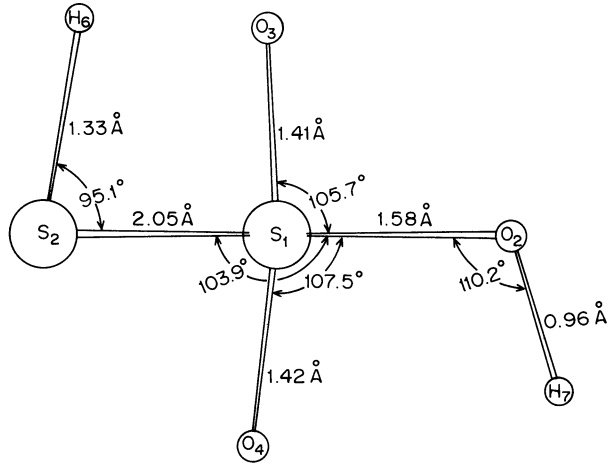


FIGURE 17. $HSSO_2OH$ II, structure **15-II**, dihedral angles: $O_4S_1O_2O_3 = 133.2°$, $S_2S_1O_2O_3 = -115.3°$, $H_6S_2S_1O_3 = -40.4°$, $H_7O_2S_1O_4 = -23.8°$

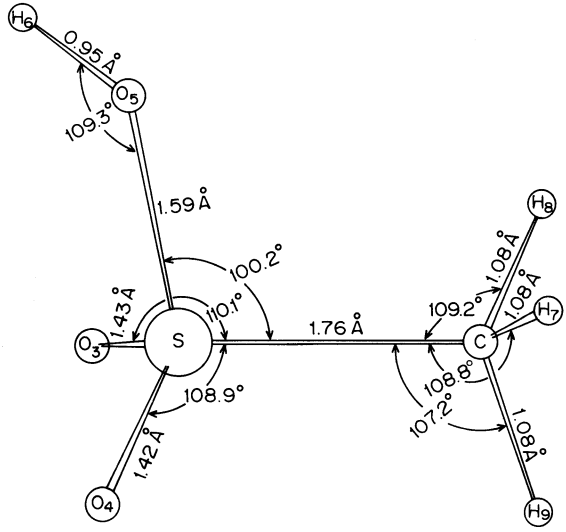
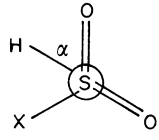


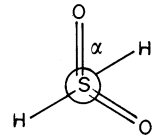
FIGURE 18. CH_3SO_2OH, structure **16**, dihedral angles: $O_4SCO_3 = 134.3°$, $O_5SCO_3 = -111.9°$, $H_6O_5SO_3 = 11.6°$, $H_7CSO_3 = 171.0°$, $H_8CSO_3 = 49.7°$, $H_9CSO_3 = -70°$

16 and 17), parallel to those of $HOSO_2OH$. The higher-energy confomer, by only (MP2/6-31 + G*) 1.0 kcal mol^{-1}, again has the larger dipole moment. The average (H—) S···O(—S) distances in **15-I** and **15-II** are both 2.82 Å, which is characteristic of the unusually short S···O non-bonded interaction distance much noted[43-45].

The apparent importance of intramolecular hydrogen bonding mentioned above can be learned from the adopted preferred conformations (**f** and **g**) of the whole sulphonic acid series. Viewed along the S—O(—H) bond, HSO_2OH (**3**, Figure 1), HSO_2SH (**7**, Figure 7), FSO_2OH (**11**, Figure 11 and $ClSO_2OH$ (**13**, Figure 14) project like **f**, and $HSSO_2OH$ (**12**-II, Figure 13), H_2NSO_2OH (**14**, Figure 15), $HSSO_2OH$ (**15**-II, Figure 17) and CH_3SO_2OH (**16**, Figure 18) have rotamer form **g**. $HOSO_2OH$ (**12**-I, Figure 12) and $HSSO_2OH$ (**15**-I, Figure 16) project as both **f** and **g** depending on along which S—O or S—S bond the projection is viewed. In each case the dihedral H—O—S=O angle α lies between 2–40°, with an average (O—)H···O(S) close-contact distance of 2.4–2.7 Å, which corresponds to the long intramolecular hydrogen-bond interaction (2.43 Å in both **12**-II and **15**-II). The H—O—S=O dihedral angle (α) differs from 0°, which would give a closer-approach hydrogen-bond distance, apparently due to repulsions between the lone-pair electrons on the O(—H) atom and the X—S or S=O bonding pairs of electrons. Also, in each case (**f** and **g**) the length of the S=O bond adjacent to the O—H bond is greater than that of the remote S=O bond, another indication of intramolecular interactions.



(**f**)



(**g**)

Similarly to HSO_2OH (**3**) and CH_3SO_2OH (**16**), we note another case of intramolecular hydrogen bonding. HSO_2OCH_3 (**9**, Figure 9) has a short (S=)O···H(—C) non-bonding distance of 2.58 Å. The interacting S=O bond is longer than the other one, as is the involved C—H bond, relative to its two brother C—H bonds. The (H—)O—S=O angle is also a relatively small 99.9°. Looking further at both CH_3SO_2H (**8**, Figure 8) and $CH_3SO_2CH_3$ (**10**, Figure 10) there is evidence, in general, of the inequivalency of the C—H bonds of the methyl groups in the sense that one of the C—H bonds is more ionic than the others. The acidity of the CH_3 group in sulphonic acids and sulphones has been noted[46] and the geometric and electronic structural aspects of this effect will be described in more detail elsewhere[47]. It should also be noted that the involvement of a stabilizing C—H hydrogen-bond interaction with an oxygen atom has been found in the formate–formic acid complex[48].

The type of correlations discussed above in the HSO_2X series between bond length/bond angles and the substituent X are also found for the XSO_2OH group of sulphonic acids (Table 2). Thus, the S=O bond lengthens (from 1.403 Å to 1.424 Å) and the O=S=O angle decreases (from 124.1° to 120.6°) as X varies in the approximate electronegativity order; F, OH, Cl, H, SH, NH_2 and CH_3. Here again the σ^*(S—X) molecular orbital should be more concentrated near the central sulphur atom and of lower energy (less anti-bonding), the more the S—X bond is polarized towards X. Such a polarized σ^* (S—X) MO should be more available to interact with, stabilize and thereby shorten the S=O bonds. The S—O(—H) bond length also increases (Table 2) in the same descending order of substituent electronegativity, for the same reasons. However, there seems to be no detectable correlation here between the X—S—O(—H) bond angle and the electronegativity order of substituents listed above, possibly because of the more complex interaction between the X group and the O(—H) atom in the XSO_2OH series compared to the S—X···H—S interaction in the HSO_2X group.

It should be noted that, in general, the S=O and S—X bonds are shorter and the O=S=O angles are smaller in the XSO_2OH series compared to XSO_2H. The former correlates with the larger atomic charge on the sulphur atom in the sulphonic acids relative to the sulphones.

The Mulliken population analysis results for atomic charges shown in Table 3 for the neutral parents, for example, are known to be basis-set dependent[3] and sometimes unrealistic. The problem can be particularly serious with an extended basis set, because the contribution attributed to a given basis function is allocated to the atom upon which that function is centred, even though that basis orbital may have its maximum charge density located close to a different center[49]. However, a comparison of population-analysis indices for a series of molecules in the same basis set has usually been found to give chemically meaningful information and is a widely used method for comparing charge distributions. This approach should also be valid here where members of a given class of compounds are being compared. However, caution should be exercised in drawing conclusions based only on the population analysis.

With this *caveat* we can now examine Table 3 in detail. One of the first observations is the remarkable near-constancy of the atomic charges for a given atom (except for the central sulphur atom). The advantage of using a common, standard basis set is very evident here. Secondly, the direction of change in the atomic charge on the central sulphur atom is related in an expected way to the electronegativity of the substituent. For example, in both series, HSO_2X and XSO_2OH, the order of decreasing charge on the X group is F, OH, (Cl, NH_2), (CH_3, SH) and H. The position of CH_3, usually considered an electron-releasing group, here appears to be anomalously out of place. This reversal of order relative to the bare hydrogen atom is reflected in the larger charge on the sulphur atom in CH_3SO_2OH (**16**) relative to HSO_2OH (**3**), and in $CH_3SO_2CH_3$ (**10**) relative to HSO_2H (**1**). Although the methyl group in substituted sulphonic acids is considered to have unusual acid properties[46], the anomalous positioning of the CH_3 group here is possibly an artificiality of the population analysis.

We also note here the large negative charge of the sulphonyl group oxygen atoms (average about -0.67) compared to fluorine (about -0.42) and the hydroxyl group (about -0.27), for example. This large negative charge on O(=S) reflects the ionic bond structure representation $S^+—O^-$, of S=O. The large and relatively uniform d-orbital population on the central sulphur atom is characteristic of these hypervalent four-coordinate sulphonyl compounds and shows that the d orbitals in these types of system are close to being real valence atomic orbitals[22], even though qualitative bonding models can be constructed without them. The divalent sulphur atoms in $HSSO_2OH$ (**15**) and HSO_2SH (**7**) have d-orbital populations of 0.08 and 0.07 electrons, respectively, compared with the hypervalent central sulphur atom d populations of 0.68 and 0.62, respectively (Table 3). These differences demonstrate most clearly the relationship between hypervalency and d-orbital occupancy.

In general, the geometric parameters shown in Table 2 are remarkedly constant for a given bond type. Thus, as has been noted[50], the S=O bond length and O=S=O bond angle are relatively invariant to surroundings or substituent group. These bond lengths can be used to characterize the type bond, where such information or its interpretation is in doubt.

V. RADICALS

The series of radicals that have been studied (Tables 4–7) can be classified into three groups: $XSO_3\cdot$, with X = H (**17**, Figure 19), F (**18**, Figure 20), OH (**19**, Figure 21), Cl (**20**, Figure 22), NH_2 (**21**, Figure 23), HS (**22**, Figure 24) and CH_3 (**23**, Figure 25); $XSO_2Y\cdot$, with X = OH, Y = S (**24**, Figure 26), X = H and Y = NH (**25**, Figure 27), Y = S (**26**, Figure 28)

TABLE 4. Energies and dipole moments of radical species

Radical		6–31 G[a]			6–31 + G*[b]		
		Energy (a.u.)		Dipole moment (*D*)	Energy (a.u.)		Dipole moment (*D*)
		UHF	UMP2		UHF	UMP2	
(17)	$HSO_3\cdot$	− 622.525441	− 623.150843	2.98	− 622.533467	− 623.170175	3.06
(18)	$FSO_3\cdot$	− 721.391411	− 722.188555	1.32	− 721.400969	− 722.211674	1.31
(19)	$HOSO_3\cdot$	− 697.399232	− 698.200071	3.21	− 697.408584	− 698.222846	3.19
(20)	$ClSO_3\cdot$	−1081.418186	−1082.176820	1.81	−1081.427346	−1082.199351	1.98
(21)	$H_2NSO_3\cdot$	− 677.569804	− 678.355320	4.64	− 677.578889	− 678.378536	4.62
(22)	$HSSO_3\cdot$	−1020.034019	−1020.781585	3.36	−1020.043690	−1020.805207	3.55
(23)	$CH_3SO_3\cdot$	− 661.582276	− 662.337897	4.27	− 661.589905	− 622.358216	4.38
(24)	$HOSO_2S\cdot$	−1020.064971	−1020.831942	3.53	−1020.076272	−1020.858083	3.61
(25)	$HSO_2NH\cdot$	− 602.688303	− 603.303459	4.27	− 602.696692	− 603.323082	4.36
(26)	$HSO_2S\cdot$	− 945.190149	− 945.778764	3.40	− 945.199732	− 945.799677	3.56
(27)	$HSO_2CH_2\cdot$	− 586.698157	− 587.288907	4.65	− 586.706218	− 587.307838	4.79
(28)	$HSO_2\cdot$	− 547.686595	− 548.169607	3.15	− 547.695019	− 548.186973	3.30
(29)	$FSO_2\cdot$	− 646.548996	− 647.205305	1.75	− 646.559788	− 647.228832	1.73
(30)	$HOSO_2\cdot$	− 622.556718	− 623.216655	3.14	− 622.566689	− 623.238640	3.15
(31)	$ClSO_2\cdot$	−1006.589490	−1007.205743	1.78	−1006.597892	−1007.224395	1.91
(32)	$H_2NSO_2\cdot$	− 602.732835	− 603.376253	4.77	− 602.743320	− 603.398842	4.79
(33)	$HSSO_2\cdot$	− 945.204639	− 945.809452	3.23	− 945.214050	− 945.829831	3.45
(34)	$CH_3SO_2\cdot$	− 586.743503	− 587.355963	4.20	− 586.751655	− 587.374414	4.39
(35)	$CH_3OSO_2\cdot$	− 661.585447	− 662.371894	4.15	− 661.595323	− 662.394903	4.22

[a]Geometry SCF optimized with no symmetry or atom equivalence constraints.
[b]In the 6–31 G* basis optimized geometry.

TABLE 5. Calculated optimized bond lengths and angles of the radical species[a]

Radical	Bond lengths (Å)								Bond angles (deg)	
	H—S	X	X—S[b]	S=O	N—H[c]	C—H[d]	O—H	S—O	O=S=O	X—S—Y[e]
(17) $HSO_3\cdot$[f]	1.318			1.412				1.596	124.6	100.6
(18) $FSO_3\cdot$[f]		F	1.539	1.400				1.580	125.8	99.3
(19) $HOSO_3\cdot$				1.412			0.956	1.593	125.2	102.8
				1.403				1.564[h]		
(20 $ClSO_3\cdot$[f]		Cl	1.986	1.406				1.591	124.7	101.7
(21) $H_2NSO_3\cdot$[f]		N	1.609	1.413	0.999			1.619	122.4	97.6
(22) $HSSO_3\cdot$	1.326	S	2.041	1.415				1.602	124.5	104.8
				1.412						
(23) $CH_3SO_3\cdot$[f]		C	1.764	1.418		1.081		1.606	123.0	102.6
(24) $HOSO_2S\cdot$		S	2.044	1.421			0.955	1.579	123.5	104.5
				1.413						
(25) $HSO_2NH\cdot$	1.328	N	1.683	1.417	1.013				122.1	98.4
				1.425						
(26) $HSO_2S\cdot$[f]	1.324	S	2.046	1.423					123.2	102.2
(27) $HSO_2CH_2\cdot$[f]	1.329	C	1.742	1.429		1.072			122.1	101.9
(28) $HSO_2\cdot$[f]	1.340			1.439					123.5	—
(29) $FSO_2\cdot$[f]		F	1.565	1.423					123.0	—
(30) $HOSO_2\cdot$				1.427			0.956	1.594	122.9	—
				1.433						
(31) $ClSO_2\cdot$[f]		Cl	2.061	1.424					122.0	—
(32) $H_2NSO_2\cdot$[c,f]		N	1.651	1.434	1.000				123.3	—
(33) $HSSO_2\cdot$	1.326	S	2.119	1.431					122.0	—
				1.432						
(34) $CH_3SO_2\cdot$[f]		C	1.794	1.443		1.081			121.6	—
(35) $CH_3OSO_2\cdot$[g]				1.434		1.079		1.583	122.1	—
				1.428						

[a]From the 6–31 G* basis optimized geometries.
[b]X = C, N, F, S or Cl atom attached to central sulphur atom.
[c]The two N—H bond lengths are equivalent, to the accuracy of the table.
[d]Average value.
[e]Y = N, C, N, or O.
[f]The S=O bond lengths are equivalent, to the accuracy of the table.
[g]O—C bond length = 1.432 Å.
[h]O(—H).

TABLE 6. Mulliken atomic charges and d-orbital occupancies on sulphur for the radical species[a]

Radical	Atom charges								d-Orbital occupancy[b]
	S	H(—S)	X[c]	H(—O)	H(—N)[d]	H(—C)[e]	O(=S)	O(—S)	
(17) $HSO_3\cdot$[f]	+1.53	+0.06[b]					−0.62	−0.34	+0.70
(18) $FSO_3\cdot$[f]	+1.85		−0.39				−0.58	−0.30	+0.76
(19) $HOSO_3\cdot$	+1.80			+0.52			−0.63	−0.33	+0.76
							−0.60	−0..76[g]	
(20) $ClSO_3\cdot$[f]	+1.61		−0.11				−0.59	−0.32	+0.72
(21) $H_2NSO_3\cdot$[f]	+1.77		−1.00		+0.44		−0.63	−0.38	+0.73
(22) $HSSO_3\cdot$[f]	+1.53	+0.14	−0.08				−0.62	−0.34	+0.69
(23) $CH_3SO_3\cdot$[f]	+1.68		−0.76			+0.25	−0.64	−0.37	+0.68
(24) $HOSO_2S\cdot$	+1.51		+0.04	+0.52			−0.67	−0.78[g]	+0.69
							−0.62		
(25) $HSO_2NH\cdot$	+1.46	+0.05	−0.59		+0.39		−0.64		+0.65
							−0.67		
(26) $HSO_2S\cdot$[f]	+1.22	+0.07	−0.02				−0.65		+0.63
(27) $HSO_2CH_2\cdot$[f]	+1.39	+0.05	−0.58			+0.26	−0.68		+0.62
(28) $HSO_2\cdot$[f]	+1.17	+0.06					−0.61		+0.49
(29) $FSO_2\cdot$[f]	+1.54		−0.41				−0.56		+0.55
(30) $HOSO_2\cdot$	+1.47			+0.51			−0.58	−0.77[g]	+0.55
							−0.63		
(31) $ClSO_2\cdot$[f]	+1.29		−0.16				−0.56		+0.51
(32) $H_2NSO_2\cdot$[f]	+1.40		−0.97		+0.42		−0.63		+0.54
(33) $HSSO_2\cdot$[f]	+1.20	+0.14	−0.12				−0.61		+0.49
(34) $CH_3SO_2\cdot$[e]	+1.29		−0.73			+0.24	−0.64		+0.48
(35) $CH_3OSO_2\cdot$	+1.48		−0.19[h]			+0.20	−0.63	−0.68	+0.56
							−0.60		

[a]From 6–31 G* basis SCF optimized wave functions.
[b]Central sulphur atom.
[c]X = C, N, F, S or Cl atom attached to the central sulphur atom. See Table 5.
[d]The two H(—N) values are equal, to the accuracy of the table.
[e]Averaged H(—C).
[f]The O(=S) values are equal, to the accuracy of the table.
[g]O(—H).
[h]Carbon atom.

TABLE 7. Orbital spin populations for the radical species[a]

Radical		$<S^2>$[b]	Atom[c]	Spin populations[d] S orbital	Spin populations[d] P orbital
(17)	$HSO_3\cdot$	0.758	O_5		0.95[g]
(18)	$FSO_3\cdot$	0.758	O_5		0.98
(19)	$HOSO_3\cdot$	0.758	O_2		0.99
(20)	$ClSO_3\cdot$	0.759	O_5		0.99
(21)	$H_2NSO_3\cdot$	0.758	O_3		0.99
(22)	$HSSO_3\cdot$	0.759	O_2		0.96
			O_3		0.04
(23)	$CH_3SO_3\cdot$	0.758	O_5		0.99
(24)	$HOSO_2S\cdot$	0.759	S_2		0.96
(25)	$HSO_2NH\cdot$	0.759	N		0.98
(26)	$HSO_2S\cdot$	0.759	S_2		0.96
(27)	$HSO_2CH\cdot$	0.762	C	0.10	0.98
			H_6[e]	−0.05	
(28)	$HSO_2\cdot$	0.775	S	0.12	0.23
			O_2[f]		0.20
			H	0.14	
(29)	$FSO_2\cdot$	0.775	S	0.21	0.29[g]
			O_2[f]		0.23
(30)	$HOSO_2\cdot$	0.773	S	0.22	0.32
			O_2		0.20
			O_3		0.18
			H		0.05
(31)	$ClSO_2\cdot$	0.773	S	0.16	0.14
			O_2[f]		0.19
			Cl		0.29
(32)	$H_2NSO_2\cdot$	0.789	S	0.22	0.32[g]
			O_2[f]		0.17
			N		0.13
(33)	$HSSO_2\cdot$	0.795	S_1	0.13	0.22
			O_2[f]		0.18
			S_2		0.32
(34)	$CH_3SO_2\cdot$	0.774	S	0.16	0.25
			O_3[f]		0.24
			C		0.11
(35)	$CH_3OSO_2\cdot$	0.772	S	0.23	0.21
			O_2		0.21
			O_3		0.20
			O_4		0.10

[a]Defined as the difference between the total α spin and total β spin Mulliken populations for each orbital; from the 6–31 G* basis results.
[b]Expectation value of the spin-squared operation. Exact value for spin-restricted wave functions = 0.75 for the spin doublet radicals listed here.
[c]See figures for atom labelling.
[d]The split valence components are summed together. Only values above 0.04 are listed.
[e]On each hydrogen atom.
[f]On each oxygen atom.
[g]Includes d-orbital population of 0.04.

and Y = CH_2 (**27**, Figure 29); XSO_2·, with X = H (**28**, Figure 7 in Ref. 8), F (**29**, Figure 30), OH (**30**, Figure 31), Cl (**31**, Figure 32), NH_2 (**32**, Figure 33), HS (**33**, Figure 34), CH_3 (**34**, Figure 35) and OCH_3 (**35**, Figure 36).

Table 7 gives the orbital spin population by atom for each of the radical species. Thus in the XSO_3· series the unpaired spin is calculated to be very strongly concentrated on the

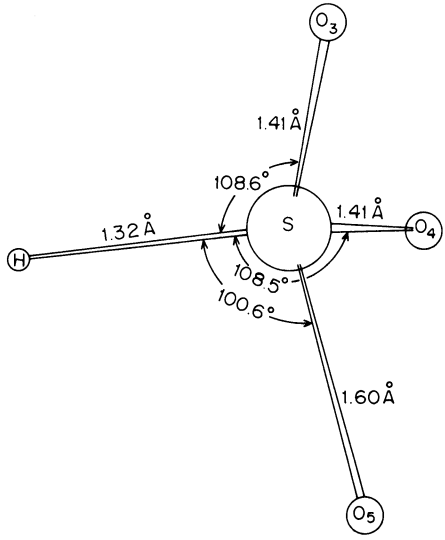


FIGURE 19. HSO_3·, structure **17**, dihedral angles: $O_4SHO_3 = +138.1°$, $O_5SHO_3 = -110.9°$

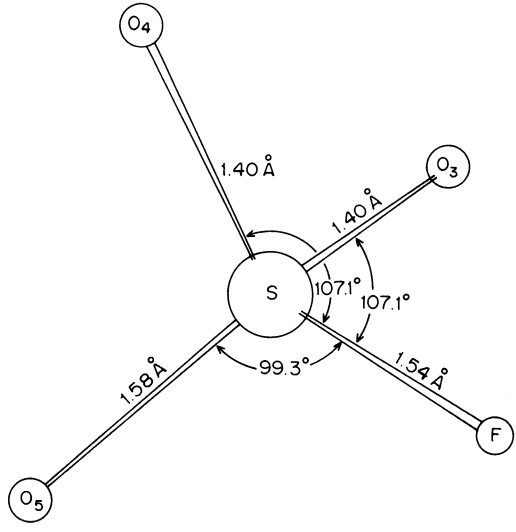


FIGURE 20. FSO_3·, structure **18**, dihedral angles: $O_4SFO_3 = 137.4°$, $O_5SFO_3 = -111.3°$

oxygen atom that is singly bonded (Table 5) to the central sulphur atom. Although this is not entirely unexpected, since the $XSO_3\cdot$ group is derived from XSO_2OH by the homolytic cleavage of the electron pair in the O—H bond, the degree of localization is probably somewhat exaggerated by the SCF method. In this regard, there are several interesting features that can be noted in comparing the geometries and atomic charges among the members of this series and in comparison with the precursor neutral species which we will now discuss.

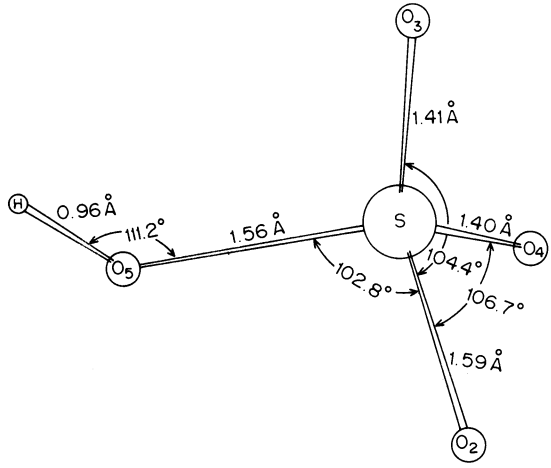


FIGURE 21. $HOSO_3\cdot$, structure **19**, dihedral angles: $O_4SO_2O_3 = 134.3°$, $O_5SO_2O_3 = -113.3°$, $HO_5SO_3 = -23.2°$

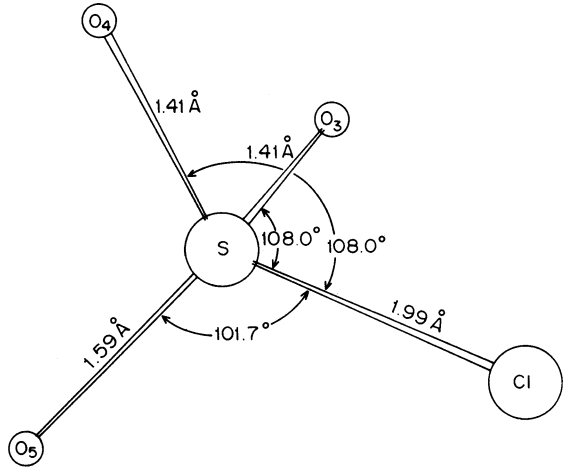


FIGURE 22. $ClSO_3\cdot$, structure **20**, dihedral angles: $O_4SClO_3 = 137.4°$, $O_5SClO_3 = -111.3°$

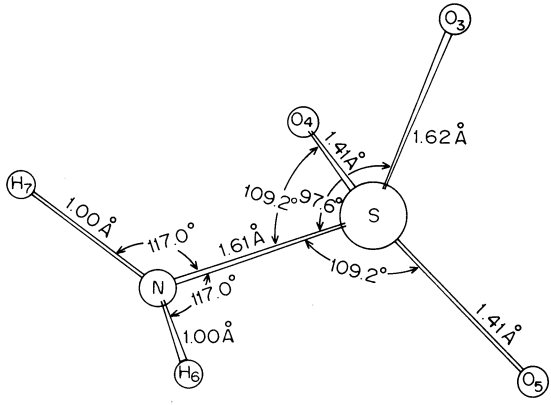


FIGURE 23. $NH_2SO_3\cdot$, structure **21**, dihedral angles: $O_4SNO_3 = 111.8°$, $O_5SNO_3 = -111.9°$, $H_6NSO_3 = 73.7°$, $H_7NSO_3 = 286.4°$

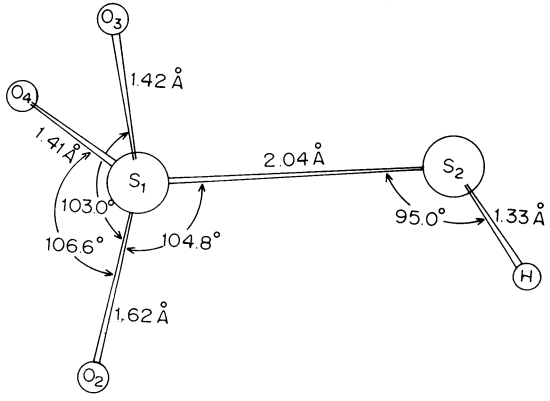


FIGURE 24. $HSSO_3\cdot$, structure **22**, dihedral angles: $O_4S_1O_2O_3 = 132.5°$, $S_2S_1O_2O_3 = -115.4°$, $HS_2S_1O_3 = -37.0°$

Generally, both S—X and S=O bond lengths decrease in going from the parent neutral (Table 2) to the corresponding radical species (Table 5) while the S—O bond length increases. These trends can be qualitatively explained in simple molecular orbital terms by the classical 3 electron, 2 MO interaction of each of the bonding X—S and S=O electron pairs with the radical electron MO. This type of interaction is considered stabilizing[51] because the net energy gain from the energy lowering of the bonding pair more than offsets the raising of the single electron energy in the anti-bonding interaction. The radical electron is localized in a mainly oxygen non-bonding MO, but with a small S—O bonding component. Thus the S—O bond lengthens upon radical formation due both to the small loss of bonding character with the decrease in the number of electrons in that MO, and to the destabilization introduced into the radical MO due to the interaction with the S—X

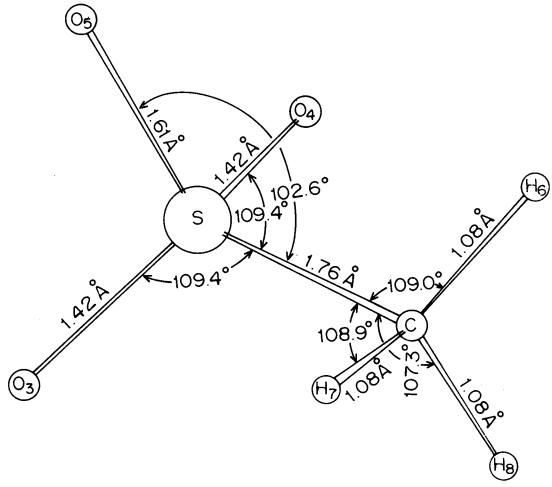


FIGURE 25. $CH_3SO_3\cdot$, structure **23**, dihedral angles: $O_4SCO_3 = 137.4$, $O_5SCO_3 = -111.3°$, $H_6CSO_3 = 172.0°$, $H_7CSO_3 = 50.6°$, $H_8CSO_3 = -68.7°$

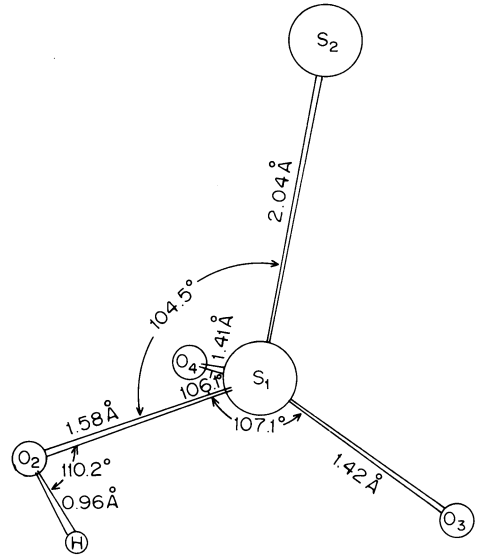


FIGURE 26. $HOSO_2S\cdot$, structure **24**, dihedral angles: $O_4SO_2O_3 = 133.6°$, $S_5SO_2O_3 = -112.3°$, $HO_2S_1O_3 = 19.8°$

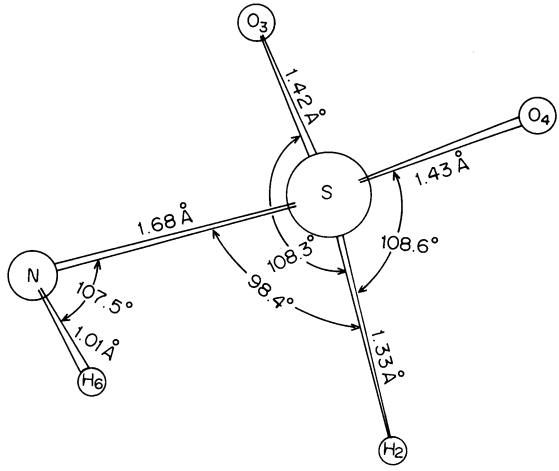


FIGURE 27. $HSO_2NH\cdot$, structure **25**, dihedral angles: $O_4SH_2O_3 = 225.3°$, $NSH_2O_3 = 112.7°$, $H_6NSH_2 = 73.4°$

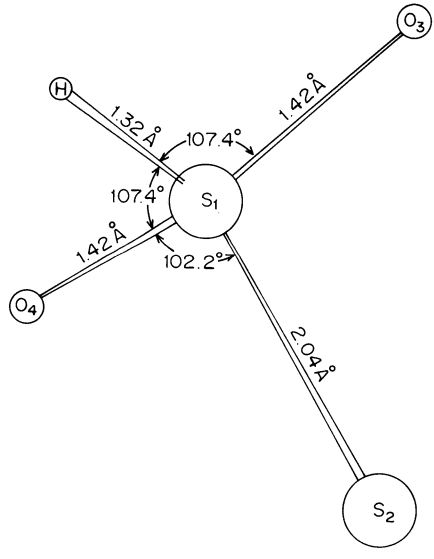


FIGURE 28. $HSO_2S\cdot$, structure **26**, dihedral angles: $O_4S_1HO_3 = 134.5°$, $S_2S_1HO_3 = -112.8°$

and S=O bonding electron pairs. These latter are stabilized by this same interaction, which can lead to a shorter bond length for each.

The shift in individual atomic charges from the neutral XSO_2OH (Table 3) to the radical $XSO_2O\cdot$ is in conformity with this analysis. Thus the charge on O(=S) and X uniformly decreases slightly (by from 0.01 to 0.06 electrons). The charge on O(—S) decreases also, but

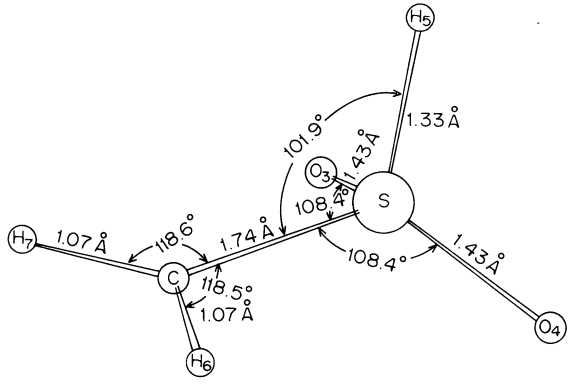


FIGURE 29. $HSO_2CH_2\cdot$, structure **27**, dihedral angles: $O_4SCO_3 = 134.5°$, $H_5SCO_3 = -112.8°$, $H_6CSO_3 = 202.5°$, $H_7CSO_3 = 23.3°$

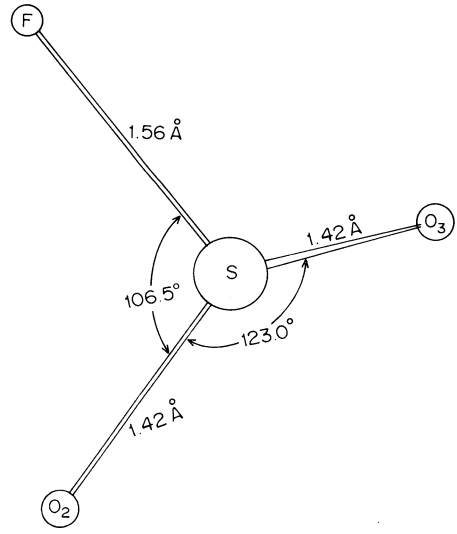


FIGURE 30. $FSO_2\cdot$, structure **29**, dihedral angle: $FSO_2O_3 = 122.9°$

always by less than the amount of charge transferred to it by the attached hydrogen atom (Table 3) in the neutral parent. Thus a small amount of charge is transferred from O(=S) and X(—S) to O(—S) by the 3 electron, 2 MO interaction model described above. The charge and d-orbital occupancy on the central sulphur atom are the same (to within 0.01e) in the neutral and radical species, independent of X.

Both O=S=O and X—S—O angles increase in going from the parent XSO_2OH

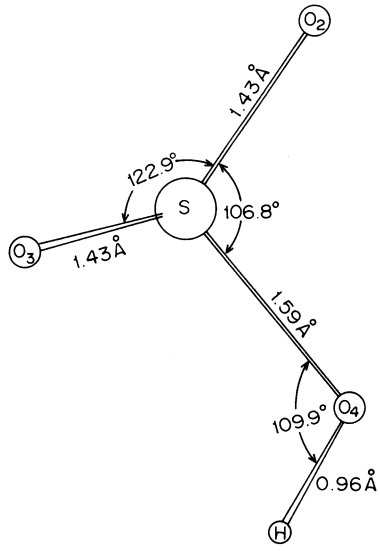


FIGURE 31. $HOSO_2\cdot$, structure **30**, dihedral angles: $O_4SO_2O_3 = -124.5°$, $HO_4SO_3 = 20.1°$

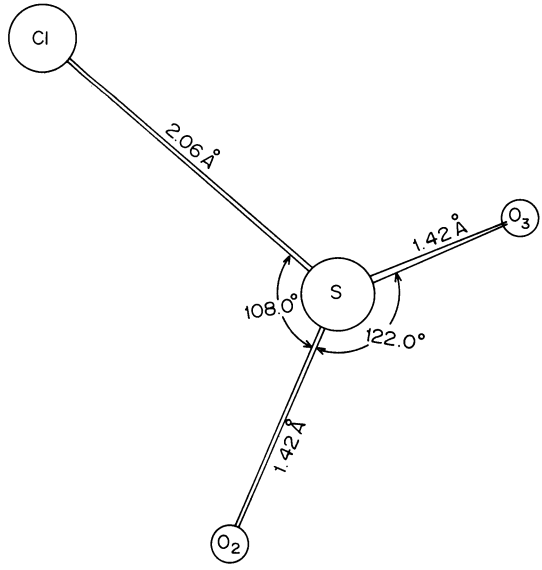


FIGURE 32. $ClSO_2\cdot$, structure **31**, dihedral angle: $ClSO_2O_3 = 125.9°$

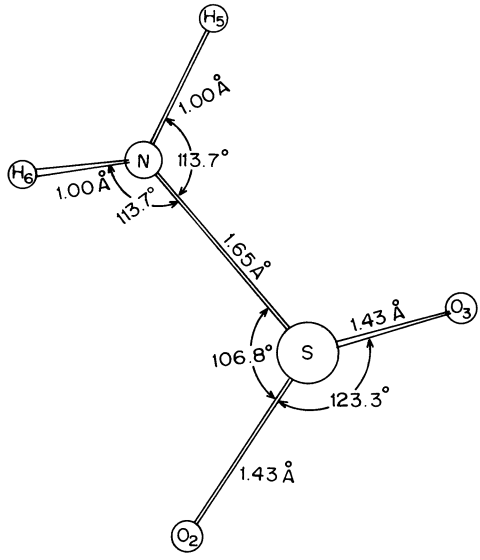


FIGURE 33. $NH_2SO_2\cdot$, structure **32**, dihedral angles: $NSO_2O_3 = 124.0°$, $H_5NSO_3 = -46.6°$, $H_6NSO_3 = 180.2°$

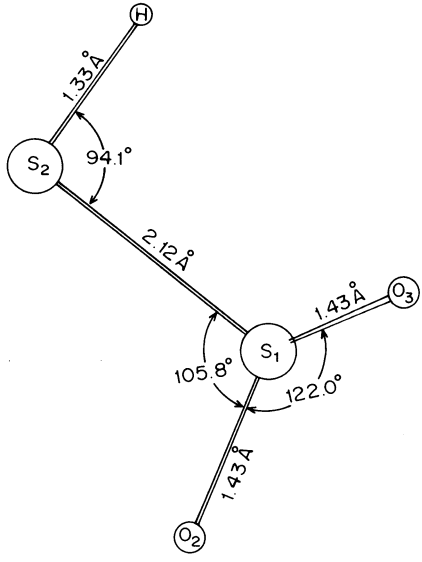


FIGURE 34. $HSSO_2\cdot$, structure **33**, dihedral angles: $S_2S_1O_2O_3 = -125.6°$, $HS_2S_1O_3 = 38.7°$

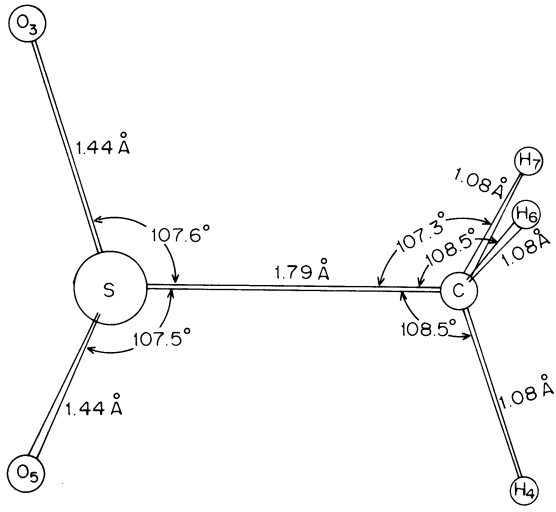


FIGURE 35. $CH_3SO_2\cdot$, structure **34**, dihedral angles: $H_4CSO_3 = 174.2°$, $H_4CSO_5 = -53.2°$, $H_6CSO_3 = 52.7°$, $H_7CSO_3 = -66.6°$

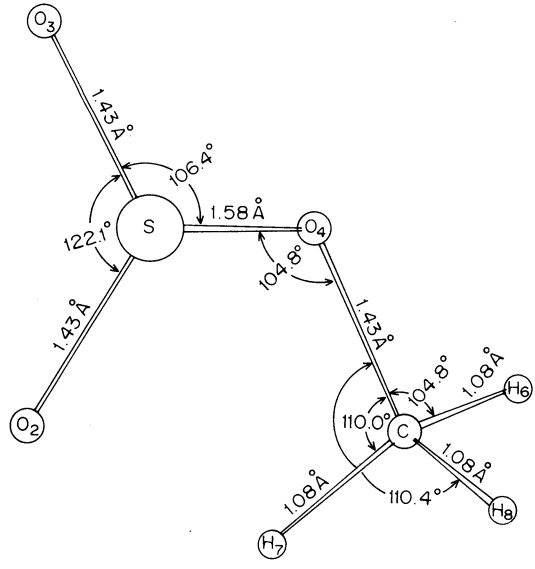
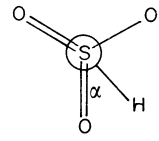


FIGURE 36. $CH_3OSO_2\cdot$, structure **35**, dihedral angles: $O_4SO_3O_2 = 126.0°$, $CO_4SO_2 = -32.5°$, $H_6CO_4S = 181.1°$, $H_7CO_4S = 61.8°$, $H_8CO_4S = -60.3°$

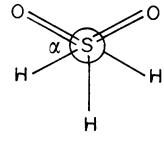
molecule to the $XSO_2O\cdot$ radical. The former change may be related to the S=O bond shortening with accompanying increased repulsion among the bonding and non-bonding electron pairs. Again, this analysis is not certain due to the small decrease of charge on O(=S) upon radical formation. Nonetheless, there is a general correlation between changes in the S=O bond length and O=S=O angles, whether comparing different-type species or following changes as a function of substituent X; when one increases, the other decreases, and *vice versa*. The X—S—O angle change is also difficult to predict, *a priori*, since the X—S bond length decreases while the S—O distance increases. In general, the bond angle changes as a function of substituent X in going from the neutral to the radical require a more detailed analysis.

The preferred rotamer conformation of the $XSO_2Y\cdot$ radical series shows the usual intramolecular hydrogen-bond interaction which is characterized by the small dihedral angle α (rotamer **h**) for $HOSO_2O\cdot$ (**19**), $\alpha = 23.2°$, $HSSO_2O\cdot$ (**22**), $\alpha = 37.0°$ and $HOSO_2S\cdot$



(**h**)

(**24**), $\alpha = 19.8$. The S = O bond distances are also differentiated by their spatial relationship to H(—O or —S), with the longer bond length involving the oxygen atom closest to that hydrogen atom. Analogously, in the $HSO_2NH\cdot$ (**25**) radical the dihedral angle between the N—H and S—H bonds is calculated to be 73.4°. The (N—)H···O(=S) distance is only 2.58 Å, with a slightly longer S=O bond length (Figure 27). On the other hand, projection along the S—C bond in $CH_3SO_2O\cdot$ (**23**) shows a completely staggered arrangement of the C—H and S—O, S=O bonds, dominated by electron pair repulsion effects. In $HSO_2CH_2\cdot$ (**27**, Figure 29) the radical electron is localized on the carbon atom (Table 7), and the dihedral angle between the S=O and C—H bonds is $\alpha = 23.3°$ (rotamer **i**).



(**i**)

The $HSO_3\cdot$ (**17**) radical that has been detected experimentally[52] is actually $HOSO_2\cdot$ (**30**, Figure 31). From Table 4 we can see that the latter is (MP2/6-31 + G*) calculated to be a substantial 43.0 kcal mol^{-1} more stable than **17**. However, the methyl substituted radical $CH_3OSO_2\cdot$ (**35**) is only 23.0 kcal mol^{-1} more stable than $CH_3SO_3\cdot$ (**23**) at the same level, and only 2.0 kcal mol^{-1} more stable at the SCF/6-31G* level at which the geometry optimizations were carried out. The $XSO_2O\cdot$ series of radicals merit further study.

The $XSO_2\cdot$ series of radicals differs from the $XSO_2O\cdot$ group in that the half-occupied MO is much more delocalized on the $XSO_2\cdot$ skeleton and, to some extent, even on the substituent X (Table 7). The naive expectation, based on the precursor H—SO_2X neutral, is that the radical electron should be localized mainly on the sulphur atom. The qualitative molecular orbitals sketched for H_2SO_2 by Gavezzotti[26] show that the S—H bonding MO is also somewhat S=O bonding. The delocalization of the radical electron in the $XSO_2\cdot$

series can be viewed as follows. Dissociation of the S—H hydrogen atom leaves an unpaired electron mainly on the central sulphur atom. This 'vertical' radical orbital can undergo interaction with the σ^* (S=O), π^*(S=O), σ^*(S—X) molecular orbitals for stabilization. The former two S=O antibonding MOs are polarized towards the sulphur atom, especially π^*(S=O), as a result of the corresponding bonding MOs being strongly polarized towards the oxygen atom. Depending on the electronegativity of X, σ^*(S=X) will be polarized towards the central sulphur atom or, at most, evenly distributed on X and S. Thus, these interactions all involve MOs with large components in the same region of space which should give them substantial interaction matrix elements.

The qualitative results of such interactions should be to substantially delocalize the unpaired spin, transfer charge from the X and O atoms to the central sulphur atom and introduce anti-bonding character into the S—X and S=O bonds. This, in fact, is what is calculationally observed. A comparison of Tables 2 and 5 shows that, in contrast with the $XSO_2O\cdot/XSO_2OH$ changes, here both the S—X and S=O bond lengths increase in going from parent to radical species, where the S=O change is larger. Analogously, comparing Tables 3 and 6, the atomic charges on S, X and O are all reduced in absolute value terms, corresponding to the transfer of charge in the direction of O, X $\longrightarrow$ S. If we add the small atomic charge on the sulphur-bonded hydrogen atom in XSO_2H (Table 6) to the sulphur atomic charge, appropriate to the H atom dissociation removing one whole electron, then the reduction in the S atom charge is particularly noticeable. As expected, the change in the atomic charge for the oxygen atom is larger than for substituent X.

The preferred conformation of the $XSO_2\cdot$ radical can be understood on the basis of the radical electron behaving like a pseudo-ligand on the sulphur atom, even though the unpaired electron is delocalized to other atoms. For X = OH and SH the angle α between S=O and ligand group X equals 20.1° and 38.7°, respectively (rotamer **j**). Viewed along the S—N bond, $H_2NSO_2\cdot$ (**32**, Figure 33), rotamer **k**, has $\alpha = 46.6°$. $CH_3SO_2\cdot$ (**34**, Figure 35), rotamer **l**, has the symmetric staggered structure shown. $CH_3OSO_2\cdot$ (**35**,

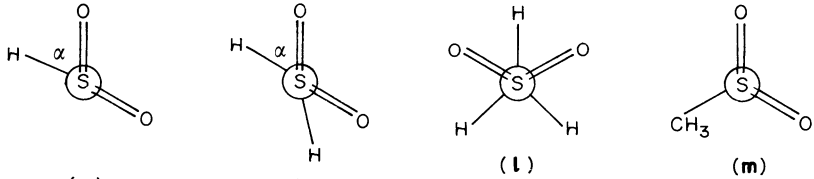


Figure 36), rotamer **m**, however, seems to have the S—C bond eclipsed with the radical electron orbital on the sulphur atom with $\alpha = 125°$. The $(S=)O_2\cdots H_7(—C)$ non-bonding distance here is only 2.59 Å, which is again indicative of a long hydrogen bond, similar to the O···H distance in $HOSO_2\cdot$ (**30**, Figure 31) of 2.43 Å. Thus intramolecular interactions would seem to explain the preferred eclipsed conformation. In $H_2NSO_2\cdot$ the closer O···H distance is 2.66 Å. Thus, again, internal hydrogen bonding is seen to influence the stability of rotamer conformation.

The experimental situation with regard to the $XSO_2^{\cdot}$ radicals has been summarized by Chatgilialoglu[53] with reference to previous theoretical work[54,55]. Electron spin resonance (ESR) spectra have been analyzed to give the percentage sulphur atom 3*s* and 3*p* character of the radical electron in $H_2NSO_2^{\cdot}$(**32**) and $CH_3SO_2^{\cdot}$(**34**). The calculated results in Table 7 for $H_2NSO_2^{\cdot}$ are larger than the values derived experimentally. The difference is mainly in the *s* character (calc. value 22%, 'exp.' value 7.5%) while the ρ character agrees

well (32% and 35%, respectively). For $CH_3SO_2^{\cdot}$ the calculated total ($s + p$) spin population percentage of sulphur is 41% but the 'experimental' value is only 31.8%.[53]

On the other hand, Bassindale and Iley[56] have analyzed experimental electron-nuclear isotropic and anisotropic coupling in sulphuryl radicals to give total sulphur atom percent s + p character in $H_2NSO_2^{\cdot}$ and $CH_3SO_2^{\cdot}$ of 55% and 41%, respectively. These derived values agree perfectly with the total s + p calculated spin populations in Table 7. However, the division between individual s and p characters is still very different.

Spin properties are notoriously difficult to calculate accurately[57]. Here, we are actually calculating spin populations, with their intrinsic uncertainties, and not the directly observed hyperfine interactions. On the other hand, analyses of the hyperfine interactions in the ESR spectra to give 'experimental' atomic orbital occupancies for the radical electron are based on a simplistic, rigid linear combination of atomic orbitals (LCAO)–MO model with the reference electron–nuclear coupling parameters taken from the free atom. No allowance is made for radial or angular polarization of the atomic orbitals in the molecular environment. Thus agreement at these levels between calculated and 'experimental' values can only be qualitative, at best.

The rotamer preference of the aminosulphonyl radical **32** from a conformational analysis of the ESR spectra[53] agrees with the symmetric rotamer **k**, while the methoxysulphonyl radical **35** was found to prefer the asymmetric structure as shown for conformer **m** above.

VI. ANIONS

Several of the anions shown in Tables 8–10 have been studied previously[27,58], but with smaller basis sets. The importance of diffuse basis functions for the proper electronic

TABLE 8. Energies and dipole moments of the anions[a]

Anion	Energy (a.u.) RHF	Energy (a.u.) MP2	− EA[b]	Dipole moment (D)[c]
(36) HSO_3^-	− 622.662904	− 623.351889	4.94	2.49
(37) FSO_3^-	− 721.556168	− 722.419738	5.66	1.15
(38) $HOSO_3^-$	− 697.542823	− 698.411312	5.13	3.11
(39) $ClSO_3^-$	− 1081.585506	− 1082.409003	5.70	1.16
(40) $H_2NSO_3^-$	− 677.704268	− 678.557586	4.87	4.03
(41) $HSSO_3^-$	− 1020.182346	− 1020.996847	5.21	3.29
(42) $HOSO_2S^-$	− 1020.180735	− 1020.990512	3.60	3.21
(43) $CH_3SO_3^-$	− 661.708244	− 662.530088	4.68	4.54
(44) HSO_2S^-	− 945.305623	− 945.930737	3.57	2.52
(45) $HSO_2CH_2^-$	− 586.742571	− 587.385099	2.10	3.26
(46) HSO_2^-	− 547.767457	− 548.276727	2.44	3.00
(47) FSO_2^-	− 646.679928	− 647.375502	3.99	2.17
(48) $HOSO_2^-$	− 622.662459	− 623.360356	3.31	1.90
(49) $ClSO_2^-$	− 1006.738023	− 1007.379916	4.23	5.22
(50) $H_2NSO_2^-$	− 602.818966	− 603.500003	2.75	2.64
(51) $HSSO_2^-$	− 945.313552	− 945.952245	3.33	2.53
(52) $CH_2SO_2^-$	− 586.816115	− 587.460968	2.36	4.41
(53) $CH_3OSO_2^-$	− 661.682919	− 662.510386	3.14	4.09

[a]Geometry SCF optimized with no symmetry or atom equivalence constraints in the 6-31 + G* basis set.
[b]Electron affinity (in eV) for radical (Table 4) → anion (this table) using the MP2/6-31 + G* energies.
[c]Relative to the molecular centre of mass.

TABLE 9. Calculated optimized bond lengths and angles of the anions[a]

Anion	Bond lengths (Å)								Bond angles (deg)	
	H—S	X	X—S[b]	S=O	N—H[c]	C—H[d]	O—H	S—O	O=S=O	X—S—Y[e]
(36) HSO_3^-[f]	1.335			1.453					114.3	104.0
(37) FSO_3^-[f]		F	1.610	1.437					115.6	102.3
(38) $HOSO_3^-$				1.448[f]			0.950	1.632	113.3	102.4
				1.439						
(39) $ClSO_3^-$[f]		Cl	2.152	1.434					115.8	102.0
(40) $H_2NSO_3^-$[c]		N	1.694	1.458	1.003				115.6	106.0
				1.449[f]						
(41) $HSSO_3^-$	1.328	S	2.135	1.445[f]					113.9	101.0
				1.444						
(42) $HOSO_2S^-$[f]		S	1.978	1.446			0.953	1.627	114.3	103.0
(43) $CH_3SO_3^-$[f]		C	1.786	1.458		1.083			113.8	104.7
(44) HSO_2S^-[f]	1.333	S	1.987	1.453					115.7	103.0
(45) $HSO_2CH_2^-$[f]	1.349	C	1.656	1.459		1.077			118.0	112.6
(46) HSO_2^-[f]	1.368			1.500					111.2	
(47) FSO_2^-[f]		F	1.699	1.459					113.2	
(48) $HOSO_2^-$				1.477			0.954	1.684	111.2	
				1.478						
(49) $ClSO_2^-$[f]		Cl	2.752	1.430					115.1	
(50) $H_2NSO_2^-$[f]		N	1.750	1.489	1.005				113.2	
(51) $HSSO_2^-$	1.332	S	2.432	1.452					114.1	
				1.453						
(52) $CH_3SO_2^-$[f]		C	1.817	1.500		1.086			113.1	
(53) $CH_3OSO_2^-$[g]				1.474		1.088		1.706	113.2	
				1.466						

[a] From the 6-31 + G* basis optimized geometries.
[b] X = C, N, F, S or Cl atom attached to central sulphur atom.
[c] The two N—H bond lengths are equivalent, to the accuracy of the table.
[d] Average value.
[e] Y = H, O or S.
[f] Two or more S=O bond lengths are equivalent, to the accuracy of the table.
[g] O—C bond length = 1.390 Å.

TABLE 10. Calculated atomic charges and d-orbital occupancies on sulphur for the anions[a]

Anion	Atom charges								d-Orbital occupancy[b]
	S	H(—S)[b]	X[c]	H(—O)	H(—N)	H(—C)	O(=S)	O(—S)	
(36) HSO_3^-[d]	+1.58	−0.06					−0.84		0.71
(37) FSO_3^-[d]	+2.31		−0.61				−0.90		0.74
(38) $HOSO_3^-$	+2.21			+0.51			−0.91[d]	−0.98	0.74
							−0.92		
(39) $ClSO_3^-$[d]	+1.45		−0.29				−0.72		0.71
(40) $H_2NSO_3^-$[e]	+2.09		−1.18		+0.41		−0.89		0.72
							−0.92[d]		
(41) $HSSO_3^-$	+1.30	+0.08	−0.17				−0.72[d]		0.70
							−0.76		
(42) $HOSO_2S^-$[d]	+1.24		−0.47	+0.50			−0.75	−0.78	0.61
(43) $CH_3SO_3^-$[d]	+1.86		−0.83			+0.21[f]	−0.89		0.69
(44) HSO_2S^-[d]	+0.96	+0.0	−0.55				−0.71		0.58
(45) $HSO_2CH_2^-$[d]	+1.27	−0.05	−0.94			+0.17[f]	−0.81		0.60
(46) HSO_2^-[d]	+0.87	−0.09					−0.89		0.40
(47) FSO_2^-[d]	+1.27		−0.55				−0.86		0.45
(48) $HOSO_2^-$	+1.11			+0.48			−0.92	−0.85	0.44
							−0.91		
(49) $ClSO_2^-$[d]	+1.01		−0.78				−0.62		0.42
(50) $H_2NSO_2^-$[d]	+1.24		−1.19		+0.41		−0.94		0.42
(51) $HSSO_2^-$[d]	+0.84	+0.05	−0.49				−0.70		0.41
(52) $CH_3SO_2^-$[d]	+0.90		−0.67			+0.18[h]	−0.90		0.40
						+0.22			
(53) $CH_3OSO_2^-$[d]	+1.20		−0.30[g]			+0.14[h]	−0.88	−0.62	0.45
						+0.19			

[a] From the 6-31 + G* basis SCF optimized wave functions.
[b] Central sulphur atom.
[c] X = C, N, F, S or Cl atom attached to the central sulphur atom. See Table 9.
[d] Two or more O=(S) are equal, to the accuracy of the table.
[e] The two H(—N) values are equal, to the accuracy of the table.
[f] Averaged H(—C) values.
[g] Carbon atom.
[h] Two H(—C) are equal, to the accuracy of the table.

structure description of anions has been amply demonstrated[5,59]. The level of theory used here to calculate the electron affinities (EAs) tabulated in Table 8 should give values that are within several tenths eV of experiment[60]. For example, the MP2/6-31 + G* calculated electron affinity of SO_2 is 1.01 eV, compared to the experimental value of 1.11 eV[61]. Here the neutral species was SCF geometry optimized in the 6–31 G* basis set and the anion was optimized directly in the 6–31 + G* basis, as with all the other anions. However, the comparision between SO_2 and SO_2^- (closed shell → radical), where the number of electron pairs is conserved, is not exactly the same as the cases studied here (radical → closed shell), where an electron pair is added in the process. Therefore, the results here are expected to be somewhat less accurate.

The trends in the values of the EAs for both the XSO_3^- and XSO_2^- series as a function of the substituent X are as expected, with the more electronegative group preferentially stabilizing the anion relative to the radical. The electron affinities of the sulphonyl radicals have not been treated before and these are the first published values. The EAs, of course, also give the first adiabatic ionization energies of the anions.

A comparison of the geometric structural parameters, bond lengths and angles in Table 9 and Figures 37–51 for the anions with the corresponding neutral parents and radical species shows uniform and interesting trends. The S=O and S—X bond lengths increase both for the XSO_3^- and XSO_2^- series, where the X—S distance is substantially elongated for X = Cl and SH, and especially in $ClSO_2^-$ (**49**, Figure 47) and $HSSO_2^-$ (**51**, Figure 49). For the XSO_2^- set these elongations are just a continuation of the trend observed in going from the neutral to the radical species, probably for the same orbital interaction reasons: stabilization of the anion MO by interaction with the anti-bonding S=O and S—X molecular orbitals.

The increase in S=O and S—X bond lengths in the XSO_3^- series in going from radical to anion can perhaps be generally explained as follows. In contrast to the corresponding radical $XSO_3\cdot$, interaction between each of the S=O and S—X bonding MOs with the

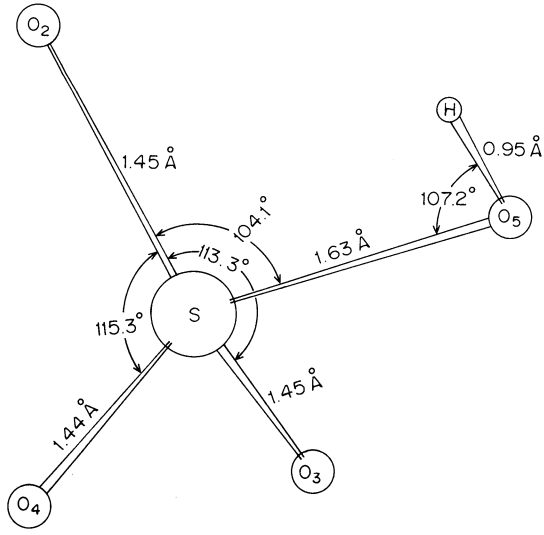


FIGURE 37. $HOSO_3^-$, structure **38**, dihedral angles: $O_4SO_2O_3 = 136.0°$, $O_5SO_2O_3 = -112.6°$, $HO_5SO_3 = -59.6°$

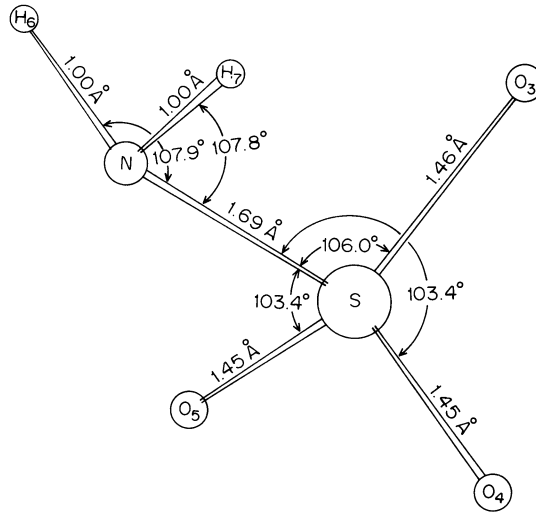


FIGURE 38. $H_2NSO_3^-$, structure **40**, dihedral angles: $O_4SNO_3 = 119.5°$, $O_5SNO_3 = -119.5°$, $H_6NSO_3 = 58.3°$, $H_7NSO_3 = 301.6°$

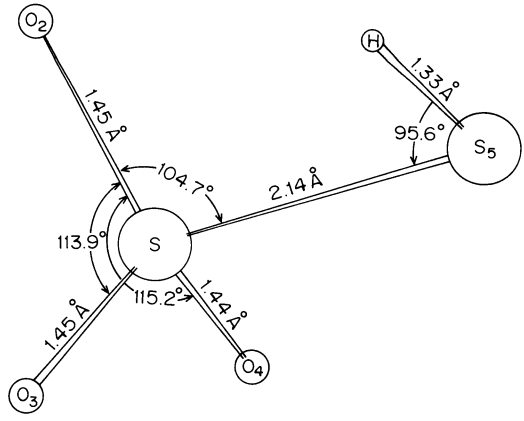


FIGURE 39. $HSSO_3^-$, structure **41**, dihedral angles: $O_4SO_2O_3 = 136.3°$, $S_5SO_2O_3 = -113.7°$, $HS_5SO_3 = -60.0°$

anion orbital (4 electron, 2 MO) is destabilizing. The dominant interactions will then be between the anion MO and the S=O and S—X anti-bonding molecular orbitals which, as in the XSO_2^- case, will stabilize the anion at the expense of increased anti-bonding character in S=O and S—X. This latter will cause bond lengthening, as observed.

In the XSO_3^- group, adding the electron gives, except for small intramolecular effects, three equivalent S=O bonds, with significant shortening of the S—O bond. The added

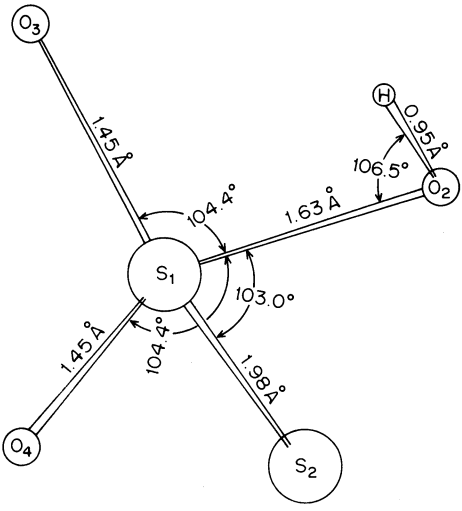


FIGURE 40. $HOSO_2S^-$, structure **42**, dihedral angles: $O_4S_1O_2O_3 = 120.3°$, $S_2S_1O_2O_3 = -119.9°$, $HO_2S_1O_3 = -59.9°$

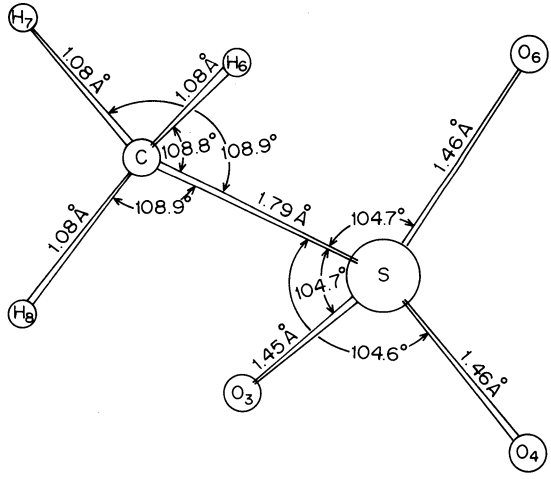


FIGURE 41. $CH_3SO_3^-$, structure **43**, dihedral angles: $O_4SCO_3 = 120.0°$, $O_5SCO_3 = -120.0°$, $H_6CSO_3 = 179.8°$, $H_7CSO_3 = 59.8°$, $H_8CSO_3 = -60.2°$

charge is distributed over all three oxygen atoms and the substituent X. Delocalization of the charge is apparently the reason that the bond length changes are generally larger for the smaller XSO_2^- than for XSO_3^-. The X—S bond lengthens considerably in both series and is particularly affected when X involves a second-row atom (Cl or SH). Thus in

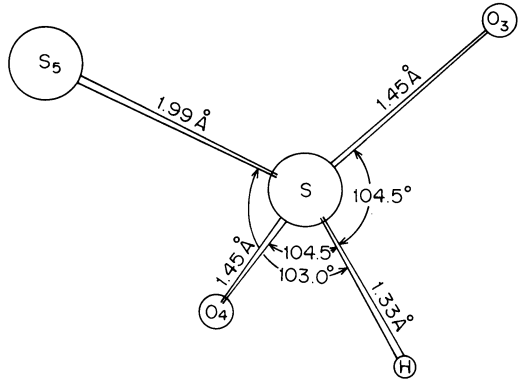


FIGURE 42. HSO_2S^-, structure **44**, dihedral angles: $O_4SHO_3 = 122.0°$, $S_5SHO_3 = -119.0°$

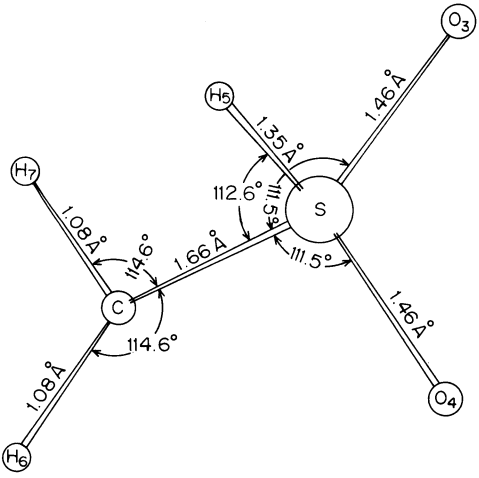


FIGURE 43. $HSO_2CH_2^-$, structure **45**, dihedral angles: $O_4SCO_3 = 134.2°$, $H_5SCO_3 = -112.9°$, $H_6CSO_3 = 183.9°$, $H_7CSO_3 = 42.1°$

$ClSO_2^-$ the S—Cl bond is stretched to 2.75 Å. It is tempting to attribute this general behaviour in S—X and particularly of the S—Cl and S—SH bonds to the relative availability of their low-lying σ^* MOs for interaction with the higher-lying bonding MOs in the anion. In contrast, in the XSO_2Y^- series, $HOSO_2S^-$ (**42**, Figure 40), HSO_2S^- (**44**, Figure 42) and $HSO_2CH_2^-$ (**45**, Figure 43), where the additional charge is somewhat more localized (Table 10) by the heteroatom, the S—Z bond lengths (Z = S or C) actually decrease (by about 0.07–0.09 Å) in going from the neutral/radical to the anion. This decrease is analogous to the resonance shortening of the S—O bond in going from the radical to the anion as mentioned above for the XSO_3^- series.

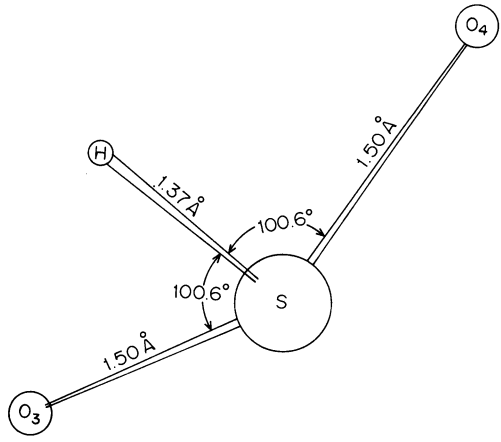


FIGURE 44. HSO_2^-, structure **46**, dihedral angle: $O_4SHO_3 = 117.2°$

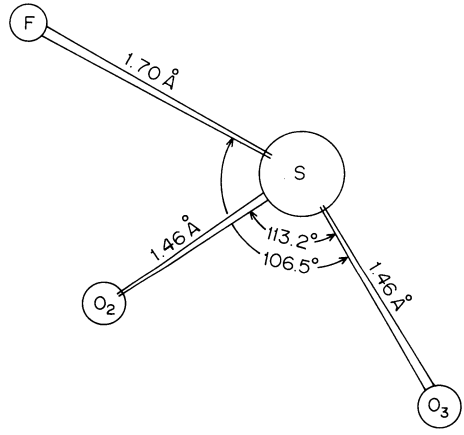


FIGURE 45. FSO_2^-, structure **47**, dihedral angle: $FSO_2O_3 = 106.5°$

The calculated Mulliken atomic charges in the 6–31 + G* basis set, listed in Table 10, generally agree with the charge distribution picture given above. Thus the oxygen atom charges become equivalent upon anion formation and part of the excess charge flows on to the substituent X in the XSO_3^- system. However, except for X = Cl and SH, the charge on the central sulphur atom increases, compared to the radical species (Table 6), which is counterintuitive. This increase in charge on sulphur is difficult to interpret, because an examination of the sulphur atom population components reveals a large negative contribution for each XSO_3^- system, except for X = Cl and SH. Thus, while it is tempting to somehow tie the 'unusual' sulphur atom charge in these two anions with the calculated elongation of the S—X bond for the X = Cl and SH members, it turns out that these

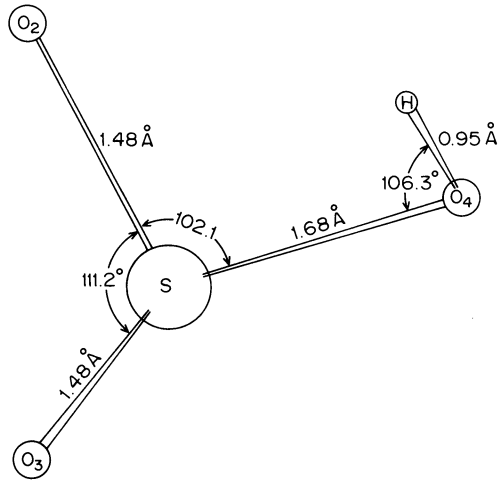


FIGURE 46. $HOSO_2^-$, structure **48**, dihedral angles: $O_4SO_2O_3 = 107.9°$, $HO_4SO_3 = 55.2°$

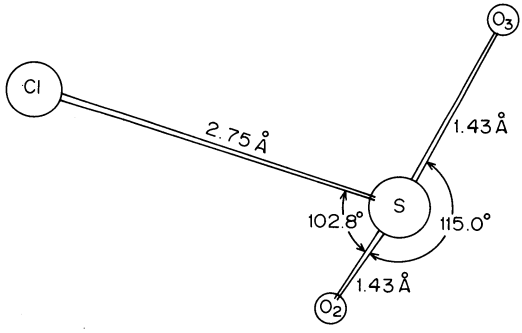


FIGURE 47. $ClSO_2^-$, structure **49**, dihedral angle: $ClSO_2O_3 = 110.9°$

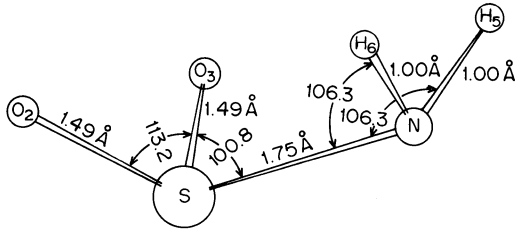


FIGURE 48. $H_2NSO_2^-$, structure **50**, dihedral angles: $NSO_2O_3 = 106.8°$, $H_5NSO_3 = 1.45°$, $H_6NSO_2 = -0.23°$

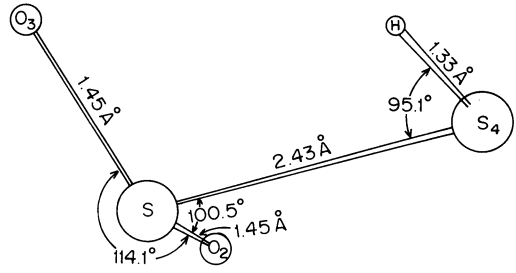


FIGURE 49. $HSSO_2^-$, structure **51**, dihedral angles: $S_4SO_2O_3 = -108.4°$, $HS_4SO_3 = 42.6°$

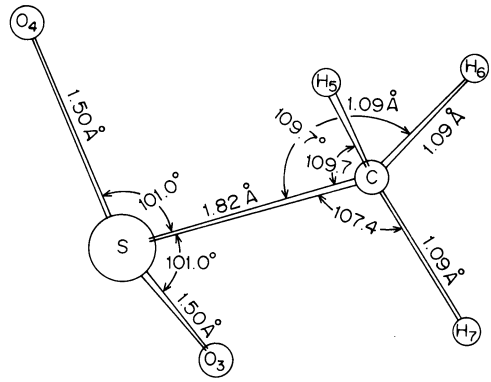


FIGURE 50. $CH_3SO_2^-$, structure **52**, dihedral angles: $O_4SCO_3 = 116.5°$, $H_5CSO_3 = 182.3°$, $H_6CSO_3 = 61.1°$, $H_7CSO_3 = -58.3°$

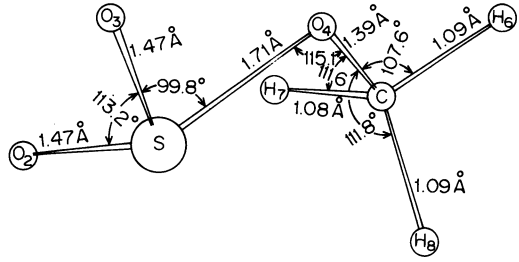
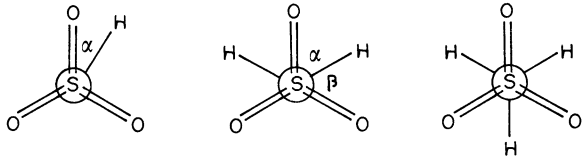


FIGURE 51. $CH_3OSO_2^-$, structure **53**, dihedral angles: $O_4SO_2O_3 = 107.8°$, $CO_4SO_2 = -54.5°$, $H_6CO_4S = 187.0°$, $H_7CO_4S = 67.2°$, $H_8CO_4S = -54.4°$

systems have uncomplicated charges on the central sulphur atom and the others in this series may be suffering from different degrees of artificiality in the population analysis which significantly affect the calculated central sulphur atom charge.

In the XSO_2^- series the atomic charge on the central sulphur atom is calculated to decrease (radical → anion) for all the substituents X, as expected. The atomic charges on X also become more negative, and this change is largest for X = Cl and SH, which does correlate with the special elongation of their bond length with the central sulphur atom. There are no obviously unusual features in the atomic orbital population components in this series but the Mulliken population analysis in an extended, diffuse basis set must be treated with caution.

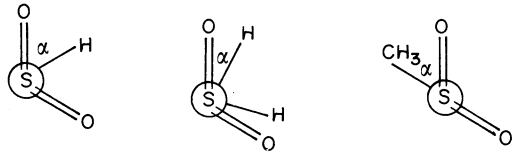
The simple XSO_3^- structures, X = H (**36**), F (**37**) and Cl (**39**), have a quasi-tetrahedral structure (Table 9), where the dihedral angles O—S—X···O are ± 120°. HSO_2S^- (**44**, Figure 42) has a similar structure. For the X = OH and SH members of this series, $HOSO_3^-$ (**38**, Figure 37), $HSSO_3^-$ (**41**, Figure 39) and $HOSO_2S^-$ (**42**, Figure 40), the preferred rotamer conformation places the hydrogen atom (in projection) between the two



oxygen atoms (**n**) where the angle α is very close to 60°. In $H_2NSO_3^-$ (**40**, Figure 38) shown in rotamer **o**, the angle α is again close to 60°. The $CH_3SO_3^-$ (**43**, Figure 41) conformation is symmetric (**p**), as expected.

The presence of intramolecular interactions in the **n** and **o** rotamers in the form of internal hydrogen bonding can be deduced from the small differences calculated for the S=O bond lengths, the atomic charges on the oxygen atoms and the relatively short non-bonding O···H distances. Thus, for example, in $HOSO_3^-$ the oxygen atom *trans* to hydrogen has a slightly shorter S=O bond length than the pair of *gauche* oxygen atoms (rotamer **n**), which are 2.58 Å from the hydrogen atom. A similar situation is found for $HSSO_3^-$. In $H_2NSO_3^-$ the oxygen atom bracketed by the two hydrogen atoms has a longer S=O bond length than the other two and each hydrogen atom is an almost equal distance from the two adjacent oxygen atoms in projection (rotamer **o**) of approximately 2.68 Å. $HSO_2CH_2^-$ (**45**, Figure 43) has the structure shown in **o** above, where the bracketed oxygen atom is replaced by H(—S) and the view is along the S—C bond. The angle β is calculated to be 42.1° with an adjacent O···H distance of 2.79 Å.

The pyramidal geometries of the simple XSO_2^- species are shown in structures **46** (**X** = H), **47** (X = F) and **49** (X = Cl) (Figures 44, 45 and 47). Both $HOSO_2^-$ (**48**, Figure 46) and $HSSO_2^-$ (**51**, Figure 49) have the structure shown in rotamer **q** with α = 55.2° and 42.6°,



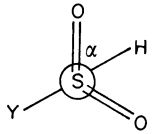
respectively. In the former case the shorter O···H distance is 2.55 Å. The cause of the small asymmetry in terms of a balance between an eclipsed confomer and a symmetric ($\alpha = 60°$) structure having equal interactions with both oxygen atoms is not clear. However, the *gauche* conformation is probably dictated by a combination of interactions between lone pairs of electrons on the central sulphur atom with O(—H), and between the hydrogen atoms with the sulphonyl oxygen atoms. This is probably also true of the eclipsed structure found for $H_2NSO_2^-$ (**50**, Figure 48) where α is only 1.5° (rotamer **r**). $CH_3SO_2^-$ (**52**, Figure 50) is very close to being perfectly staggered, viewed along the S—C bond, if the lone pair on sulphur is taken into account. Finally, $CH_3OSO_2^-$ (**53**, Figures 51) has a *gauche* conformation (**s**), viewed along the S—O bond, where the S=O bond *cis* to O—C is longer (Table 9) than the *trans* S=O bond. This is probably due to the (C—)H···O (=S) interaction where the H···O_2 non-bonding distance is only 2.61 Å.

VII. CATIONS

The optimized geometric structures in Table 12 show that in the sulphonic acid (**56** and **62**) and sulphone cations the hole created by the ionized electron is localized on one of the sulphonyl oxygen atoms, unless another group, such as SH (**59**) or OCH_3 (**61**), has a more available electron for ionization. This localization (as opposed to a symmetric distribution of the hole over both oxygen atoms in the $>SO_2$ fragment) is due to the lack of a sufficiently strong bonding interaction or coupling between the (initially) equivalent oxygen atoms[62]. Thus comparing Table 12 with Table 2, the ionized oxygen atom has its previously short S=O bond distance increased to an almost normal S—O single bond length (1.58–1.59 Å) while the remaining S=O bond shrinks by 0.02–0.03 Å. The S—X bond length generally decreases upon ionization relative to the nautral (Table 2), except for X = SH and OCH_3 where the S—S and S—O bond distances increase considerably. The calculated atomic charges (Table 13) parallel the geometry changes and the localization of the hole state is confirmed by the orbital spin populations shown in Table 14.

The geometric structural changes described above can be interpreted as follows. The ionizing electron in XSO_2H (except for X = SH and OCH_3) is coming out of the polarized π bond on S=O, which reduces its ionic bonding character. The d-orbital occupancy (Table 13) decreases by almost 0.1 electron relative to the neutral parents (Table 3), which should be some measure of the degree of covalent d-orbital participation in the ionic bond. By analogy to the $XSO_2O\cdot$ systems, this MO is now available for a 3 electron, 2 MO interaction which stabilizes the S=O and S—X bonds, and perhaps also relieves a small amount of anti-bonding character in the S—X bond[26,63]. For X = SH and OCH_3 the loss of the ionized electron weakens the S—X bond considerably.

The three simple cations, HSO_2H^+ (**54**, Figure 52), HSO_2F^+ (**55**, Figure 53) and HSO_2Cl^+ (**57**, Figure 55), have their O=S=O angles reduced and H—S—Y angles increased upon ionization. The preferred geometric conformation of the more complex cations follows the pattern already noted. HSO_2OH^+ (**56**, Figure 54) looks like rotamer **t**



(**t**)

(Y=H) in projection along the S—O bond where $\alpha = 44.1°$ and the H(—O) is closer to the oxygen atom of the S=O bond with the larger negative charge. In HSO_2SH^+ (**59**,

TABLE 11. Energies of the cations

Cation	Energy (a.u.)				Dipole moment (D)[c]
	6 − 31G*[a]		6 − 31 + G*[b]		
	UHF	UMP2	UHF	UMP2	
(54) HSO_2H^+	(−547.904800	−548.346405	−547.908445	−548.355259)	4.62
	(−547.832597	−548.333433	−547.837749	−548.343495)[d]	
(55) HSO_2F^+	−646.749086	−647.365184	−646.755170	−647.379121	3.54
	(−646.710012	−647.334497	−646.717085	−647.349128)[d]	
(56) HSO_2OH^+	−622.785198	−623.404871	−622.790856	−623.417793	2.68
	(−622.737511	−623.365491	−622.743646	−623.378466)[d]	
(57) HSO_2Cl^+	−1006.792906	−1007.367979	−1006.799301	−1007.381830	3.31
	(−1006.739911	−1007.354183	−1006.747087	−1007.370094)[d]	
(58) $HSO_2NH_2^+$	−602.973234	−603.577948	−602.978266	−603.590360	5.26
	(−602.932825	−603.550864	−602.944650	−603.585590)[d]	
(59) HSO_2SH^+	−945.433701	−946.033817	−945.441406	−946.049364	4.24
	(−945.411910	−946.008463	−945.419364	−946.025111)[d]	
(60) $HSO_2CH_3^+$	−586.985279	−587.555827	−586.989248	−587.566159	4.70
	(−586.919832	−587.545419	−586.924737	−587.557192)[d]	
(61) $HSO_2OCH_3^+$	−661.810644	−662.573710	−661.816622	−662.588987	6.64
	(−661.757261	−662.517309	−661.764943	−662.534277)[d]	
(62) $CH_3SO_2OH^+$	−661.864495	−662.613406	−661.870476	662.628129	3.06
	(−661.816700	−662.576784	−661.823234	−662.591606)[d]	

[a]Geometry SCF optimized with no symmetry or atom equivalence constraints.
[b]In the 6 − 31G* basis geometry optimized for the cation.
[c]Relative to the centre of mass.
[d]In the neutral species geometry.

TABLE 12. Calculated optimized bond lengths and angles of the cations[a]

Cation	Bond lengths (Å)								Bond angles (deg)	
	H—S	X	X—S[b]	S=O	N—H	C—H[c]	O—H	S—O	O=S=O	H—S—Y[d]
(54) HSO_2H^+	1.330			1.399 1.583					120.6	106.0
(55) HSO_2F^+	1.322	F	1.500	1.382 1.566					113.2	100.6
(56) HSO_2OH^+	1.319			1.392 1.575			0.970	1.518	110.8	99.2
(57) HSO_2Cl^+	1.326	Cl	1.931	1.395 1.581					115.6	104.9
(58) $HSO_2NH_2^+$	1.321	N	1.568	1.398 1.579	1.006[e]				111.0	
(59) HSO_2SH^+[f]	1.324	S	2.365	1.398[g]					128.4	94.7
(60) $HSO_2CH_3^+$	1.329	C	1.777	1.406 1.589		1.083			117.8	108.3
(61) $HSO_2OCH_3^+$[h]	1.321			1.391[g]		1.080		1.889	128.9	90.2
(62) $CH_3SO_2OH^+$		C	1.760	1.400 1.586		1.083	0.968	1.531	108.1	

[a]From the 6 – 31G* basis optimized geometries.
[b]X = C, N, F, S or Cl.
[c]Average value.
[d]Y=H or O.
[e]The two N=H bonds are equivalent, to the accuracy of the table.
[f]Non-central S—H bond length = 1.334 Å.
[g]The two S=O bonds are equivalent, to the accuracy of the table.
[h]O—C bond length = 1.456Å.

TABLE 13. Mulliken atomic charges and d-orbital occupancies on sulphur in the cations[a]

Cation	Atomic charges								d-Orbital occupancy
	S	H(—S)	X[b]	H(—O)	H(—N)	H(—C)[c]	O=(—S)	O—(—S)	
(54) HSO_2H^+	+1.26	+0.22					−0.48 −0.23		0.50
(55) HSO_2F^+	+1.69	+0.22	−0.30				−0.42 −0.18		0.61
(56) HSO_2OH^+	+1.60	+0.21		+0.59			−0.47 −0.22	−0.70	0.62
(57) HSO_2Cl^+	+1.31	+0.23	+0.13				−0.45 −0.22		0.55
(58) $HSO_2NH_2^+$	+1.53	+0.19	−0.98		+0.50 +0.51		−0.50 −0.25		0.60
(59) HSO_2SH^+	+1.23	+0.20[d] +0.23	+0.34				−0.50[e]		0.61
(60) $HSO_2CH_3^+$	+1.39	+0.20	−0.79			+0.32	−0.51 −0.26		0.50
(61) $HSO_2OCH_3^{+f}$	+1.55	+0.20				+0.30	−0.51[e]	−0.36	0.63
(62) $CH_3SO_2OH^+$	+1.74		−0.78	+0.58		+0.32	−0.51 −0.26	−0.73	0.60

[a]From the 6–31G* basis SCF optimized wave functions.
[b]X = C, N, F, S or Cl atom attached to central sulphur atom. See Table 12.
[c]Averaged.
[d]Central sulphur atom.
[e]The two O(=S) values are equal, to the accuracy of the table.
[f]C(—O) charge = −0.28.

TABLE 14. Orbital spin populations for the radical cations[a]

Cation	$\langle S^2 \rangle^b$	Atom[c]	Spin population[d] p orbital
(54) HSO_2H^+	0.759	O_4	1.00
(55) HSO_2F^+	0.758	O_3	0.98
(56) HSO_2OH^+	0.758	O_4	0.99
(57) HSO_2Cl^+	0.759	O_3	0.96
(58) $HSO_2NH_2^+$	0.759	O_3	0.94
(59) HSO_2SH^+	0.776	S_5	0.98
(60) $HSO_2CH_3^+$	0.759	O_4	0.95
(61) $HSO_2OCH_3^+$	0.764	O_5	0.98
(62) $CH_3SO_2OH^+$	0.758	O_3	0.97

[a]See footnote *a* in Table 7.
[b]See footnote *b* in Table 7.
[c]See footnote *c* in Table 7.
[d]See footnote *d* in Table 7.

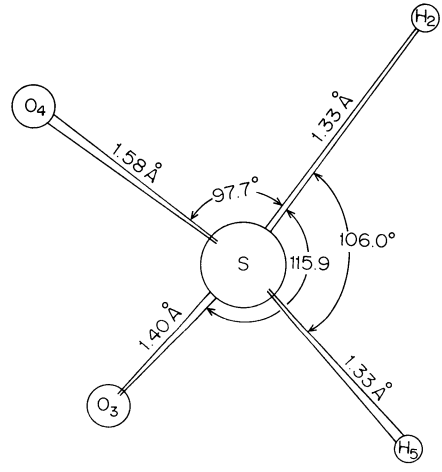


FIGURE 52. HSO_2H^+, structure **54**, dihedral angles: $O_4SH_2O_3 = 129.5°$, $H_5SH_2O_3 = -130.2°$

Figure 57) H(—S) is more symmetrically placed between the two S=O bonds with $\alpha = 66.9°$. The O(—H) or S(—H) lone-pair electrons are also a factor in determining the specific angle α. Analogously, α for $HSO_2OCH_3^+$ (**61**, Figure 59) is 66.8°. Viewed along the S—N and S—C bonds, respectively, both $HSO_2NH_2^+$ (**58**, Figure 56) and $HSO_2CH_3^+$ (**60**, Figure 58) have the staggered conformation, again taking into account the nitrogen atom lone pair in the former case. $CH_3SO_2OH^+$ (**62**, Figure 60) has $\alpha = 77.4°$ in rotamer **t** with a closest (S=)O···H(—O) distance of 2.72 Å. Viewed along the S—C bond the conformation is staggered.

The calculated adiabatic ionization energies in the 6–31 + G* basis set, combining the numbers in Tables 1 and 2, are shown in Table 15. The vertical ionization potentials (IPs)

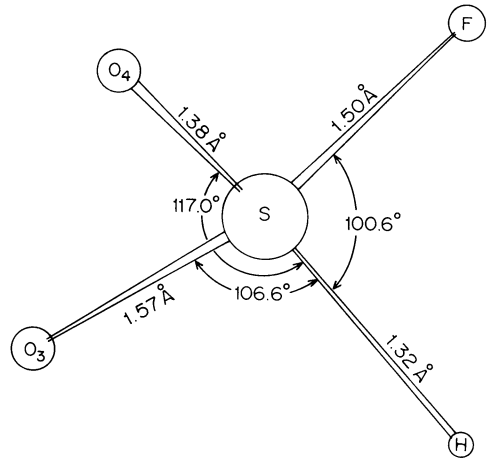


FIGURE 53. HSO_2F^+, structure **55**, dihedral angles: $O_4SHO_3 = 127.8°$, $FSHO_3 = -104.0°$

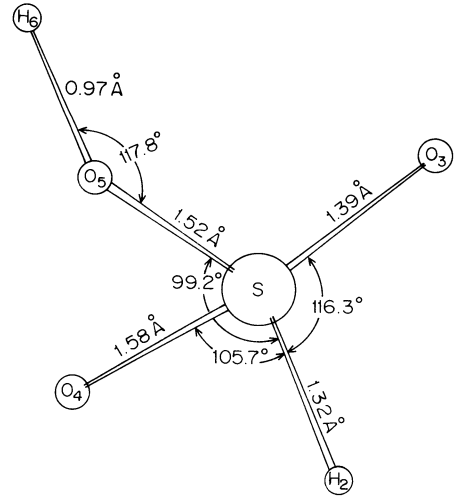


FIGURE 54. HSO_2OH^+, structure **56**, dihedral angles: $O_4SH_2O_3 = 123.4°$, $O_5SH_2O_3 = -130.5°$, $H_6O_5SO_3 = 44.1°$

are also tabulated, based on the energies of the cation states in the neutral parent optimized geometries. The difference between the adiabatic and vertical ionization energies is expected to be a measure of the geometry changes upon electron ionization. Both the SCF and MP2 energies are shown. The latter are expected to be more accurate

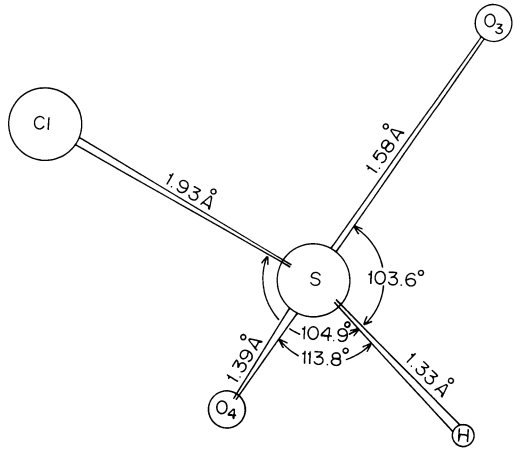


FIGURE 55. HSO_2Cl^+, structure **57**, dihedral angles: $O_4SHO_3 = 126.3°$, $ClSHO_3 = 102.7°$

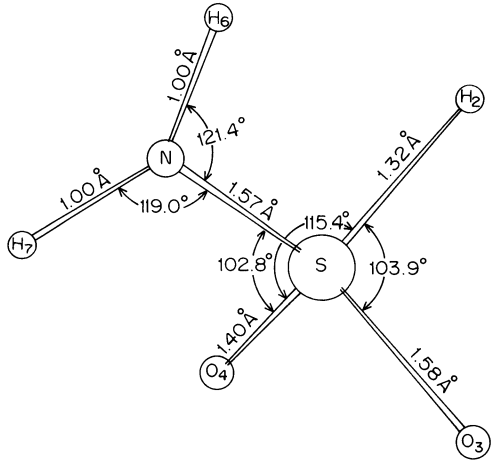


FIGURE 56. $HSO_2NH_2^+$, structure **58**, dihedral angles: $O_4SH_2O_3 = 238.2°$, $NSH_2O_3 = 107.9°$, $H_6NSO_3 = 87.8°$, $H_7NSO_3 = -80.7°$

numerically, due to their presumably taking into account the major correlation energy difference between electronic states that differ by one electron. Thus, the MP2 IPs are usually larger than the SCF values because MP2 is expected to preferentially stabilize the neutral precursor relative to the ion by taking into account the additional electron correlation of the species with the larger number of electrons. This effect is neglected in the direct SCF method of calculating ionization energies. However, it should be remembered that the geometries were not optimized at the MP2 level.

Examining Table 15 now, we see large discrepancies between the SCF calculated

TABLE 15. Ionization potentials[a]

Cation		Adiabatic		Vertical	
		SCF	MP2	SCF	MP2
(54)	HSO_2H^+	10.2	11.6	12.2	11.9
(55)	HSO_2F^+	11.1	12.6	12.2	13.4
(56)	HSO_2OH^+	10.3	11.7	11.6	12.8
(57)	HSO_2Cl^+	10.6	12.0	12.0	12.3
(58)	$HSO_2NH_2^+$	9.9	11.3	10.8	11.4
(59)	HSO_2SH^+	9.8	10.2	10.4	10.8
(60)	$HSO_2CH_3^+$	9.6	11.1	11.4	11.3
(61)	$HSO_2OCH_3^+$	10.3	11.3	11.7	12.8
(62)	$CH_3SO_2OH^+$	9.6	11.1	10.9	12.1

[a]Energies (in eV) taken from 6-31 + G* basis set results.

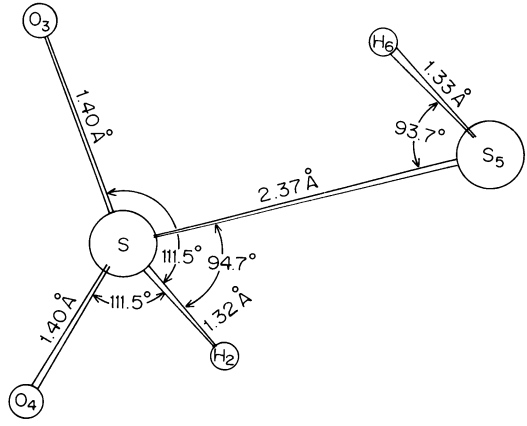


FIGURE 57. HSO_2SH^+, structure **59**, dihedral angles: $O_4SH_2O_3 = 150.9°$, $S_5SH_2O_3 = -104.6°$, $H_6S_5SO_3 = 66.9°$

adiabatic–vertical energy differences (Δ) and the MP2 values of Δ. The former are large (1–2 eV) and reflect the relatively large geometry changes, particularly in the S—O or S—S bond distances, calculated at the SCF level for the ions, relative to the neutral species. The MP2 energy differences are usually considerably smaller (0.3–1.0 eV), and sometimes unrealistically so in light of these large geometry changes. An exception is $HSO_2OCH_3^+$ (**61**), where Δ for both SCF and MP2 methods is the same. However, for $H_2SO_2^+$ (**54**), for example, the 0.3 eV value of Δ is unrealistically small considering the 0.16 Å lengthening of the sulphur–oxygen bond (Table 2 → Table 12) upon ionization. Thus the SCF values of Δ are more indicative of the expected spectroscopic Δ values while the MP2 ionization energies are expected to be more accurate.

This dependence in reliability for the SCF and MP2 levels of theory on the specific calculated property is probably due to the lack of geometry optimization at the MP2 level

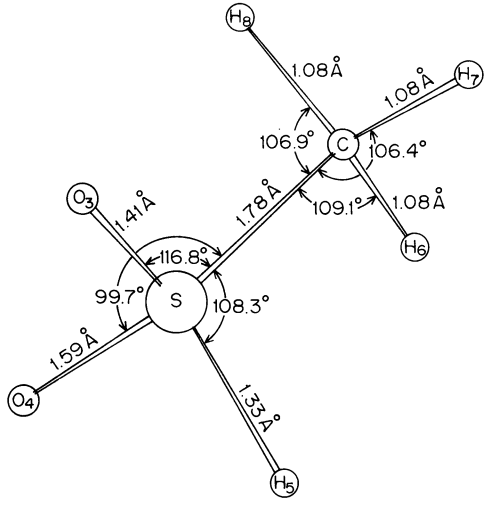


FIGURE 58. $HSO_2CH_3^+$, structure **60**, dihedral angles: $O_4SCO_3 = 128.0°$, $H_5SCO_3 = -129.3°$, $H_6CSO_3 = 177.0°$, $H_7CSO_3 = 55.8°$, $H_8CSO_3 = -62.0°$

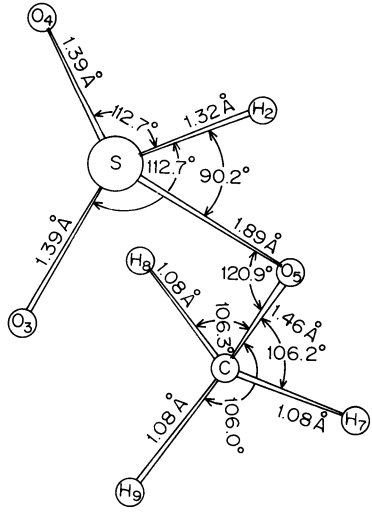


FIGURE 59. $HSO_2OCH_3^+$, structure **61**, dihedral angles: $O_4SH_2O_3 = 155.9°$, $O_5SH_2O_3 = -102.0°$, $CO_5SO_3 = 66.8°$, $H_7CO_5S = 179.3°$, $H_8CO_5S = 58.4°$, $H_9CO_5S = -60.0°$

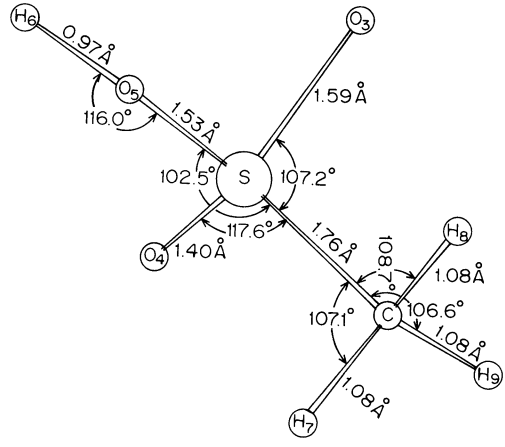


FIGURE 60. $CH_3SO_2OH^+$, structure **62**, dihedral angles: $O_4SCO_3 = 121.9°$, $O_5SCO_3 = -107.9°$, $H_6O_5SO_3 = 77.4°$, $H_7CSO_3 = 174.9°$, $H_8CSO_3 = 54.4°$, $H_9CSO_3 = -66.1°$

of the cation. As has been shown by comparison with experiment, the geometries of the parent neutrals are accurately reproduced at the SCF level in the 6–31 G* basis set. This is possibly not true of the cations. We have therefore gradient-optimized the geometry of $H_2SO_2^+$ (**54**) at the MP2/6–31 G* level and find changes of the order of 0.03 Å in bond lengths and about 2° in bond angles, relative to the SCF geometry-optimized cation structure (Table 12). The result is that, relative to the SCF-optimized neutral species structure, the SCF adiabatic energy increases by only 0.1 eV but the MP2 adiabatic energy decreases by 0.4 eV, increasing the MP2 value of Δ in the expected direction. MP2 optimization of the neutral H_2SO_2 structure will probably further increase the MP2 value of Δ, so that the MP2 value for the adiabatic–vertical energy difference will tend to converge towards the SCF calculated value.

Experimentally, the first vertical ionization energy of $(CH_3)_2SO_2$ is found at 10.65 eV[53]. The closest species in Table 11 is $HSO_2CH_3^+$ (**60**). Extrapolating the trend in MP2 vertical ionization energies for HSO_2H^+ (11.9 eV) and $HSO_2CH_3^+$ (11.3 eV) in Table 15 gives an expected approximate 10.7 eV vertical IP for dimethyl sulphone, which is close to experiment.

The effect of substituent X in XSO_2H^+ on the MP2/6–31 G* vertical ionization energies in Table 15 is in the order: F, OH, OCH_3, Cl, H, NH_2, CH_3 and SH, in decreasing value of IP. Substituting CH_3 for F is calculated to reduce the vertical ionization potential by 2.1 eV ($HSO_2F \rightarrow HSO_2CH_3$). Experimentally, going from $(CH_3)_2SO_2$ to CH_3FSO_2 reduces the first IP by 1.9 eV[63].

VIII. THERMOCHEMICAL QUANTITIES

In order to be able to compare calculated thermochemical quantities with experimental values it is necessary to take into account not only electronic energy differences, as tabulated here, but also the vibrational, rotational, translational and work (PV) energy differences[5,64]. The largest term is usually the vibrational energy difference, which is taken as a sum of zero-point vibrational energies for each molecular species in the chemical

reaction. The difference between reactants and products can be significant for small molecules[64] and must be considered for more accurate work[65]. Here, we will use only the total electronic energy differences in calculating thermochemical quantities and review trends in similar chemical systems[66]. The thermodynamic quantities needed to complete the electronic energy difference calculations to enthalpy differences can be added as needed. In any event, high accuracy may require a larger basis set and higher level of theory than used here[65].

Table 16 tabulates the (negative of the) calculated proton affinities (PAs) of the XSO_3^-, XSO_2^- and XSO_2Y^- series of anions to form the neutral species, in the direction shown by equation 1. The SCF and MP2/6–31 + G* energy values from Tables 1 and 8 have been used. Zero-point energy differences will generally favour the neutral species and reduce the calculated PAs. The numbers in Table 16 can be used to describe relative acidities or trends in deprotonation. For example, the (uncorrected) MP2 proton affinity of $HSO_2CH_2^-$ (**45**) is shown in Table 16 at 376.3 kcal mol^{-1}. The experimental enthalpy value for the similar $CH_3SO_2CH_2^-$ anion is 366.6 kcal mol^{-1}[67], which is relatively close. Analogously, the PA of HS^- from Table 17 can be calculated as 352.1 (SCF) or 351.6 (MP2) kcal mol^{-1} compared to the experimental value of 351.7 ± 4.2 kcal mol^{-1}[67]. The corresponding numbers for OH^- (Table 17) are 402.1, 389.4 and 390.8 ± 0.4 kcal mol^{-1}[67]. Thus the calculated gas-phase acidities in Table 16 are in reasonable correspondence with experiment. Similarly, good results have been obtained at a comparable level of basis set and theory, including the energy corrections mentioned above, for PO_3^- and NO_3^-[18].

$$A-H \longrightarrow A^- + H^+ \qquad (1)$$

By examining trends in Table 16, we now find that the range of PAs for attachment to the oxygen atom in the XSO_3^- series (SCF = 303 → 324 kcal mol^{-1}; MP2 = 296 → 312 kcal mol^{-1}, and to sulphur in XSO_2^- or XSO_2S^- (SCF = 283 → 330 kcal mol^{-1}; MP2 = 278 → 321 kcal mol^{-1}) are similar. The MP2 method generally gives lower calculated PA values than the SCF. This implies that the anion is a more highly correlated system and therefore the SCF method treats it less well than the neutral protonated species. In contrast to the large difference in experimental PA values between HS^- and HO^- (~ 39 kcal mol^{-1}), the calculated differences here between attachment to S and O are much smaller and not always in the same direction. The valency of the sulphur atom does not seem to play a significant role and the MP2 calculated difference in PAs between hypervalent and divalent S is not large. The PA values in Table 16 increase in the

TABLE 16. Proton affinities[a]

	XSO_3^{-b}		XSO_2^{-c}		XSO_2Y^{-d}		
X	SCF	MP2	SCF	MP2	SCF	MP2	Y
H	317.5	311.4	324.5	317.4	310.9	309.1	S
					376.3	368.5	CH_2
F	303.0	296.4	304.3	292.3			
OH	315.1	308.0	317.7	306.1	312.5	309.2	S
Cl	303.3	303.9	283.2	277.9			
NH_2	320.7	313.6	328.0	316.5			
HS	311.5	305.2	305.9	295.6			
CH_3	323.5	312.0	330.1	320.9			

[a]In kcal mol^{-1}; from 6-31 + G* energies in Tables 1 and 8; see equation 1.
[b]Proton attached to O.
[c]Proton attached to S.
[d]Proton attached to Y.

TABLE 17. Energies of miscellaneous atoms and fragments[a]

Species	Energy (a.u.)[b]	
	SCF	MP2
F^-	−99.417376	−99.621589
Cl^-	−459.538279	−459.668021
OH^-	−75.375649	−75.585294
HS^-	−398.105533	−398.226886
NH_2^-	−55.517628	−55.705858
SO_2^-	−547.215421	−547.716995
H·	−0.498233	−0.498233
F·	−99.370019	−99.496176
Cl·	−459.447320	−459.551020
OH·	−75.385786	−75.526566
HS·	−398.063794	−398.160819
NH_2·	−55.560299	−55.694017
HF	−100.012553	−100.198690
HCl	−460.059450	−460.190964
H_2O	−76.016520	−76.205847
H_2S	−398.666588	−398.787178
NH_3	−56.188321	−56.360060
SO_2	−547.173351	−547.679698
SO_3[c]	−621.985513	−622.667280

[a]Molecular fragment SCF geometry optimized in the 6-31G* basis (neutral species) or in the 6-31 + G* basis (anions).
[b]Using the 6-31 + G* basis set.
[c]Closed-shell singlet state.

substituent (X) order: F, Cl, HS, OH, H, NH_2 and CH_3. Generally, the more electronegative substituent preferentially stabilizes the anion (A^-) relative to AH. An exception to the above order is found for X = Cl in the XSO_2^-/XSO_2H series where the calculated PA is anomalously low as judged by electronegativity arguments.

$$B-H \longrightarrow B\cdot + H\cdot \qquad (2)$$

Homolytic bond dissociation energies (BDEs) for the detachment of a hydrogen atom (radical), are shown in Table 18. This type of comparison is expected to be less accurate than PAs, because different numbers of pairs of electrons are involved on the two sides of equation 2[66]. For example, the gas-phase BDE of H_2O is calculated from Table 17 at 114 kcal mol^{-1}, where the experimental value, corrected for zero-point vibrational energy which was not taken into account in the theoretical calculation, is 126 kcal mol^{-1}[5]. Thus, as expected, the calculation underestimates BDEs because of the relatively poorer description of the B—H system relative to B· + H·. A larger basis set and higher level of theory are required to achieve better accuracy for BDEs[68]. Nonetheless, we can examine the BDE values as a function of substituent X, and compare sulphur-bonded to oxygen-bonded H atom dissociation.

The range of BDEs in Table 18 for dissociation from a given atom is much narrower than for the PAs. For hydrogen atom dissociation from an oxygen atom the calculated BDEs are smaller than in H_2O, whose exact experimental value is 117.9 kcal mol^{-1} [69]. The corresponding spectroscopic value for hydrogen atom dissociation from H_2S is 75.2 kcal mol^{-1}[69], while the average value for homolytic dissociation in H—SO_2X (Table 18) is ~65 kcal mol^{-1}. For H—SSO_2X the calculated BDE value in Table 18 is

TABLE 18. Homolytic hydrogen-atom bond dissociation energies (BDE)[a]

X	Energy (kcal mol^{-1})			
	Reaction I[b]	Reaction II[c]	H—Y	Reaction III[d]
H	112.8	61.0	—	—
F	114.4	71.7	—	—
OH	113.6	69.9	H—O	112.8[e]
Cl	122.8	62.8	—	—
NH_2	113.3	67.4	H—NH	114.9
HS	111.8	59.8	H—S	78.7
CH_3	112.2	62.6	H—CH_2	104.3

[a]From MP2/6-31 + G* energies in Tables 1 and 4. Energy of H· taken as −0.498233 a.u.
[b]$XSO_2O—H \rightarrow XSO_3\cdot + H\cdot$. Lowest energy conformer from Table 1.
[c]$H—SO_2X \rightarrow XSO_2\cdot + H\cdot$.
[d]$H—YSO_2H \rightarrow \text{-}YSO_2H\cdot + H\cdot$.
[e]Same as top entry under Reaction I.

78.7 kcal mol^{-1}, close to the experimental value for H—SH. Thus both the ranges and absolute values of the calculated BDEs are reasonable, in light of existing experimental information. The calculated BDE for H_2S from Table 17 is 80.4 kcal mol^{-1}.

The calculated BDEs shown in Table 18 can be compared directly with experiment in two cases,

$$FSO_2O—H \longrightarrow FSO_2\cdot + H\cdot \quad (3)$$

$$HOSO_2O—H \longrightarrow HOSO_2O\cdot + H\cdot \quad (4)$$

Using the experimental heats of formation tabulated by Benson[9] and 52 kcal mol^{-1} for the hydrogen-atom heat of formation[5], the experimental BDEs for reactions 3 and 4 are 115 and 104 kcal mol^{-1}, respectively. Table 18 shows a calculated 114 kcal mol^{-1} for both processes.

The dissociation of OH· from sulphuric acid (equation 5) can be calculated from Tables 1, 4 and 17 as 86 kcal mol^{-1}. The corresponding experimental number is 88 kcal mol^{-1} [9]. Analogously, for equation 6, the experimental enthalpy of dissociation is estimates at 36 kcal mol^{-1} [9] while a calculation using the energies tabulated in Tables 4 and 17 gives 20.3 kcal mol^{-1}. Here, the number of electron pairs is conserved in the reaction but the location of the unpaired spin is completely different in reactants and products, being localized on the SO_2 fragment in $HOSO_2\cdot$ and on OH· in the products. The $X—SO_2\cdot \longrightarrow X\cdot + SO_2$ reaction has also been investigated by Boyd and coworkers[34].

$$HOSO_2—OH \longrightarrow HOSO_2\cdot + OH\cdot \quad (5)$$

$$HO—SO_2\cdot \longrightarrow OH\cdot + SO_2 \quad (6)$$

All the calculated BDEs discussed here use the MP2/6–31 + G* energies and do not include any of the correction terms mentioned above that are necessary for a quantitative comparison with experiment. Nonetheless, the calculated thermodynamic quantities seem to be at least qualitatively correct.

Many more general types of chemical reactions can be composed from energy Tables 1,4,8,11 and 17, including abstractions that preserve the number and types of electron pairs, as in equations 7 and 8, and dissociations like equations 9 and 10, for comparison with experiment, where available, and predictive usefulness. We leave these to the interest and inclination of the reader.

$$XSO_3H + OH\cdot \longrightarrow XSO_3\cdot + H_2O \quad (7)$$

$$XSO_2H + SH\cdot \longrightarrow XSO_2\cdot + H_2S \quad (8)$$

$$XSO_n\cdot \longrightarrow X\cdot + SO_n \ (n = 2, 3) \quad (9)$$

$$XSO_n^- \longrightarrow X^- + SO_n \ (n = 2, 3) \quad (10)$$

IX. SUMMARY

The geometric and electronic structural properties of a large number of prototypical sulphonic acids and their derivatives, obtained by *ab initio* quantum chemical methods, have been surveyed. Trends in the calculated properties are correlated using simple models, indices and concepts. The relationship between d-orbital occupancy, hypervalency and coordination is discussed.

The d-orbital occupation of a central sulphur atom increases with its degree of valency due to a combination of spatial polarization needs in the molecule and the stabilization of atomic spectroscopic states. However, hypervalency depends more on size and geometric factors than on d-orbital occupancy. The S=O bond generally has the $S^+—O^-$ structure as its major resonance component.

The optimized molecule bond lengths and angles are found to be in uniformly good agreement with experiments, where available, including rotamer conformation. Strong evidence for internal hydrogen-bonding interactions at (S=)O—H(—Z) interatomic distances of about 2.5–2.8 Å (even for Z = carbon) is indicated by differential S=O and Z—H bond lengths and terminal atom charges. The preferred rotamer conformations seems to be the result of a balance between the non-bonded O···H attractive interactions and repulsion among lone-pair and bonding-pair molecular orbitals.

The XSO_2Y series of molecules (Y = OH, H) have been examined for trends in geometric structure changes, both as a function of substituent X (H, CH_3, F, Cl, OH, NH_2, SH and OCH_3) and as a function of species (neutral, radical, anion and cation). There is a global correlation between changes in the S=O bond length and O=S=O angle; when one increases the other decreases, and *vice versa*. Generally, changes in bond distances with substituent X or type species can be correlated with the expected results of interactions among the bonding, non-bonding and anti-bonding molecular orbitals in these systems.

In the $XSO_3\cdot$ series the radical electron is localized on the precursor oxygen atom, while in $XSO_2\cdot$ the unpaired spin is delocalized mainly over the SO_2 fragment. In XSO_3^- the three S=O bonds are equivalent, except for small intramolecular effects. In both XSO_3H^+ and XSO_2H^+ the electron hole is again localized on one of the sulphonyl oxygen atoms, unless another group such as SH or OCH_3 has a more available electron for ionization.

Atomic charges calculated from the Mulliken populations are usually consistent with the orbital interaction analyses and geometry changes as a function of substituent and species. The XSO_3H series sometimes shows a negative population for a specific basis orbital on the central sulphur atom which can complicate interpretation of the atomic charges. Calculated spin populations in $XSO_2\cdot$ radicals are not in very close agreement with ESR derived values, probably due to the lack of a common basis for comparison.

Calculated ionization energies, electron affinities, proton affinities, homolytic bond dissociation energies and other thermochemical quantities are tabulated and discussed. Agreement with experiment, where available, is very reasonable.

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CHAPTER 2

Stereochemistry, conformation, and chiroptical properties of sulfonic acids and derivatives

KENNETH K. ANDERSEN

Department of Chemistry, University of New Hampshire, Durham, NH 03824, USA

I. INTRODUCTION

This discussion of the stereochemistry of sulfonic acids and closely related groups is almost exclusively confined to stereochemistry which arises from the sulfonic acid group (or closely related group) itself and not necessarily from the remainder of the molecule. That is, chiral sulfonic acids whose dissymmetry is independent of the sulfonic acid functional group, but due to some other feature such as the presence of stereogenic carbon atoms, are not covered. Only those molecules in which the sulfur atom is stereogenic and chirotopic (the terms chiral or asymmetric are often used in place of stereogenic) will be considered[1]. When the descriptors *R* and *S* are used, they refer to the configuration of the sulfur atom.

The sulfonic acid group has three equivalent oxygen atoms, assuming that the proton exchanges readily among the three. The sulfur atom in this group is stereogenic only when three isotopes of oxygen are present. For all practical purposes these isotopes must be the three stable isotopes ^{16}O, ^{17}O, and ^{18}O, i.e. **1**. The sulfur atom is also stereogenic if one of the three oxygen atoms in **1** is replaced by another heteroatom, or if one of the three is bonded to a relatively nonexchangeable group such as an alkyl or aryl group, e.g. **2**. The sulfur atom in derivatives in which two of the oxygen atoms have

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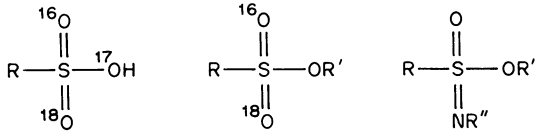
been replaced by two nonidentical groups or atoms is stereogenic independent of any isotopic substitution, e.g. **3**.



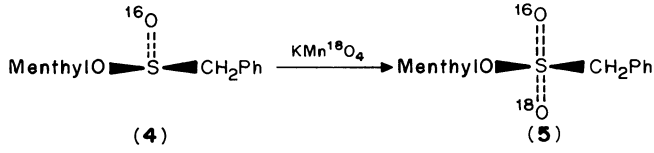
(**1**) (**2**) (**3**)

II. SULFONIC ACIDS

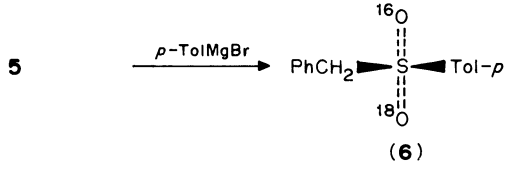
Sulfonic acids of type **1**, chiral by virtue of isotopic substitution, seem not to have been prepared. There is no reason why they could not be synthesized with high isotopic content since both ^{17}O and ^{18}O labeled oxygen and water of high isotopic purity are available. For example, hydrolysis of an ester of type **2**, where *R'* is aryl, using ^{17}O-labeled water might be a source of **1** of known configuration. The natural occurrence of **1** as a racemic modification is very small and is calculated to be 753 parts per billion[2].

III. SULFONATE ESTERS

An example of a sulfonate ester (**5**) of type **2** was prepared by permanganate oxidation of sulfinate ester **4** of configuration *R* (equation 1)[3]. It was assumed by analogy with oxidation at sulfur atoms in other molecules that the oxidation proceeded with retention of configuration, thus establishing the absolute configuration of **5** as *S*. Treatment with *p*-tolylmagnesium bromide converted **5** to (−)-^{16}O, ^{18}O-benzyl *p*-tolyl sulfone (**6**) whose absolute configuration had previously been established as *S* (equation 2). This showed that nucleophilic substitution at the sulfonyl sulfur atom in **5** proceeded with inversion of configuration.



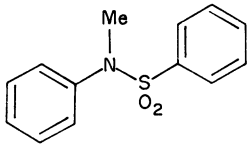
(**4**) (**5**) (1)



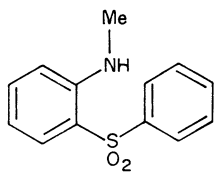
(**6**) (2)

It is generally believed that nucleophilic substitution at sulfonyl sulfur proceeds with inversion of configuration either through an S_N2-like transition state or intermediate in which the nucleophile, sulfonyl sulfur atom and leaving group are collinear. Substituion, possibly with retention, might still take place if the three groups were arranged far from the ideal 180° angle[4,5]. Several compounds (**7a**, **8a** and **9a**) were prepared in which any intramolecular substitution could not go via a collinear arrangement of the three groups. Treatment of **7a** with an alkyllithium to create a nucleophilic center *ortho* to the amino

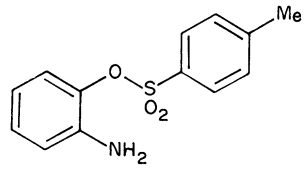
group led to intramolecular formation of the *o*-amino-sulfone **7b**.[5] This rearrangement might proceed through a nonlinear transition state or intermediate. Sulfonate **9a** gave the sulfonamide **9b** when the nitrogen was deprotonated, but this apparent rearrangement product was formed intermolecularly, not intramolecularly[4]. Sulfonate **8a** rearranged intramolecularly to the sulfonamide **8b**, but this apparent rearrangement probably followed an elimination–addition pathway rather than one involving nucleophilic substitution at sulfur[4].



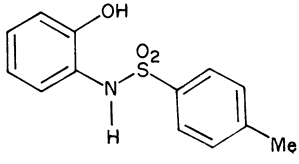
(**7a**)



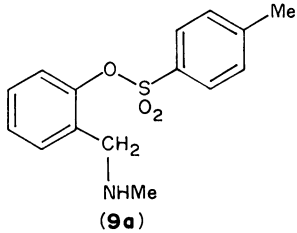
(**7b**)



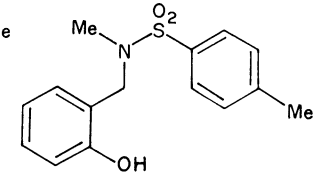
(**8a**)



(**8b**)



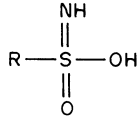
(**9a**)



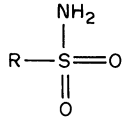
(**9b**)

IV. SULFONIMIDIC ACIDS AND DERIVATIVES

Sulfonimidic acids have the general structure **10**, but they exist in their tautomeric form as sulfonamides, **11**. If the oxygen atoms of **11** (or **10**) were isotopically dissimilar then the sulfur atom would be stereogenic, but molecules of this type have not been prepared[6,7].

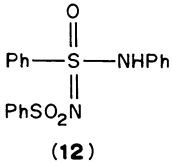


(**10**)

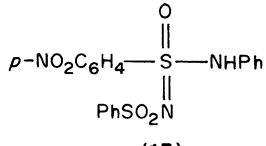


(**11**)

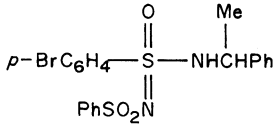
Levchenko and her coworkers first prepared sulfonimidic acid derivatives and studied their chemistry[8,9]. They also provided the first optically active examples of these compounds (**12**, **13** and **14**) by resolution with optically active α-phenethylamine[9]. Both enantiomers of **12** and **13** and all four diastereomers of **14** were obtained in optically pure form.



(**12**)



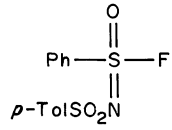
(**13**)



(**14**)

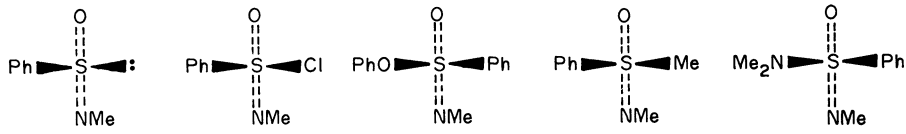
Several optically active derivatives of sulfonimidic acids have also been used in stereochemical studies. These examples will be discussed.

Sulfonimidoyl fluoride **15** was synthesized from the corresponding chloride by displacement with fluoride ion[10]. This stable compound crystallized as huge 1 to 3 g crystals which showed optical rotation. It was possible to predict the sign of rotation from the shape of each crystal.



(15)

Treatment of (*S*)-*N*-methylbenzenesulfinamide (**16**) with chlorine in pyridine-ether gave (*R*)-*N*-methylbenzenesulfonimidoyl chloride (**17**) with retention of configuration. Compound **17** was not isolated but treated with sodium phenoxide to give (*S*)-phenyl *N*-methylbenzenesulfonimidate (**18**). Reaction of ester **18** with methyllithium yielded (*S*)-*N*-methyl methyl phenyl sulfoximine (**19**). With dimethylamine, **17** gave (*R*)-*N*,*N*,*N*′-trimethylbenzenesulfonimidamide (**20**). The formation of **18**, **19** and **20** all proceeded with inversion at sulfur[11–13].

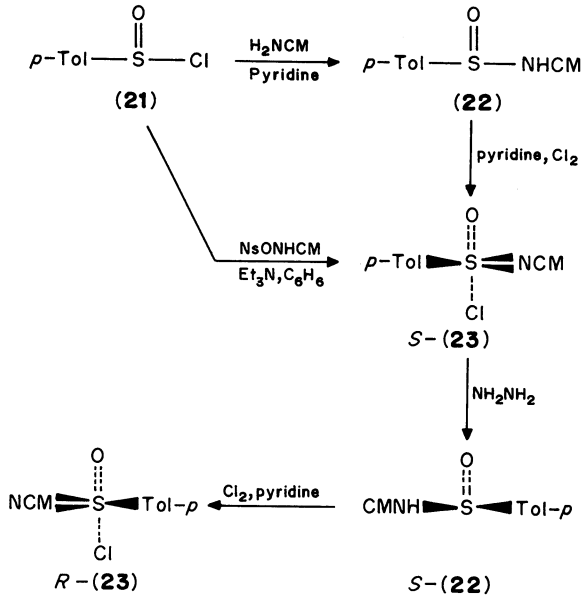


S-(**16**) *R*-(**17**) *S*-(**18**) *S*-(**19**) *R*-(**20**)

Another approach to chiral arenesulfonimidoyl chlorides started with racemic *p*-toluenesulfinyl chloride (**21**), which was converted to a mixture of diastereomers following either of two routes (Scheme 1)[14]. The first, and superior, method required two steps. (−)-Menthyl *N*-hydroxycarbamate (H_2NCM), **21** and pyridine gave sulfinamide **22** as a mixture of epimers. Subsequent treatment with pyridine and chlorine or with *tert*-butyl hypochlorite gave **23** as an epimeric mixture from which optically pure (*S*)-**23** was isolated by crystallization. In the second method, **21** was treated with (−)-menthyl *N*-*p*-nitrobenzenesulfonoxycarbamate (NsONHCM) and triethylamine in benzene to give (*S*)-**23** (the configurational notation refers to sulfur and not to the chiral menthyl group); the *R* epimer was not isolated.

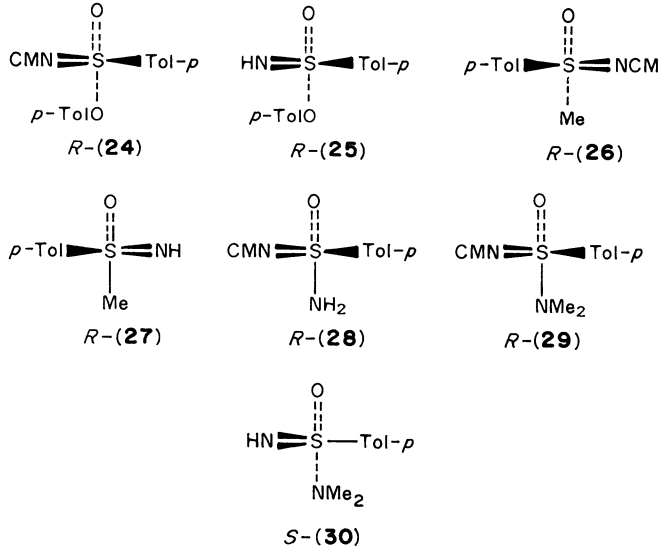
Isomer (*R*)-**23** was prepared from sulfonimidoyl chloride (*S*)-**23** in two steps. First (*S*)-**23** was treated with hydrazine to give (*S*)-**22**. This reaction proceeded with inversion of configuration. Chlorination of (*S*)-**22** gave (*R*)-**23** with retention.

Sulfonimidoyl chloride (*S*)-**23** reacted with inversion of configuration when treated with potassium *p*-cresolate, yielding ester (*R*)-**24**. Concentrated sulfuric acid removed the carbomenthoxy group to give (*R*)-**25** with retention of configuration. A similar sequence was carried out starting with (*R*)-**23**. Methylmagnesium bromide transformed ester (*R*)-**24** to sulfoximine (*R*)-**26**, which gave (*R*)-**27** upon reaction with sulfuric acid. This sequence was also carried out starting with (*S*)-**24**. Reaction of (*S*)-**23** with sodium amide and dimethylamine gave (*R*)-**28** and (*R*)-**29**, respectively. Sulfuric acid removed the carbomenthoxy group from (*R*)-**29** with retention accompanied by some racemization to give **30**.



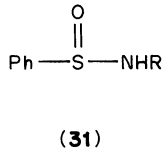
CM = CO_2menthyl-(−) NS = p-$O_2NC_6H_4SO_2$

SCHEME 1

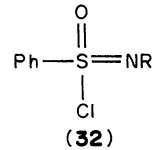


Sulfonimidates can be converted to sulfoximines, which are useful in synthesis, as mentioned above. Chlorination of a 3:1 diastereomeric mixture of sulfinamides (**31**), epimeric at sulfur, with *N*-chlorobenzotriazole gave diastereomeric sulfonimidoyl

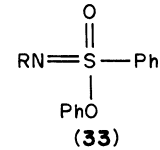
chlorides (**32**). Treatment of **32** with sodium phenoxide gave a 1.8:1.0 diastereomeric mixture of **33** in 85% yield[15]. The chlorination proceeded with racemization. Treatment of diastereomers **33** with methyllithium gave a mixture of sulfoximines, which were separated chromatographically into **34** (14% yield) and **35** (28% yield).



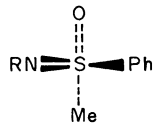
(**31**)



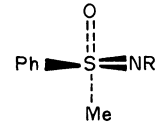
(**32**)



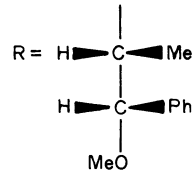
(**33**)



(**34**)



(**35**)

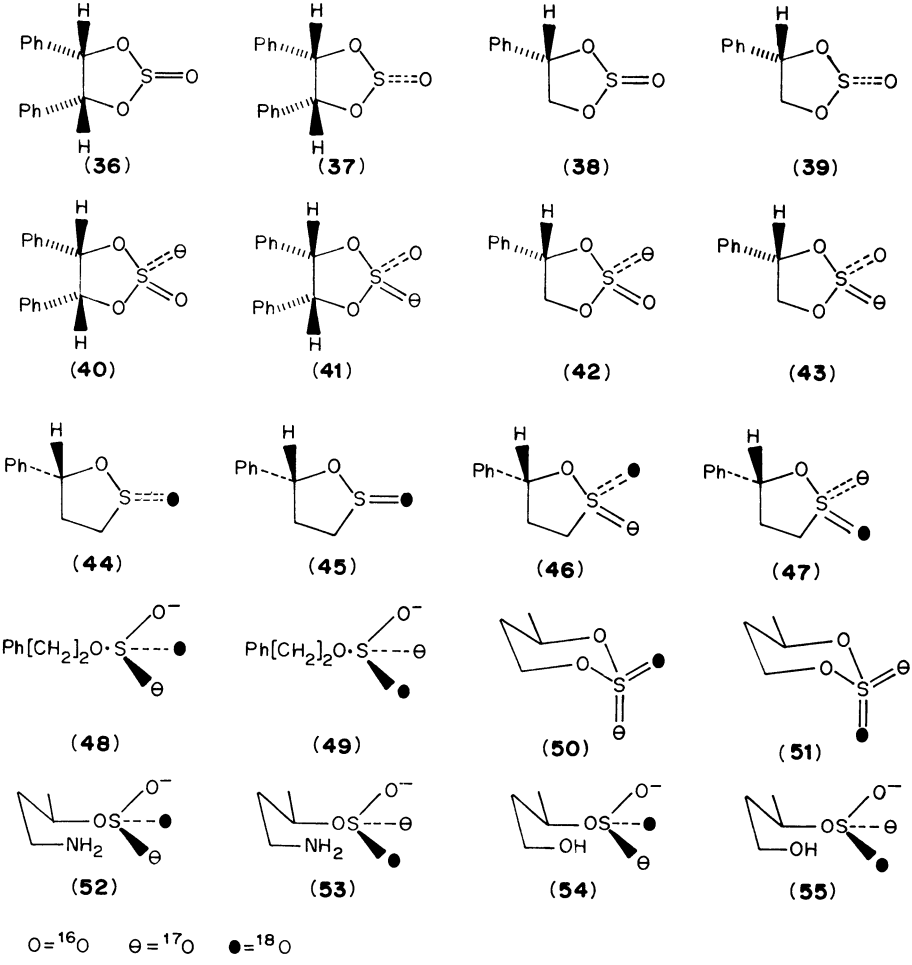


V. SULFATE ESTERS AND DERIVATIVES

Sulfate esters are not, strictly speaking, derivatives of sulfonic acids but of sulfuric acid and so are not properly under the purview of this chapter. However, it should be possible to extend to sulfonates the recent achievements of Lowe and coworkers on the stereochemistry of sulfates, based on the use of oxygen isotopes[16–22].

Several five- and six-membered cyclic sulfites were readily oxidized to their corresponding cyclic sulfates by ruthenium tetroxide. When ruthenium [^{17}O] tetroxide was used, diastereomeric five-membered sulfites (**36**, **37**, **38** and **39**) gave their respective diastereomeric sulfates (**40**, **41**, **42** and **43**) whose configurations were established by lanthanide-induced chemical shifts of their ^{17}O NMR spectra[16]. This demonstrated that the oxidation proceeded with retention of configuration at sulfur. Two cyclic sulfites (**44** and **45**), epimeric at sulfur and labeled with ^{18}O at their oxo oxygens, were oxidized to their cyclic sulfates (**46** and **47**, respectively) by ruthenium [^{17}O] tetroxide[18]. Reduction of **46** using tetrabutylammonium borohyride gave 2-phenylethyl (*S*)-[^{16}O, ^{17}O, ^{18}O]sulfate (**48**); **47** gave the enantiomer, 2-phenylethyl (*R*)-[^{16}O, ^{17}O, ^{18}O]sulfate (**49**). Both anions were isolated as their tetrabutylammonium salts. These sulfates are the first examples of sulfates chiral by virtue of stereogenic sulfur atoms alone.

Cyclic sulfates **50** and **51**, prepared from (3*R*)-1,3-butanediol, gave amines **52** and **53**, respectively, upon being treated with ammonia in methanol[20,21]. Deamination of **52** gave alcohol **54**; **53** gave **55**. Reaction with sulfuryl chloride regenerated the cyclic sulfates but with a change in the original isotopic distribution. The symmetric and antisymmetric sulfonyl stretching frequencies for the mixture of isotopomers were measured using FT IR. Since different spectral patterns in these regions were obtained for the two recyclized sulfates, it was possible to distinguish between them. They are configurationally different isotopic mixtures of isotopomers. FT IR measurement of the symmetric and asymmetric sulfonyl stretching frequency regions led to a stereochemical analysis of [^{16}O, ^{17}O, ^{18}O]sulfate monoesters.



VI. CONFORMATIONAL ANALYSIS

Dipole moment measurements have been used to determine the conformations of alkyl sulfonates, *S*-alkyl thiosulfates, sulfonic acid anhydrides and sulfonic acid thioanhydrides[23]. The gauche conformation in which the R-SO_2-XR′ dihedral angle is 60° is favored over the conformation in which the angle is 180°. The gauche conformation also controls the conformation in the anhydrides where four conformations are possible. The conformation with two 180° dihedral angles and the conformation with one 60° and one 180° angle were deemed unimportant. Of the two remaining conformations both with two 60° angles, the C_2 form is preferred over the C_s form.

Electron diffraction and microwave spectroscopy have been used to determine the conformational preferences for some simple, volatile sulfonic acids and derivatives. The findings have been summarized by Hargittai[24]. Compounds **56** to **61** exist as staggered conformers.

CH_3-SO_2Cl	CCl_3-SO_2Cl	CF_3-SO_2Cl
(**56**)[25,26]	(**57**)[27]	(**58**)[28]

CH_3-SO_2F	CH_3-$SO_2N(CH_3)_2$	CF_3-SO_2OH
(**59**)[29,30]	(**60**)[31]	(**61**)[32]

VII. CHIROPTICAL PROPERTIES

The sulfonic acid group is not a UV chromophore. Since simple sulfonic acids do not absorb in the UV, stereogenic examples would give no CD absorption and only plain ORD curves at best. As a consequence, published studies of their chiroptical properties are nonexistent. For example, no ORD measurements on sulfonate ester **5** were carried out, since it was felt that the menthyl group would dominate the rotation and obscure any contribution from the sulfonyl group. The contribution of the stereogenic sulfonyl group to the rotation was believed to be within experimental error. After the menthyl group had been removed by converting the ester to the sulfone (**6**), the rotation induced by the sulfonyl group of **6** was detected, but the magnitude of the rotation was very small.

The chiroptical influence of a nonstereogenic sulfonic acid group would be to asymmetrically perturb a UV active chromophore in the molecule in which it is found. 10-Camphorsulfonic acid is an example. However, this type of influence is outside the purview of this chapter.

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Chapter 3

Mass spectrometry of sulfonic acids and their derivatives

SIMONETTA FORNARINI

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università di Roma 'La Sapienza', 1-00185 Rome, Itlay

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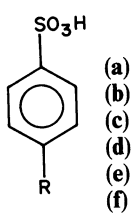
I. INTRODUCTION

The mass spectrometric behavior of sulfonic acids and sulfonic derivatives has not achieved a comprehensive description since 1967, when few data on the EI mass spectra of sulfonic esters and sulfonamides were available[1]. Since then, several reports have dealt with compounds possessing a sulfonic functionality, most of them spurred by their important role as environmental chemicals and biochemicals, surfactants, dyes or drugs. This chapter refers to those studies published from 1968 to early 1989. The great practical interest of such sulfonic derivatives has oriented mass spectrometric studies mostly towards analytical aspects. The vaporization and ionization of samples which may be nonvolatile or prone to decomposition and the identification of diagnostic molecular and/or fragment ions were major problems addressed. When mass spectra were discussed, the fragmentation patterns were often based on reasonable hypotheses and on the interpretation of metastable transitions while ion structures relied on high-resolution measurements and isotopic labelling. Techniques such as collisional activation (CA), which could aid in ion structure elucidation, were employed to induce fragmentation and to characterize the ions obtained by 'soft' ionization methods, e.g. field desorption (FD), fast atom bombardment (FAB) or chemical ionization (CI). Little detailed information is available on the gas-phase ion chemistry and ion thermochemistry of these compounds.

Though not strictly related, the last section of this chapter is devoted to sulfenic acid derivatives, which were not extensively studied by mass spectrometry, despite the fact that they are key intermediates in organosulfur chemistry, representing a link between compounds with bivalent sulfur and those containing sulfur in higher oxidation states.

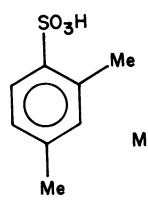
II. SULFONIC ACIDS

The electron impact (EI) mass spectra of sulfonic acids may be studied, provided special care is taken to control their thermal decomposition in the inlet system of the mass spectrometer. In his early study of the mass spectral fragmentation pattern of *p*-toluenesulfonic acid, Wiley[2] noticed a dependence of the relative intensity of the molecular ion on the temperature and time involved in sample volatilization. *o*-Toluenesulfonic acid failed to give a reproducible mass spectrum[3]. More recently, Borthakur and Rao[4] found the *S*-benzylisothiouronium salts of alkylbenzenesulfonic acids to be useful precursors, from which the free acids could be obtained in pure form by decomposition

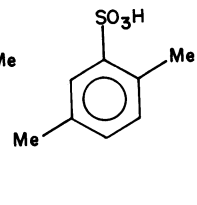


R
(a) H
(b) Me
(c) Et
(d) *i*-Pr
(e) *t*-Bu
(f) *t*-Amyl
(g) MeO

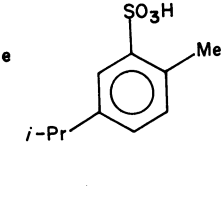
(1)



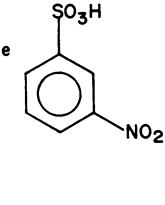
(2)



(3)



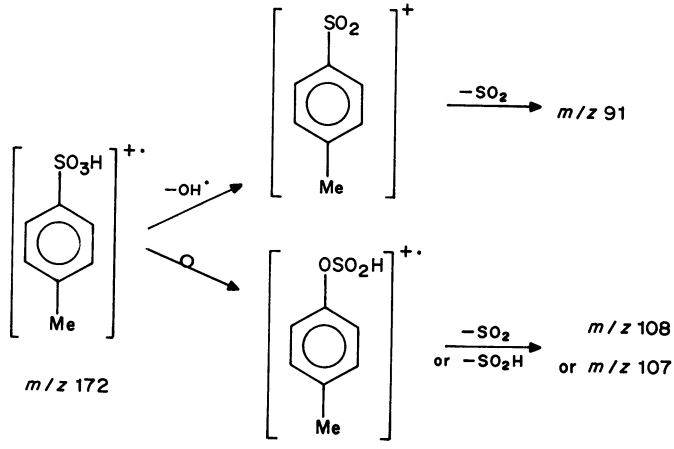
(4)



(5)

under the operational mass spectrometric conditions. By these means, the mass spectral features of compounds **1a–f**, **2–4** were studied. The 70 eV mass spectra of **1a**, **1b**, **1g** and **5** were also reported by Soothill and Williams[5], using purified commercial sulfonic acids.

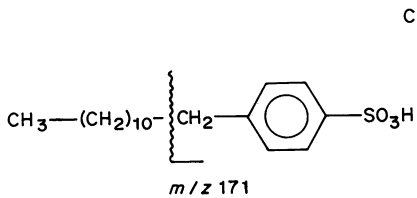
There was general agreement on the qualitative features of the mass spectra of alkylbenzenesulfonic acids. The molecular ion was the base peak for **1a** and **1b** according to References 2 and 5. However, its relative intensity decreased as the alkyl chain increased in length (**1c–f**) or number (**2–4**). Branching at the benzylic position gave rise to enhanced loss of alkyl groups, e.g. the $[M-15]^+$ ions were most intense for compounds **1d** and **1e**. Desulfonation was observed from all alkylbenzenesulfonic acids leading to prominent $[M-SO_3H]^+$ ions, from which further hydrocarbon fragments could originate. Loss of SO_3H probably involved a two-stage process with cleavage of SO_2 from the observed $[M-OH]^+$ ions[5], although the latter ions, formally corresponding to $[ArSO_2]^+$ ions, were weak, except in the case of compound **1g**. A rearrangement process was implied in the formation of abundant $[M-SO_2]^+$ and $[M-SO_2H]^+$ ions and suggested the involvement aryl migration from sulfur to oxygen in the parent molecular ion prior to fragmentation. Such rearrangements were characteristically found in the fragmentation patterns of sulfones[6]. For the methoxy-substituted sulfonic acid **1g**, the one-step relationship $[M]^{+\cdot} \rightarrow [M-SO_2H]^+$ was supported by the presence of a metastable peak. The major fragmentation channels and proposed ion structures for the representative spectrum of **1b** are shown in equation 1. The peak at *m/z* 107 in the mass spectrum of **1b** was proven to correspond to $[C_7H_7O]^+$ by precise mass evaluation[2]. Compound **5** behaved differently from the other sulfonic acids examined, in that its primary fragmentation involved the nitro group.



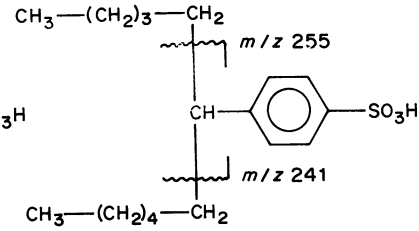
(1)

The mass spectra of isomeric *p*-$C_{12}H_{25}C_6H_4SO_3H$ have been recorded[7] using samples of their sodium salts, introduced into the ionization chamber by a direct inlet probe, in admixture with an equal amount of $KHSO_4$. The resulting spectra of the free acids were dominated by fragmentations of the alkyl chains, which revealed patterns diagnostic of their branching. Straight-chain *p*-dodecylbenzenesulfonic acid (**6**) was characterized by ions at *m/z* 171, due to benzylic cleavage of the C_{11} alkyl chain, and at *m/z* 172, due to benzylic cleavage with hydrogen rearrangement, plus a homologous series of ions corresponding to carbon–carbon bond cleavages progressively farther from the aryl ring. Doublets at *m/z* 241/242 and *m/z* 255/256 characterized the linkage position of the aromatic ring in *p*-(1-pentylheptyl)benzenesulfonic acid (**7**). While the molecular ion

was the base peak in the 15 eV mass spectrum of **6**, polybranched alkyl chains gave feeble molecular ions even at low electron energy.

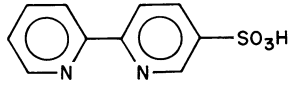


(6)



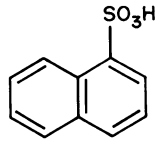
(7)

Metastable transitions and high resolution mass data supported the major fragmentation routes in the 70 eV mass spectrum of 2,2′-bipyridyl-5-sulfonic acid (**8**)[8]. High-mass ions derived from the molecular ion (*m/z* 236, 100%) by loss of SO_3 (*m/z* 156, 28%), HCN (*m/z* 209, 2%), O_3 (*m/z* 188 , 12%) and SO_2 (*m/z* 172, 8%) were observed.

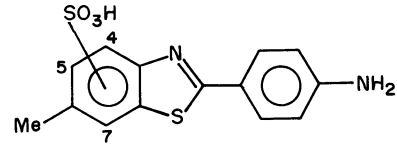


(8)

In recent years, however, newer techniques for the mass analysis of samples of low volatility have been exploited. The FAB method has been successfully applied to naphthalene-1-sulfonic acid (**9**)[9] and to isomeric 2-(4-aminophenyl)-6-methylbenzothiazolesulfonic acids with the —SO_3H group in the 4, 5 or 7 position (**10a–c**)[10]. The positive-ion FAB spectrum of **9** showed abundant $[M + H]^+$ ions and ions corresponding to $[M - SO_3]^+$. Negative-ion FAB spectra were more informative and were less contaminated by ions from the matrix. Thus, the negative-ion spectrum of **9** was dominated by $[M - H]^-$ ions accompanied by $[M - H - SO_2]^-$ and $[M - H - SO_3]^-$. The presence of the sulfonic group was confirmed by characteristic ions at *m/z* 80 and *m/z* 81 ($[SO_3]^{-\bullet}$ and $[HSO_3]^-$). In addition to $[M - H]^-$, the negative-ion FAB spectra of **10a–c**, desorbed from a triethanolamine (TEA) liquid matrix, contained weaker dimeric ions, $[2M - H]^-$ and $[M - H + TEA]^-$.



(9)



(10)

Two FD studies of sulfonic acids in the positive-ion mode have been published. Schülten and Kümmler[11] examined a variety of sulfonic acids, including alkanesulfonic acids, substituted benzenesulfonic acids, naphthalenesulfonic acids and anthraquinonesulfonic acids. Their results can be summarized as follows: (a) all the compounds gave high molecular ion intensities, normally with less intense $[M + H]^+$ ions, except

alkanesulfonic acids, which gave only $[M+H]^+$ ions rather than $[M]^{+\cdot}$ ions; (b) $[M-SO_3]^+$ ions, of structural significance, were often observed, their intensity increasing at higher emitter currents; (c) trace impurities of alkali metal ions could dominate the spectra, because of the known sensitivity of FD to their presence; (d) cluster ions ($[nM+H]^+$) were observed, which assisted the correct assignment of molecular weights.

Mathias and coworkers[12] observed considerable variations in the peak intensities with the anode heating current. Their FD spectrum of naphthalene-1,6-disulfonic acid showed no significant $[M]^{+\cdot}$, a base peak corresponding to $[M+H]^+$ and a major ion formally due to $[2M+H-SO_2-SO_3]^+$. At lower anode current, cluster ions became dominant and $[2M+H]^+$ was the base peak. Cluster ions were found under negative-ion FD conditions as well[13]. Anions of arenemonosulfonic acids dissolved in a polar organic matrix desorbed easily to yield abundant $[M-H]^-$ ions. Association with one or more molecules gave rise to cluster ions $[nM-H]^-$ for many of the compounds studied. The degree of clustering appeared to increase at lower emitter current and was noteworthy in the case of benzene- and 2-methyl-5-nitrobenzenesulfonic acid, where clusters up to $[5M-H]^-$ were observed. Naphthalene di- and trisulfonic acids were more awkward samples to deal with. The negative-ion FD spectra of 2-naphthalenesulfonic acid, naphthalene-2,6-disulfonic acid and naphthalene-1,3,6-trisulfonic acid were reported by Higuchi and coworkers[14]. The emitter was loaded with neat samples which melted and decomposed at increasing currents. Nevertheless, the reported spectra showed peaks due to $[nM-H]^-$ ions, with $n=1$–4.

Secondary ion mass spectrometry (SIMS) has also found application in the analysis of organic compounds not prone to thermal evaporation. By this technique sulfanilic acid gave fair abundancies of $[M-H]^-$ ions[15], when bombarded with low primary-ion current densities on a silver target. Sulfonic acids were successfully tested by atmospheric-pressure ion evaporation mass spectrometry and found to produce characteristic negative cluster ions[16].

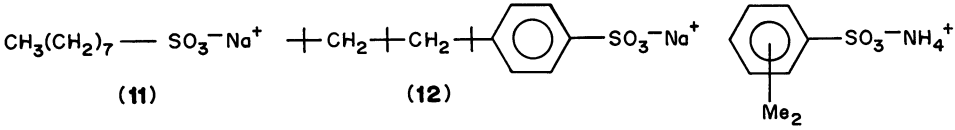
In contrast to analytical applications or to studies of unimolecular decay processes, the mass spectrometric study of ion–molecule reations requires high pressure or long residence times for reactive encounters to take place. High pressure mass spectrometry and ion cyclotron resonance (ICR) techniques have been used to determine the proton affinity (PA) of trifluoromethanesulfonic acid, by establishing whether proton transfer reactions to reference bases do occur, using the so-called bracketing technique[17]. A PA value of 172 ± 2 kcal mol^{-1} was obtained, close to the PA value of sulfuric acid, indicating that the effect of a trifluoromethyl substituent on the basicity of these compounds is similar to that of a hydroxyl group. The protonation site of these acids was suggested to be the hydroxyl oxygen, based on the observation that their PA value is close to that of other hydroxy compounds, such as H_2O, CH_3OH or HNO_3, and significantly larger than those of SO_2 and SO_3. It should be remarked, however, that the hydroxyl group of nitric acid appears to be more basic than the nitro oxygen atom by only few kcal mol^{-1} [18]. Work aimed at clarifying this problem and exploring the gas-phase ion molecule chemistry of simple sulfonic acids and esters is under way.

III. SULFONIC SALTS

A. Alkanesulfonate and Alkylbenzenesulfonate Salts

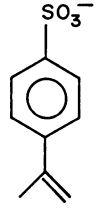
Sulfonic salts are not amenable to ionization by conventional mass spectrometric methods which require prior thermal volatilization of the samples. Two routes were envisaged to overcome the volatility problem: either the sulfonic acid salt was chemically converted to a volatile derivative, e.g. chloride or ester, whose mass spectrometric

behavior is discussed under the specific headings, or the sulfonic salt was ionized by techniques able to desorb it from a solid or liquid matrix. Among these, the FAB method shares with 'soft' ionization techniques the capability of yielding molecular weight information but also the usual absence of structurally informative fragment ions in the spectra. For this reason Lyon, Gross and coworkers have used FAB in conjunction with tandem mass spectrometry (MS/MS) to characterize alkanesulfonate and alkylbenzenesulfonate salts[19]. The possibility of obtaining CAD spectra of individual ions makes this combined technique especially powerful for the analysis of mixtures of sulfonate salts such as those found in commercial samples of anionic surfactants. The positive ion FAB spectra of specimen compounds **11** and **12** were reported to show cluster ions of formula $[n\mathrm{M} + \mathrm{Cat}]^+$, where M indicates the whole molecular formula of the salt and Cat is the cation. Compound **13** exhibited a single major peak corresponding to $[\mathrm{M} + \mathrm{H}]^+$. The anions $[\mathrm{M} - \mathrm{Cat}]^-$ were significantly present in the negative-ion FAB spectra. The CAD spectra of these FAB-generated negative ions showed the presence of a peak at m/z 80, $[SO_3]^-$, indicative of a sulfonate.



(11) **(12)** **(13)**

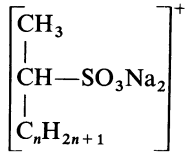
Other ions were present which could aid structural identification: the CAD spectra of the negative ions of **13** and of toluenesulfonic acid were characterized by methyl losses and by a rearrangement process which resulted in the loss of SO_2, while dissociation of the anion of the branched sodium alkylbenzenesulfonate **12** yielded an abundant ion at m/z 197, to which was assigned the probable structure **14**. The presence of this ion was found diagnostic for homologues, sharing the feature of two methyl branches at the benzylic carbon atom. The possibility of distinguishing between linear or branched alkylbenzenesulfonate salts has important implications in environmental analysis, as these compounds are widely used anionic surfactants with different properties. In fact, branching in the alkyl chain makes these detergents not biodegradable, encouraging the use of the less persistent linear alkylbenzenesulfonate salts.



(14) *m/z* 197

The first application of MS/MS for direct analysis of anionic surfactants mixtures is due to Levsen and coworkers, who used FD as the ionization method[20]. The full-scan FD spectra of pure sodium sulfonates have been reported by Large and Knof[21] and Schülten and Kümmler[11]. The following features were commonly observed[11]: (a) ions formed by cation attachment to the salt, $[\mathrm{M} + \mathrm{Cat}]^+$, gave intense signals, accompanied by usually weaker $[\mathrm{M}]^{+\bullet}$, although the intensities of $[\mathrm{M}]^{+\bullet}$ tended to increase with increasing molecular size; (b) ions corresponding to $[\mathrm{M} + \mathrm{H}]^+$ were observed; (c) the

formation of large cluster ions $[nM + Cat]^+$ was typical, e.g. $n = 1–6$ for sodium benzenesulfonate ($n = 1–5$ according to Reference 21), the relative ion cluster intensities decreasing with increasing size. The molecular weight information from these FD spectra was, however, much superior to the structural information available from weak, if ever present, fragment ions. Thus, $[M + Na]^+$ from a mixture of alkylbenzenesulfonates of the general formula $C_nH_{2n+1}SO_3Na$ were selected for CAD analysis[20a,b]. The spectra were dominated by the ion at m/z 126, $[Na_2SO_3]^+$ formed by loss of the alkyl chain. From this ion, a series of fragment ions of the general formula $[C_mH_{2m}SO_3Na_2]^+$ extended up to the main beam, which aided the determination of the chain length. A strong ion signal at m/z 154 was informative of the chain branching in sulfonates of type $R^1R^2CHSO_3Na$, originating from loss of R^2 and identifying R^1 with a methyl group. In the lower mass range a dominating sodium ion (m/z 23) was accompanied by ions attributed to formulas $[Na_2O]^+$ (m/z 62) and $[CH_3SO]^+$ (m/z 63). The major fragmentation routes of these compounds of formula $C_nH_{2n+1}CH(CH_3)SO_3Na_2$ (**15**), cationized by sodium attachment, are summarized in equation 2a. They were paralleled by the fragmentations of the corresponding alkylbenzenesulfonate salts (**16**), shown in equation 2b. The ion at m/z 230, formed by benzylic cleavage, was the counterpart of the ion at m/z 154 in the alkanesulfonate series. Fragment ions which characterized the aromatic moiety were found at m/z 202, due to complete loss of the alkyl substituent, and at m/z 91. The fragment ion series $[C_mH_{2m}C_6H_4SO_3Na_2]^+$, extending from m/z 230 to the parent ion, corresponded to the $[C_mH_{2m}C_6H_4SO_3HNa]^+$ series from CAD of $[M + H]^+$ ions. In the latter case, however, there appeared a substantial contribution of unimolecular (metastable) decomposition, which persisted in the absence of a collision gas. It is possible that the cation formed by proton rather than Na^+ attachment had a lower intrinsic stability or higher energy content.

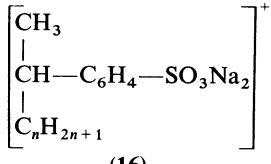


(**15**)
$n = 12–15$

CAD

m/z 23	$[Na]^+$
m/z 62	$[Na_2O]^+$
m/z 126	$[Na_2SO_3]^+$
m/z 154	$[CH_3CHSO_3Na_2]^+$

(2a)



(**16**)
$n = 6–11$

CAD

m/z 23	$[Na]^+$
m/z 62	$[Na_2O]^+$
m/z 126	$[Na_2SO_3]^+$
m/z 202	$[C_6H_4SO_3Na_2]^+$
m/z 230	$[CH_3CHC_6H_4SO_3Na_2]^+$

(2b)

From an analytical standpoint, it could be concluded that FD combined with MS/MS allowed the assessment of individual components in a mixture of anionic surfactants, identifying the cation, the sulfonate group and the length and the branching of the alkyl chain. The analytical scope of the methodology has been applied to the trace determination of surfactants in surface water[20c] with the selective desorption of anionic surfactants of the alkylbenzenesulfonate type at higher emitter heating current.

A comparative study of the potential of FD, FAB and desorption chemical ionization (DCI) techniques for the analysis of linear alkanesulfonate and alkylbenzenesulfonate

salts can be found in Reference 22. Positive-ion FAB spectra of **15** and **16** were found to yield both molecular weights with $[M + Na]^+$ ions and some structurally informative fragments, e.g. *m/z* 153 for species **15** and *m/z* 91, *m/z* 202, *m/z* 229 for compounds **16** with *m/z* 126 ($[Na_2SO_3]^+$) reflecting the functional group and the nature of the cation. Abundant ions below *m/z* 100 were due, in most cases, to hydrocarbon fragments, their intensities depending on the experimental conditions adopted. On the contrary, fragment ions were absent in the DCI spectrum of **15**, which showed only $[M + Na]^+$ ions and weaker $[M + H]^+$ ions, and in the negative ion FD spectra of **15** and **16** which revealed only signals due to the intact anions. The latter finding holded for the negative-ion FD mass spectra of a series of alkyl- and alkenylbenzenesulfonate salts obtained with or without use of a polyethylene oxide matrix[23].

The absence of fragment ions characterized the thermal surface ionization mass spectra of the sodium salts of alkylbenzenesulfonic acids[24]. The observed $[nM + Na]^+$ ions, $n = 1$–2, were suggested to derive from a stepwise process involving evaporation of neutral clustered molecules followed by ionization and dissociation on the surface of the hot wire.

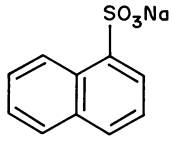
Linear sodium alkanesulfonates, $C_nH_{2n+1}SO_3Na$, $n = 2$–12, were examined by means of the filament heated in-beam (FHIB) method[25]. Aqueous solutions of the sulfonates were dried on the tungsten filament of the FHIB device. The resulting mass spectra showed few ions, with $[M + Na]^+$ base peak in most cases, prominent $[Na]^+$ peaks and signals due to clusters $[nM + Na]^+$, decreasing in intensity with increasing *n*. In addition to the above ions, the FHIB electron impact mass spectrum of unsubstituted sodium benzenesulfonate was reported to contain abundant fragment ions, assigned to $[C_6H_6]^+$, $[SO_2Na]^+$ and $[C_6H_5SO]^+$ [26]. The same method was said to differentiate between linear and branched alkylbenzenesulfonate salts, on the basis of their different pattern of fragmentations involving the alkyl chain, e.g. sodium linear *p*-n-dodecylbenzenesulfonate showed a smooth curve of decreasing intensities for homologous fragments from the most abundant $[C_3H_5C_6H_4SO_3Na_2]^+$ up to $[M + Na]^+$, while in the same mass range C_{12}-*p*-branched alkylbenzenesulfonate salts showed discontinuities due to preferred fragmentations at the branching sites[26].

Laser irradiation of the alkali salts of linear alkanesulfonic acids, $C_nH_{2n+1}SO_3Cat$, $n = 6$, 10, 12, 16, produced positive-ion mass spectra consisting of few intense signals, as recorded by a time-of-flight mass spectrometer[27]. The major organic ion was $[M + Cat]^+$ accompanied by less abundant dimers $[2M + Cat]^+$. For $n = 6$, the spectra[27b] were dominated by the alkali metal ion signals $[Cat]^+$, their relative intensities in each spectrum decreasing with increasing ionization potentials, in the series Cs > Rb > K > Na. The first ionization potential of the corresponding element determined also the relative intensities of positive metal ions (Na^+, Mg^+, K^+, Ca^+) emitted from alkanesulfonate films on a gold foil under O_2^+ bombardment[28]. The range of this SIMS study of alkanesulfonate salts was forcedly restricted to the low mass region (10–250 a.m.u.) because of instrumental limitations. Within this range, the organic moiety, isohexadecylsulfonate, gave rise only to weak fragments with poor reproducibility.

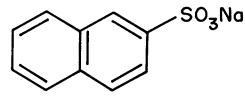
B. Arenesulfonate Salts

A variety of substituted naphthalenes and anthraquinones, bearing one or more sulfonate salt groups, have been investigated by FAB, FD and electrodynamic ionization techniques. The interest in these compounds originated from their important role as dye intermediates. The FD mass spectra of compounds **9a**, **18**, **20**[11] and **17**, **19**, **21** and **22**[12], among other arenesulfonate salts, have been described. Their main features were similar to those of benzene- and alkylbenzenesulfonate salts, with $[M + Cat]^+$ usually being the base

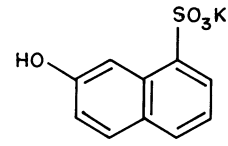
peak and dimer ions $[2M + Cat]^+$, becoming most abundant at lower anode heating currents[12].



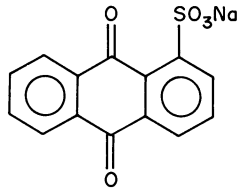
(9a)



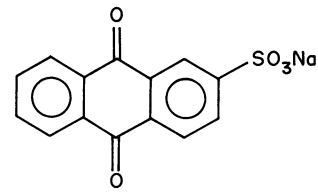
(17)



(18)



(19)



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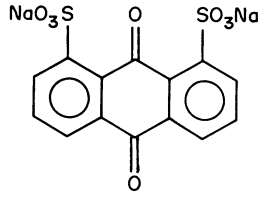
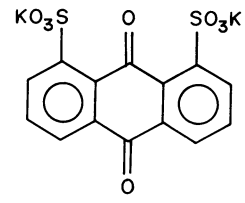
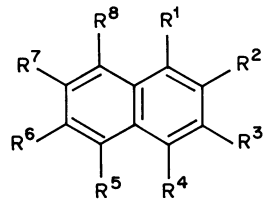


(21)



(22)

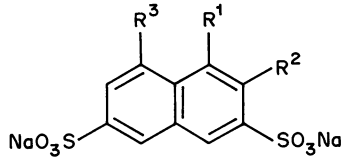
The presence of cluster ions was much less relevant in the FAB mass spectra of a number of naphthalene mono-, di- and trisulfonate salts, i.e. compounds **9a** and **23a–j**[9]. These compounds appeared well suited to FAB ionization and gave good spectra in both the positive- and negative-ion mode. However, negative-ion spectra were usually more informative and contained less interference by glycerol molecules from the matrix. In fact, in the positive-ion mode, glycerol clusters dominated the spectra and $[M + Cat]^+$ ions were of low intensity, particularly with the growing number of sulfonate groups. $[M + H]^+$ ions predominated over $[M + Cat]^+$ ions when the cation Cat^+ was the ammonium ion, as in compound **23a**. Fragment ions corresponding to $[M + H - SO_3]^+$ and $[M - SO_3]^+$ were formed from di- and trisulfonate salts **23c–j**. In the negative-ion FAB spectra, the free anion $[M - Cat]^-$ gave typically the base peak and the ions at m/z 80 and m/z 81 ($[SO_3]^-$ and $[HSO_3]^-$) were found diagnostic for sulfonated species. In addition to these ions, characteristic fragments were found, corresponding to: (a) $[M - Cat - SO_2]^-$ and $[M - Cat - SO_3]^-$ for monosulfonate salts **9a**, **23a** and **23b**; (b) $[M - Cat - SO_3Cat]^-$, $[M - Cat - SO_3 + H]^-$ and $[M - SO_3Cat - SO_2Cat + H]^-$ for disulfonate salts **23c–f**; (c) relatively intense $[M - Na - SO_3Na + H]^-$ for trisulfonate salts **23g–j**. Tetrasulfonate salts **23k** gave a weak negative-ion spectrum with $[M - Na]^-$ ions and peaks at m/z 80 and m/z 81 barely discernible against the background.



(23)

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
(a)	H	SO_3NH_4	H	H	H	H	H	H
(b)	SO_3Na	NH_2	H	H	H	H	H	H
(c)	SO_3K	SO_3K	H	H	H	H	H	H
(d)	H	SO_3Na	H	H	H	H	SO_3Na	H
(e)	H	NH_2	H	SO_3Na	H	H	SO_3Na	H
(f)	H	NH_2	H	SO_3Na	H	H	H	SO_3Na
(g)	SO_3Na	H	SO_3Na	H	H	SO_3Na	H	H
(h)	NH_2	H	SO_3Na	H	SO_3Na	H	SO_3Na	H
(i)	H	NH_2	H	SO_3Na	H	SO_3Na	H	SO_3Na
(j)	OH	H	SO_3Na	H	H	SO_3Na	H	SO_3Na
(k)	SO_3Na	H	SO_3Na	H	SO_3Na	H	SO_3Na	H

The superiority of the negative-ion mode was also clear from the FD mass spectra of **9a** and **17** and of the potassium salts of benzenesulfonic acid, 1-methylphenanthrenesulfonic acid and perylenesulfonic acid[13,29], where the unclustered anions were the only significant species desorbed from the respective salts, dissolved in a polyethylene oxide matrix. Only weak negative-ion signals could be obtained from the application of electrodynamic ionization mass spectrometry to the disodium salts of 2-naphthol-3,6-disulfonic acid (**24a**) and of 4,5-dihydroxy-2,7-naphthalenedisulfonic acid (**24b**)[30].



(24) (a) $R^1 = R^3 = H$, $R^2 = OH$

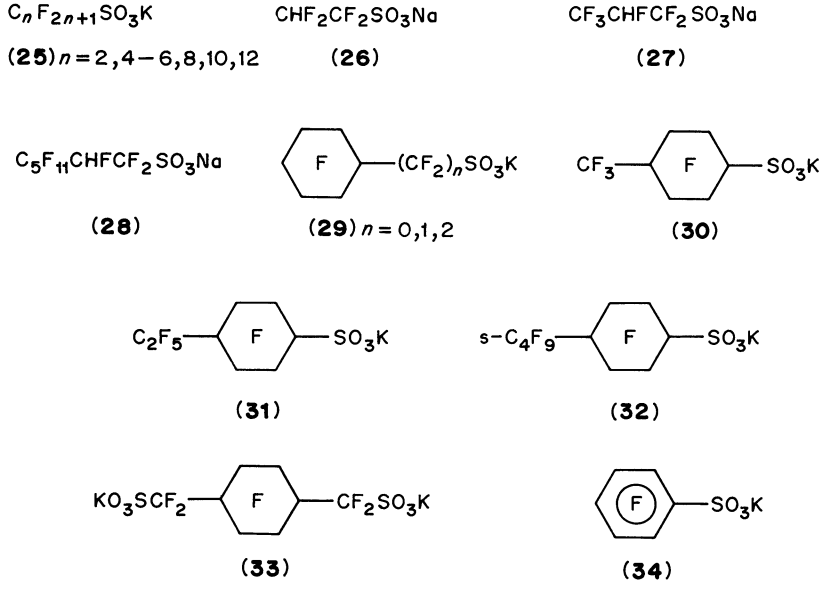
(b) $R^1 = R^3 = OH$, $R^2 = H$

The negative-ion laser desorption (LD) mass spectrum of sodium 2,4,6-trinitrobenzenesulfonate has been reported to contain ion peaks corresponding to: $[NO_2]^-$ (34% relative abundance), $[CNO]^-$ (8%), $[CN]^-$ (34%), $[M + O - SO_3Na]^-$ (100%), $[M - Na]^-$ (74%) and $[M - SO_3Na]^-$ (42%)[31]. The formation of the ion ascribed to $[M + O - SO_3Na]^-$, which found counterparts in the series of nitroarenes under study, was suggested to arise from an ion–molecule reaction, taking place in the high-pressure region adjacent to the laser-irradiated portion of the sample surface. An indirect support for this hypothesis was found in a parent–daughter ion relationship observed by Fourier

Transform ICR. Double resonance experiments established a link between the $[NO_2]^-$ ion and $[M + O - Cl]^-$ product ion for the corresponding process in the case of 2,6-dinitrochlorobenzene.

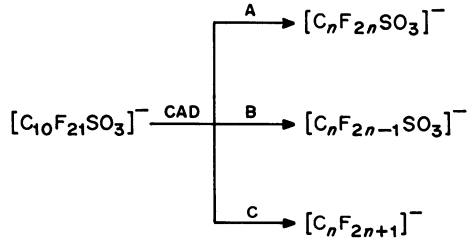
C. Fluoroalkanesulfonate Salts

Lyon, Gross and coworkers investigated the mass spectrometric behavior of cyclic and acyclic fluoroalkanesulfonates **25–33** and pentafluorobenzenesulfonate **34**, upon FAB ionization and CAD analysis of selected negative ions[32]. Positive- and negative-ion full-scan FAB spectra were relatively simple, typically void of significant fragment ions. In the positive-ion mode, cation (Cat = Na or K) attachment of the salt molecule (M) afforded the dominant ion in the spectrum, $[M + Cat]^+$, with clusters $[nM + Cat]^+$ extending to high n values. The observation of high mass clusters appeared to be limited by the spectrometer mass range since, when this was fairly extended, compound **31** showed clusters up to $[8M + Cat]^+$. The propensity of sulfonate salts to be desorbed in such aggregates has encouraged their use as high mass standards, as reported below. Glycerol molecules (G) from the matrix caused some interference, yielding additional cluster ions $[M + G + Cat]^+$, $[G + Cat]^+$ and $[G - H + 2Cat]^+$. The latter two ions appeared at m/z 131 and m/z 169, when Cat = K, and could be erroneously regarded as due to $[C_3F_5]^+$ and $[C_3F_7]^+$ fragments, characteristic of perfluoroalkyl chains.

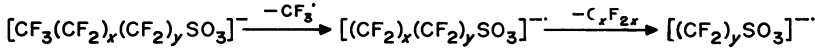


The negative-ion FAB mass spectra showed the free anion $[M - Cat]^-$ as the base peak. As in the positive-ion spectra, extensive clustering, $[nM - Cat]^-$, and limited, if any, fragmentation was observable. Both positive- and negative-ion spectra appeared contaminated by the presence of chemical impurities, lower homologues in the case of acyclic perfluoroalkanesulfonate salts, unsaturated and, possibly, ring-opened compounds in the cyclic perfluoroalkanesulfonate salts. A structurally diagnostic loss of neutral SO_3 in the negative-ion spectra characterized cyclic compounds with the sulfonate group directly attached to the ring.

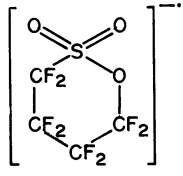
While positive- and negative-ion FAB spectra gave information on the molecular weight, purity and identity of the cation, CAD was applied to FAB-generated free anions to gain structural information. The CAD mass spectra of long-chain perfluoroalkanesulfonate anions, exemplified by perfluorodecanesulfonate ion, typically showed three series of peaks, summarized in equation 3. The 50 a.m.u. spacings between peaks in each series corresponded to a CF_2 group. Ions of the general formula $[C_nF_{2n}SO_3]^-$, extending from m/z 80, $[SO_3]^-$, to the main beam, pertained to the first series A and were suggested to originate from initial cleavage of F, CF_3 or C_2F_5 from the parent anion, followed by loss of C_xF_{2x} (e.g. equation 4), rather than by single direct homolytic cleavage. This series showed a peak of maximum intensity at m/z 280, ascribed to a stable six-membered ring structure (**35**) rather than an open-chain distonic radical anion (**36**). An alternative mechanism to series A ions, involving concerted ring formation with perfluoroalkyl radical loss (equation 5) was disfavored for entropic reasons. A second series B corresponded to $[C_nF_{2n-1}SO_3]^-$ ions, formally originating by perfluoroalkane losses from the parent anion. In analogy with carboxylate anions, loss of $F_2 + C_nF_{2n}$ was suggested to occur, to form an unsaturated sulfonate anion. The third series C comprised perfluoroalkyl carbanions, $[C_nF_{2n+1}]^-$, involving loss of SO_3 from the parent anion, followed by parallel and/or sequential losses of C_nF_{2n}.



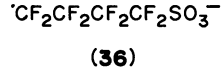
(3)



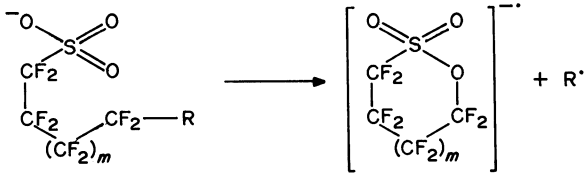
(4)



(**35**)

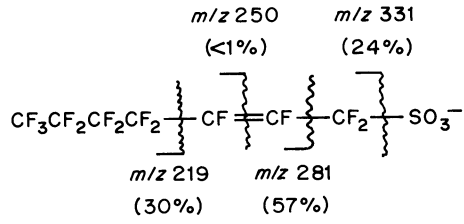


(**36**)



(5)

The anions of the 2-hydro-compounds **27** and **28** exhibited largely different CAD spectra, with respect to their perfluoro analogues. As expected, they were dominated by the elimination of HF, already discernible as a unimolecular process. The fragment ion thus produced from compound **28** corresponded to perfluoroheptenesulfonate anion **37**, and was stable, but upon CAD, it yielded fragment ions whose abundancies were consistent with the location of the double bond between carbons $C_{(2)}$ and $C_{(3)}$.



(37)

While abundant $[SO_3]^-$ ions at m/z 80 in the CAD spectra of the free anions of linear perfluoroalkanesulfonate salts were a common feature, which could be exploited as an analytical tool, their intensity was greatly reduced in the case of cyclic perfluoroalkanesulfonate salts **29**[32b]. Rather, upon CAD, the $[M—Cat]^-$ ions from compounds **29** underwent C – S bond cleavage with predominant negative charge retention on the perfluoroalkyl moiety. On a thermodynamic basis, sulfur trioxide should always be lost as neutral molecule due to its lower electron affinity value (EA = 1.7 eV) when compared with perfluoroalkyl radicals [e.g. $EA(CF_3) = 1.9–2.1$ eV]. The loss of neutral SO_3 was the major fragmentation process displayed by cyclic perfluoroalkanesulfonate salts, which appeared less prone to fragment than their acyclic counterparts. Monosubstituted perfluoroalkanesulfonates **29**, $n = 1–2$, could be distinguished from their disubstituted isomers **30** and **31** by the presence of a significant perfluoroalkyl carbanion peak at m/z 281 in their CAD spectra. The $[M - K]^-$ ion from the disulfonated compound **33** exhibited a most intense unique fragmentation of the elements of neutral SO_3K. The anion of pentafluorobenzenesulfonate **34** underwent cleavage of neutral SO_3 while benzenesulfonate anion cleaved with charge retention on sulfur trioxide. The latter anion showed also extensive rearrangement to lose SO_2.

The tendency of sulfonic salts to desorb and give rise to cluster ions has been exploited by Fenselau and coworkers[33] in their quest for high mass reference ions for the FAB ionization technique. To achieve high mass ions, cesium was chosen as the cation and a perfluoroalkylsulfonate as the anion. When the sample concentration was optimized, clusters $[nM + Cs]^+$ were observed, with n values as high as 29 ($M = C_6F_{13}SO_3Cs$). Higher mass clusters of greater intensity were obtained by increasing monomer size rather than by increasing the n value. In fact, signal intensities fell off with the n value, but did so less steeply with the increasing mass of cluster ion. These features made cesium perfluoroalkanesulfonates suitable as high mass reference compounds, when compared to commonly used CsI, under close experimental parameters.

Despite its low volatility, silver trifluoromethanesulfonate (**38**) gave an EI mass spectrum with intense $[M + Ag]^+$ ions, leading to the suggestion that **38** vaporized as a dimer[34]. FD mass spectra of both **38** and silver methanesulfonate (**39**) showed the presence of cluster ions $[nM + Ag]^+$, with $n = 1–6$ for **38** and $n = 1–7$ for **39**[35a]. Each cluster ion yielded multiple peaks with relative intensities determined by the presence of the silver isotopes. A mixture of the two compounds showed a FD mass spectrum comprising additional clusters with mixed anions. Thus, the resulting spectrum had relatively intense

peaks distributed throughout the mass range examined and was exploited as high resolution mass standard in FD mass spectrometry[35b].

CF_3SO_3Ag (38) CH_3SO_3Ag (39)

Photodissociation with 514.5 nm photons was tried on $[(MeSO_3Ag)_3Ag]^+$, $[(MeSO_3Ag)_2Ag]^+$ and $[(CF_3SO_3Ag)_2Ag]^+$ cluster ions, generated by FD[36]. The three ions failed to produce any evidence of photodissociation activity, which could otherwise be a tool for structure determinations.

D. Sulfonic Salts of Organic Cations

FAB ionization has been applied to alkylammonium sulfonates **40**–**50**, some of these compounds being of interest as selective solvents and stationary phases in gas chromatography[37]. The mass spectra, obtained from samples dissolved in glycerol, were characterized by: (a) the free ammonium ion as almost always the base peak; (b) clusters of the general formulas $[nM + Cat]^+$ and $[nM + H]^+$; (c) fragment ions deriving from the ammonium ion, i.e. hydrocarbon fragments and ions formally corresponding to $[RNH{=}CH_2]^+$ and $[R_2N{=}CH_2]^+$, with R being a former alkyl substituent on nitrogen. Fragmentations originating from the tetra-n-butylammonium ion have been described[37b]. Proton-bound clusters $[nM + H]^+$ decreased in intensity with increasing alkyl substitution on nitrogen. It may be recalled here that the FAB mass spectrum of **13** showed exclusively the protonated cluster[19]. Increasing the number of substituents on nitrogen also resulted in smaller n values, other factors held constant.

$TsO^-\overset{+}{N}HMe_3$ (40) $TsO^-\overset{+}{N}Et_nH_{4-n}$ (41) $TsO^-\overset{+}{N}Pr_nH_{4-n}$ (42)

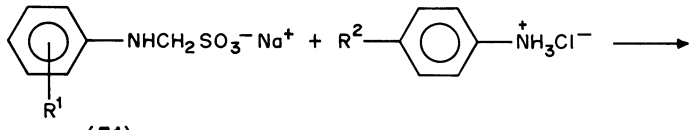
$TsO^-\overset{+}{N}Bu_nH_{4-n}$ (43) $TsO^-\overset{+}{N}(C_6H_{13})H_3$ (44) $TsO^-\overset{+}{N}(c\text{-}C_6H_{11})H_3$ (45)

$TsO^-\overset{+}{N}(CH{=}CHCH_2)_2H_2$ (46) $TsO^-\overset{+}{N}BuHMe_2$ (47) $MeSO_3^-\overset{+}{N}Bu_4$ (48)

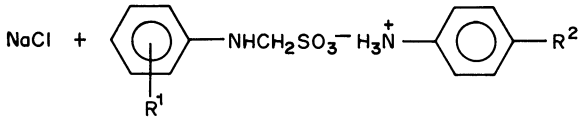
$EtSO_3^-\overset{+}{N}Bu_4$ (49) $CF_3SO_3^-\overset{+}{N}Bu_4$ (50)

The FD mass spectra of the di-n-butylammonium salts of a few naphthalene- and anthraquinonesulfonic acids have been reported[38]. The spectra were dominated by the $[Bu_2NH_2]^+$ ion ($[Cat]^+$). Naphthalene-1-sulfonic acid dibutylammonium salt showed a major $[M + Cat]^+$ ion while more abundant ions were $[M + H]^+$ in the spectrum of naphthalene-2,6-disulfonic acid di-dibutylammonium salt and $[M - Cat + 2H]^+$ in the spectrum of naphthalene-1,3,6-trisulfonic acid tri-dibutylammonium salt.

By mixing sodium anilinomethanesulfonates **51** with anilinium or *p*-toluidinium chloride in equimolar ratio, anilinium or *p*-toluidinium anilinomethanesulfonates **52** were obtained (equation 6)[39]. Despite their thermal instability at temperatures close to their low melting points, conventional EI mass spectra were recorded for compounds **52** and compared with those of compounds **51**.



(51)



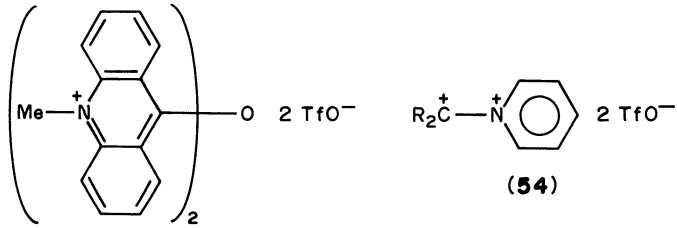
(6)

(52)

R^1 = H, *p*-Me, *p*-MeO, *o*-Cl, *m*-Cl, *p*-Cl, *p*-Br

R^2 = H, Me

Very low basicity and nucleophilicity made the trifluoromethanesulfonate anion (TfO^-) the counterion of choice for labile cationic species as in dication salts **53** and **54**, which were characterized by FD, FAB and ^{252}Cf-Plasma Desorption mass spectrometry[40]. In the FD mass spectrum of **53**, the noteworthy presence of the dication itself ($[D]^{2+}$) was found, giving the base peak, accompanied by a cation triflate cluster $[D{\cdot}OTf]^+$ and fragment ions, involving cleavage at the ether bond.



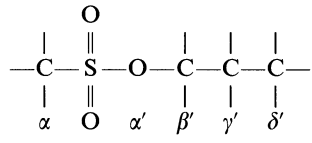
(53) (54)

IV. SULFONIC ESTERS

A. Alkyl and Aryl Esters of Methane- and Trifluoromethanesulfonic Acids

The EI mass spectra of several methyl and ethyl alkanesulfonates have been discussed[41] and reviewed[1]. In a later work[42], Truce and Christensen examined the mass spectra of a series of alkyl methanesulfonates, $MeSO_3R$, focussing on possible rearrangement processes involving the R group. In the discussion of fragmentation processes, the sites involved in bond ruptures are designated as shown in structure **55**, α'-cleavage meaning S—O bond rupture, β'-cleavage C—O bond rupture, etc. Upon EI ionization, the first member of the series, methyl methanesulfonate, in addition to simple α- and α'-cleavages, underwent an α'-cleavage with a hydrogen rearrangement process (equation 7), forming an ion at *m/z* 80. The second member of the series, ethyl methanesulfonate, gave instead a prominent ion at *m/z* 97, ascribed to a β'-cleavage with transfer of two hydrogen atoms (equation 8). The latter fragment ion was found to be a common feature in the mass spectra of linear alkyl methanesulfonates, with R ranging from n-propyl to n-octyl. Deuterium

labelling showed that the hydrogen atoms transferred did not originate from specific sites in the alkyl chain. Secondary alkyl methanesulfonates did not produce ions at *m/z* 80 or *m/z* 97 of noticeable intensity, direct β'-cleavage to yield $[R]^+$ ions becoming far more favorable. All primary esters underwent direct γ'-cleavage, giving rise to ions at *m/z* 109, which shifted to *m/z* 123 in the presence of a β'-methyl branch (equations 9 and 10). A unique fragment ion, which appeared in the mass spectrum of *i*-butyl methanesulfonate at *m/z* 111, was associated to γ'-cleavage with hydrogen rearrangement (equation 11). Cyclopentyl and cyclohexyl methanesulfonates did not show any fragments associated to hydrogen migration; instead they underwent direct β'-cleavage and subsequent fragmentation of the alkyl group.



(55)

$$[MeSO_2OMe]^{+\cdot} \xrightarrow{\sim H} [MeSO_2H]^{+\cdot} + CH_2O \quad (7)$$
m/z 80

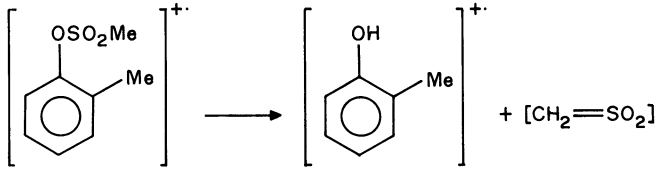
$$[MeSO_2OEt]^{+\cdot} \xrightarrow{\sim 2H} [MeSO_3H_2]^{+} + C_2H_3^{\cdot} \quad (8)$$
m/z 97

$$[MeSO_2OCH_2R]^{+\cdot} \longrightarrow [MeSO_2OCH_2]^{+} + R^{\cdot} \quad (9)$$
m/z 109

$$[MeSO_2OCH(Me)R]^{+\cdot} \longrightarrow [MeSO_2OCHMe]^{+} + R^{\cdot} \quad (10)$$
m/z 123

$$[MeSO_2OCH_2CHMe_2]^{+\cdot} \longrightarrow [MeS(OH)_2OCH_2]^{+} + C_3H_5^{\cdot} \quad (11)$$
m/z 111

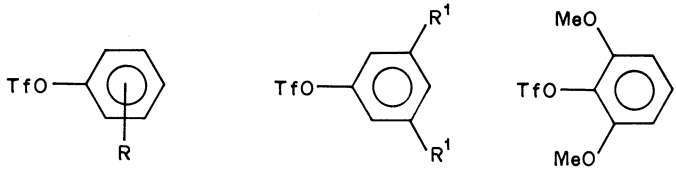
The mass spectra of aryl methanesulfonates were examined[42] with the expectation of observing enhanced intensities for the ions at *m/z* 80 and *m/z* 97, if an *ortho* methyl group were present, e.g. in *o*-tolyl methanesulfonate (**56**). However, neither ions were formed but an intense signal at *m/z* 108 was ascribed to the radical cation of *o*-cresol (equation 12), produced by loss of a neutral sulfene molecule. The ion at *m/z* 108 was the base peak in the mass spectrum of *m*-tolyl methanesulfonate, showing that the presence of a methyl group in the *ortho* position was not essential for its formation. The mass spectrum of **56** was



(12)

(**56**) *m/z* 108

further characterized by a most intense signal at m/z 107, formally due to $[o\text{-}MeC_6H_4O]^+$, and by a weaker peak due to $[M - SO_2]^+$. The latter fragment ions corresponded to the major dissociation pathway in the low-energy (18 eV) mass spectra of aryl trifluoromethanesulfonates **57** and **58**[43], being formed from the molecular ion either by direct S—O bond cleavage or by rearrangement with loss of SO_2 (equation 13).

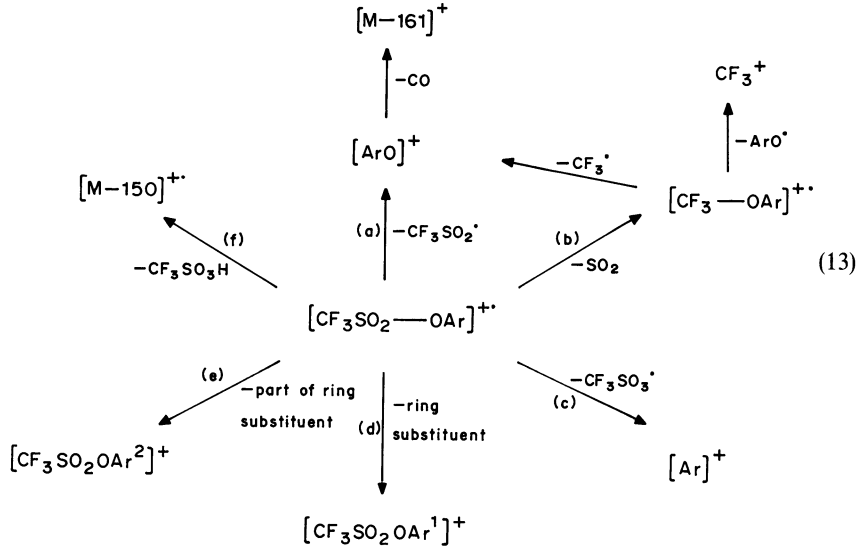


(57) **(58)** **(59)**

R = H, *o*-Me, *m*-Me, *p*-Me, *o*-MeO, *m*-MeO, *p*-MeO, *o*-Cl, *p*-Cl, *m*-Br, *p*-Br, *m*-F, *m*-NH_2, *p*-NH_2, *m*-CN, *p*-CN, *m*-NO_2, *p*-NO_2, *o*-cyclopropyl

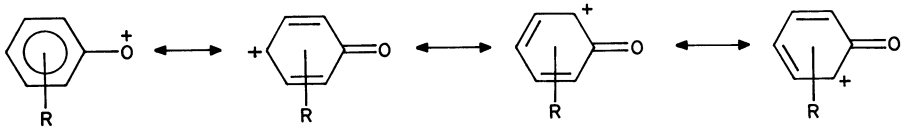
R^1
(**a**) MeO
(**b**) *i*-Pr
(**c**) cyclopropyl
(**d**) methylcyclopropyl

In their paper Derocque and Jochem[43] reported the standard 70 eV mass spectra of compounds **57**–**59**, but discussed the main fragmentation routes, summarized in equation 13, on the basis of low-energy mass spectra, metastable ion analysis and exact mass measurements. In the 18 eV mass spectra, the dissociation pathways (a) and (b) in equation 13 represented nearly the only decomposition modes of the molecular ions of *meta*- and *para*-substituted aryl triflates **57**. Their relative abundancies appeared to depend on the Hammett σ value of the substituent, the intensity of $[ArO]^+$ ions increasing



(13)

with increasing electron-donating ability of the ring substituent. This observation led to the suggestion that the $[ArO]^+$ species retained a cyclic structure, corresponding to aryloxenium ions **60**. However, application of the Hammett relationship to mass spectrometric data, in particular to unimolecular fragmentation patterns, is questionable. Metastable transitions revealed a direct link between the molecular ions of **58b–d** and the fragments corresponding to $[Ar]^+$ ions, which were expected to retain the cyclic structure and whose ease of formation and relative stability have been discussed in terms of 'through bond' stabilization by *meta* electron-donating substituents.

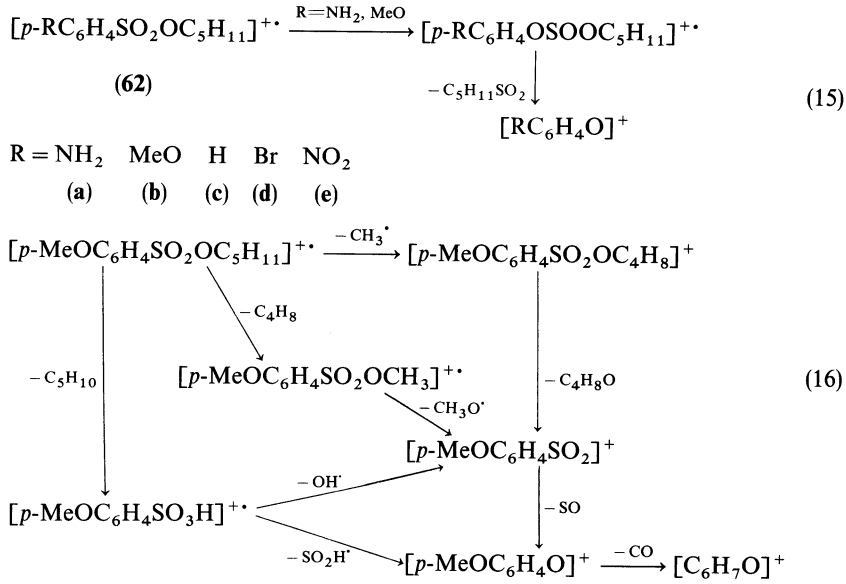


(60)

B. Alkyl and Aryl Esters of Arenesulfonic Acids

Whereas sulfonic esters of n-pentanol showed significant yields of $[M - C_5H_9]^+$ ions, formally corresponding to the protonated sulfonic acid[42], neopentyl arenesulfonates upon EI ionization preferentially underwent elimination of C_4H_7[44,45]. The loss of C_4H_7 from neopentyl *p*-toluenesulfonate (**61**), yielding an ion of the same formula as protonated methyl tosylate, was found to be 30 times more favorable than the loss of C_5H_9 (equation 14). ^{13}C or ^2H labels in the 1 position of the neopentyl group were retained by the $[M - C_4H_7]^+$ ion, whose formation therefore appeared to involve the migration of two hydrogen atoms from the methyl groups with rupture of the labile C—CMe_3 bond. The relative abundance of this ion was greatly reduced by replacement of the *para*-methyl group by either electron-withdrawing or electron-donating substituents, as shown in a comparative study of the mass spectra of neopentyl esters of *para*-substituted benzenesulfonic (**62a–e**) and benzoic acids[45]. The main peaks in the mass spectra of **62a** and **62b** corresponded to $[M - C_5H_{10}]^+$ ions, which underwent further loss of OH and SO_2H, as shown by metastable transitions, thus behaving similarly to the molecular ion of *p*-methoxybenzenesulfonic acid[5]. Distinct $[ArO]^+$ ions also appeared in the mass spectra of **62a** and **62b**. A metastable peak showed a direct link with $[M]^{+\cdot}$, in the case of **62a**, suggesting that an aryl group migration from sulfur to oxygen took place in the molecular ion (equation 15). However, rearranged molecular ions were by no means the only precursors to $[ArO]^+$, as shown by the fragmentation pattern based on the metastable peaks in the mass spectrum of **62b** (equation 16). Whether the $[ArSO_2]^+$ ions, formed by different pathways, had undergone partial or total rearrangement before fragmentation could not be established. For the same ring substituent R, $[M - C_9H_{11}O]^+$ ions were of much smaller relative abundance in the arenesulfonate series than in the benzoate series and apparently derived from a stepwise loss of $CH_3^\cdot$ and C_4H_8O.

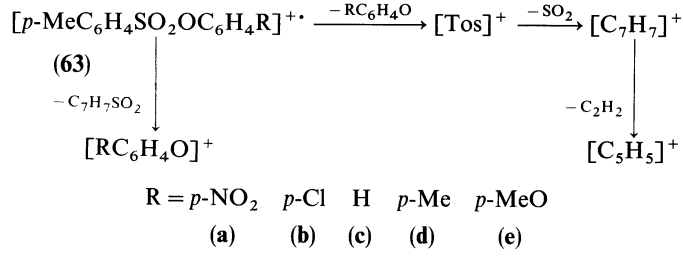
$$[TsOCH_2CMe_3]^{+\cdot} \underset{(61)}{\longrightarrow} \begin{cases} \xrightarrow[(9\%)]{} [TsOCH_3 + H]^+ + C_4H_7^\cdot \\ \xrightarrow[(0.3\%)]{} [TsOH_2]^+ + C_5H_9^\cdot \end{cases} \qquad (14)$$



(15)

(16)

No rearrangement processes appeared to take place in the relatively simple 80 eV mass spectra of aryl tosylates **63a–e**[46], characterized by (a) distinct molecular ions; (b) base peaks at m/z 91, except for **63e** which showed an ion corresponding to $[ArO]^+$ as the most intense peak; (c) fragmentation routes initiated by S—O bond fission to give the $[ArO]^+$ ion, favored by electron-donating substituents (equation 17).



(17)

The mass spectra of arylsulfonylmethyl arenesulfonates and arylsulfonylmethyl trifluoromethanesulfonates have been discussed[47] and reviewed[6]. Their fragmentation patterns were typical of those of the two functionalities, sulfone and sulfonate, plus an additional fragmentation mode, yielding abundant $[M - CH_2O]^{+\cdot}$ ions.

The positive- and negative-ion mass spectra of ethyl benzenesulfonate have been reported[48]. In the positive-ion mode, the parent radical cation either eliminated ethyl radical and neutral SO_2 sequentially or rearranged with loss of SO_2, formally yielding the radical cation of phenol. In the negative-ion mode, the molecular anion underwent loss of C_6H_5 or C_2H_5O.

o- and *p*-toluenesulfonic acids were derivatized to the more volatile ethyl esters, to allow their determination by conventional mass spectrometry[49]. Their mass spectra were dominated by $[C_7H_7]^+$ ions with less intense $[C_5H_5]^+$ and $[M]^{+\cdot}$ ions. The sulfur-containing fragments marked the difference between the two isomers, the most

abundant ions having a *m/z* ratio of 155 from the *para* isomer, and *m/z* 137 and 172 from the *ortho* isomer. The presence of appropriate metastable peaks indicated that several pathways could contribute to the formation of ions at *m/z* 137 from ionized methyl *o*-toluenesulfonate[3]:

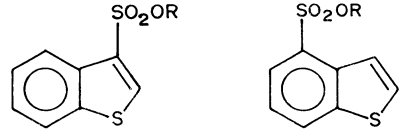
$$\text{(a) } [M]^{+\cdot} \xrightarrow{-MeO^{\cdot}} [M - OMe]^{+} \xrightarrow{-H_2O} m/z\ 137;$$

$$\text{(b) } [M]^{+\cdot} \xrightarrow{-MeOH} [M - MeOH]^{+\cdot} \xrightarrow{-OH^{\cdot}} m/z\ 137;$$

$$\text{(c) } [M]^{+\cdot} \xrightarrow{-OH^{\cdot}} [M - OH]^{+} \xrightarrow{-MeOH} m/z\ 137;$$

$$\text{(d) } [M]^{+\cdot} \xrightarrow{-H_2O} [M - H_2O]^{+\cdot} \xrightarrow{-MeO^{\cdot}} m/z\ 137.$$

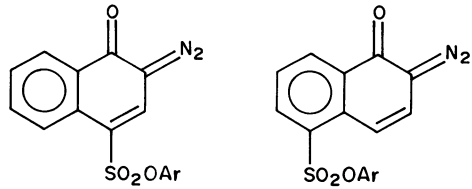
The following arenesulfonic acids were converted to methyl esters, to be examined by standard EI mass spectrometry[50]: *p*-dodecylbenzenesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-1,3,5-trisulfonic acid, 2-chloroaniline-4-sulfonic acid, 3,4-dichloroaniline-2-sulfonic acid, anthraquinone-1-sulfonic acid, anthraquinone-1,5-disulfonic acid, 1,4-dihydroxyanthraquinone-2-sulfonic acid and 1,2-dihydroxyanthraquinone-3-sulfonic acid. The mass spectra of their methyl esters showed the molecular ions and charged fragment ions from the cleavage of the sulfonate group(s) either at the Ar—S bond or at the S—OMe bond. Similarly, the mass spectra of heptafluorobutyl sulfonates **64a** and **64b**[51] were characterized by: (a) a prominent molecular ion, base peak for **64a**; (b) $[M - SO_3R]^+$ ions, base peak for **64b**; (c) $[M - OR]^+$ ions; (d) $[CF_3]^+$ ions at *m/z* 69.



R=$CH_2CF_2CF_2CF_3$ **(64a)** **(64b)**

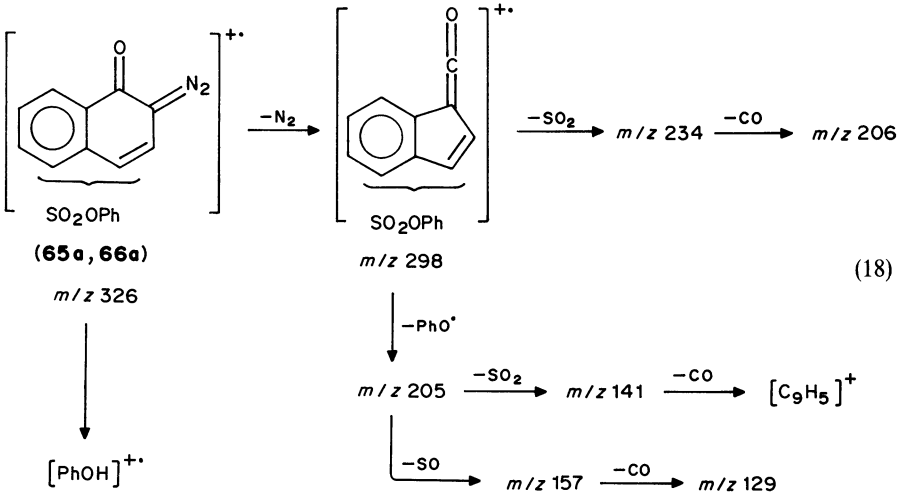
The EI, positive and negative CI and FAB mass spectra of compounds **65** and **66** have been studied[52]. Their EI-induced decomposition closely paralleled their photo-induced decomposition, in terms of the tendency to lose N_2 to form, presumably, a ketene species by Wolff rearrangement. The main peaks in the EI mass spectra of **65a** and **66a** have been rationalized within the framework of equation 18, where many transitions were associated to metastables and the composition of all ions was verified by high-resolution mass measurements. The molecular ions of **65a** and **66a** gave well-defined peaks and underwent loss of N_2, forming ions at *m/z* 298, which were ascribed an indenoketene structure, in analogy to the product from the photolytic Wolff rearrangement. The ion at *m/z* 298 was much more abundant in the mass spectrum of **65a** than in that of **66a**. In addition to $[M - N_2]^+$ ions, the mass spectra of **65** and **66** showed ions formally corresponding to $[M - N_2 + 2H]^+$. The latter were found to derive from a reduction process initiated on the surface of the direct insertion probe, as indicated by deuterium incorporation when the active sites on the tip surface were saturated with deuteriated water. The FAB mass spectra of **65** and **66**, studied in both glycerol and 3-nitrobenzyl alcohol, showed $[M + H]^+$ and $[M + H - N_2]^+$ ions. Again, reduction of

the parent molecule was implied in the formation of $[M + 2H - N_2]^+$ and $[M + 3H - N_2]^+$ ions.



(65) (66)

(a) Ar = Ph
(b) Ar = *o*-$PhCOC_6H_4$
(c) Ar = *m*-$PhCOC_6H_4$
(d) Ar = *p*-$PhCOC_6H_4$

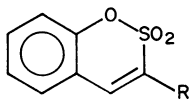


(18)

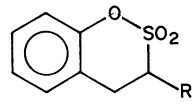
C. Cyclic Esters Bearing the Sulfonic Function in a Heterocyclic Ring

Several benzo-anellated cyclic sulfonates (**67**–**71**) were synthesized and characterized by their 70 eV mass spectra[53]. Compounds **67** and **68** typically underwent loss of SO_2 from the molecular ion, to give $[M - 64]^+$ ions, with a corresponding metastable peak. The other features of the spectrum closely resembled the fragmentation pattern of the related benzofuran, including metastable transitions, a reasonable finding since the $[M - SO_2]^+$ ion formally corresponded to the radical cation of the benzofuran. The fragmentation scheme of **67a**, shown in equation 19, is a representative example. The sultones **70a** and **70b** showed a similar mass spectral behavior, in that initial loss of SO_2 gave rise to fragmentation patterns comparable to those of the corresponding benzofuranones. A

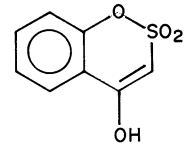
competing fragmentation route involved elimination of a sulfene moiety (CH_2SO_2) as shown in equation 20 for compound **70a**.



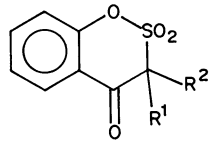
(67) (**a**) R=H
(**b**) R=Me
(**c**) R=Br



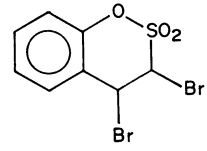
(68) (**a**) R=H
(**b**) R=Me



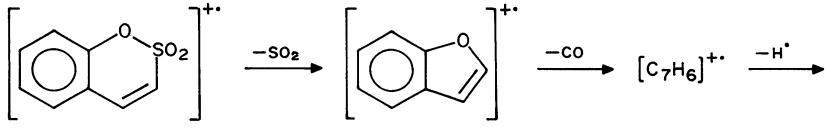
(69)



(70) (**a**) $R^1=R^2=H$
(**b**) $R^1=H, R^2=Me$
(**c**) $R^1=Me, R^2=Br$



(71)



(67a)

m/z 182 (82%)

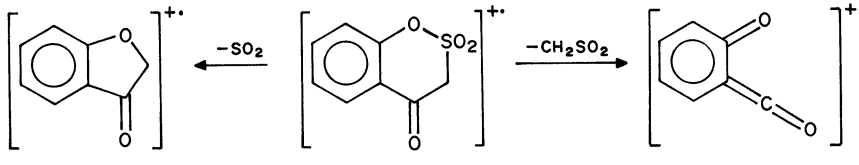
m/z 118 (100%)

m/z 90 (96%)

$$[C_7H_5]^+ \xrightarrow{-C_2H_2} [C_5H_3]^+ \qquad (19)$$

m/z 89 (77%)

m/z 63 (40%)



(20)

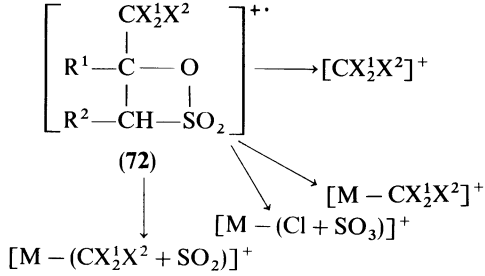
(70a)

m/z 134 (18%)

m/z 198 (71%)

m/z 120 (100%)

The mass spectra of trihalomethyl β-sultones **72** have been examined and compared with those of isomeric vinyl methanesulfonates[54]. Molecular ions were absent in all spectra. A preferential fragmentation site did not involve the four-membered 1,2-oxathietane-2,2-dioxide ring, but rather the $C-CX^1_2X^2$ bond, yielding trihalomethyl cations $[CX^1_2X^2]^+$ and the $[M-CX^1_2X^2]^+$ ions. The former ions represented the base peak in all cases, except for compound **72c**. The latter ions could eliminate neutral SO_2 leading to prominent fragments of the formula $[M-(CX^1_2X^2+SO_2)]^+$, probably formed in a stepwise process. In the case of compound **72f**, both $[M-(CCl_2F+SO_2)]^+$ and $[M-(CClF_2+SO_2)]^+$ ions were observed. A further major fragmentation mode involved loss of (halogen + SO_3) from the molecular ion, at least partly in a concerted fashion, as indicated by the appropriate metastable peak. Thus, in addition to $[M-(Cl+SO_3)]^+$ ions, which were present in the mass spectra of all compounds examined, compound **72b** gave $[M-(Br+SO_3)]^+$ ions and compounds **72d–f** gave $[M-(F+SO_3)]^+$ ions. The main fragmentation routes of β-sultones **72**, summarized in equation 21, did not share many features with those of isomeric vinyl methanesulfonates.



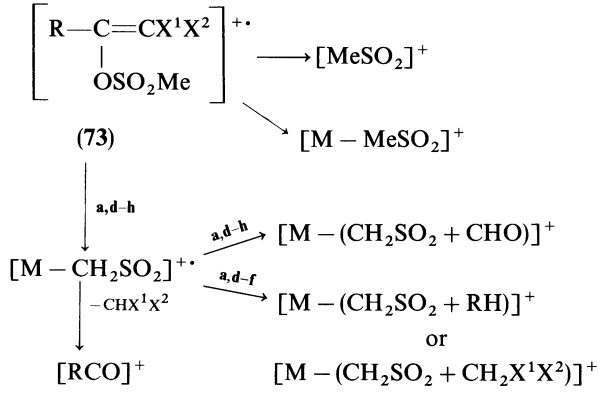
(21)

	R^1	R^2	X^1	X^2
(a)	H	H	Cl	Cl
(b)	H	Br	Cl	Cl
(c)	H	Me	Cl	Cl
(d)	CF_2Cl	H	F	Cl
(e)	CCl_2F	H	Cl	F
(f)	CF_2Cl	H	Cl	F

D. Vinyl Methanesulfonates

The 80 eV mass spectra of halogenated vinyl methanesulfonates **73a–h** showed distinct molecular ions, although their intensity was low for fluorine-containing compounds[55]. Their fragmentation pattern, summarized in equation 22, was characterized by S—O bond cleavage, to give $[MeSO_2]^+$ and $[M-MeSO_2]^+$ ions. The methylsulfonyl cation $[MeSO_2]^+$ was the base peak for all compounds examined with two exceptions. Compounds **73d** and **73g** showed a base peak at *m/z* 43 and *m/z* 105, respectively, corresponding to $[RCO]^+$ ions, i.e. acetylium (R = Me) and benzoylium (R = Ph) ions. The $[RCO]^+$ ions were proposed to derive from a stepwise process, involving loss of a neutral sulfene molecule from the molecular ion, forming $[M-CH_2SO_2]^+$ ions, which were observed from all chlorine-containing compounds, followed by loss of CHX^1X^2. Loss of CH_2SO_2 could alternatively be followed by elimination of chloromethanes ($CH_2X^1X^2$) or RH or CHO. The proposed fragmentation routes were purely speculative, since they

even lack the support of metastable transitions. Characteristic fragments of alkyl methanesulfonates[42] at *m/z* 80 and *m/z* 97 were not significant in the mass spectra of **73a–h**.



(22)

	R	X^1	X^2
(a)	CCl_3	H	H
(b)	CF_3	H	H
(c)	CF_3CF_2	H	Me
(d)	Me	Cl	Cl
(e)	CH_2Cl	H	Cl
(f)	$CHCl_2$	Cl	Cl
(g)	Ph	Cl	Cl
(h)	H	Cl	Cl

E. Sulfonic Esters of Polyhydroxy Compounds

Pomonis and Nelson[56] investigated the EI mass spectra of polymethylene glycol dimethanesulfonates **74**. None of them provided molecular ions. Common ions in the mass spectra of **74** are shown in equation 23. The fragment ion at *m/z* 109 shifted to *m/z* 123 ($[MeSO_3CHMe]^+$) in the mass spectrum of **75**, while the ion at *m/z* 111 showed an increased intensity in the mass spectrum of **76**, due to the formation of $[MeSO_3CD_2]^+$. The mass spectra of **74–76** displayed a few other ions, whose formation involved some kind of a rearrangement process. A well-defined peak at *m/z* 175, common to all compounds examined except **74a**, corresponded to the elemental composition of $C_2H_7O_5S_2$ and when formed from **76** did not incorporate deuterium. Hence, it was traced to migration of one methanesulfonate group to the second one, yielding protonated methanesulfonic acid anhydride. The presence of such a compound as pyrolytic degradation product could not be excluded, however. The intensities of ions of the general formula $[(CH_2)_{n-1}CH]^+$ and $[(CH_2)_{n-1}CHO]^+$ depended on *n* and on the presence of methyl branching. The origin of the ion at *m/z* 97 in the mass spectra of **74b–d** and **75** was attributed to a nonspecific transfer of two hydrogen atoms together with a C—O bond rupture leading to protonated methanesulfonic acid, in agreement with the reports of Truce and Christensen[42]. High-resolution measurements assigned the formula $[C_2H_7O_3S]^+$ in the mass spectra of **74–76**, with the exception of **74a**, to the ion at *m/z* 111.

It was suggested to involve C—O bond cleavage with migration of a hydrogen atom from an inner methylene group and of a S-methyl group from one of the methanesulfonate groups to the oxygens of the second, to form protonated methyl methanesulfonate.

$MeSO_2O(CH_2)_nOSO_2Me$ (74)

n	2	3	4	5	9
	(a)	(b)	(c)	(d)	(e)

$MeSO_2OCH(CH_2)_2CHOSO_2Me$ (75)

$MeSO_2OCD_2(CH_2)_2CD_2OSO_2Me$ (76)

$[MeSO_2O(CH_2)_nOSO_2Me]^{+\cdot}$ → $[MeSO_2]^+$ *m/z* 79; $[MeSO_2OCH_2]^+$ *m/z* 109; $[Me]^+$ *m/z* 15 (23)

Buchs and coworkers[57] have investigated the possible routes leading formally to ionized and protonated *p*-toluenesulfonic acid in the mass spectrum of the ditosylate derivative of 1,4-butanediol **77a**. When the selectively deuteriated compounds **77b–d** were examined, the observed mass shifts were not compatible with simple hydrogen(s) migration from the methylene chain to the tosylate group. Rather, the mass shifts in the spectra of the labelled compounds were rationalized in terms of multiple pathways, shown in equations 24 and 25, supported by metastable transitions and by an extremely weak signal at *m/z* 326, corresponding to the proposed intermediate, *p*-toluenesulfonic anhydride (**78**).

$TsO(CH_2)_4OTs$ (77a) $TsOCD_2(CH_2)_2CD_2OTs$ (77b) $TsOCH_2(CD_2)_2CH_2OTs$ (77c)

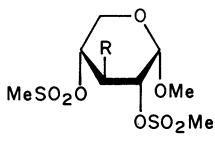
$TsO(CD_2)_4OTs$ (77d)

$[TsO(CH_2)_4OTs]^{+\cdot}$ → $[TsOH]^{+\cdot}$; $[TsO(CH_2)_4]^+$ → $[C_7H_6SO_2O(CH_2)_4]^{+\cdot}$; $[TsOTs]^{+\cdot}$ → $[TsOH]^{+\cdot}$; $[C_7H_6SO_3H_2]^{+\cdot}$ (24)

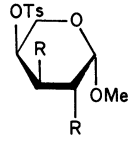
(78)

$[TsO(CH_2)_4OTs]^{+\cdot}$ → $[TsOH_2]^+$; $[TsO(CH_2)_4]^+$ (25)

The mass spectra of some methanesulfonic and *p*-toluenesulfonic esters of pentose derivatives **79** and **80** have been reported, with fragmentation schemes based on metastable transitions[58]. Compounds **79a–d** exhibited weak molecular ions and a base peak at *m/z* 79, due to $[MeSO_2]^+$. A distinct peak at *m/z* 97 corresponded to $[MeSO_3H_2]^+$. Alternatively, the methanesulfonyl group was involved in the elimination of neutral moieties, i.e. CH_2SO_2, $MeSO_3H$ and $MeSO_2OSO_2Me$, in complex fragmentation series. Compound **80a** underwent thermal detosylation even at the lowest probe temperature. Compounds **80b** and **80c** showed weak or no molecular ions and pronounced signals derived from the tosylate group at *m/z* 155 and *m/z* 91. An interesting ion at *m/z* 215 in the mass spectrum of **80b** could be ascribed to a protonated mixed anhydride $[TsOAc + H]^+$. The fragmentation pattern of **80c** was dominated by fragmentations involving the benzoyl group.

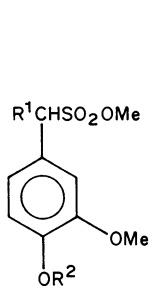


(**79**) (**a**) R = OSO_2Me
(**b**) R = OAc
(**c**) R = OH
(**d**) R = OD



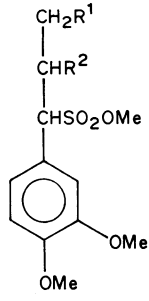
(**80**) (**a**) R = OH
(**b**) R = OAc
(**c**) R = OCOPh

McCarthy and coworkers studied the mass spectra of eight monomeric (**81–84**) and seven dimeric lignin-related methanesulfonates, which were prepared as acetylated and methylated derivatives[59]. Molecular ions were of low abundance and the sulfonate group cleaved predominantly at the C—S bond. Ions corresponding to $[M - (MeSO_3 + CH_2CO)]^+$ gave rise to the most abundant peak for those compounds bearing an acetoxy substituent on the aryl ring.



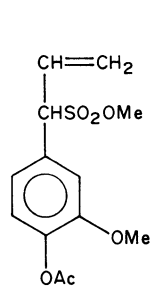
(**81**)

(**a**) (**b**) (**c**) (**d**)
R^1 = H Me Et Et
R^2 = Ac Ac Ac Me

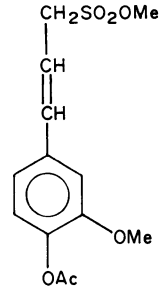


(**82**)

(**a**) $R^1 = OSO_2Me$, R^2 = H
(**b**) R^1 = H, R^2 = OAc



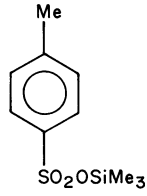
(**83**)



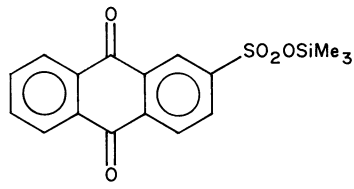
(**84**)

F. Trimethylsilyl and Trimethylgermyl Sulfonates

Trimethylsilylation is a typical procedure to increase the volatility of polar compounds and allow their analysis by standard GLC-MS. Eagles and Knowles[60] have tested their trimethylsilylation method in the preparation of trimethylsilyl aromatic and aliphatic sulfonates **85–89**. The molecular ion was weak, absent in the case of **87**, but the determination of the molecular weight could be aided by the usually most abundant $[M - Me]^+$ ion, a typical fragment from trimethylsilyl derivatives. In the case of **85** and **86**, further fragmentation of $[M - Me]^+$ involved loss of SO_2 and SO_3. In the fragmentation pattern of compounds **88** and **89**, the sulfonate moiety cleaved at the C—S bond, with or without hydrogen migration.



(85)



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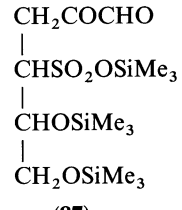

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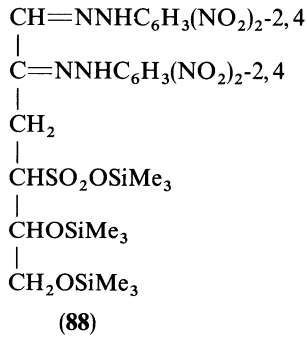
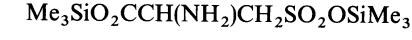


(88)



(89)

Stokke and Helland[61] gave the ten ion listings for the EI mass spectra of the (poly)trimethylsilyl derivatives of a few miscellaneous sulfonic acids. Their common feature was a dominating $[M - Me]^+$ fragment, representing the base peak for many of them.

Trimethylgermyl methanesulfonate (**90**) and trifluoromethanesulfonate (**91**) have been

(90)

(91)

characterized by their mass spectrum and shown to be monomeric compounds[62]. For both species the molecular ion was missing. Fragment ions containing germanium appeared as multiplets, due to the natural abundance isotopic distribution of the element.

The $[Me_3Ge]^+$ ion, prominent in the mass spectrum of **90**, was the strongest from **91**. $[M-15]^+$ ions were more pronounced in the mass spectrum of **90**, but their origin was ascribed mainly to the Me_3Ge group. Weak signals corresponded to $[Me_3GeOSO]^+$ ions arising from Me or CF_3 migration from sulfur to oxygen, followed by S—O bond cleavage, as found for alkyl alkanesulfonates[41]. The presence of small amounts of $[Me_2GeF]^+$ and $[GeF]^+$ ions was indicated in the case of **91**, suggesting fluorine transfer to germanium.

G. Thiosulfonic Esters

Thiosulfonates may be thermally labile in the sample introduction system of a mass spectrometer, so that care must be exercised to ascertain the ionic, rather than the thermal, origin of fragment ions in their mass spectra.

Block and coworkers[63] investigated the fragmentation pathways of alkyl alkanethiosulfonates, with the aid of selective deuteriation, metastable peaks and exact mass determinations. The mass spectra of various symmetrical (**92b, e–i**) and unsymmetrical (**93d–f**) alkyl alkanethiosulfonates have also been reported[64]. The mass spectral fragmentation pattern of ethyl methanethiosulfonate (**93a**), shown in equation 26, implied a number of rearrangement processes[63a]. The formation of similar amounts of ions at *m/z* 63, $[MeSO]^+$, and at *m/z* 77, $[EtSO]^+$, was indicative of an isomerization of ionized **93a** to a sulfenic–sulfinic mixed anhydride (**94**) or α-disulfoxide, MeS(O)S(O)Et, structure prior to fragmentation.

RSO_2SR

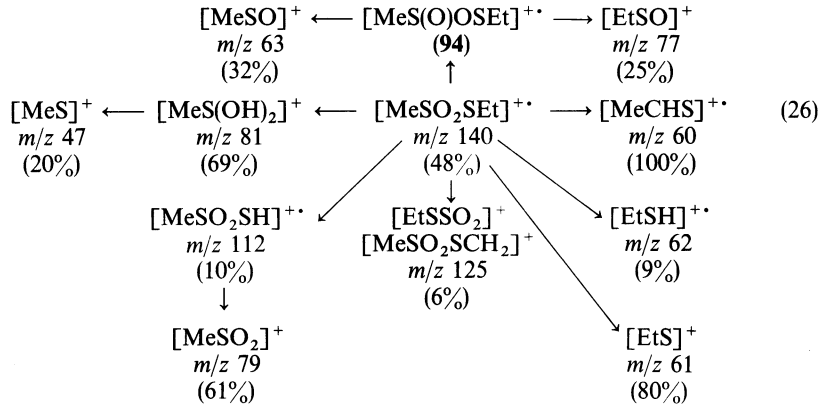
(**92**)

R =	Me	Et	CH_3CD_2	CD_3CH_2	*n*-Pr	*i*-Pr	*s*-Bu	*i*-Bu	*t*-Bu	$PhCH_2$
	(**a**)	(**b**)	(**c**)	(**d**)	(**e**)	(**f**)	(**g**)	(**h**)	(**i**)	(**j**)

$R^1SO_2SR^2$

(**93**)

R^1 =	Me	Me	Et	*i*-Pr	*i*-Pr	*i*-Pr
R^2 =	Et	CD_3	Me	*n*-Bu	*s*-Bu	*i*-Bu
	(**a**)	(**b**)	(**c**)	(**d**)	(**e**)	(**f**)



(26)

Fragment ions corresponding to $[MeSO]^+$ and $[CD_3SO]^+$ were also found for **93b**, but ions corresponding to this isomerization process were not significant from the higher homologues. A double hydrogen rearrangement led to $[RS(OH)_2]^+$ ions, formally protonated alkanesulfinic acid, which were significantly intense in the mass spectra of compounds **92a** and **93a** at *m/z* 81, compound **93b** at *m/z* 83 and compounds **92b** and **93c** at *m/z* 95. The two transferred hydrogens were found to originate preferentially from the carbon atom adjacent to sulfur, in either a concerted or a stepwise process, when specifically deuteriated compounds **92c** and **92d** were examined. The elimination of SO_2 from the molecular ion of **92j** yielded an ion corresponding to $[(PhCH_2)_2S]^{+\bullet}$, as confirmed by a metastable peak, but this process was not relevant for other thiosulfonates. Ions corresponding to the ionized thiol, $[RSH]^+$ or $[R^2SH]^+$, base peak for **92b**, could also arise from pyrolytic contribution. In the case of higher homologues **92e–i** and **93d–f** the mass spectrum was dominated by the alkyl cation $[R]^+$ or $[R^2]^+$ and fragments derived therefrom[64].

Corina and coworkers[65] gave the EI mass spectra of two fluorinated ethyl methanethiosulfonates (**95** and **96**), which showed distinct molecular ions and preferential S—S bond cleavage, in analogy with unsubstituted **93a**. However, the extent of fluorine substitution affected the site of charge retention, so that base peaks at *m/z* 78, $[CH_2FCHS]^+$, and *m/z* 79, $[MeSO_2]^+$, were found for **95** and **96**, respectively.

$MeSO_2—SCH_2CH_2F$ (**95**) $\qquad$ $MeSO_2—SCH_2CF_3$ (**96**)

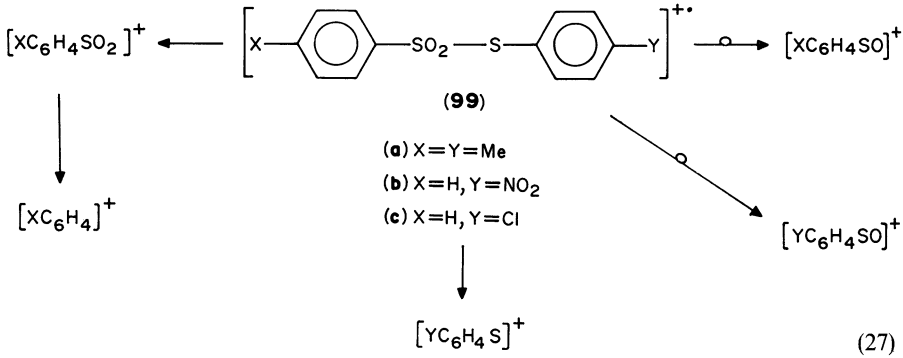
Freeman and Angeletakis[66] reported the EI and CI mass spectra and tentative fragmentation patterns of thiosulfonates **92j**, **97** and **98**. With the exception of **97a** and **98c**, molecular ions were of low intensity in the El mass spectra. However, CI (*i*-C_4H_{10}) of **97** and **98** yielded abundant $[M + H]^+$ ions as base peaks, with the exception of **98b**, whose base peak at *m/z* 201 was ascribed to loss of SO_2 from $[M + H]^+$. Compound **98c** was the unsubstituted parent of aryl arenethiosulfonates **99**, investigated by Oae and coworkers[67]. The El mass spectra of **99**, whose major fragmentation routes are summarized in equation 27, were characterized by the following features: (a) fairly intense molecular ions; (b) strong ions due to direct cleavage of the S—S bond; (c) ions whose formation implied a formal oxygen migration process from the sulfone sulfur to the thiol sulfur.

$R—SO_2—SPh$ (**97**)

(**a**) R = neo-C_5H_{11}
(**b**) R = $PhCH_2$

$Ph—SO_2—SR$ (**98**)

(**a**) R = neo-C_5H_{11}
(**b**) R = $PhCH_2$
(**c**) R = Ph



(27)

The mass spectra of alkyl methanethiosulfonates carrying various functionalities (**100–102**) have been studied by Corina and coworkers[65,68]. The fragmentation of ionized polymethylene dimethanethiosulfonates **100** was characterized by S—S bond cleavage with charge retention on the thiol fragment. The *trans*-sulfonylation process, which led to formal protonated methanesulfonic acid anhydride from the oxygen analogues[56], was not observed, with the possible exception of the molecule with $n = 8$.

$MeSO_2\text{-}S(CH_2)_nS\text{-}SO_2Me$ (**100**), $n = 5–12$

$MeSO_2\text{-}S(CH_2)_nR$ (**101**)

$MeSO_2\text{-}SCH_2CO(CH_2)_nR$ (**102**)

V. SULFONIC DERIVATIVES WITH N—S BONDS

A. Sulfonamides

1. *Positive-ion mass spectra of sulfonamides*

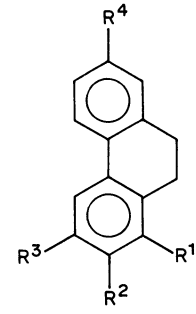
The mass spectral behavior of arenesulfonamides has been extensively studied[1,3,69–73].

The EI mass spectra of various sulfonamides (**103a–g, 104**) have been investigated, revealing, in some cases, the occurrence of skeletal rearrangement processes[69]. Based on

$R^1C_6H_4SO_2NHR^2$ (**103**)

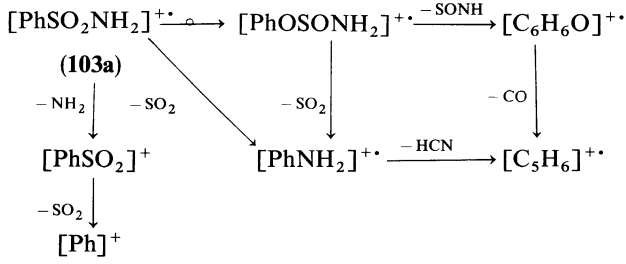
	R^1	R^2
(a)	H	H
(b)	*p*-Me	H
(c)	H	n-Bu
(d)	*p*-Me	n-Bu
(e)	*p*-Me	*t*-Bu
(f)	H	*o*-MeC_6H_4
(g)	H	$PhSO_2$
(h)	*o*-Me	H
(i)	*o*-Me	Ph
(j)	*p*-Me	Me
(k)	*p*-Me	Et
(l)	*p*-Me	n-Pr
(m)	*p*-Me	cyclo-C_6H_{11}
(n)	*p*-Me	Ph

	R^1	R^2	R^3	R^4
(a)	H	$MeSO_2NH$	H	H
(b)	H	TosNH	H	H
(c)	H	$MeSO_2NH$	NO_2	H
(d)	H	$MeSO_2NH$	H	NO_2
(e)	NO_2	TosNH	H	H
(f)	H	TosNH	NO_2	H
(g)	H	TosNH	H	NO_2



(**104**)

high-resolution measurements and the presence of metastable ions, a fragmentation pattern for the parent, unsubstituted benzenesulfonamide **103a** could be drawn, as in equation 28. Thus, the mass spectrum of benzenesulfonamide was characterized by (a) direct bond cleavages, with sequential loss of NH_2 and SO_2, which yielded the base peak at *m/z* 77, and (b) fragmentations with rearrangements, implied in the eliminations of SO_2 and SONH from the molecular ion. A 1,2-phenyl migration from sulfur to oxygen in the radical cation of **103a** was postulated, to account for the latter processes. The same behavior was shown by *p*-toluenesulfonamide, while an *ortho* effect was discernible in the fragmentation pattern of *o*-toluenesulfonamide **103h**[3]. In fact, at variance with the *para* isomer, loss of NH_3, rather than NH_2, occurred, with the transferred hydrogen coming exclusively from the methyl group, without any prior randomization among amino, methyl and ring hydrogens. The resulting $[M - NH_3]^{+\cdot}$ ion then eliminated OH, yielding an ion at *m/z* 137.

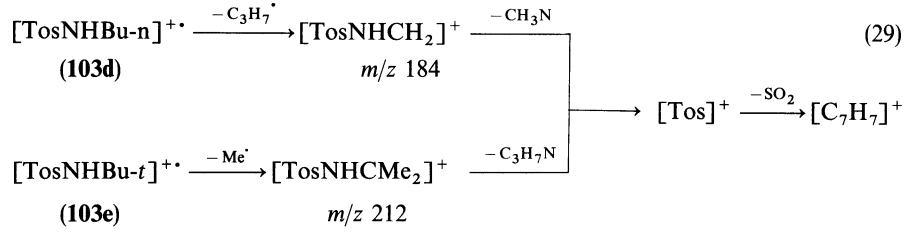


(28)

The fragmentation of *N*-alkyl and *N,N*-dialkyl tosylamides **103d, 103e**[69], **103k, 103l**, and **105b–f**[70] was characterized by '*β*-cleavage' to nitrogen, with loss of the larger alkyl group being favored. The two isomeric *N*-butyl tosylamides **103d** and **103e** could thus be distinguished, because of their different fragmentation patterns, as shown in equation 29[69]. The simplest members of this series, i.e. **103j** and **105a**, could not fragment by '*β*-cleavage', but underwent only N—S bond fission, with formation of major $[Tos]^+$ ions and minor $[CH_4N]^+$ or $[C_2H_6N]^+$ ions[70].

$TosNR^1R^2$
(105)

	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
R^1	Me	Me	Et	Me	Me	Me	Me	Et
R^2	Me	Et	Et	n-Pr	*i*-Pr	n-Bu	Ph	Ph



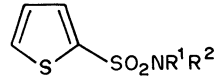
(29)

Arenesulfonamides bearing *N*-aryl substituent(s) showed in their mass spectra: (a) abundant molecular ions; (b) relatively minor fragments involving rearrangement, at $[M - 64]^+$ (loss of SO_2) and/or at $[M - 65]^+$ (loss of HSO_2); (c) predominant fragments

due to direct cleavage of the N—S bond, with the charge preferentially retained on either the tosyl or the amine moiety depending on substitution. For example, in the fragmentation of the molecular ion of **103f**, the nitrogen-containing fragment exclusively retained the charge[69], while the mass spectra of **103n**, **105g** and **105h** showed also substantial $[Tos]^+$ ions[70]. Basically the same behavior was exhibited by dihydrophenanthrene sulfonamides **104**. The presence of *ortho* effects emerged from comparison of the mass spectra of isomers **104e–g**[69].

Aftalion and Proctor[71] examined the mass spectra of several tosylamides, derived from cyclic and aromatic amines, in the attempt to draw some generalizations on the electronic or conformational requirements which rendered the molecular ion prone to loss of SO_2.

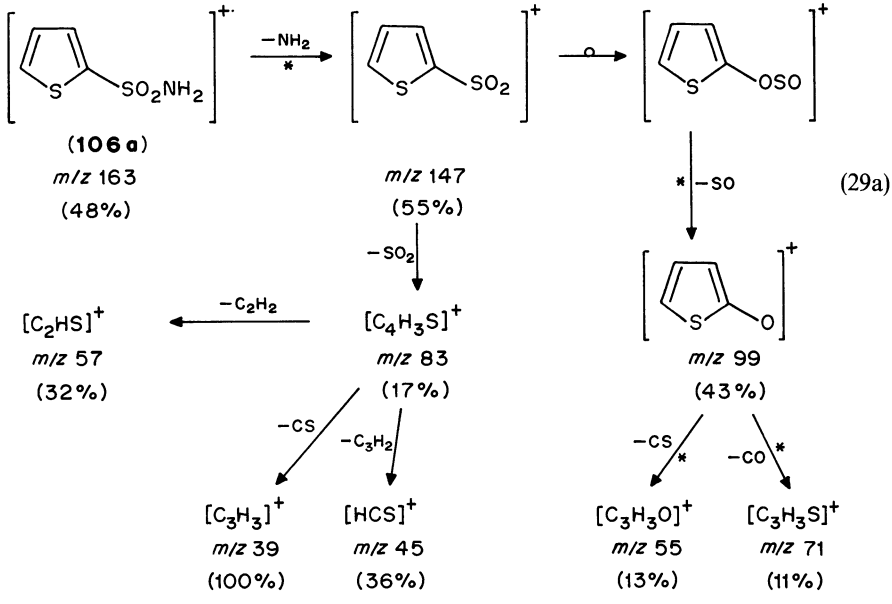
The fragmentation routes of 2-thiophenesulfonamide (**106**), *N*-cyclohexyl-2-thiophenesulfonamide (**107**) and *N*-methyl-*N*-phenyl-2-thiophenesulfonamide (**108**) have been examined at both 20 eV and 70 eV ionizing electron energy[74]. Equation (29a) shows the proposed fragmentation pattern of **106** with the observed metastable transitions and ion abundancies, normalized to the base peak at 70 eV. The molecular ion of **107** cleaved at the N—S bond, forming $[C_6H_{11}NH]^+$ ions, and at the cyclohexyl group, yielding $[M-43]^+$ ions. In this case, the thiophenesulfonyl cation could originate either from N—S bond cleavage or by further fragmentation of $[M-43]^+$ ions, as suggested by the appropriate metastable peak. In the 70 eV mass spectrum of **108**, the amine moiety $[PhNMe]^+$ corresponded to the base peak, while a prominent peak corresponding to $[M-SO_2]^+$ ions became the most intense at 20 eV.



(**106**) $R^1 = R^2 = H$

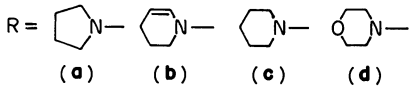
(**107**) $R^1 = H$, $R^2 = c\text{-}C_6H_{11}$

(**108**) $R^1 = Me$, $R^2 = Ph$

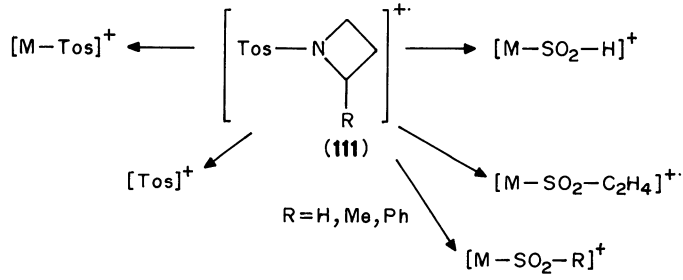


The mass spectra of sulfonamides, whose amido nitrogen pertains to an aliphatic cycle, have been investigated both in the EI[70,71,75,76] and CI[77] modes.

The mass spectra of the tosyl derivatives of cyclic amines (**109, 110**) were characterized by intense molecular ions[70], base peaks corresponding to $[M - Tos]^+$ and abundant fragments due to the tosyl group at *m/z* 155, *m/z* 91 and *m/z* 65. Fragmentation of the amine moiety, prior to N—S bond fission, was not significant, with the exception of **109a** and **109c** which yielded abundant $[M - 1]^+$ ions.



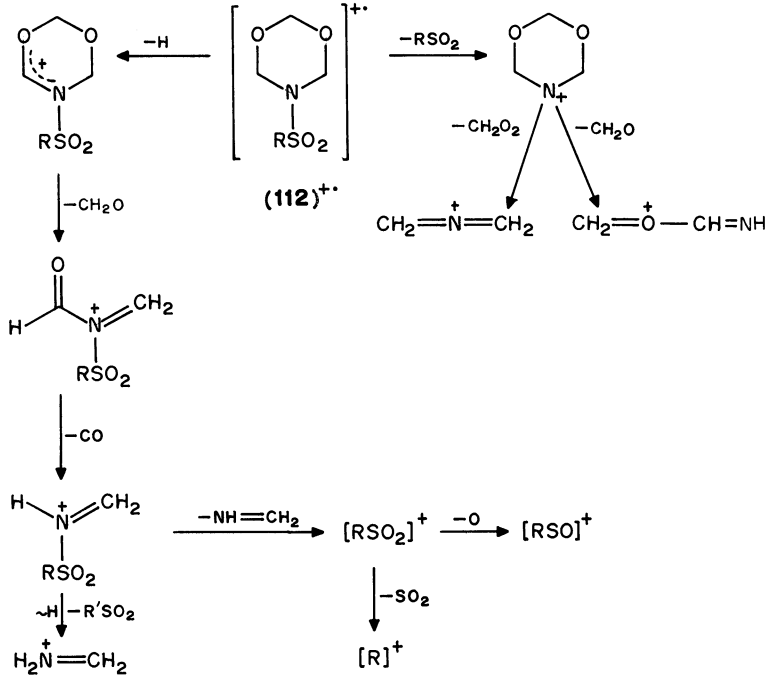
In the mass spectra of tosylated azetidines **111**, the main fragmentation at the N—S bond was accompanied by cycle fragmentations, involving skeletal rearrangements with SO_2 expulsion, as shown in equation 30[75]. The mass spectrum of *N*-methanesulfonyl azetidine has been compared with that of *N,N*-dimethyl methanesulfonamide, both displaying a methyl cleavage process from the molecular ion, in addition to the usual N—S fission[75].



(30)

N—S bond rupture was found to be competitive with loss of a hydrogen atom from the weak molecular ions of *N*-alkanesulfonyl- and *N*-arenesulfonyl-dihydro-1,3,5-dioxazines **112**[76]. Equation 31 summarizes the major common fragmentation paths, with postulated ion structures, as emerged from the occurrence of metastable ions, high-resolution mass measurements and deuterium labelling.

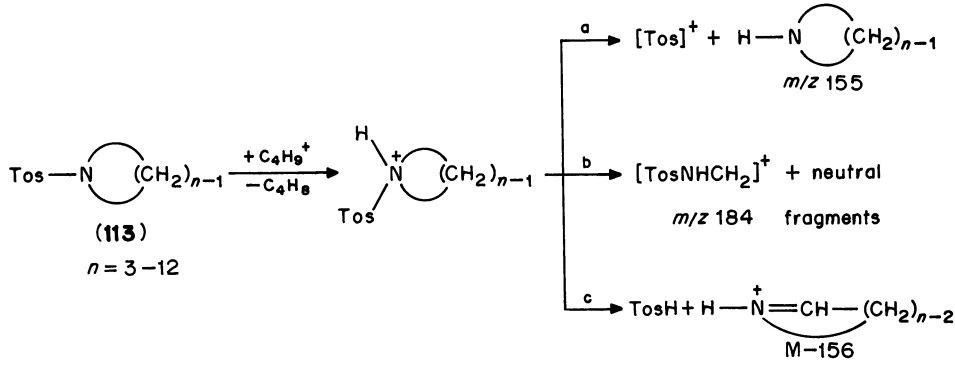
Little fragmentation characterized the CI spectra of *N*-tosylazacycloalkanes **113**, with isobutane as reactant gas[77]. The *t*-butyl cation thus ensured mild protonation of **113**, with formation of $[M + H]^+$ ions of low excess internal energy, whose unimolecular decompositions were observed in the 1st and 2nd field free regions of a double focusing mass spectrometer and compared with those of protonated open-chain *p*-toluenesulfonamides. $[M + H]^+$ ions decomposed along three main pathways (equation 32), common to all ring sizes: (a) N—S bond cleavage, forming $[Tos]^+$ ions and neutral amines; (b) ring fission, to give a common peak at *m/z* 184, corresponding to $[TosNHCH_2]^+$; (c) elimination of the constituents of toluenesulfinic acid. Several pieces of evidence pointed to a nitrogen-protonated $[M + H]^+$ ions, retaining the aza-ring structure; among them were the one



(31)

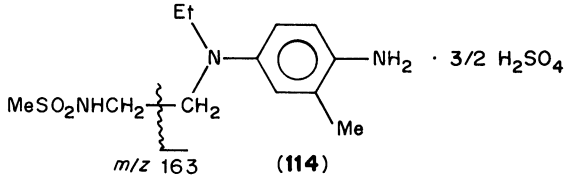
R = Me, Et, n-C_5H_{11}, $PhCH_2$, Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *m*-$O_2NC_6H_4$, *p*-$AcNHC_6H_4$, *p*-$MeO_2CC_6H_4$, 2-naphthyl

mass unit shift for the ions at *m/z* 184 and $[M - 156]^+$ ions when a deuteriated Bronsted acid, i.e. $(CD_3)_2COD^+$, was the CI reactant ion and the markedly different decomposition pattern of open-chain protonated tosylamides, dominated by an alkene elimination process. Reaction 32b, leading to the ion at *m/z* 184, involved ring fission and a correlation was sought with the strain energy of the ring. As expected, the relative intensity of the *m/z* 184 fragment, plotted against ring size *n*, followed a trend consistent with the strain energy of the corresponding isoelectronic cycloalkane, characterized by a deep minimum at $n = 6$.



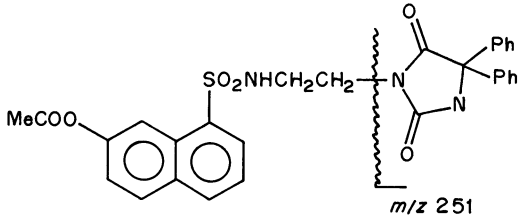
(32)

From the analytical standpoint, sulfonylation of biogenic amines has been exploited as a procedure for obtaining suitable derivatives for mass spectrometric assay. Approximately 80 amines of biological and medical interest have been converted to 5-dimethylamino-1-naphthalenesulfonamides (dansylamides) and characterized by their mass spectra, following separation by thin layer chromatography[72]. Direct analysis of dansylamides in mixtures, based on the determination of their molecular weights, has been accomplished at 12 eV electron energy[73]. The volatility requirements for combined GLC-MS analysis of sulfonamides have been fulfilled by peralkylation procedures[78]. The FAB technique overcame the vaporization problems associated with a salt-like species such as sulfonamide **114**, a color developing agent[79]. The positive-ion FAB spectrum of **114** showed a most intense peak, corresponding to the protonated free base, $[B + H]^+$, and an ion at *m/z* 641, $[2B + H + H_2SO_4]^+$, informative of the salt type. The most abundant fragment ion of the free base, at *m/z* 163, was due to '*β*-cleavage' to the amido nitrogen, as typical for *N*-alkylsulfonamides[69,70], with the charge retained by the *p*-phenylenediamino fragment.



(**114**)

Laser desorption has been used to desorb and ionize a nonvolatile sulfonamide; the LD mass spectra of *N*-2-(5,5-diphenyl-2,4-imidazolinedion-3-yl)ethyl-7-acetoxy-1-naphthalenesulfonamide (**115**) were characterized by cation attachment, forming $[M + K]^+$ and $[M + Na]^+$ ions in the positive-ion mode, and by $[M - C_2H_3O]^-$ ions in the negative-ion mode[80]. Continuous-wave irradiation by a second CO_2 laser induced the $[M - C_2H_3O]^-$ ions to photodissociate producing an ion at *m/z* 251. According to its elemental composition, it resulted from cleavage of the C—N bond adjacent to the imidazole ring.



(**115**)

2. Negative-ion mass spectra of sulfonamides

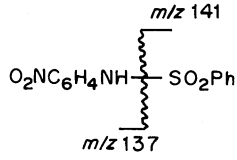
The molecular anions of several arenesulfonamides are endowed with fair stability, so that informative negative-ion spectra have been obtained. Bowie and coworkers[48] examined the negative-ion mass spectra of arenesulfonamides **103a,b,d,e,i** and of $PhSO_2NHSO_2Ph$ (**116**), under conditions (70 eV electron energy and 10^{-6} Torr source pressure) sought to minimize the possible occurrence of skeletal rearrangements in the molecular anions. Thus, the molecular anions fragmented by direct cleavages, losing either

the NHR^2 neutral moiety or a hydrogen atom, the latter process typically giving the base peak. Deuterium labelling showed that the hydrogen atom lost originated from the amino group. The mass spectra, characterized by $[M]^{-\cdot}$, $[M-H]^-$, $[R^1C_6H_4SO_2]^-$, $[R^1C_6H_3SO]^-$ and $[R^1C_6H_3S]^-$ ions, did not exhibit remarkable differences between the two butyl isomers **103d** and **103e** at variance with their positive-ion spectra[69]. The most abundant species in the negative-ion mass spectra of **103a** and **116** was the common ion at *m/z* 156 (equation 33).

$$[PhSO_2NH_2]^{-\cdot} \xrightarrow{-H^\cdot} [PhSO_2NH]^- \xleftarrow{-PhSO_2^\cdot} [PhSO_2NHSO_2Ph]^{-\cdot} \quad (33)$$

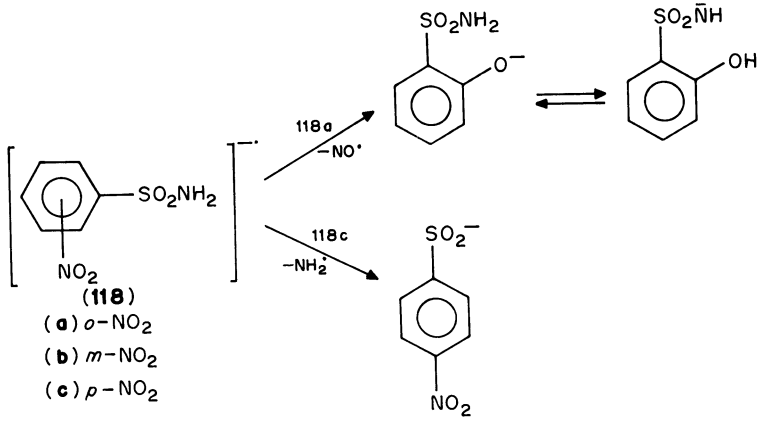
$(\mathbf{103a})^{-\cdot}$ *m/z* 156 $(\mathbf{116})^{-\cdot}$

An example of structural discrimination was found in the mass spectra of isomeric *N*-nitrophenyl benzenesulfonamides **117**[81]. Common features of the mass spectra of *ortho*, *meta* and *para* isomers were the presence of $[M-H]^-$ ions, more intense than the molecular anion, and the presence of fragments at *m/z* 137 and *m/z* 141, originating from N—S bond rupture. However, the ratio of the intensities of the latter ions was markedly higher for the *ortho* and *para* compounds, which reflected the stabilization of the *m/z* 137 anion by a nitro group in a conjugatively effective relationship. The *ortho* isomer was further differentiated by the elimination of hydroxyl radical, to form $[M-OH]^-$ ions.



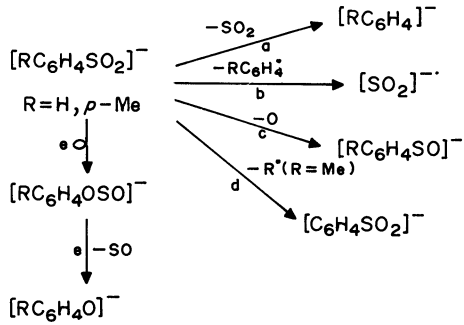
(117)

Intense signals for the molecular anions were obtained with relatively high pressures of inert gases in the ion source, favoring the production of low-energy electrons[82]. Under these conditions, pronounced increase in the ion current of the molecular anions of isomeric nitrobenzenesulfonamides **118** was achieved. An *ortho* effect emerged from the comparison of the mass spectra of **118a** and **118c**, displaying the exclusive loss of either NO or NH_2 from the parent anion (equation 34).



(34)

The $[ArSO_2]^-$ ions, produced by dissociative secondary electron capture from sulfonamides **103c** and **103d**, dissociated both by simple cleavage (equation 35a–d) and by rearrangement (equation 35e) processes, as shown by their CAD MIKE spectra[83].



(35)

Bowie and coworkers[84] have reported the kinetic energy releases for metastable negative-ion decomposition of *p*-nitrobenzenesulfonamide **118c**. The simple cleavage process

$$[M]^{+\cdot} \xrightarrow{-NH_2^{\cdot}} [M - NH_2]^-$$

was followed by dissociation with skeletal rearrangement:

$$[M - NH_2]^- \xrightarrow{-SO} [M - NH_2 - SO]^-$$

However, caution was necessary to assess the unimolecular rather than collision-induced character of these consecutive metastable reactions[85].

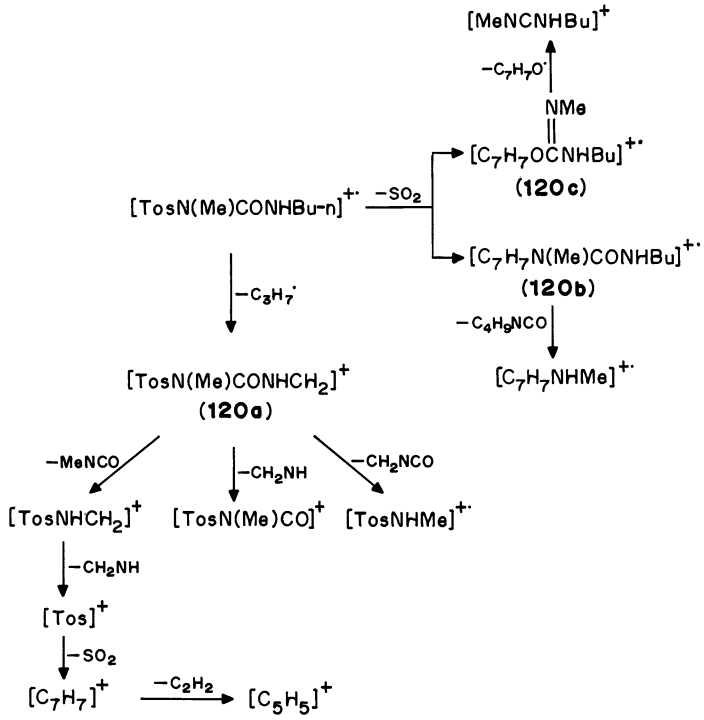
SIMS[15] and atmospheric-pressure ion evaporation MS[16] have found application for the production of negative ions, $[M - H]^-$, or ion clusters, $[M - H + (H_2O)_n]^-$, from biologically important sulfonamides.

B. Sulfonylureas

The mass spectrometric behavior of *N*-butyl-*N'*-tosylurea (**119**) has been studied, with special concern to the rearrangement process implied in the formation of $[M - SO_2]^+$ ions[86,1]. However, its relevance as hypoglycemic agent has stimulated a re-examination of the mass spectrum of the *N*-methyl derivative **120**[87]. The mass spectrum of **121** has also been reported[87]. Paying care to the possibility of thermal degradation to sulfonamide, the major fragmentation pathways of ionized **120** were rationalized within the framework of equation 36, with the support of appropriate metastable ions and high-resolution mass data. A tendency to extrusion of stable neutral molecules with skeletal rearrangement could be seen not only in the loss of SO_2, probably leading to isomeric ions **120b** and **120c**[86,1], but also in the elimination of the constituents of methyl isocyanate from ion **120a**. Compound **121** exhibited a similar fragmentation pattern with the additional presence of ions due to losses of methyl groups from precursors still containing the acetyl group.

TosNHCONHBu-n (**119**) TosN(Me)CONHBu-n (**120**)

p-$AcC_6H_4SO_2N(Me)CONHC_6H_{11}$-c (**121**)

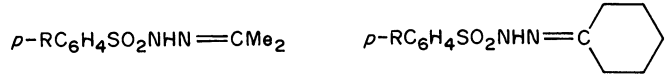


(36)

Skeletal rearrangement with loss of SO_2 was also observed in the mass spectra of arenesulfonylthioureas, but alkanesulfonylthioureas failed to produce this fragmentation mode[88,6].

C. Sulfonyl Hydrazones, Sulfonyl Hydrazides and Sulfonyl Azides

Upon EI ionization, sulfonyl hydrazones of the general type $ArSO_2NH—N=CR^1R^2$ typically underwent N—S bond cleavage, with charge retention on either the arenesulfonyl or the nitrogen-containing fragment, with or without hydrogen rearrangement[89,1]. When R^1 and R^2 were aliphatic groups, the ion corresponding to $[R^1R^2CN_2H]^+$ was the base peak for most of the compounds examined. The intensity of the $[R^1R^2CN_2H]^+$ ion relative to the molecular ion was studied for two series of arenesulfonyl hydrazones, **122** and **123**, as a function of the *para* substituent R[90]. A trend was found, favoring an increased intensity of the daughter ion as the group R became more electron-withdrawing. A similar trend was exhibited by the $[N_2H_3]^+$ fragment ion versus molecular ion intensities, in a series of substituted benzenesulfonyl hydrazides[91], $RC_6H_4SO_2NHNH_2$, whose mass spectrometric behavior has been reviewed[6].

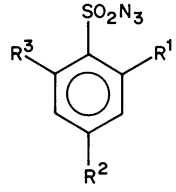


(122) (123)

R=H, Me, OMe, Cl, Br

While the thermal and photochemical decomposition mode of sulfonyl azides **124** and **125** was associated to loss of N_2, forming nitrenes, the mass spectral fragmentation of their radical cations was characterized by cleavage of azide radical, $N_3^{\bullet}$[92]. $[M-N_3]^+$ ions were abundant from all compounds examined, corresponding to the base peak for **124**, while $[M-28]^+$ accounted for 1% or less of the base peak intensity. Loss of N_3 from the molecular ion, confirmed by a metastable peak in the case of **125a, c, d**, was followed by elimination of SO_2, forming $[M-SO_2N_3]^+$ ions, base peaks in the mass spectra of **125a,b,d** (equation 37). The dissociation of **125e** was characterized uniquely by the loss of a fragment of 43 mass units from the molecular ion, traced to the concerted elimination of CH_3N_2 by exact mass measurements and the presence of a metastable transition. Fluorobenzenesulfonyl azide (isomer not given)[93] underwent the same fragmentation sequence which ultimately ended with an ion at *m/z* 75, probably resulting from the loss of HF from $[M-SO_2N_3]^+$.

$MeSO_2N_3$
(124)



(125)

	R^1	R^2	R^3
(a)	H	H	H
(b)	H	Me	H
(c)	H	NO_2	H
(d)	Me	Me	Me
(e)	*i*-Pr	*i*-Pr	*i*-Pr

The fragmentation pattern of 2-thiophenesulfonyl azide has been examined at both 20 eV and 70 eV electron energy[74] and was found to parallel that of the corresponding amide **106** (equation 29a). The 70 eV mass spectrum was dominated by the $[M-N_3]^+$ ion which became the base peak at 20 eV. Also in this case, no significant extrusion of molecular nitrogen took place.

$$[M]^{+\bullet} \xrightarrow{-N_3} [M-N_3]^+ \xrightarrow{-SO_2} [M-SO_2N_3]^+ \qquad (37)$$

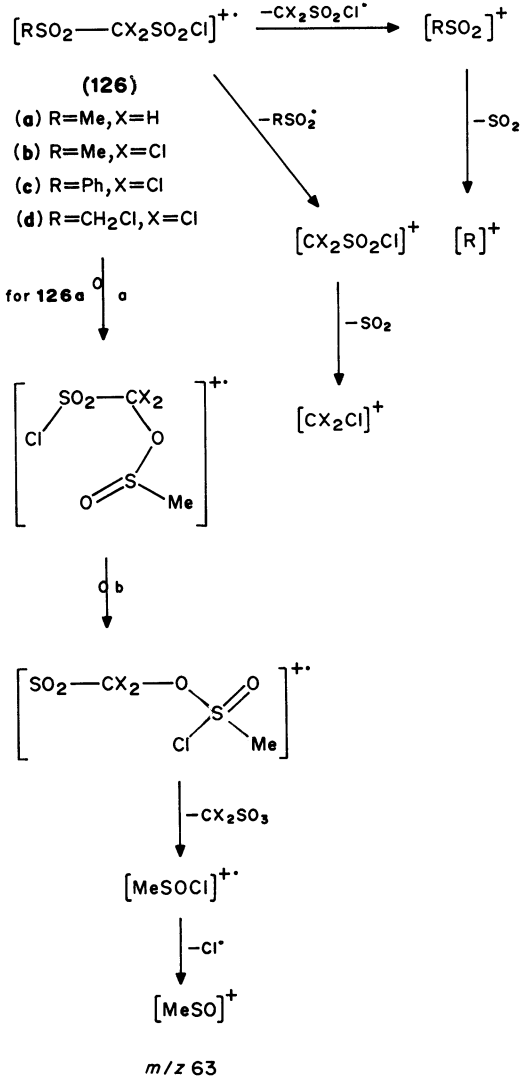
VI. SULFONYL CHLORIDES

A. Alkanesulfonyl Chlorides

The EI fragmentation pattern of sulfonyl chlorides has been rationalized within the framework of equation 38. However, the 30 eV mass spectra of simple alkanesulfonyl chlorides[94] required only pathway a in equation 38 to account for the major peaks, corresponding to: (a) $[M-Cl]^+$ ions, base peak when R = Me, Et; (b) $[M-(Cl+SO_2)]^+$ ions, i.e. alkyl cations, base peak when R = n-Pr, n-Bu; (c) $[M]^{+\bullet}$ of low intensity or absent. In the case of $PhCH_2SO_2Cl$, the molecular ion peak was discernible, but $[M-Cl]^+$ was not, the fragment at *m/z* 91 being the almost only significant ion at 30 eV.

$$\begin{array}{ccc} [RSO_2Cl]^{+\bullet} & \xrightarrow[-SO_2]{b} & [RCl]^{+\bullet} \\ \Big\downarrow{\scriptstyle a}\ Cl^{\cdot} & & \Big\downarrow{\scriptstyle b}\ Cl^{\cdot} \\ [RSO_2]^+ & \xrightarrow[-SO_2]{a} & [R]^+ \end{array} \qquad (38)$$

Sulfonyl-substituted compounds **126a–d** exhibited a much different mass spectral behavior, dominated by the sulfone fragmentation at the RSO_2-CX_2SO_2Cl bond and by the presence of fragment ions involving chlorine atom migration, as depicted in equation 39[94,95]. In particular, the formation of the ion at *m/z* 63 has been interpreted as resulting from a sulfone–sulfinate ester rearrangement[6] of the molecular ion (equation 39a) followed by chlorine migration (equation 39b). The relative abundance of the $[CX_2Cl]^+$ ions was greatly enhanced by chlorine substitution at CX_2, as expected from the stabilizing effect of chlorine on the intermediate charge retaining fragment $[CX_2SO_2Cl]^+$.



(39)

B. Arenesulfonyl Chlorides

1. Positive-ion mass spectra of arenesulfonyl chlorides

The EI mass spectra of arenesulfonyl chlorides have been reported in several studies, giving sometimes overlapping information[3,5,69,74,96–98]. Fragmentation occurred primarily at the S—Cl bond, followed by more or less easy loss of SO_2, as described in equation 38a. Other fragmentation modes depended on the nature and the position of substituents. The formation of rearrangement ions, involving loss of SO_2 and C—Cl bond formation, as shown in equation 38b, was first observed in the mass spectra of **127a,d,h**[69], although $[M - SO_2]^{+\cdot}$ ions represented only 3–4% of the base peaks corresponding to $[M - Cl]^+$ or $[M - (SO_2 + Cl)]^+$. Significant yields of $[M - SO_2]^+$ ions were found in the 30 eV mass spectra of 1- and 2-naphthalenesulfonyl chlorides[94].

$$RC_6H_4SO_2Cl$$

(127)

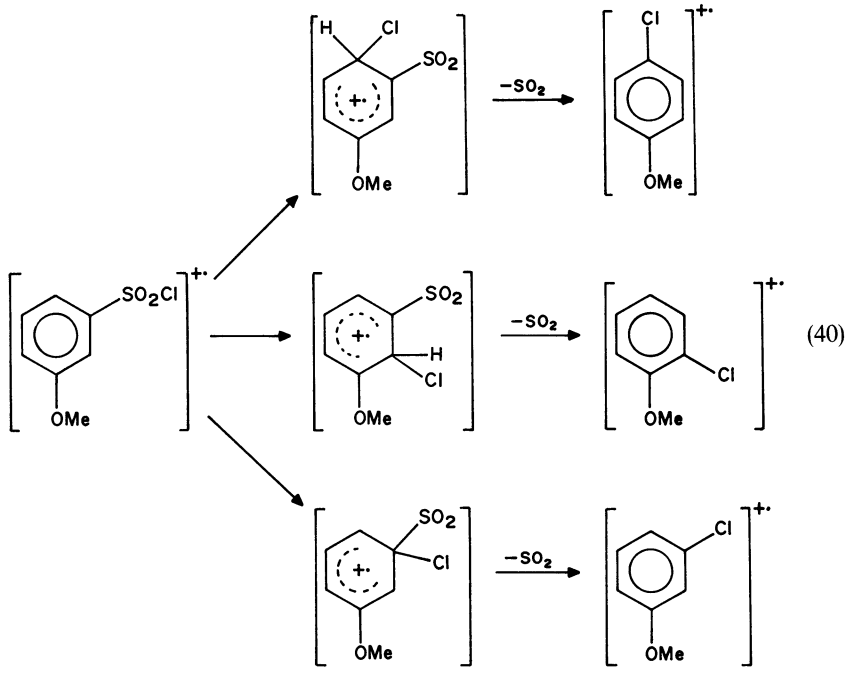
R = H	*o*-Me	*m*-Me	*p*-Me	*o*-MeO	*m*-MeO	*p*-MeO	*o*-NO_2
(a)	**(b)**	**(c)**	**(d)**	**(e)**	**(f)**	**(g)**	**(h)**

R = *m*-NO_2	*p*-NO_2	*p*-Cl	*p*-Br	*p*-CN	*m*-CF_3	*p*-$(CH_2)_n$Ar
(i)	**(j)**	**(k)**	**(l)**	**(m)**	**(n)**	**(o)**

A noticeable difference in the relative abundance of $[M - SO_2]^+$ ions emerged from the comparison of the 70 eV mass spectra of the isomeric methoxybenzenesulfonyl chlorides **127e–g**[96]. The distinctly greater intensity of this ion in the mass spectrum of the *meta* isomer stimulated a study of its structural features by MIKE spectrometry. Selected $[M - SO_2]^+$ ions from **127f** were found to decompose unimolecularly by losing Me, CH_2O and Cl fragments. Since these $[M - SO_2]^+$ ions formally corresponded to the molecular ions of chloroanisoles, the MIKE spectra of $[M]^{+\cdot}$ ions from isomeric chloroanisoles were recorded and compared to the MIKE spectrum of the $[M - SO_2]^+$ fragment from **127f**. From a semiquantitative matching of these spectra, the conclusion was drawn that, for SO_2 cleavage to occur, the chlorine atom migrates to the carbon atoms either *ortho* or *ipso* to the SO_2Cl group yielding a mixture of ionized chloroanisoles, as depicted in equation 40.

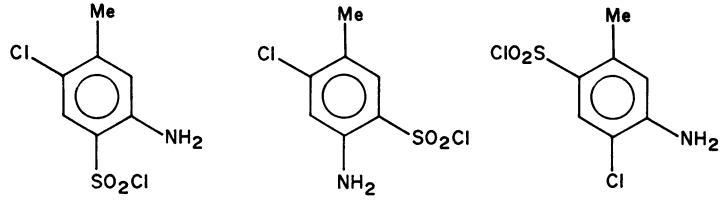
Soothill and Williams[5] observed that the $[M - Cl]^+$ ions produced by direct cleavage from ionized **127g** underwent stepwise loss of SO and oxygen atom, in addition to SO_2 elimination, all processes confirmed by metastable transitions. With *meta*- or *para*-nitro substituents, as in **127i–j**, the fragmentation proceeded according to equation 38a and no rearranged ions were present in their 70 eV mass spectra[5]. The *ortho* isomer **127h** behaved differently, in that the loss of a chlorine atom was followed by predominant loss of NO, rather than of SO_2; alternatively, sequential losses of SO_2 and NO_2 from the molecular ion produced fairly abundant ions, whose exact mass corresponded to $[C_6H_4Cl]^+$.

The presence of appropriate metastable peaks suggested that $[M - Cl]^+$ ions from *o*-toluenesulfonyl chloride, **127b**, underwent a unique elimination of H_2O, together with the predominant loss of SO_2, common to the *meta*[97] and *para*[69] isomers. Several arenesulfonyl chlorides, **127c, g, l–o**, synthesized by an improved methodology, have been characterized by their 70 eV mass spectra, basically described by equation 38a[97]. Arenesulfonyl chlorides **127o**, with the Ar group equal to *p*-methoxyphenyl or 4,8-dimethoxy-1-naphthyl and $n = 1–3$, cleaved predominantly at the benzylic position of the charge retaining methoxy-substituted fragment, upon EI ionization.



(40)

The mass spectral data of arenesulfonyl chlorides **128a–c**, derivatives suitable for GLC analysis of the corresponding acids, have been reported[98]. Abundant molecular ions and base peaks corresponding to $[M - SO_2Cl]^+$ were accompanied by fragment ions whose relative abundancies characterized the individual isomers. The 20 eV and 70 eV mass spectra of 2-thiophenesulfonyl chloride were remarkably similar to those of the corresponding amide and azide, in that $[M - Cl]^+$ ions either lost SO_2 or eliminated SO to form rearranged $[M - Cl - SO]^+$ ions[74]. Route b in equation 38 accounted for a peak corresponding to $[M - SO_2]^{+\cdot}$ of only 4% intensity relative to the base peak at *m/z* 39, in the 70 eV mass spectrum. In the case of benzo[*b*]thiophene-3- and 4-sulfonyl chlorides, the 70 eV mass spectrometric pattern could be interpreted according to equation 38 with $[M - SO_2]^{+\cdot}$ and $[M - Cl]^+$ ions of comparable intensities[51].



(128a) **(128b)** **(128c)**

2. Negative-ion mass spectra of arenesulfonyl chlorides

The negative-ion mass spectrum of *p*-toluenesulfonyl chloride, **127d**, has been reported[48]. The molecular anion gave a peak of low intensity and fragmented by loss of

C_7H_7 as major channel and by loss of a chlorine atom as minor process. However, the base peak was represented by the chloride anion, as commonly observed in the negative-ion spectra of halo compounds.

The CAD MIKE spectra of $[ArSO_2]^-$ ions deriving from methyl-deuteriated **127d** and from unlabelled *p*-toluene-*N*-butylsulfonamide (**103d**) displayed the same decomposition pattern and the expected mass shifts[83], pointing to the same structure, or mixture of structures.

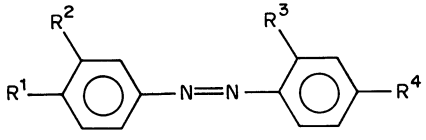
VII. (BIO)ENVIRONMENTALLY SIGNIFICANT SULFONIC ACIDS AND SULFONIC DERIVATIVES

A. Sulfonated Dyes

Polar and ionic groups such as SO_3H or $SO_3^-Cat^+$ are purposely introduced into complex organic dye molecules, to promote water solubility properties. However, sulfonic acids have very low volatilities and their salts are extremely involatile. This is a problem, if their mass spectrometric analysis is to be performed by conventional EI ionization, which requires the sample to volatilize into the ion source. To overcome such an obstacle, a large number of azo dyes containing sulfonic acid groups have been converted into methyl esters by extraction from water as tetrabutylammonium salts and methylation by methyl fluorosulfate, which did not affect other nucleophilic centres in the molecules[99]. These methyl derivatives, of the general type $Ar^1—N=N—Ar^2$, with Ar^2 typically representing a hydroxynaphthyl group, were endowed with sufficient volatility and stability to record their EI mass spectra. Most of these arylazonaphtholsulfonic acid methyl esters gave strong molecular ions at 70 eV, but the most complex species gave detectable $[M]^{+\bullet}$ ions only at 12 or 20 eV. Dissociation on EI occurred primarily at the C—N bonds as shown in equation 41. The two diazonium ions thus formed underwent loss of N_2 to give $[Ar^1]^+$ and $[Ar^2]^+$. The branching between a and b in equation 41 was determined by the substituents on the arylamine and naphthol moieties. The presence of methoxysulfonyl groups inhibited the retention of the positive charge, especially when formally located on an adjacent site. Additional signals appeared at *m/z* ratios corresponding to $[Ar^1NH]^+$, $[Ar^1NH_2]^+$ and $[Ar^2NH_2]^+$. Aside from these main fragmentation routes, further structure-specific fragmentations of diagnostic value were observed and attempts were made to rationalize them.

$$[Ar^1—N=N—Ar^2]^{+\bullet} \begin{cases} \xrightarrow{a} [Ar^1N_2]^+ + Ar^{2\bullet} \\ \xrightarrow{b} Ar^{1\bullet} + [Ar^2N_2]^+ \end{cases} \quad (41)$$

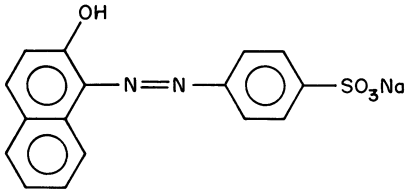
The development of desorption ionization techniques allowed the direct examination of nonvolatile, thermally labile species, previously inaccessible to MS. Thus, the volatility of sulfonated dyes **129a–c**, and **130–134**, even when converted to the free acids, remained too low to give EI mass spectra, with the possible exception of **129a**, and their analysis was performed by FD MS[100]. Compounds **129b,c**, **130**, **131** and **134a,b** gave cluster ions of the general formula $[nM + Cat]^+$, with major peaks for $n = 0$–1. To produce FD mass



(129)

(a) $R^1 = SO_3^-Na^+$, $R^2 = H$, $R^3 = R^4 = OH$
(b) $R^1 = SO_3^-Na^+$, $R^2 = R^3 = H$, $R^4 = NMe_2$
(c) $R^1 = R^3 = H$, $R^2 = SO_3^-Na^+$, $R^4 = NHPh$

spectra, some dyes had to be converted to free acids, either by ion exchange or by addition of ammonium sulfate to the dye solution to be applied to the FD emitter. In this way, FD mass spectra displaying $[M - Cat + H]^+$ ions were obtained from **129a** and **132** while compound **133** failed to give a meaningful spectrum, probably because of the presence of two sulfonic groups.



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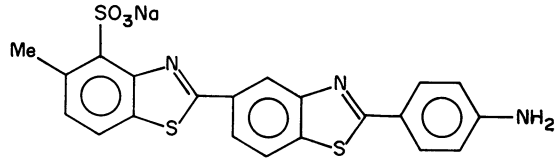

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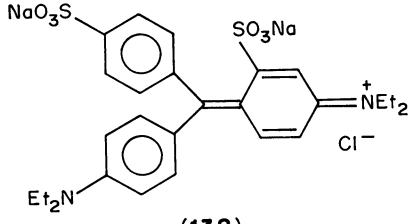

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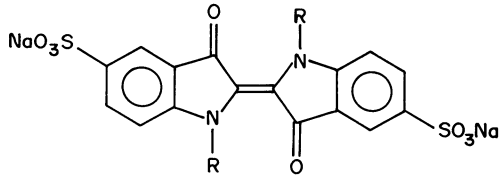
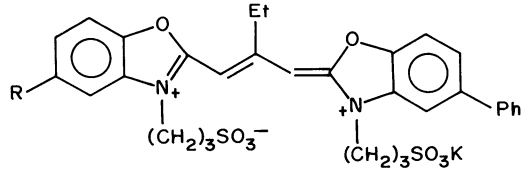


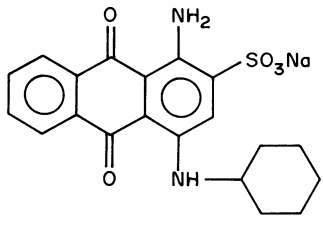
(133)



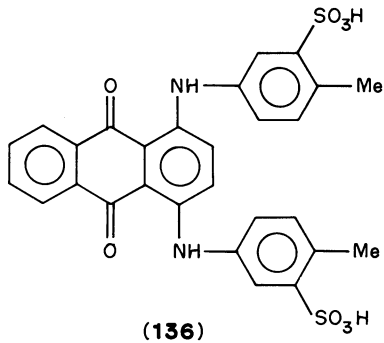
(134) (a) R = Me
(b) R = Ph

Mathias and coworkers[12] discussed the FD mass spectra of four dyes: two anthraquinone derivatives, **135** and **136**, and two azo dyes, **137** and **138**. Molecular weight information could be obtained from the presence of molecular ($[M]^{+\cdot}$) and/or cluster ions ($[nM + Cat]^+$), although only a weak $[M]^{+\cdot}$ ion was found for **136** and only a doubly charged $[M + 2K]^{2+}$ ion was present in the FD mass spectrum of **138**. The FD spectrum of **135** was further characterized by a base peak corresponding to $[M - H - SO_3Na]^+$ while $[M - SO_3]^+$ and $[M - 2SO_3]^+$ ions dominated the spectrum of **136**. Extensive cleavage of the azo linkage was observed from **138**. Similar features were observed by Schülten and Kümmler in their FD mass spectrometric study of sulfonic acids and sulfonates, which included some dyes and dye intermediates[11].

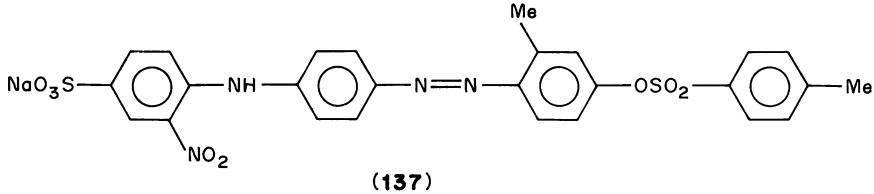
Monaghan and coworkers have addressed the mass spectral analysis of sulfonated azo dyes by means of the FAB technique[101]. Both positive- and negative-ion FAB spectra of compounds ranging from simple monoazo monosulfonates to complex bisazo pentasulfonated species could be recorded, although weaker spectra were obtained from highly sulfonated compounds. The negative-ion mode was found more suitable for this



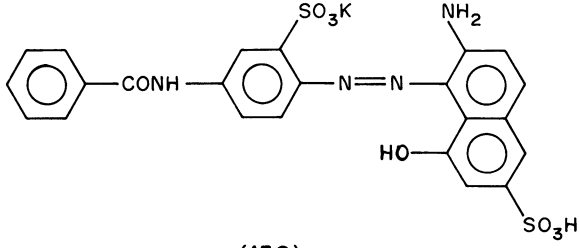
(135)



(136)



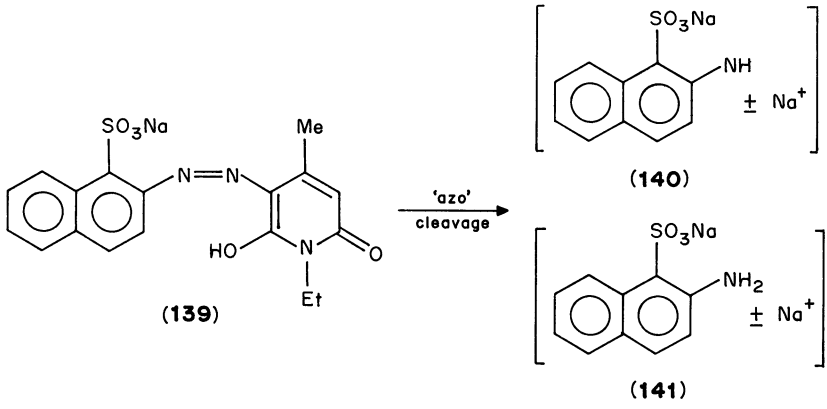
(137)



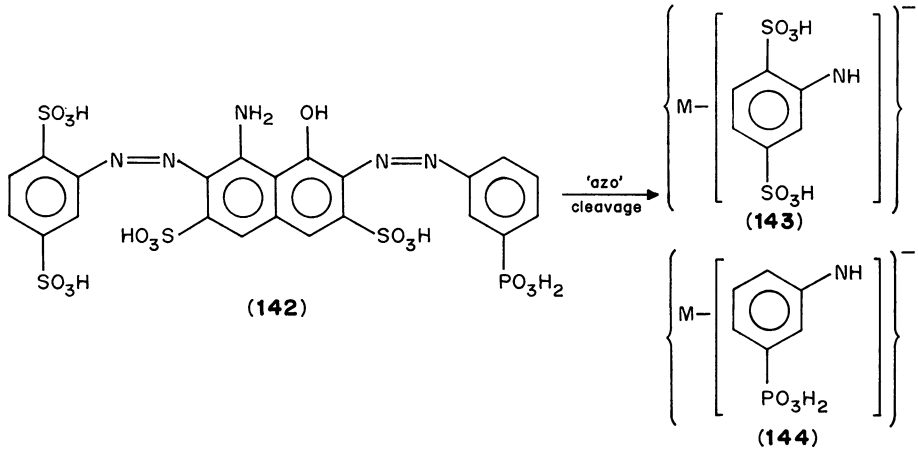
(138)

class of compounds, displaying greater sensitivity and less interference by the glycerol cluster ions. All the compounds examined gave abundant $[M + Na]^+$ and $[M - Na]^-$ ions, thus allowing their molecular weights to be established. The presence of sulfonic groups gave rise to the characteristic negative ions at *m/z* 80 and *m/z* 81 ($[SO_3]^-$ and $[HSO_3]^-$) and weaker signals could be assigned to $[M + Na - SO_3]^+$ and $[M + H - SO_3]^+$ in the positive-ion and $[M - Na - SO_3]^-$ in the negative-ion mode, respectively. The azo linkage was again a preferential fragmentation site. The cleavage ions were more abundant in the negative-ion mode, decreased as the number of sulfonate groups increased and typically contained the sulfonate group(s), the complementary ions from the unsulfonated moiety never being detected. The 'azo cleavage ions' from **139**, the simplest member in this series of azo dyes, have been assigned structures **140** and **141**, which accounted for the ions at *m/z* 267 and *m/z* 268, in the positive-ion mode, and for the ions at *m/z* 221 and *m/z* 222, in the negative-ion mode.

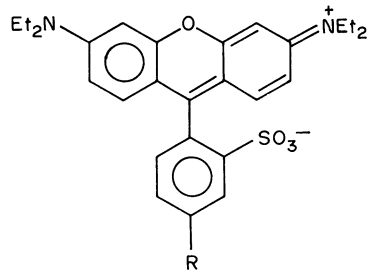
Fragmentation of bisazo species of formula $Ar^1—N=N—C_{10}H_6—N=N—Ar^2$ occurred at both azo linkages, thus yielding valuable structural information. The FAB method has also been applied to sulfonated azo dyes incorporating a phosphonic acid



group, to impart the capability of covalent bond formation with the hydroxyl groups of cotton fibers[101b,c]. Good spectra were obtained from these completely involatile samples, ranging in complexity from monosulfonated/monophosphonated monoazo dyes to monophosphonated/tetrasulfonated bisazo compounds. Their major features resembled those of sulfonated dyes. Characteristic negative ions of phosphonated species were present at *m/z* 63 and *m/z* 79 ($[PO_2]^-$ and $[PO_3]^-$). Negative-ion spectra were confirmed to be superior to positive-ion spectra, probably because of the inherent stability of phosphonated/sulfonated anions. Positive-ion spectra, however, could provide valuable complementary information. The presence and position of azo groups was indicated, once again, by predictable fragments. Thus, in the negative-ion FAB spectrum of bisazo species **142**, intense ions were found at *m/z* 515 and *m/z* 595, assigned to azo cleavage ions **143** and **144**.



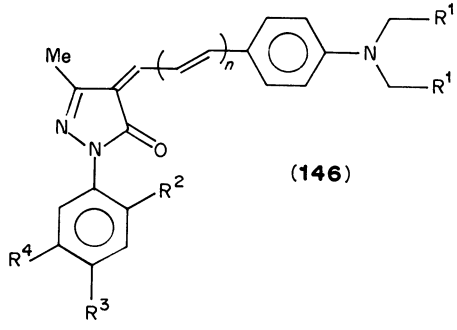
The positive-ion FAB spectra of xanthane dyes **145a,b** were found to be reproducible and to contain structurally significant ions, although changes in the glycerol solution of the sample could exert a strong influence[102]. The prominent $[M + H]^+$ ions dissociated by losing SO_3 or the substituted phenyl ring, as confirmed by metastable linked scanning.



(**145**) (**a**) R = SO_3Na

(**b**) R = SO_3H

The FAB mass spectra of five sulfonated merocyanine dyes, **146a–e**, have been reported[103]. Molecular weight information was given by $[M + H]^+$ and $[M - Li + 2H]^+$ positive ions and by $[M - Li]^-$ anions, base peaks in the negative-ion mode. Clusters with glycerol molecules or glycerol fragments were also observed. While azo dyes showed similar fragmentation patterns both in the positive- and negative-ion mode, merocyanine dyes underwent primary loss of the sulfonic group from positive ions and elimination of a methyl or methylene unit from negative ions.



(**146**)

	R^1	R^2	R^3	R^4	n
(**a**)	H	H	SO_3Li	H	1
(**b**)	H	H	H	SO_3Li	0
(**c**)	H	Cl	H	SO_3Li	0
(**d**)	Ph	H	SO_3Li	H	0
(**e**)	H	Cl	H	SO_3Li	1

Several sulfonated dyes with different structural features have been examined by ^{252}Cf plasma desorption mass spectrometry, using a time-of-light mass spectrometer[104]. Sodium arenesulfonate dyes gave weak or no $[M - Na]^-$ ions but, in the positive-ion mode, $[M + Na]^+$ ions were often abundant and fragmented along predictable lines. Disulfonated dyes failed to provide good spectra. Tetrabromophenol blue, incorporating a sultone ring, gave an intense negative-ion spectrum, while the probable existence of pyrogallol red in a sultone form was suggested by the relative peak intensities in its positive-ion spectrum.

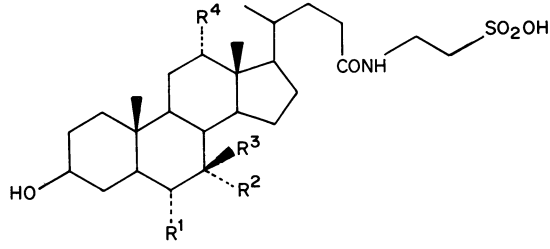
Thermospray ionization was found to be a suitable 'soft' ionization process for the direct determination of dyes of widely different chemical structures[105]. Among them, a commercial sample of the sulfonated azo dye **129a** showed a positive-ion spectrum consistent with a predominant sulfonic acid form of this dye. In fact, the base peak corresponded to the protonated sulfonic acid at *m/z* 295. Upon low-energy CAD, this ion produced a peak at *m/z* 173, which could be attributed to the azo cleavage species $[HO_3S—C_6H_4—NH_2]^{+\cdot}$. In the negative-ion mode, abundant anions at *m/z* 293 were

present. The CAD spectrum of these ions displayed a single strong daughter ion at m/z 171, corresponding again to an azo cleavage ion.

The environmental impact and health risks connected to the industrial wastes of dye manufacturers require an efficient method for the trace analysis of mixtures of dyes in aqueous solutions. LC/MS has the potential of providing a suitable analytical procedure. The LC/MS analysis of sulfonated azo dyes was found to be amenable using either thermospray ionization[106] or atmospheric pressure ionization (API)[107]. Flory and coworkers[106] obtained negative-ion thermospray ionization mass spectra for di- and tetrasulfonated azo dyes and investigated the effect of varying several parameters on the thermospray response. Doubly charged anions, $[M-2Na]^{2-}$, gave usually the most intense peaks when the dyes were analyzed in pure water. The presence of increasing amounts of ammonium acetate buffer introduced protonated ions, i.e. $[M-2Na+H]^-$, and contaminant ions, besides lowering the sensitivity when the concentration was over 10^{-2} M. Henion and coworkers[107] coupled HPLC to their triple quadrupole mass spectrometer, equipped with an API source, using different pneumatic nebulizers. The mild ionization of mono- and disulfonated azo dyes generated $[M-H]^-$ ions of the free acids with little or no fragmentation. Upon CAD in the second quadrupole, these $[M-H]^-$ ions gave the daughter ions expected from azo cleavage, and $[SO_3]^-$ ions of diagnostic value for this class of compounds.

B. Taurine Conjugated Bile Acids and Salts

Underivatized bile acids are carboxylic acids, synthesized in the liver from cholesterol, sharing the same molecular framework, with differences only in the number and position of hydroxyl and ketone functions on the steroid ring system. They also exist in the bile as glycine and taurine conjugates. The CI (NH_3) mass spectrum of free taurine, 2-aminoethanesulfonic acid, has been reported[108] to show the protonated molecule, $[M+H]^+$, and proton bound dimer ions, $[2M+H]^+$. 'Soft' ionization techniques have been exploited for the mass spectral examination of taurine conjugates of bile acids, e.g. **147a–f**, whose trivial names are given.

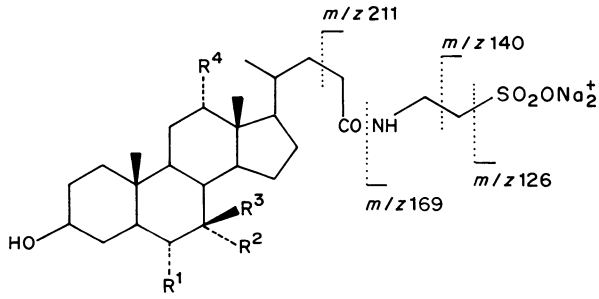


(147)

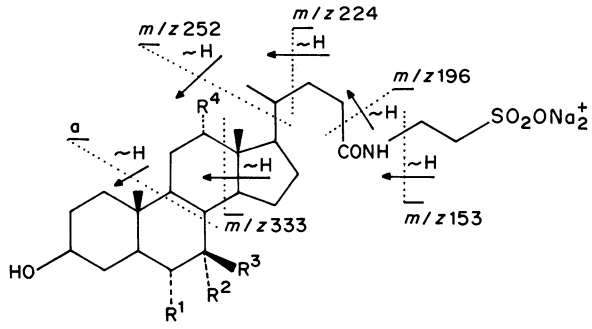
	R^1	R^2	R^3	R^4	
(a)	H	OH	H	H	taurochenodeoxycholic acid
(b)	H	H	H	OH	taurodeoxycholic acid
(c)	H	OH	H	OH	taurocholic acid
(d)	H	H	OH	H	tauroursodeoxycholic acid
(e)	OH	H	H	H	taurohyodeoxycholic acid
(f)	H	H	H	H	taurolithocholic acid

The application of FD MS to the sodium salts of **147a–c** has shown $[M + Na]^+$ ions and intense doubly charged ions, which enabled identification of their molecular weights[109].

LD has been used by Day and coworkers[110] in their study of the mass spectrometry of bile acids. In the high mass region, the LD mass spectra of the sodium salts of **147a–c** contained only $[M - Na]^-$ ions, in the negative-ion mode, and $[M + Na]^+$ ions, in the positive-ion mode. These molecular species apparently failed to fragment. Similar molecular weight information was provided by the FAB technique, whose mass spectra typically lacked significant fragmentation and yielded no structural characterization. For this reason FAB has been combined with tandem mass spectrometry and FAB-desorbed positive and negative ions of bile salts have been characterized by their CAD mass spectra[111,112]. The FAB mass spectra of the sodium salts of **147a,b,d,e** showed abundant $[M + Na]^+$ ions which were analyzed by CAD MIKES[111]. The major daughter ions derived by side-chain fragmentation, either by simple homolysis, as shown in structure **148**, or by cleavage accompanied by hydrogen migration, as shown in structure **149**. Structural differentiation between isomers was sought in the middle mass region (*m/z* 300–450), expected to record ions derived from fragmentation of the polycyclic nucleus. *β*-ring rupture along a in **149**, with hydrogen rearrangement, produced an ion at *m/z* 387 from **147a,d,e** and *m/z* 403 from **147b**. The intensities of smaller peaks revealed no measurable differences between the two stereoisomers **147a,d** while subtle variations could distinguish **147e**.

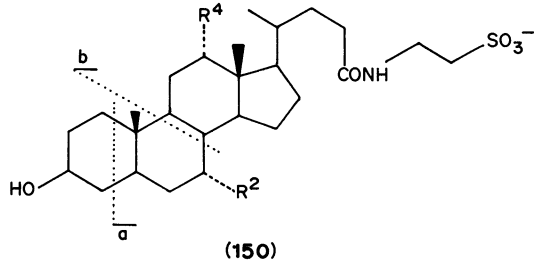


(148)



(149)

The negative-ion FAB spectra of **147a,c,f** were characterized by abundant $[M-H]^-$ ions with little additional fragmentation, with the exception of $[M-H-16]^-$ ions from **147f**. CAD spectra of these $[M-H]^-$ ions were obtained by colliding the selected ion beam with helium, in the third field-free region of a triple sector mass spectrometer[112]. Apart from water loss, the major daughter ions involved ring cleavages, as indicated in structure **150**, rather than fragmentation of the side-chain. The charge resided on the fragment containing the sulfonic group but no significant loss of SO_3 was observed. Instead, the preferential cleavage along a occurred at the ring most remote from the site formally bearing the negative charge. Loss of SO_3 was a significant unimolecular and collision activated process from the $[M-H]^-$ ions of taurolithocholate 3-sulfate, the eliminated SO_3 most probably deriving from the sulfate group.



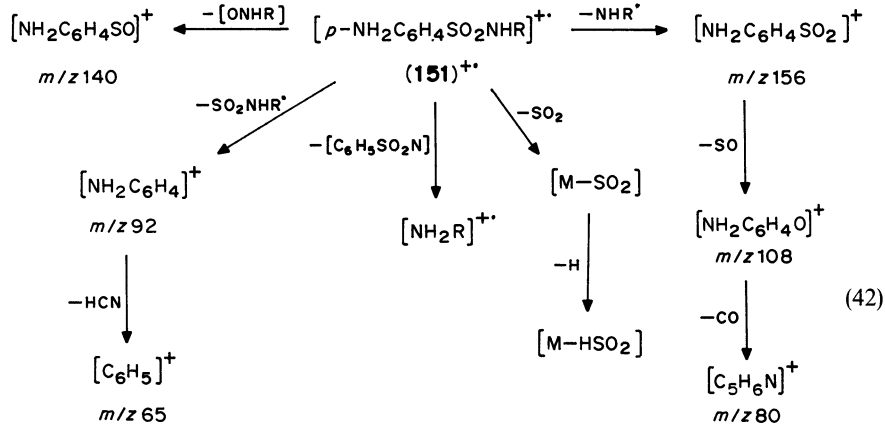
(150)

Bile acids and their conjugates have been separated and mass analyzed by a direct combination of micro HPLC and FAB MS[113], allowing the introduction of the total effluent into the mass spectrometer through a fused silica capillary tubing, ending with a stainless steel frit. The liquid mobile phase was vaporized on the surface of the frit, while the solute and the glycerol matrix were left on the surface and were subjected to FAB.

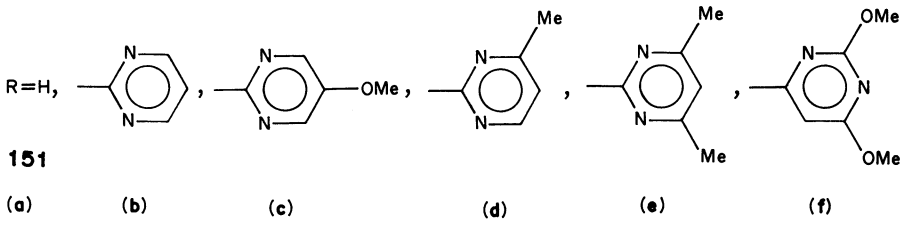
C. Sulfonamide Drugs

Several methods of analysis of sulfonamides of pharmaceutical interest have been developed, involving their identification by mass spectrometry[114–122].

The EI mass spectra of many substituted sulfonamides of the general type p-$NH_2C_6H_4SO_2NHR$, components of pharmaceutical preparations, have been reported[114,115,121,122]. In the known[1] mass spectrum of sulfanilamide (**151a**) Cambon and

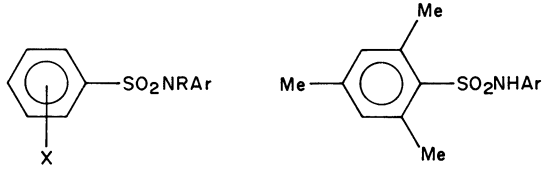


(42)

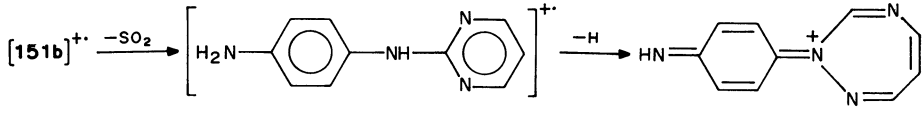


coworkers[114] recognized two contributions to the peak at *m/z* 108 (equation 42, R = H), by high-resolution mass measurements. A 90% fraction was due to $[M-(SO+NH_2)]^+$ ions while a remaining 10% fraction arose from loss of SO_2 from the molecular ion. Representative sulfanilamides (**151b–d**) showed a similar fragmentation pattern, summarized in equation 42, with ion intensities characterized by prominent $[M-SO_2]^+$ and $[M-HSO_2]^+$ ions.

The mass spectra of several arenesulfonamides of the general type **152** and **153**, where Ar indicates a heteroaryl group containing at least one aza group, have been studied, with the aim of establishing which structural features rendered the losses of SO_2 and HSO_2 from $[M]^{+\cdot}$ a preferential fragmentation pathway. In fact, it was known that the only *N*-arylsulfonamides which showed abundant $[M-SO_2]^+$ and $[M-HSO_2]^+$ ions were sulfadiazine (**151b**) and related compounds[69,123]. A ring expansion mechanism had been postulated, leading to a stable cation, as shown in equation 43.

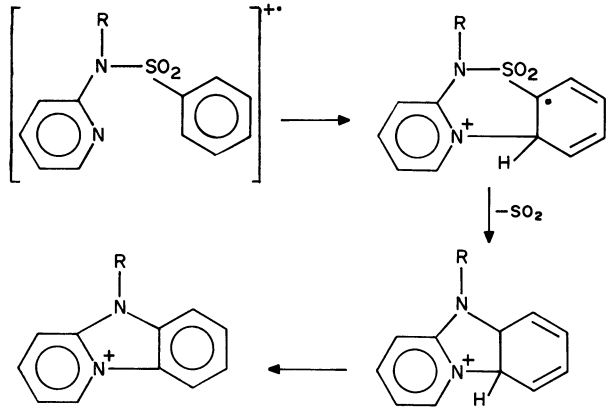


(152) (153)



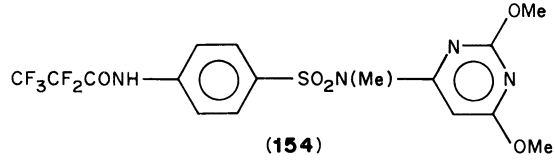
(43)

Broxton[124] confirmed the elemental composition of $[M-65]^+$ ions as due to loss of HSO_2, confirmed[114] a prominent metastable transition linking $[M-SO_2]^+$ to $[M-HSO_2]^+$ and observed that at least one aza group ortho to the amino group in the heteroaryl moiety was necessary to produce intense $[M-SO_2]^+$ and $[M-HSO_2]^+$ ions. He concluded that an alternative cyclization–elimination mechanism (equation 44), first postulated for benzamide derivatives, could better account for the experimental findings. The *ortho* aza group was seen as acting as a nucleophile, its efficiency being diminished by electron-withdrawing substituents on the heteroaryl ring. The attacked position of the benzene ring, *ortho* to the sulfonyl group, subsequently eliminated a hydrogen atom, in the case of compounds **152**, leading to $[M-65]^+$ ions, or a methyl group, in the case of compounds **153**, forming $[M-79]^+$ ions. The details of the elimination of SO_2 are still an unanswered question, however.



(44)

As indicated in equation 42, a set of ions at *m/z* 156, *m/z* 140, *m/z* 108, *m/z* 92, *m/z* 80 and *m/z* 65 could be considered diagnostic of a probable sulfonamide drug. However, ions corresponding to the NHR portion of the molecule and the molecular ion itself were not always present with significant intensities in the EI mass spectra. Complementary information was provided by CI (CH_4)MS in pulsed positive ion–negative ion mode[115]. The positive-ion spectrum showed the protonated amine $[NH_3R]^+$ and protonated molecule $[M + H]^+$ as typically the two most intense ions, providing information on the molecular weight and the amine moiety. The sulfonyl portion of the molecule was characterized by a common negative ion at *m/z* 155, formally due to $[M - NHR - H]^-$, arising from N—S bond cleavage with hydrogen rearrangement from the molecular anion, which was usually not observed. The relative abundancies of positive and negative ions depended strongly on the substituents on the amido nitrogen. With no substituents, as in **151a**, the negative ion at *m/z* 155 was least intense, but the intact sulfonyl moiety yielded a positive ion at *m/z* 156. This behavior was confirmed by the positive-ion and negative-ion CI (CH_4) analysis of **151e** by combined LC/MS, using a moving belt interface[116]. Sulfadimethoxine (**151f**) was analyzed by GLC/CI MS as its methyl pentafluoropropionyl derivative (**154**)[117], using stable isotope dilution and multiple ion detection to confirm its presence in tissue extracts. The most intense peak at *m/z* 170 in the CI (*i*-C_4H_{10}) mass spectrum of **154**, corresponding to the protonated amine $[MeNR + 2H]^+$, was accompanied by ion signals at *m/z* 471 ($[M + H]^+$), *m/z* 304 ($[M - MeNR + H]^+$), *m/z* 240 ($[M - SO_2NMeR + H]^+$). Underivatized **151b,d,e** were separated by supercritical fluid chromatography, interfaced to MS, which allowed recording of their EI and CI (CH_4) mass spectra[118]. Under the conditions adopted, no molecular ions were observed in the EI mode but CI (CH_4) gave both abundant $[M + H]^+$ and $[M + Et]^+$ ions.



(**154**)

The application of MS/MS offers the advantage of simplifying cleanup procedures. To this end, CAD MIKES was applied to the detection of sulfonamide drugs and decomposition spectra were reported from $[M + H]^+$ ions produced under CI (*i*-C_4H_{10})[119]. Equation 45 summarizes the most significant pathways leading to fragment

ions, whose composition has been confirmed by high-resolution mass measurements in individual cases. Additional fragment ions characteristic of the sulfonyl moiety and common to the EI mass spectra were found at *m/z* 140, *m/z* 108 and *m/z* 92. CAD MIKE spectra displayed also dissociation routes associated with particular functionalities present in the molecule and exhibited isomer distinctions.

$$[NHRSO_2]^+ \longleftarrow [p\text{-}NH_2C_6H_4SO_2NHR + H]^+ \longrightarrow [M + H - H_2SO_2]^+ \quad (45)$$

$$\text{or } [M + H - HSO_2]^+$$

$$[NHR + 2H]^+ \qquad [NH_2C_6H_4SO_2]^+$$

$$\text{or } [NHR + H]^{+\cdot}$$

Henion and coworkers used a MS/MS technique for the determination of sulfonamide drugs by LC in series with a triple quadrupole mass spectrometer[120], equipped with an atmospheric-pressure chemical ionization ion source for direct liquid introduction. CAD mass spectra were obtained by selecting $[M + H]^+$ ions with the 1st quadrupole, performing CAD with N_2 as the collision gas in the 2nd quadrupole and mass analyzing the fragment ions in the 3rd quadrupole. The LC MS/MS mass spectra of sulfonamide drugs obtained by this methodology conformed to the indicative pattern described by equation 45.

VIII. SULFENIC COMPOUNDS

A. Sulfenic Acids and Esters

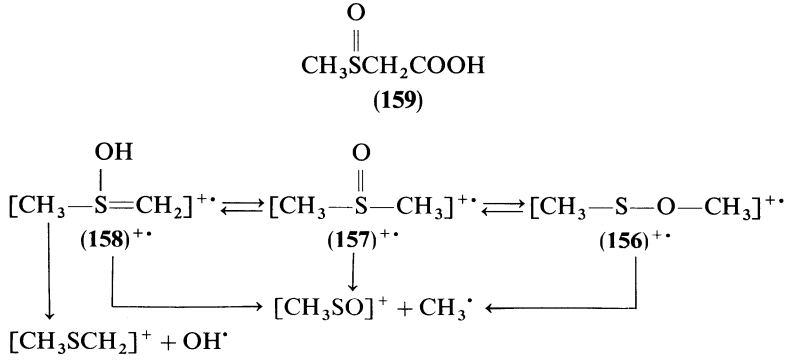
Tureček and coworkers[125] have recently investigated by mass spectrometry the gas-phase thermochemical properties of four sulfenic acids **155a–d**. These unstable compounds, which may exist in an isomeric sulfoxide-like structure, R—S(O)—H, have been prepared by flash vacuum pyrolysis of the corresponding *t*-butyl or 3-buten-1-yl sulfoxides. The course of the pyrolysis was monitored in continuum by a double focusing mass spectrometer, equipped with a micro oven, and the EI mass spectra of the expected products **155a–d** were obtained after subtracting the spectrum of the olefin formed from the mass spectrum of the pyrolysate. The sulfenic acids examined afforded abundant molecular ions, base peak for **155b**, and $[M - OH]^+$ fragments, base peak for **155a,c**. The favorable cleavage of OH was suggested to indicate a sulfenic acid, rather than sulfoxide-like, structure for ionized **155a–d**. The expected loss of a hydrogen atom from a possible sulfoxide isomer was significant only in the case of **155a**, where it could more conceivably arise from the methyl group of the sulfenic form. The values of threshold ionization energies, determined from ionization efficiency curves, ranged from 9.07 ± 0.03 eV for **155a** to 8.45 ± 0.03 eV for **155d**, lower than expected for sulfoxide-like forms. The linearity of the ionization efficiency curves of **155a,d** pointed to a sulfenic structure for the respective neutral molecules, while in the case of **155b,c** the contribution of one or more other isomeric structure(s) emerged. The goal of establishing the heats of formation of neutral **155a–d** was pursued both by MNDO calculations and experimentally, devising a

R—S—OH
(155)

(a) R = Me
(b) R = $H_2C{=}CH$
(c) R = $HC{\equiv}C$
(d) R = Ph

thermochemical cycle, which used the appearance energies of ionized sulfenic acids, formally obtained by loss of propene from the radical cations of the corresponding n-propyl sulfoxides.

Carlsen and Egsgaard[126] have investigated the unimolecular and the collision activated dissociation of methyl methanesulfenate (**156**) and dimethyl sulfoxide (**157**), upon EI ionization, to examine the possibility of interconversion of their radical cations and isomerization to the ionized aci tautomer of dimethyl sulfoxide (**158**), as depicted in equation 46. A model ion for ionized **158** was obtained by elimination of CO_2 from the radical cation of methyl carboxymethyl sulfoxide (**159**). The ions at *m/z* 78, thus generated from the three different neutral precursors, underwent the same major losses of OH and methyl radicals, the latter enhanced by collisional activation and probably more energy demanding. The loss of hydroxyl radical appeared distinctly more facile from the ions deriving from **159**, which was in agreement with their enol structure. The rearrangement of ionized **156** and **157** to the radical cation of **158** was inferred, if the OH elimination were to proceed via a structure possessing this group. Selective deuterium labelling showed that methyl cleavage occurred from the individual isomers, without prior isomerization. In particular, the dissociation spectrum of $[CH_3—S—O—CD_3]^{+\cdot}$ could be rationalized by losses of intact CH_3 and CD_3 radicals.

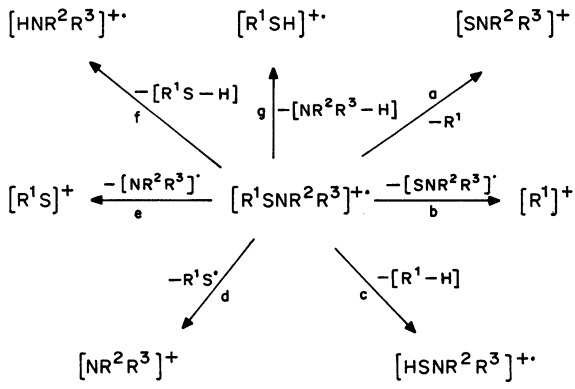


(46)

B. Sulfenamides

The EI-induced fragmentation of sulfenamides typically involved C—S and N—S bond fission[127,128]. In their study of the chemistry of sulfenamides, Heimer and Field[128] examined the mass spectra of 12 sulfenamides of the general type $R^1SNR^2R^3$, with R^1 = Et, n-Bu, *t*-Bu or $AcNH(CH_2)_2$, while R^2 and R^3 comprised alkyl, aryl or heterocyclic groups. Four major fragmentation processes were common to most of them: C—S cleavage, paths a and b in equation 47, C—S cleavage with hydrogen migration (path c), N—S cleavage (paths d and e), N—S cleavage with hydrogen rearrangement (path f).

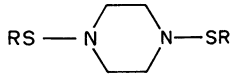
The fragmentation pathways in equation 47 may offer a scheme to illustrate the mass spectra but do not imply the actual occurrence of specific fragmentation routes; e.g. the product ions of path d may derive as well from path c followed by loss of SH radical. All the sulfenamides investigated afforded molecular ions; their intensities and the relative abundances of fragment ions depended strongly on the substituents R^1,R^2,R^3. The 2-acetamidoethyl compounds showed molecular ions of low intensity and N—S cleavage ions usually dominated the mass spectra. Unsaturated substituents on nitrogen yielded abundant ions from N—S bond rupture with hydrogen migration. With R^1 = *t*-Bu preferential cleavage at the C—S bond occurred, with or without hydrogen rearrangement.



(47)

The 70 eV mass spectra of aryl sulfenamides Ar^1SNHAr^2, all showing strong parent ions, also conformed to the formal fragmentation pattern of equation 47[129]. The most abundant fragment ions involved N—S bond cleavage with retention of charge on the nitrogen-containing fragment to form $[Ar^2NH]^+$ ions, representing the base peak in most cases. With respect to the sulfenamides examined by Heimer and Field, two additional fragmentation pathways were detected, leading to the formation of $[Ar^1SH]^{+\cdot}$ (path g) and $[Ar^1NAr^2]^+$ ions, the latter involving elimination of SH from the molecular ion, as indicated by the presence of the appropriate metastable peak. This finding, which implied an aryl group migration from sulfur to nitrogen, represented a further example of the tendency of radical cations of organosulfur compounds to undergo rearrangements. In the $CI(CH_4)$ mode, abundant $[M+H]^+$ ions and weaker $[M+Et]^+$ and $[M+C_3H_5]^+$ adduct ions were accompanied by still strong fragment ions dominated by $[Ar^2NH_2]^{+\cdot}$ and $[Ar^2NH_3]^+$.

The mass spectral behavior of several sulfenamides and related compounds, containing divalent sulfur bonded to nitrogen (**160–168**), has been studied by Harpp[130], Raban[131] and their coworkers.

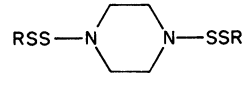


(160)

(a) R=Et

(b) R= *t* -Bu

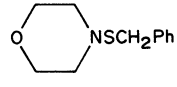
(c) $R=PhCH_2$



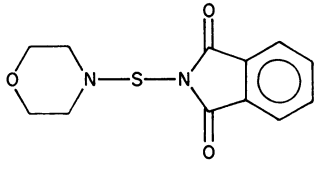
(161)

(a) R= *i* -Pr

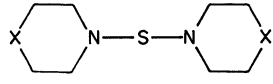
(b) R= *t* -Bu



(162)



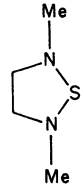
(163)



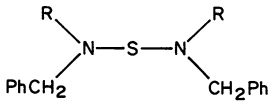
(164)

(a) $X=CH_2$

(b) X=O



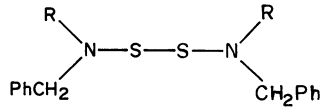
(165)



(166)

(a) R=Me

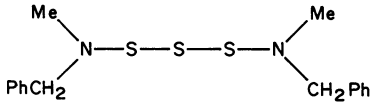
(b) R= *i*-Pr



(167)

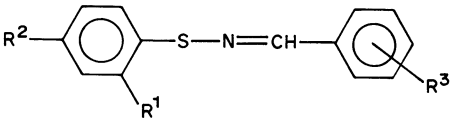
(a) R=Me

(b) R= *i*-Pr



(168)

The mass spectra were fairly complex in most cases. Sulfenamides **160** and **162** were characterized by intense molecular ions, base peak for **160a**, while the base peaks for **160b, c** and **162** originated from C—S bond cleavage with predominant retention of charge on the hydrocarbon fragment, corresponding to stable $[C_4H_9]^+$ and $[C_7H_7]^+$ ions. Extensive N—S bond cleavage occurred from ionized **160c**, with or without hydrogen rearrangement and retention of charge on either sulfur- or nitrogen-containing fragments (paths d–f in equation 47). In the case of the ethyl analogue **160a**, only path d was important while compounds **160b, c** showed abundant $[C_4H_{10}N_2]^+$ and $[C_4H_9N_2]^+$ ions deriving from ready rupture of the second N—S bond. In the case of the *t*-butyl derivative **160b**, C—S bond fission according to path g in equation 47 was a prominent process which could take place also on the second C—S bond or be accompanied by N—S bond rupture from the other sulfenamide functionality. Thus, a combination of the fragmentation processes summarized in equation 47 accounted for most daughter ions appearing in the mass spectra of **160a–c**, in addition to species involving fission of the piperazine ring. N—S bond scission dominated also the fragmentation pattern of compounds **163–166**, containing the N—S—N moiety. The charge was retained by either fragment in the case of **164**, while nitrogen-containing cations predominated in the mass spectrum of **166**. Of the two different sulfenamide bonds in *N*-morpholinothiophthalimide **163**, the imide–sulfur linkage cleaved more readily. In the mass spectrum of 2,5-dimethyl-1,2,5-thiadiazolidine **165**, the principal modes of dissociation resulted from the usual N—S bond rupture in conjunction with cleavage of a C—C bond. *N,N'*-bisalkyldithiopiperazines **161a, b** gave rise to abundant $[M]^{+\cdot}$ and $[R]^+$ ions, while N—S bond fission yielded nitrogen-containing ions. Fission of the S—S bond also contributed significantly to the mass spectra of **161a, b**, occurring at one or both linkages or in

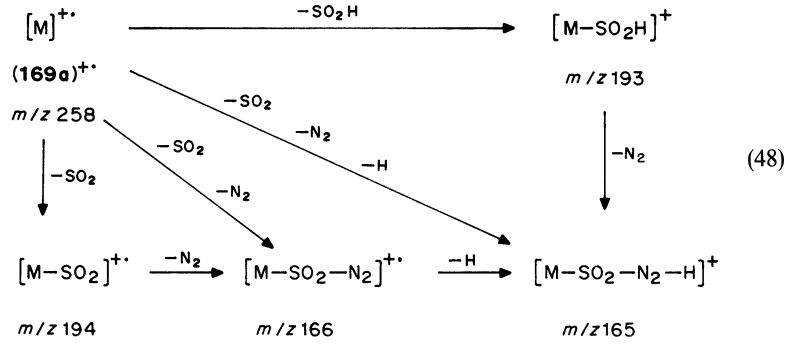


(169)

	R^1	R^2	R^3
(a)	NO_2	H	H
(b)	H	NO_2	H
(c)	NO_2	H	*p*-Cl
(d)	NO_2	H	*p*-NO_2
(e)	NO_2	H	*m*-NO_2
(f)	NO_2	H	*p*-Me
(g)	NO_2	H	*p*-MeO
(h)	NO_2	H	*o*-MeO
(i)	NO_2	Cl	H
(j)	NO_2	Cl	*p*-MeO
(k)	H	NO_2	*o*-NO_2
(l)	H	NO_2	*p*-NO_2

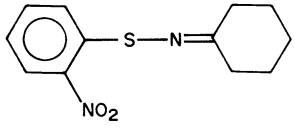
conjunction with cleavage of the sulfenamide bond on the opposite side of the molecule. In the mass spectra of **167** and **168**, minor fragment ions appeared to result from sulfur elimination.

Ramana and coworkers[132] have investigated the role of structural parameters on the loss of SO_2 and N_2, peculiar to the molecular ions of certain *N*-arylidene-nitrobenzenesulfenamides (**169a–l**). The 70 eV mass spectrum of *N*-benzylidene-2-nitrobenzenesulfenamide **169a** was characterized by an intense peak at *m/z* 166, corresponding to $[M - SO_2 - N_2]^+$ ions and a base peak at *m/z* 165, corresponding to $[M - SO_2 - N_2 - H]^+$ ions, as indicated by high-resolution measurements. Linked scans established the parent daughter relationships shown in equation 48, where the concerted expulsion of SO_2 and N_2 from the molecular ion, followed by loss of a hydrogen atom, contributed most significantly to the formation of the ions at *m/z* 166 and *m/z* 165.

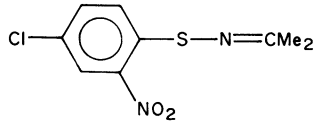


(48)

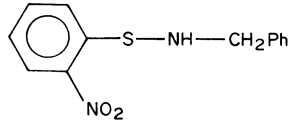
This fragmentation mode was minor or absent under the following conditions: (a) in the absence of an *ortho*-nitro group on the S-aryl ring, as in compounds **169b, k, l**; (b) when the *N*-arylidene group was replaced by a *N*-alkylidene, as in compounds **170** and **171**; (c) when the imine functional group was saturated, as in compound **172**.



(170)



(171)



(172)

If other substituents were present on the aryl rings, i.e. $R^2 \neq H$ or $R^3 \neq H$, loss of R^2 or R^3 became competitive with hydrogen loss. In the case of compound **169j**, chlorine atom expulsion was strongly favored over loss of the methoxyl group from $[M - SO_2 - N_2]^+$ ions. All these observations led to the suggestion that initial transfer of two oxygen atoms from the nitro group to the sulfur atom yielded a rearranged molecular ion, from which the expulsion of SO_2 and N_2 occurred with concomitant ring expansion at either of the aryl rings. Alternative structures, corresponding to fluorene radical cation for the ion at *m/z* 166 and fluorenyl ion for *m/z* 165, were rather disproven by the different behavior displayed upon CAD by the two ionic species, when derived from EI ionization of fluorene and from EI-induced dissociation of *N*-benzylidene-2-nitrobenzenesulfenamide.

IX. ACKNOWLEDGMENTS

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CHAPTER 4

Ultraviolet photoelectron spectroscopy of organic sulfur compounds

J. BARRIE PEEL

Department of Chemistry and Research Centre for Electron Spectroscopy, La Trobe University, Bundoora, Victoria 3083, Australia

I. INTRODUCTION

A. Principles of Photoelectron Spectroscopy

Ultraviolet photoelectron spectroscopy (UPS) has established its place in the lexicon of chemical spectroscopies as the technique which uniquely reveals the valence electronic structure of the isolated molecule. It has been particularly successful for organic systems

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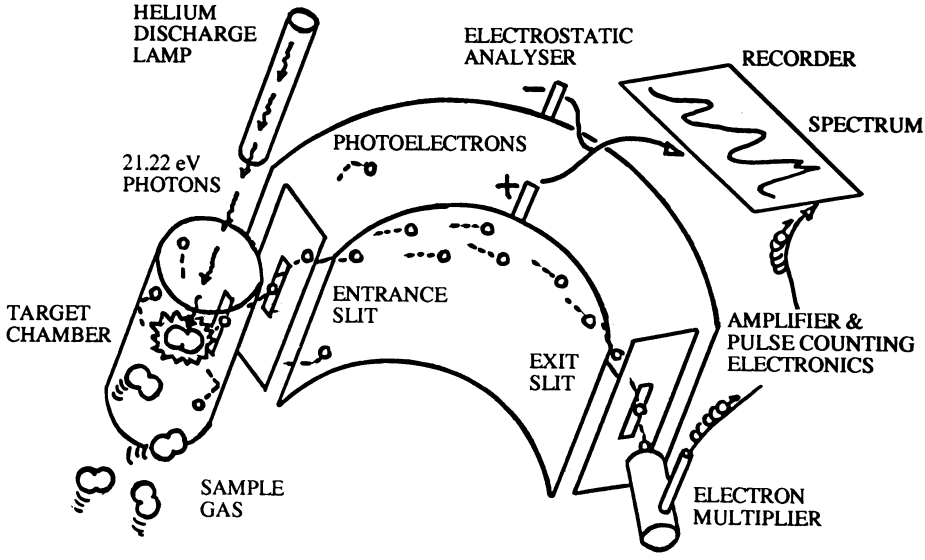


FIGURE 1. Ultraviolet photoelectron spectrometer for gaseous samples

where it has both verified and refined the description of electronic interactions which are fundamental to our understanding of molecular structure and reactivity. Its original form, as developed by Turner[1], is represented in Figure 1. Here He(I) radiation from a low pressure discharge in flowing helium gas is directed into a flowing sample gas of about 1 Pa in pressure. While this is ideally suited for organic gases and liquids, it is also convenient for organic solids, even those of higher melting point, because a heated inlet system utilizing controlled temperatures up to 500 °C is usually able to provide the required vapor pressure. As little as 2–3 mg of compound can be sufficient to obtain a reasonable spectrum, but a typical spectrometer can run efficiently using about 10 mg per hour, allowing the measurement of a number of spectra.

A valence photoelectron (PE) spectrum consists of a number of bands representing electrons of different kinetic energies (KE) produced by the different ionization channels available to the 21.22 eV photons of He(I) radiation. At this energy the valence p electrons of all elements are accessible as are the valence s electrons of some of the least electronegative elements. The energy scale is more conveniently converted to that of ionization energy (IE) using the relationship which recognizes the IE as the fundamental physical property of interest and allows the expression of data, obtained using various monochromatic ionizing lines (represented by $h\nu$) on a common scale.

$$\mathrm{IE} = h\nu - \mathrm{KE}$$

The principles and applications of UPS have been described in the monographs by Turner and coworkers[1], Eland[2] and Rabalais[3], and in the extensive series edited by Brundle and Baker[4]. Of particular use to the experimentalist is the handbook of spectra compiled by Kimura and coworkers[5].

B. Spectrum Analysis

The essential feature of the interpretation of a PE spectrum and an important reason for the success of the technique is the role of molecular orbital (MO) theory in both its qualitative and quantitative aspects. The qualitative description of ionization bands as associated with particular atoms or groups of atoms, or with particular bonds in a molecule relates closely to the chemist's picture of the molecule. The quantitative description, where the data from MO calculations are related to the experimental observations, commences with the Koopmans approximation, that the IEs of a molecule are in 1:1 correspondence with its orbital eigenvalues (ε) according to the relation illustrated in Figure 2.

$$IE_i = -\varepsilon_i$$

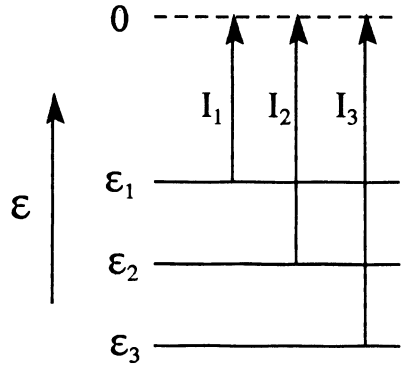


FIGURE 2. The Koopmans approximation

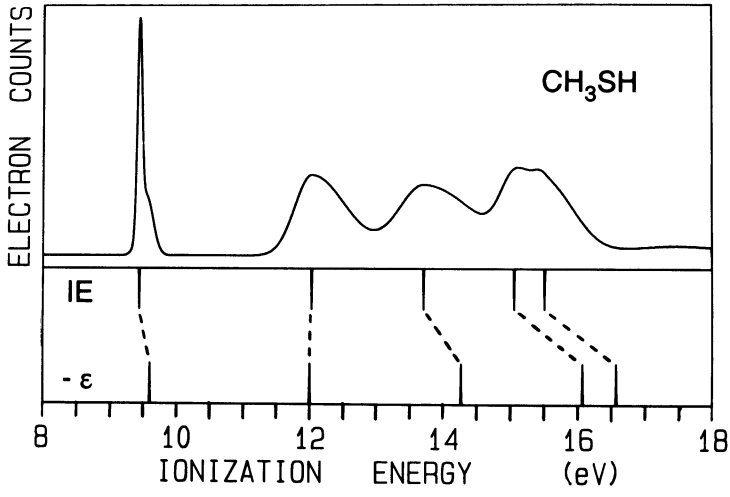


FIGURE 3. The photoelectron spectrum of CH_3SH: comparison of vertical ionization energies and calculated molecular orbital eigenvalues

This leads to more precise calculations of each IE as the energy difference of the molecule and its relevant cation states according to

$$IE_i = E(M_i^+) - E(M)$$

The independent-electron approximation, implicit in Hartree–Fock (HF) theory and the Koopmans approximation which derives from it, is shown to be an acceptable model for the description of outer-valence electron ionization in molecules, as illustrated in Figure 3 for CH_3SH, but is inadequate for ionization of the inner-valence electrons.

For small molecules the outer-valence bands generally exhibit vibrational fine structure which, in favorable cases, can be analyzed to provide a description of the geometry and fundamental vibrations of the cation state involved. For larger molecules, this band structure is either too complex or is not measurable at the spectroscopic resolution available. Here, knowledge of the cation states is limited to their vertical IEs and the spectrum is interpreted using the Koopmans approximation as a representation of the MO structure of the neutral molecule.

C. Summary of Review

The photoelectron spectroscopy of organic sulfur compounds was reviewed in detail by Gleiter and Spanget-Larsen in 1979[6]. At that time most of the published work in this area involved compounds of divalent sulfur, particularly those in which sulfur is bonded to one or two carbon atoms. Consequently, the review was confined to the cases of saturated sulfides, unsaturated sulfides and thiocarbonyls, though some polyvalent sulfur compounds were included.

The present review first updates the earlier survey in considering divalent sulfur compounds involving sulfur bonded only to carbon. Many of the compounds of this type are unstable intermediates produced by thermolytic techniques. The publications in this area indicate the utility of the UPS technique in monitoring the products of gas-phase reactions[7]. Second, compounds in which sulfur exhibits higher valence, such as when also bonded to oxygen, are considered. These are mostly relatively stable compounds such as sulfoxides and sulfones. The third group of compounds considered are those where sulfur is bonded to other heteroatoms including nitrogen or a halogen. A literature search did not reveal any UPS studies on sulfonic acids, esters or amides and only a few on sulfonyl halides, which are included here. For most of the molecules discussed here a complete (up to 18 eV) He(I) photoelectron spectrum is available.

D. Helium(II) Studies

A useful variation of the UPS technique using He(I) radiation is that involving He(II) radiation. The 40.8 eV photons of He(II) are produced in a standard He(I) light source when the pressure of the helium gas is lowered. The relative intensity of He(II) which results is somewhat low compared with He(I), so good-quality spectra can only be obtained when larger amounts of sample are available. The comparison of He(I) and He(II) spectra in the outer-valence region is particularly interesting for sulfur compounds, because a relative diminution in band intensity occurs in going from He(I) to He(II) when the ionized electron is associated with a MO possessing sulfur character. A comparison of He(I)/He(II) relative band intensity ratios offers a direct probe of sulfur orbital participation in the valence MOs of the molecule. Earlier examples involving organic sulfur compounds include studies on benzenethiol[8], thiirane[9] and thiophene[10], but more recent UPS studies of sulfur compounds discussed in this review have rarely utilized this technique.

E. Substituent Effects

While the interpretation of a PE spectrum is generally aided by reference to theoretical MO data considered within the framework of the Koopmans approximation, the description of IE trends in series of related molecules is, independently, an important element in spectral assignment. The influence of substituent effects including orbital interactions on IE shifts is the basis for this approach.

The outer-valence orbitals of most molecules, as revealed in UPS measurements and described by HF theory as linear combinations of atomic orbitals (the LCAO approximation), are often characterized by localized nonbonding character, such as the sulfur lone-pair, n_S, in $(CH_3)_2S$, or by localized bonding character, such as π_{CS} associated with the thiocarbonyl group. The prototype IEs, $I(n_s)$ in H_2S and $I(\pi_{CS})$ in CH_2S, can be considered as reference points, and the inclusion of substituent groups in place of the hydrogen atoms results in their variation. These shifts arise from the ionic and covalent interactions which are the basis of organic structural and mechanistic theory. Because of the use of LCAO–MO data to parallel UPS measurements, it is convenient to describe these effects within this formalism.

The ionic or inductive effect is associated with a shift of electronic charge due to a difference in electronegativity between two atoms or groups in a molecule. The charge shift has its origin in covalent interactions involving one or more lower energy σ bonding MOs. A simple example is the highly polar bond in hydrogen fluoride, HF, where the σ MO is represented by $c_1 1s + c_2 2p$ with $c_1 < c_2$. This inequality effectively moves electron density to the F atom, and the shift of electron density within the σ bonding MO results in an inductive effect on the higher energy localized nonbonding π orbitals on F. When electron density is withdrawn from an atom, a nonbonding orbital on that atom will exhibit an increased IE. The addition of electron density has the opposite effect, with the increased electron–electron repulsion energy causing a lowering of localized orbital IE.

The covalent or resonance interactions considered as substituent effects are often secondary effects, in that a localized atomic or group orbital may already have covalent character within the MO picture. The secondary covalent effect arises from additional orbital mixing arising from interaction with an orbital associated with the substituent. This interaction is largest when the participating basis orbitals are close (or identical) in energy, and diminishes with increased energy separation. However, spatial overlap between the basis orbitals is required, which means that they must be of the same symmetry, that is, belong to the same irreducible representation of the point group of the molecule. The overlap may be categorized in different ways depending on the relative positions of the interacting groups. If adjacent bonded atoms are involved this is the normal direct overlap; if the basis orbitals are located on nondirectly bonded atoms, a through-space (TS) overlap between them may be sufficient to produce interaction; if the groups are well-separated so that through-space overlap is negligible, a through-bond (TB) effect involving the participation of other orbitals, necessarily of the same symmetry, can facilitate the interaction. The interacting orbitals may be equivalent, say two n_S orbitals, or inequivalent, such as n_S interacting with π_{CC}, in which case two IEs of interest are analyzed. An interacting orbital may be of higher IE than the orbital of interest, and not readily identified among the closely-spaced bonding orbitals often associated with strongly overlapped PE bands. This is normally the case with the hyperconjugative effect, say of bonding CH orbitals acting on a localized nonbonding orbital such as n_S. The interaction of lower-lying σ orbitals of an alkyl framework with those of substituent groups is usually referred to as 'hyperconjugation', while the general term 'conjugation' refers to the interaction of π orbitals and/or n orbitals.

A further property of PE bands of relevance in this analysis is the breadth of the band, normally measured as the full-width-at-half-maximum (FWHM). A narrow band is

indicative of an effectively nonbonding and localized MO, whereas a strongly bonding or antibonding orbital appears as a broad PE band of up to 1 eV in FWHM. A change in bandwidth associated with substitution is interpreted as a change in orbital composition normally involving admixture of substituent orbital character, which may be either bonding or antibonding in its effect.

F. Sulfur Nonbonding Ionizations

The original studies of simple thiols and sulfides, both aliphatic and alicyclic, indicated the feature of interest to be the first ionization band associated with the nonbonding valence p orbital on S[6]. As illustrated in Figure 4, the n_S band is of narrow profile in both H_2S ($I_1 = 10.48$ eV) and CH_3SH ($I_1 = 9.41$ eV) so the IE shift of -1.07 eV is due to the inductive effect of CH_3 in which electron density moves onto the S atom. However in $(CH_3)_2S$ ($I_1 = 8.72$ eV), as well as a further inductive shift, the n_S band is subject to broadening due to CH hyperconjugative interaction. With increased alkyl substitution

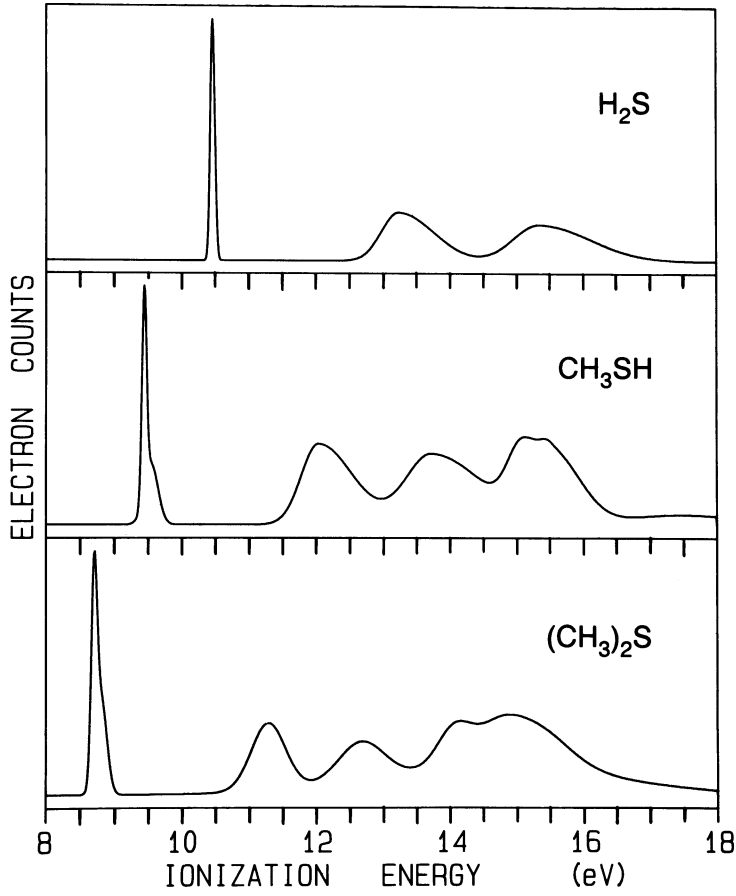
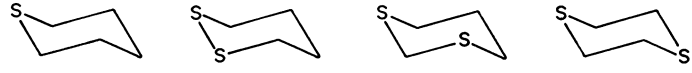


FIGURE 4. Photoelectron spectra of H_2S, CH_3SH and $(CH_3)_2S$

these effects are increased, but the MO is still able to be considered as of dominant n_S character, with the PE band usually well-separated from the higher ionizations.

Interaction between equivalent n_S orbitals is exemplified by the three dithianes, $C_4H_8S_2$, **2–4** described by Gleiter and Spanget-Larsen[6], where the n_S IEs (Figure 5) can be compared with that of thiane, $C_5H_{10}S$ (**1**) ($I_1 = 8.45$ eV), though the latter is likely to be subject to greater CH hyperconjugative effects.



(1) (2) (3) (4)

The simplest interaction between two equivalent n_S orbitals involves the TS mechanism illustrated by the MO scheme in Figure 6, where the equivalent basis orbitals φ_1 and φ_2 result in symmetry-adapted linear combinations $\varphi^+ = (1/\sqrt{2})(\varphi_1 + \varphi_2)$ called the symmetric or + combination involving positive overlap, and $\varphi^- = (1/\sqrt{2})(\varphi_1 - \varphi_2)$ called the asymmetric or − combination involving negative overlap. This is the basis of the n_S^-/n_S^+ splitting of 0.95 eV observed for 1,2-dithiane (**2**) despite the fact that the chair conformation of the six-membered ring involves a dihedral angel of $\sim 85°$ between the directions of two S 3p orbitals.

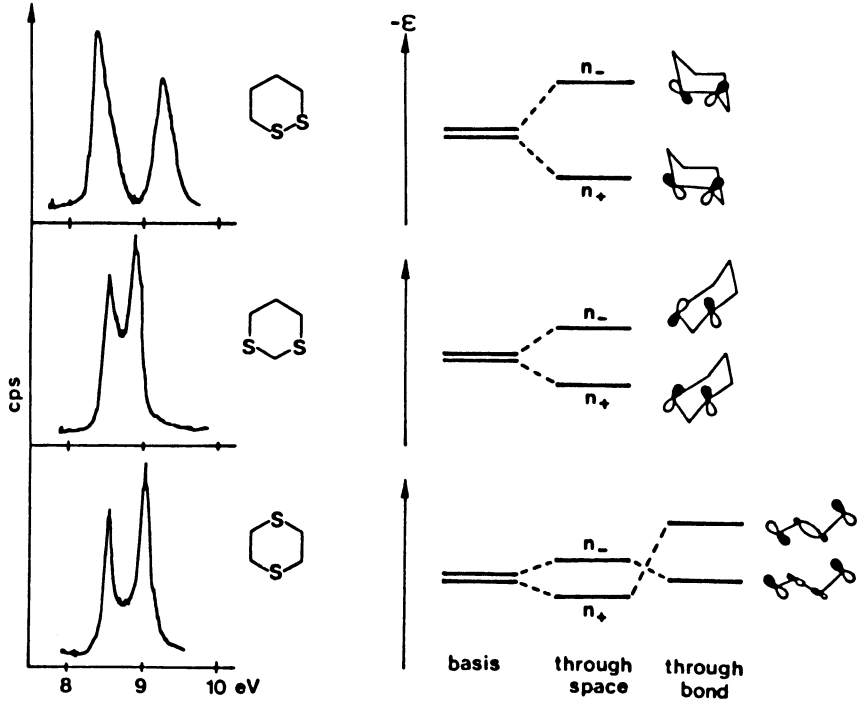


FIGURE 5. The n_S bands in the PE spectra of the dithianes illustrating 'through-space' and 'through-bond' effects. Reproduced by permission of Springer-Verlag from Reference 6

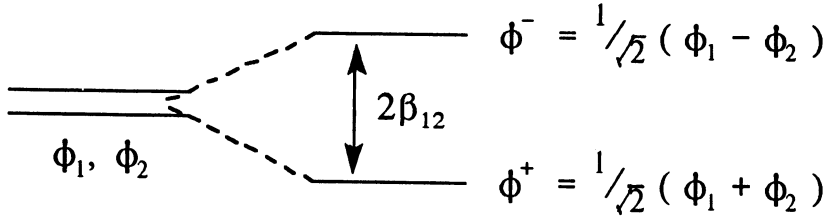


FIGURE 6 The through-space interaction scheme

The strength of the interaction is given by the resonance integral β_{12}, which is half of the IE difference. If the TS interaction is unaffected by other mechanisms, the mean IE of φ^- and φ^+ should be the same as that of φ_1 in the related molecule containing only one group. In 1,2-dithiane the mean of the first and second IEs is 8.83 eV, which is somewhat greater than the $I_1 = 8.45$ eV of thiane, and closer to the $I_1 = 8.65$ eV of thietane, C_3H_6S, which involves comparable CH hyperconjugation.

In 1,3-dithiane (**3**), the splitting is reduced to 0.41 eV consistent with a TS interaction over a larger distance. However, the splitting of 0.45 eV in 1,4-dithiane (**4**) is larger than expected considering the greater spatial separation of the n_S orbitals. This is explained by the intervention of a through-bond interaction, which not only allows a greater interaction between the orbitals but interchanges their natural order from $I(n_S^-) < I(n_S^+)$ to $I(n_S^+) < I(n_S^-)$.

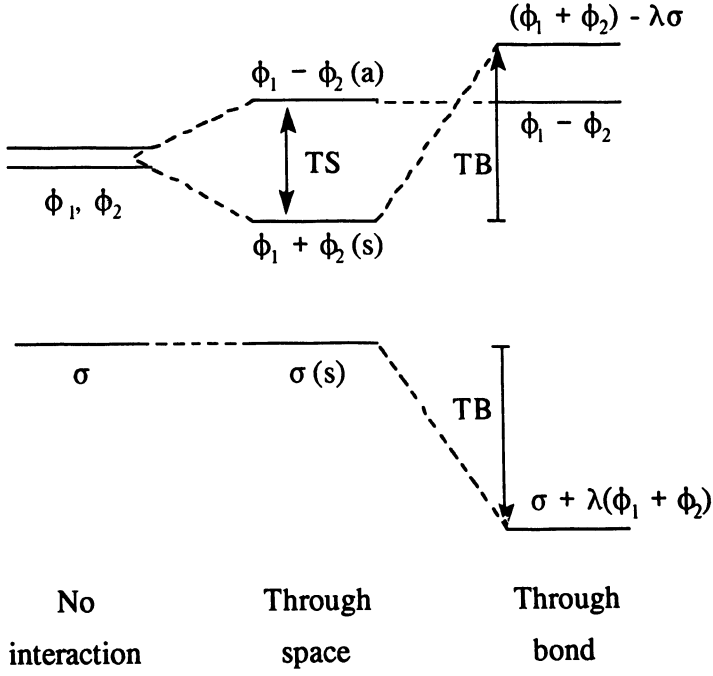
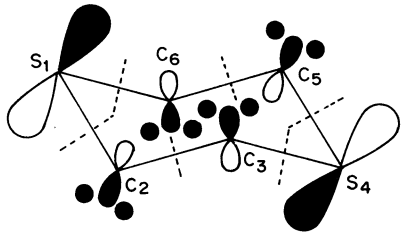


FIGURE 7. The through-bond interaction scheme

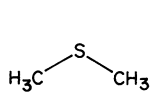
Through-bond interaction involves a third reasonably-localized orbital of an appropriate symmetry to overlap with either or both of the natural ± combinations of the equivalent group orbitals. The simplest case is illustrated in Figure 7. In the case of 1,4-dithiane, the bonding σ orbitals associated with the C_2—C_3 and C_5—C_6 bonds are of the same symmetry as the n_S^+ orbital, so that, despite the inequivalence represented by their different energies, the strong through-bond interaction raises the n_S^+ orbital above the n_S^- orbital. The n_S^+ orbital can then be represented as $n_S^+ - \lambda(e_g)$, with the antibonding admixture provided by one ethane-like e_g MO of each of the —CH_2—CH_2— groups, representing the through-bond destabilization.



The orbital interactions which involve inequivalent groups can also be described in terms of inductive and resonance contributions. However, resonance interactions, whether they are of the through-space or through-bond types, require that the interacting group orbitals be of similar energy and the same symmetry. The overlap criterion is always important, but the energy criterion is generally more sensitive. However, while two localized groups may be of different energies in one molecule, inductive effects in a related molecule can bring their energies closer and facilitate a resonance interaction.

G. Sulfur–Oxygen Interactions

Among the many classes of organic sulfur compounds containing sulfur–oxygen bonds, those which have been amenable to study in the gas phase by UPS are mostly either sulfoxides, RR′S=O, or sulfones RR′S(=O)$_2$. The properties of the formal S = O double bond in each of these general compounds is best seen in a comparison with the analogous monosulfide, RR′S. A comparison of the PE spectra and associated MO wavefunctions for $(CH_3)_2S$ (**5**), $(CH_3)_2SO$ (**6**) and $(CH_3)_2SO_2$ (**7**) illustrates the variation in the nature of the localized n_S orbital in terms of the incorporation of the π_{SO} and n_O orbitals associated with the S = O moiety. An important aspect of this comparison involves the differences in symmetry and geometry of these molecules. So **5** and **7** are of C_{2v} symmetry, but **6** is of C_s symmetry. There is variation in the CSC bond angles, being 98.9° in **5**, 96.6° in **6** and 103.3° in **7**. There are also variations in the C—S and S = O bond lengths. The low IE region of their PE spectra, shown in Figure 8, are characterized by one band in **5**, the highly localized $n_S(b_1)$ with $I_1 = 8.68$ eV[5], but two bands in **6**, at $I_1 = 9.01$ eV and $I_2 = 10.17$ eV[11], and four bands in **7** with I_1 to I_4 being respectively 10.65, 11.18, 11.65 and 12.00 eV. These



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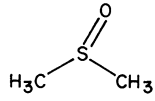

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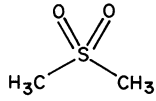

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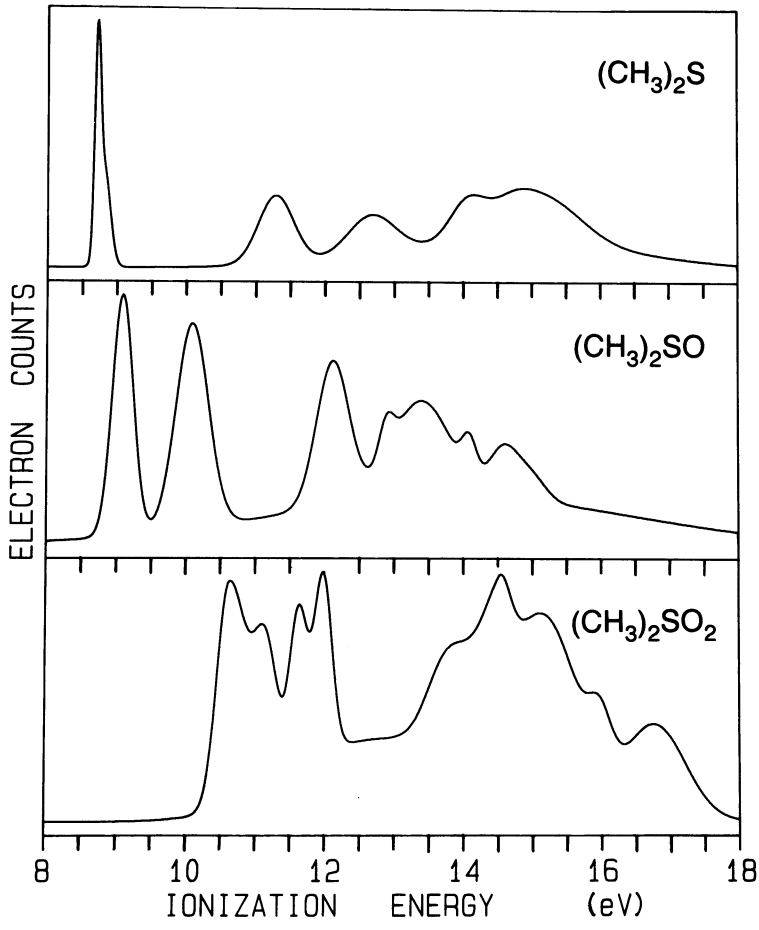


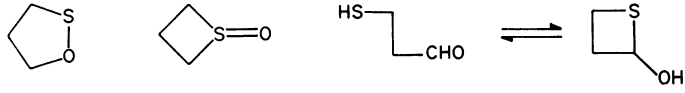
FIGURE 8. Photoelectron spectra of $(CH_3)_2S$, $(CH_3)_2SO$ and $(CH_3)_2SO_2$

latter values, obtained by Bock and coworkers[12], show small variations with the earlier results of Muller and Schweig[13] who obtained vertical IEs of 10.80, 11.15, 11.75 and 12.07 eV, respectively. The first band in **6** is assigned as of dominant n_S character, but with considerable antibonding admixture of n_O, to give $n_S - n_O$ and a recognizably broader band than in **5**. The second band of **6** is of π_{SO} character with some added CH hyperconjugative contribution. In **7** the S atom has lost its localized n_S electrons and with the approximately tetrahedral disposition of bonds the S 3p orbitals are associated with σ bonding. The uppermost MOs are then mostly of O 2p origin, involving in particular the two orbitals from each O atom which lie perpendicular to the related S = O bonds. The n_O orbitals lie in the SO_2 plane and the π_O orbitals (including a minor proportion of S character) are perpendicular to these. A combination of through-space and through-bond

interactions leads to the assignment $4b_1(\pi_O^+ - \sigma_{CS}^-) < 4b_2(n_O^-) < 6a_1(n_O^+ - \sigma_{CS}^+) < 2a_2(\pi_O^-)$, involving the appropriate $\pm$ combinations of the oxygen orbitals, for the four low IE bands.

Hence the outer MO structures in RR'S, RR'S = O and RR'S(= O)$_2$ are significantly different, so in considering their PE spectra the three classes of compounds are best treated separately. Nevertheless, a comparative study of interest is that by Heilbronner and coworkers[14] which concerns the conformational effects of large substituents in these systems. The PE spectra of the alkyl phenyl sulfides, sulfoxides and sulfones are compared for increasing size of the alkyl group from methyl to ethyl to *t*-butyl. The results are interpreted to indicate that in the sulfides the *S,R*-bond is twisted out of the planar conformation with increasing size of the alkyl group, whereas in the sulfoxides and sulfones the preferred conformation, with the *S,R*-bond perpendicular to the phenyl group plane, seems to be independent of the size of R. These conclusions are in agreement with previous conjectures concerning the preferred conformations of alkyl phenyl sulfoxides and sulfones.

The S—O single bond is associated with instability and only one molecule containing this structure, 1,2-oxathiolane (**8**), has been studied to date by UPS. In the investigation by Jorgensen and Carlsen[15], the product of the gas-phase pyrolysis of 3-(phthalimidothio)-1-propanol was identified by its PE spectrum as that of **8**, since the other possible products, thietane-1-oxide (**9**) and 3-mercaptopropanal/thietan-2-ol (**10a**–**10b**) are eliminated as they and their spectra are known from other syntheses. MNDO calculations show that **8** is essentially planar, so the large splitting of 2.38 eV observed between the first (I_1 = 8.51 eV) and second (I_2 = 10.89 eV) bands arises from a maximized conjugative interaction of the parallel n_S and n_O orbitals. The observation that these bands are broadened coincides with the description of the outermost MOs as asymmetric $\pm$ combinations, $n_S - n_O$ and $n_O + n_S$ respectively.



(**8**) (**9**) (**10a**) (**10b**)

Another unique molecule, also the only member of its class studied to date using UPS, is $CH_2{=}S{=}O$, 'sulfine' (thioformaldehyde S-oxide). In contrast to other known thiocarbonyl S-oxides, 'sulfine' had defied synthesis until Bock and coworkers[16] achieved its generation by pyrolysis of each of 1,3-dithietane-1-oxide and methanesulfinyl chloride, and its identification by UPS. By comparison with the isoelectronic SO_2 and the isovalence-electronic S_2O, and using the results of *ab initio* calculations, the low IE bands of $CH_2{=}S{=}O$ are readily assigned as I_1 = 10.3 eV (π_{nb}, 3*a*″) and I_2 = 10.7 eV ($n_S - n_O$, 13*a*′).

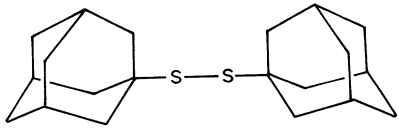
II. SULFIDES

A. Saturated Thiols, Sulfides and Disulfides

The majority of UPS studies of saturated sulfides and disulfides were reported during the 1970s and included in the review by Gleiter and Spanget-Larsen[6]. The small number of more recent studies are discussed here.

As described earlier, the n_S ionization is the feature of interest in the PE spectra of the sulfides. This has hence been utilized as a convenient probe to monitor the effects of group substitution, as illustrated in a study by Block and coworkers[17] of the silicon β-effect based on substitution by trimethylsilyl groups in CH_3SH, $(CH_3)_2S$ and thiirane ($I_1 = 9.03$ eV), and comparisons made with the analogous *t*-butyl substitutions. Substitution of the trimethylsilyl group for one, two and three of the hydrogens of methanethiol lowers the I_1 by 0.50, 0.91 and 1.28 eV, respectively, or 0.50, 0.46 and 0.43 eV, respectively, *per trimethylsilyl group* in these three compounds. By way of comparison, substitution of two hydrogens of methanethiol by *t*-butyl groups lowers the I_1 by 0.73 eV, or 0.37 eV per *t*-butyl group. The authors concluded that in particular tris(trimethylsilyl)methanethiol, $(Me_3Si)_3CSH$ ($I_1 = 8.18$ eV) should possess high electron density at sulfur and should be an excellent donor toward soft electrophiles.

In organic disulfides, the adjacent sulfur atoms provide n_S orbitals whose interaction is indicative of the stereochemistry of the attached structure. In symmetric systems the n_S^-/n_S^+ splitting based on the IEs of the antibonding ($n_S^- = n_S - n_S$) and bonding ($n_S^+ = n_S + n_S$) MOs varies as a function of the CSSC dihedral angle[18]. The 'natural' S—S dihedral angle for strain-free disulfides is well-established as 80–85°. Placement of the disulfide moiety in a ring can cause reduction of θ(CSSC) to nearly 0°. Remarkably few torsional angles larger than 85° have been observed. A study by Jorgensen and Snyder[19] on di-*t*-adamantyl disulfide (**11**) as representative of bulky disulfides showed an energy difference ($I_2 - I_1$) of 0.51 eV suggesting a dihedral angle of θ(CSSC) = 103°. Calculations suggest that *trans* disulfides may only be realizable with much larger alkyl substituents.



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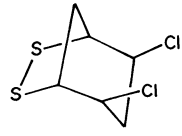

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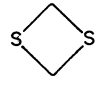

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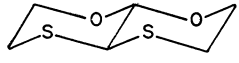


(14)

(15)

By comparison *cis*-disulfides are more readily synthesized by incorporation of a S—S moiety in a relatively rigid polycyclic hydrocarbon framework, such as provided by the bicyclooctanes. The PE spectrum measured for 2,4-dichloro-6,7-dithiabicyclo[3.2.1]octane (**12**) by Jorgensen and McCabe[20] shows the largest sulfur lone-pair energy gap ever observed (Figure 9). The splitting is measured as 2.11 eV confirming the *cis* conformation and directly providing a β_{SS} value of ~ -2.1 eV, previously available only by extrapolation. However, there is evidence that the second band, n_S^+, is affected by through-bond interaction with a σ_{CS} orbital.

Longer range n_S–n_S interactions, where the S atoms are separated by one or more carbons, are expected to be much weaker. However, if through-bond effects occur they can completely obscure the smaller through-space effect. One of the simplest molecules which

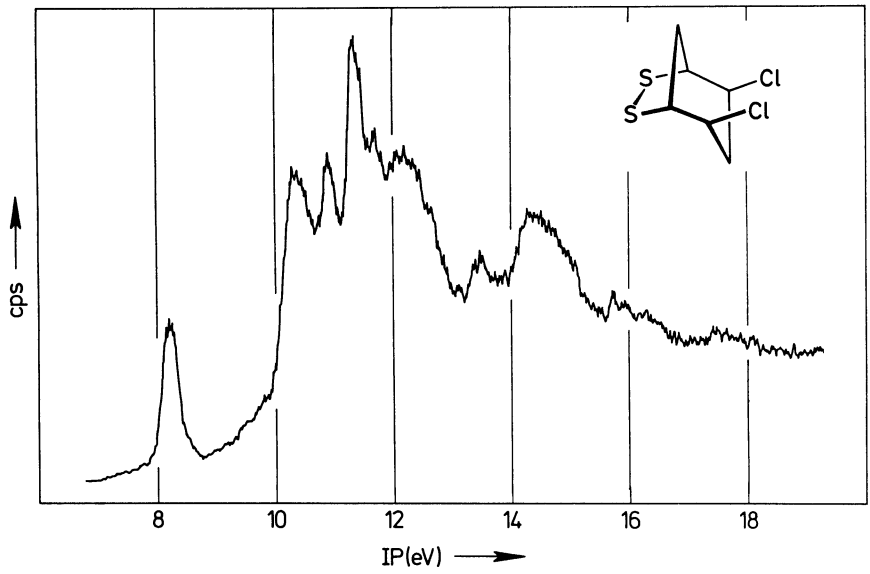


FIGURE 9. Photoelectron spectrum of 2,4-dichloro-6,7-dithiabicyclo[3.2.1]octane (**12**). Reproduced by permission of Pergamon Press from Reference 20

demonstrates this behavior is 1,3-dithietane (**13**), which was synthesized by Block and coworkers[21] by reduction of its S-oxide, and investigated by UPS. The first and second PE bands are clearly of n_S character, and comparison with the PE spectra of thietane and cyclobutane shows that replacement of each of the two CH_2 groups of the latter by sulfur adds one low IE band to the spectrum, while simultaneously removing the degeneracy of the e_u ring orbitals. A MINDO calculation of Koopmans IEs fully supports this assignment which, as shown in Figure 10, has $I_1 = 8.95$ eV ($n_S^+ - \sigma_{CH_2}^+$) and $I_2 = 9.43$ eV (n_S^-) with through-bond σ_{CH_2} interaction reversing the through-space order of the n_S^-/n_S^+ ion states.

The first *anti, anti* acetal to be studied by UPS, *trans*-1,8-dioxadecalin, was compared with that of *trans*-1,8-dioxa-4,5-dithiadecalin (**14**) by Jorgensen and Norskov-Lauritsen[22]. In the latter a large n_O^-/n_O^+ splitting of 0.65 eV, which is interpreted using a through-bond model involving the C—C bonds, is contrasted with a small n_S^-/n_S^+ gap of 0.29 eV. The observation that the lowest of these overlapped n_S bands is relatively broadened indicates that through-bond interaction is responsible for this splitting.

Through-bond effects on the n_S IEs in 1,2,4-trithiolane (**15**) are shown to be subtly affected by methyl substitution as observed in the PE spectra obtained by Bock and coworkers[23] for 3,5-dimethyl-1,2,4-trithiolane and tetramethyl-1,2,4-trithiolane.

B. Unsaturated Thiols and Sulfides

In unsaturated organic sulfides the sulfur nonbonding orbital, n_S, can show strong resonance interaction with an adjacent π_{CC} orbital. However, the interaction can be reduced if the alignment or symmetry of the relevant localized orbitals are unfavorable.

For aliphatic compounds n_S/π_{CC} interactions have been widely studied. The UPS of mono- and bis(methylthio)acetylene measured by Bock and coworkers[24] show the latter

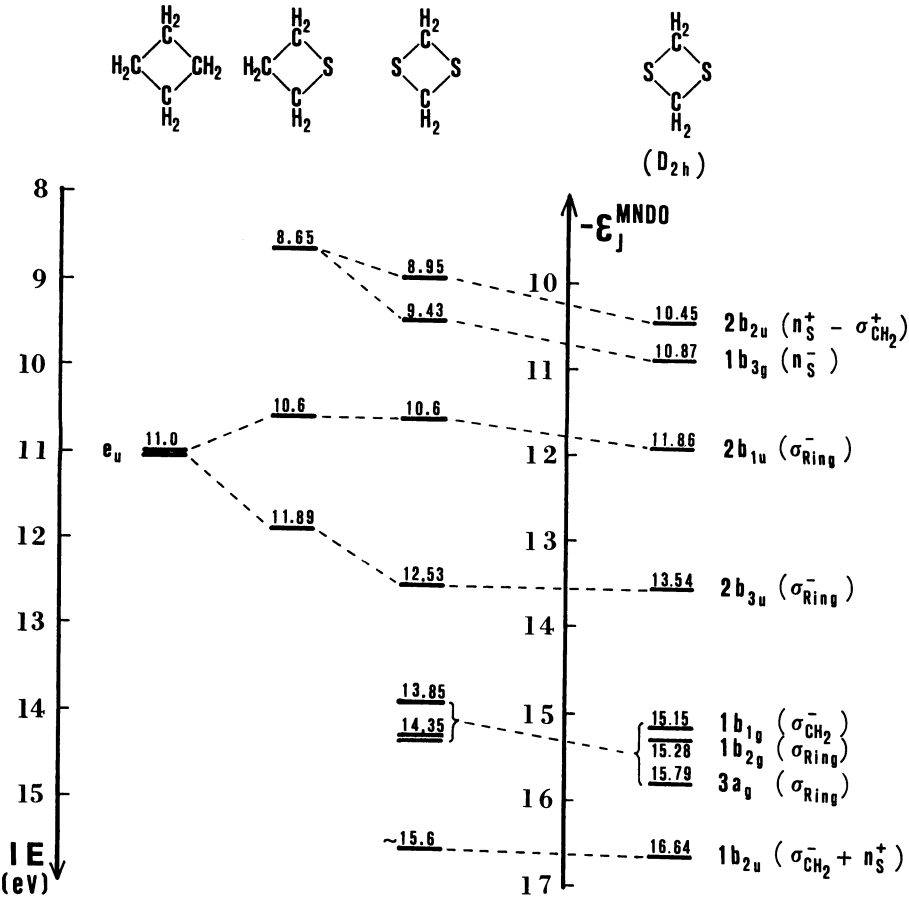
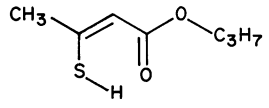


FIGURE 10. Correlation of calculated and experimental IEs of 1,3-dithietane (**13**) and comparisons with IEs of related molecules. Reprinted with permission from Reference 21. Copyright (1982) American Chemical Society

to be of C_2 symmetry with a SCCS dihedral angle of ~86°. In HC≡CSCH$_3$ the strong n_S/π_{CC} interaction lifts the degeneracy of the acetylenic π orbitals. The first IE (8.81 eV) is mainly of S lone-pair character, being represented as $n_S - \pi_{CC}$, with the complementary $\pi_{CC} + n_S$ orbital assigned as the third IE (11.62 eV). The second IE (10.34 eV) is of the other, relatively unperturbed acetylenic π_{CC} orbital. In CH$_3$SC≡CSCH$_3$, which is generated by gas-phase pyrolysis of 3,4-bis(methylthio)cyclobutene-1,2-dione, the π_{CC} MOs by contrast are near-degenerate and, because of the dihedral angle being close to 90°, each interacts exclusively with one of the n_S orbitals. However, the spectrum shows a small splitting of 0.30 eV for the $n_S - \pi_{CC}$ bands indicating a small interaction producing the two resulting orbitals $(n_S - \pi_{CC}) \pm (n_S - \pi_{CC})$. The complementary $\pi_{CC} + n_S$ basis orbitals also exhibit a small splitting of 0.32 eV assigned analogously to the $(\pi_{CC} + n_S) \pm (\pi_{CC} + n_S)$ mixtures.

A similar n_S–π_{CC} interaction in the example of propyl-3-mercaptocrotonate (**16**) studied by Jorgensen and coworkers[25] provides an isolated first band at 8.81 eV. While this β-thioxo ester may show interconverting enol–enethiol tautomers, observation of the PE spectrum confirms that it is practically exclusively of enethiol structure.



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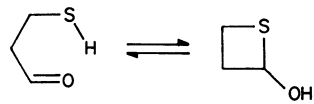
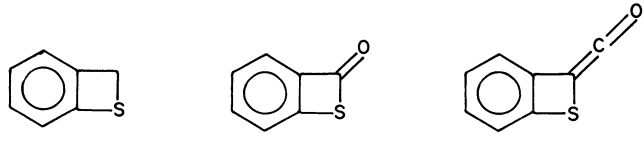


(10a) (10b)

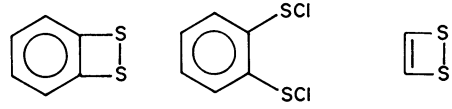
Likewise, in the case of 3-mercaptopropanal (**10a**), which is generated by thermal decomposition of the corresponding oligomer, the PE spectrum is expected to indicate the possible presence of its tautomer thietan 2-ol (**10b**). The spectrum obtained by Jorgensen and coworkers[26] is characterized by two well-resolved low-energy peaks at 9.45 and 10.28 eV, which are assigned as thiol n_S and carbonyl n_O ionizations. It is concluded that the gas-phase molecule exists in the intramolecular hydrogen-bonded form comprising a relatively weak SH--O linkage. A minor peak at 8.9 eV is clearly due to a minor constituent, but the authors conclude that this shoult be ascribed to the oligomeric species which is likely to contain a sulfide moiety with an α-hydroxy group.

Cyclic unsaturated sulfides find the sulfide group participating commonly in four-, five-, six- or seven-membered rings. A number of thietes and dithietes have been studied by UPS. For the related benzothiete (**17**), thiobenzpropiolactone (**18**) and benzothiete ketene (**19**), each generated by high-temperature pyrolysis by Schultz and Schweig[27,28], a strong n_S–π interaction involving the outermost degenerate e_{1g} orbitals of benzene is observed. Whereas **17** shows three well-resolved bands of $A''(\pi)$ symmetry as $I_1 = 8.24$ eV, $I_2 = 9.32$ eV and $I_3 = 10.31$ eV, the additional carbonyl group in **18** inductively raises these IEs to 8.56, 9.94 and 10.87 eV, respectively, while the n_O orbital of $A'(\sigma)$ symmetry strongly overlaps the second IE at 9.94 eV. In **19** the n_O orbital is of $A''(\pi)$ symmetry contributing to the π_{CCO} MOs of the ketene moiety, and hence interacting in a complex pattern with the outer $A''(\pi)$ orbitals of the benzothiete unit.



(17) (18) (19)

Benzo-1,2-dithiete (**20**) is a transient molecule which has been produced in the low-pressure gas-phase pyrolysis of 1,3-benzodithiol-2-one by Schweig and coworkers[29], and of 1,2-benzenedisulfenyl chloride (**21**) by Bock and Rittmeyer[30]. The constrained *cis* geometry of the disulfide group produces $n_S^-(a_2)$ and $n_S^+(b_1)$ group orbitals which interact respectively with the $\pi(e_{1g}) = a_2 + b_1$ orbitals of the benzene unit. Because the $\pi(b_1)$ orbital of benzene has a greater density at the 1 and 2 positions, the b_1 interaction is expected to be stronger than the a_2 interaction. As illustrated by the PE spectrum shown in Figure 11, the a_2 separation for $I_1 = 8.46$ eV and $I_3 = 10.17$ eV is measured as 1.71 eV, whereas the b_1 separation for $I_2 = 8.77$ eV and $I_4 = 11.2$ eV is obtained as 2.4 eV, in agreement with this prediction.



(20) (21) (22)

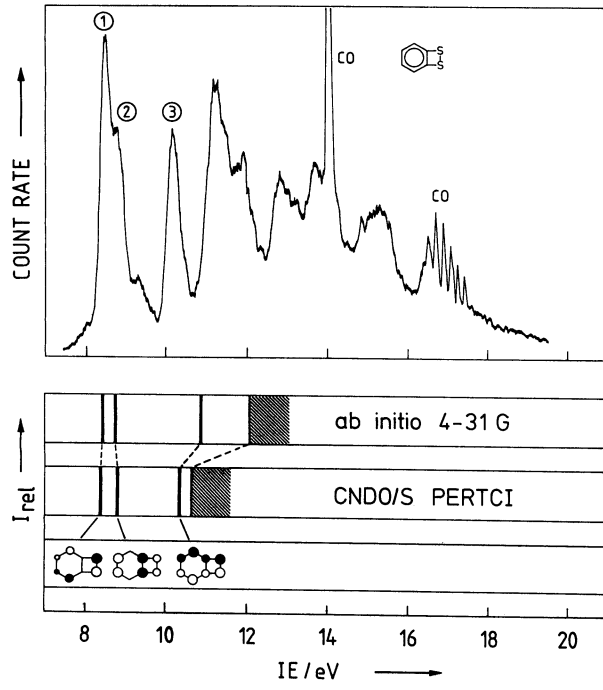
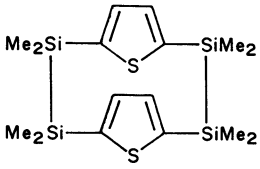


FIGURE 11. Correlation of experimental and calculated IEs of benzodithiete (**20**). Reprinted with permission from Reference 29. Copyright (1982) American Chemical Society

The parent 1,2-dithiete (**22**), synthesized by Schweig and coworkers[31] using vapor pyrolysis of 1,3-dithiol-2-one, is shown by UPS to be favored over its high- energy isomer dithioglyoxal. The PE spectrum of **22** shows strongly overlapped low IE bands at $I_1 = 9.05\,\text{eV}$ and $I_2 = 9.36\,\text{eV}$. On the basis of MO calculations these are assigned, in the Koopmans approximation, to b_1 and a_2 orbitals, respectively. The planar geometry is expected to produce well-separated $n_S^-(a_2)$ and $n_S^+(b_1)$ orbitals of the disulfide group, but interaction of the latter with the ethylenic $\pi(b_1)$ orbital results in a $n_S^+ - \pi$ combination which is lowered sufficiently in IE to become the first IE of 1,2-dithiete. The complementary $\pi + n_S^+$ orbital appears at 12.61 eV, as I_5, overlapping the lower IE pair of $I_3 = 11.83\,\text{eV}$ and $I_4 = 12.31\,\text{eV}$ which are associated with the $n_S - n_S$ (b_2) and $n_S + n_S$ (a_1) combinations of sulfur orbitals of σ type. The sulfur contribution to all five bands is shown by their diminution in the He(II) spectrum measured for the substituted molecule, 3,4-bis(trifluoromethyl)-1,2-dithiete. The PE spectrum of 3,4-dimethyl-1,2-dithiete analogously shows the expected lowered IEs, by an average of 0.5 eV, due to the hyperconjugative effect of the methyl substituents.

The thiophene ring is a common feature of aromatic sulfur compounds and numerous molecules incorporating this unit have been studied by UPS[6]. Recent studies have extended this effort.

Octomethyltetrasila[2.2](2,5)thiophenophane (**23**) is an analogue of the [2.2]paracyclophanes and its PE spectrum, measured by Gleiter and coworkers[32], shows a smaller through-space and a larger through-bond interaction between the two rings than for the latter. The through-bond interaction yields a different low IE orbital sequence as a result.



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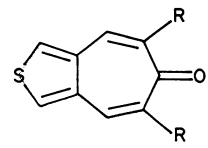
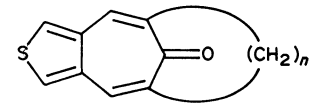


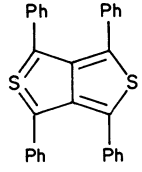
(24) R=H
(25) R=CH_3



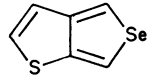
(26) $n=5$
(27) $n=6$

The thiophene-fused tropones studied by Gleiter and coworkers[33] are heterotropones and the PE spectra of 6*H*-cyclohepta[*c*]thiophen-6-one (**24**), 5,7-dimethyl-6*H*-cyclohepta[*c*]thiophen-6-one (**25**), 5,7-pentamethylene-6*H*-cyclohepta[*c*]thiophen-6-one (**26**) and 5,7-hexamethylene-6*H*-cyclohepta[*c*]thiophen-6-one (**27**) can be compared with the spectra of both the benzologue tropones and of thiophene. Using experimental correlations and the results of semiempirical MO calculations, the first five ionization bands have been assigned as $\pi < \pi < n < \pi < \pi$. The n MO, the highly localized nonbonding orbital of oxygen lying in the plane of the tropone rings, is characterized by a distinct sharp band, but the n_S orbital of sulfur is delocalized over the π network.

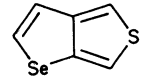
The least stable of the four isomeric thienothiophenes is thieno[3,4-*c*]thiophene, which has defied all efforts towards its isolation. Its tetraphenyl derivative (**28**) has been synthesized and its PE spectrum, obtained by Schweig and coworkers[34], is interpreted as verifying that all of these 'nonclassical' condensed thiophenes are aromatic like thiophene itself. The HOMO of **28** is of a_u symmetry and appears at the very low IE of 6.19 eV. When referenced against its counterpart in naphthalene, it is shown to be missing stabilization from the π^* orbitals, which is the explanation for its high reactivity.



(28)



(29)



(30)

While the more stable thieno[3,4-*b*]thiophene has been isolated with difficulty, its mono-seleno analogues, **29** and **30**, appear to be more stable. The PE spectra measured by Gleiter and coworkers[35] for these two isomers are closely similar, but the small differences in their correlating IEs of bands 1 to 4 relate simply to the relative contributions of n_S and n_{Se} to each π orbital, with Se character providing an influence toward lower IE. This is seen most convincingly in the comparison of both molecules with their diseleno analogue shown in Figure 12.

The PE spectrum of 2,5-dihydrothiophene (**32**) measured by Schmidt and Schweig[36], and shown in Figure 13, is in striking contrast to that of thiophene (**31**)[10] in that the n_S interaction with the ethylenic moiety in **32** is enhanced in comparision with that containing the butadiene moiety in **31**. This can be seen in Figure 14 to involve the effect of CH hyperconjugation on the n_S energy, which is absent in **31**, but of considerable influence in **32** and the fully saturated tetrahydrothiophene **33**. The conjugative interaction of the n_S

(31)

(32)

(33)

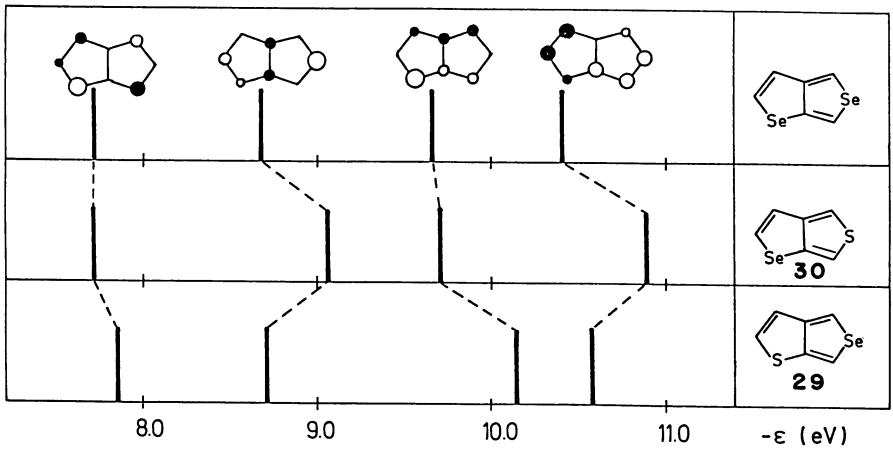


FIGURE 12. Correlation of π-MO eigenvalues of the seleno analogues of thieno[3,4-*b*]thiophene. Reproduced by permission of VCH Verlagsgesellschaft from Reference 35

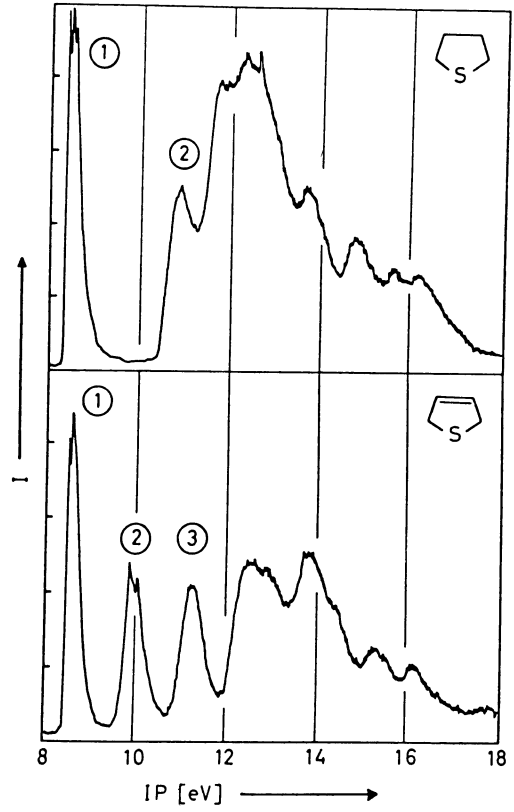


FIGURE 13. Photoelectron spectra of tetrahydrothiophene (**33**) and 2,5-dihydrothiophene (**32**). Reproduced by permission of Pergamon Press from Reference 36

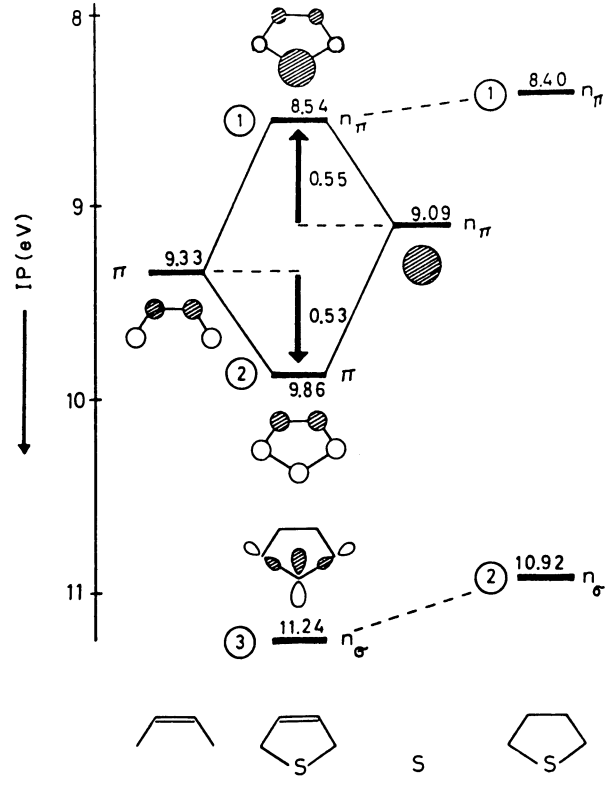
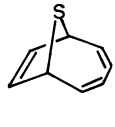


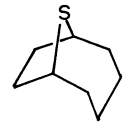
FIGURE 14. Correlation of experimental IEs of 2,5-dihydrothiophene (**32**) and tetrahydrothiophene (**33**) illustrating the n_S/π_{CC} interaction in **32**. Reproduced by permission of Pergamon Press from Reference. 36

and π_{CC} orbitals is enhanced when their basis energies are close. Because CH hyperconjugation in **32** lowers the n_S IE, and the ethylenic IE is intermediate between the two π IEs of the butadiene moiety, the n_S–π interaction is responsible for the relatively low first IE of 8.54 eV. This band is dominated by n_S character, while the corresponding band in thiophene is the second band at 9.52 eV.

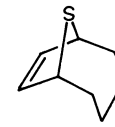
In 9-thiabicyclo[4.2.1]nona-2,4,7-triene (**34**), the n_S orbital is spatially located such that conjugation with each of the ethylene and butadiene moieties might be expected. In their analysis of the PE spectrum of **34**, Schweig and coworkers[37] have measured the spectra of the related molecules 9-thiabicyclo[4.2.1]nonane (**35**), 9-thiabicyclo[4.2.1]non-7-ene (**36**) and 9-thiabicyclo[4.2.1]nona-2,4-diene (**37**). Based on comparisons with the results of CNDO/S calculations, the spectra show that there is localized π interaction between sulfur and ethylene, but not with the butadiene moiety. Hence the butadiene orbitals $\pi_{4,a}$ and $\pi_{4,s}$ are not conjugated with the ethylene orbital $\pi_{2,s}$ in the parent molecule bicyclo[4.2.1]nona-2,4,7-triene (**38**), and this transfers to **34** with S substitution in the 9-position. However, the basis energy of $\pi_{2,s}$ at 9.02 eV places it much closer to the n_S energy of 8.16 eV than the $\pi_{4,s}$ at 10.55 eV, which greatly reduces the magnitude of any n_S–$\pi_{4,s}$ interaction. While $\pi_{4,a}$ at 8.36 eV is close to n_S in energy, its antisymmetric form prevents its interaction with n_S.



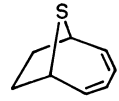
(34)



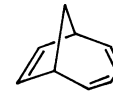
(35)



(36)



(37)

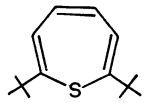


(38)

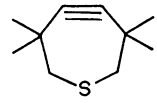
A variation of sulfur in a five-membered ring is provided by 2,3-dihydro-2,3-dimethylenethiophene (**39**), which is shown by its PE spectrum, measured by Munzel and Schweig[38], to be the only component present in the isomerization equilibrium with 1,2-dihydrocyclobuta[*b*]thiophene (**40**). The results of MNDO–PERTCI calculations, performed by the authors, and which accompany the spectrum illustrated in Figure 15, show that strong interaction of n_S with the outer π_{CC} orbitals in **39** results in strong overlapping of the second and third bands in its spectrum. The calculated spectrum for its isomer **40** is strikingly different, with a reduced degree of n_S–π_{CC} interaction providing a first IE rather higher than that for **39**.

(39) (40)

The thiepins involve sulfur contributing to a 8π system of a seven-membered ring structure. Of the hetero-8π systems, oxepin, azepine and thiepin, the latter is the most elusive. While thiepin itself is unstable due to its ready extrusion of sulfur, its derivative 2,7-di-*t*-butylthiepin (**41**) is thermally stable. Its PE spectrum, measured by Gleiter and coworkers[39], has been compared with those of its 4-methyl and 4,5-dimethyl derivatives. The spectra of each of these molecules is characterized by four low IE bands of which the second and third bands are strongly overlapped. The first IEs of the three molecules are at 7.7, 7.6 and 7.5 eV, respectively, showing the expected downward trend associated with the methyl substitution. While an X-ray structure of **41** shows it to be of boat conformation, the n_S–π_{CC} interactions can still be treated using a simple HMO model. The three π_{CC} orbitals of the hexatriene moiety include two of *a'* symmetry able to interact with the n_S orbital. Because of their relative energies, this interaction is small, so that the third band at 9.3 eV is assigned as the n_S ionization. *Ab initio* calculations provide Koopmans IEs which show fair agreement with this assignment, except for disagreement over the sequence of the two close-lying orbitals corresponding to the second and third bands.



(41)



(42)

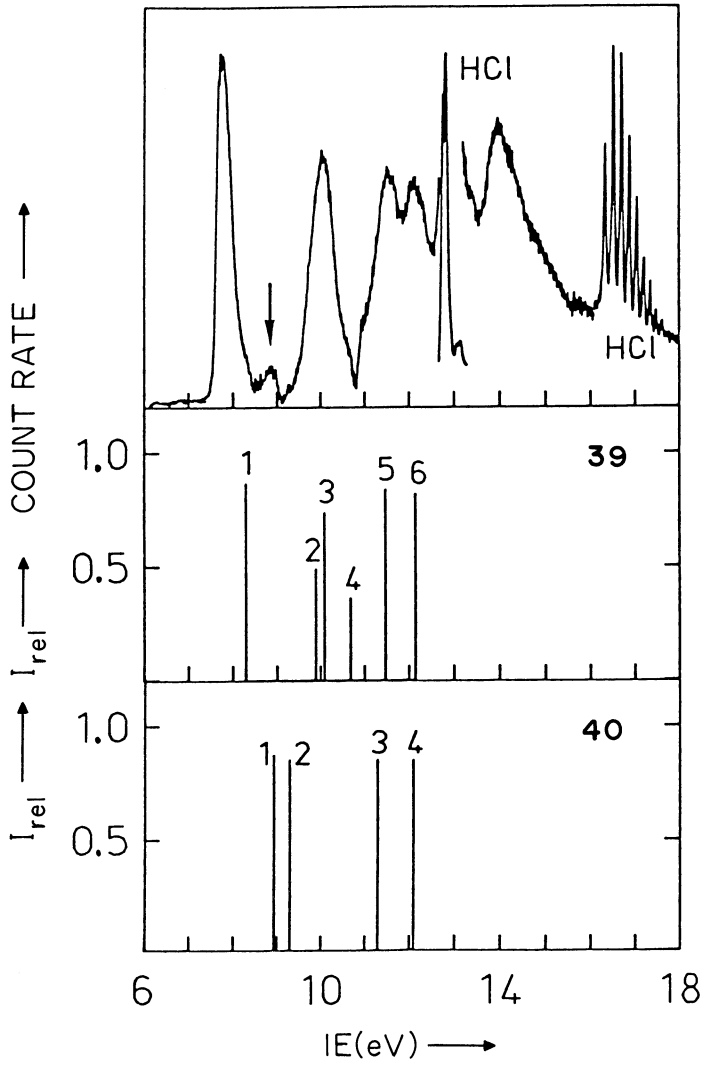
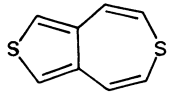


FIGURE 15. High-temperature photoelectron spectrum of the products of the thermolysis at 600 °C of 2-(chloromethyl)-3-methylthiophene (upper spectrum) compared with calculated (MNDO–PERTCI) vertical IEs of **39** and **40**. The arrow indicates the presence of unreacted precursor. Reproduced by permission of VCH Verlagsgesellschaft from Reference 38

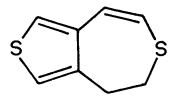
A further example of sulfur in a seven-membered ring is 3,3,6,6-tetramethyl-1-thiacycloheptyne (**42**) in which the PE spectrum obtained by Schweig and coworkers[40] shows a splitting of the degenerate acetylenic π MOs due to ring strain. This splitting depends strongly on the angle representing the deviation from collinearity around the triple bond. The measured splitting of 0.31 eV is close to that obtained for the analogous hydrocarbon (0.32 eV), with the n_S orbital showing no interaction with the π system.

C. Unsaturated Disulfides

The thienothiepins comprise two fused rings, one five-membered and the other seven-membered, each containing one sulfur atom. The n_S–n_S interaction in thieno[3,4-*d*]thiepin (**43**) shown in the spectrum (Figure 16) measured by Gleiter and coworkers[39] is assisted by through-bond effects. The effectively planar molecule has π MOs of b_1 and a_2 symmetry, so the $n_S(b_1)$ orbitals interact through the two $\pi(b_1)$ orbitals. The first three IEs in the system, assigned as $4b_1$ (7.42 eV), $2a_2$ (8.52 eV) and $3b_1$ (9.75 eV), are shown in Figure 17 to correlate with the analogous bands of azulene. The spectrum of the related dihydro compound (**44**), though of reduced C_s symmetry, shows analogous IEs at the marginally lower values of 7.67, 8.73 and 9.38 eV, respectively.

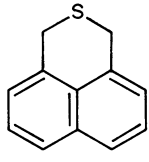


(**43**)

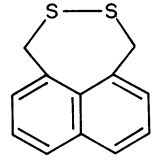


(**44**)

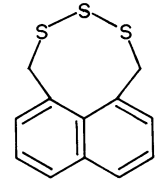
The sulfur-bridged peri-naphthalenes studied by Jorgensen and coworkers[41] include the mono-, di- and tri-sulfides, 2*H*,6*H*-naphtho[1,8-*cd*]thiin (**45**), 3*H*,7*H*-naphtho[1,8-*de*]-1,2-dithiepin (**46**) and 4*H*,8*H*-naphtho[1,8-*ef*]-1,2,3-trithiocin (**47**), respectively. Their PE spectra are compared with that of 1,8-dimethylnaphthalene, and interpreted in terms of the first three π ionizations which are clearly distinguished in the spectrum of the latter. The spectrum of **45** includes an additional n_S band as its second band at 8.42 eV. The n_S orbital is effectively localized, showing no interaction with the naphthalene π MOs. The disulfide **46** is shown by DNMR data, assisted by molecular mechanics calculations, to be of an unsymmetrical twist-boat conformation, with a S—S dihedral angle of around 40°. In its PE spectrum the $n_S \pm n_S$ combination bands are located as the second (8.14 eV) and fifth (9.89 eV) bands, with the associated MOs effectively independent of the naphthalene π bands assigned to the first (7.78 eV), third (8.90 eV) and fourth (9.67 eV) vertical ionizations. Calculations at the CNDO/S level confirm this assignment except that the n_S^+ ionization might be associated with either the fourth or fifth bands. The ΔIE for n_S^+ and n_S^- is then obtained as either 1.53 or 1.75 eV, which translate to a θ(CSSC) torsional angle of either 43° or 37°, respectively. This provides reasonable agreement with the molecular mechanics value of 44° for the dihedral angle in the twist-boat geometry. The PE spectrum of the trisulfide **47** shows three broad bands in the low IE region but, by maintaining the correlation of aromatic π levels, the IEs at 8.3, 10.0 and 10.2 eV are assigned as the n_S lone-pair combination orbitals. However, the force field calculations indicate that a boat structure, of C_s symmetry, is only 0.6 kcal mol^{-1} more stable than the corresponding chair conformation, so the spectrum recorded at 90–97 °C is probably broadened due to the presence of both conformers.



(**45**)



(**46**)



(**47**)

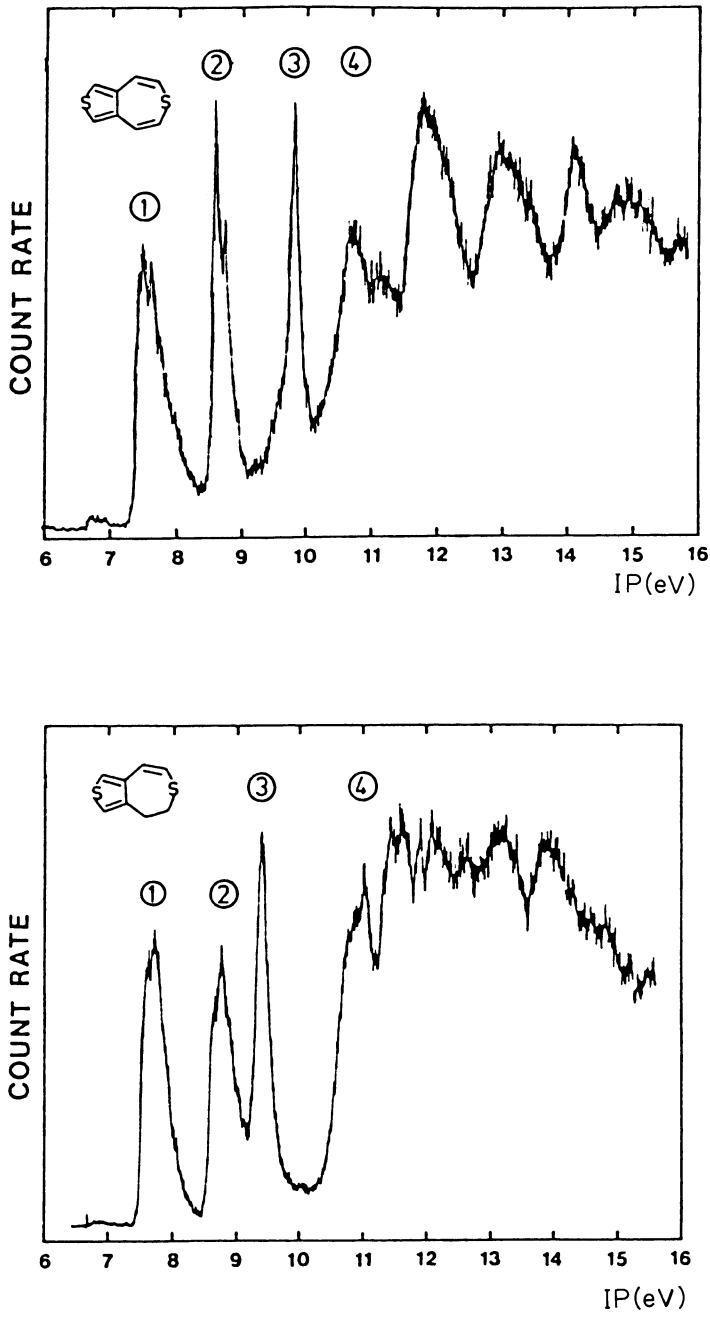


FIGURE 16. Photoelectron spectra of **43** and **44**. Reprinted with permission from Reference 39. Copyright (1985) American Chemical Society

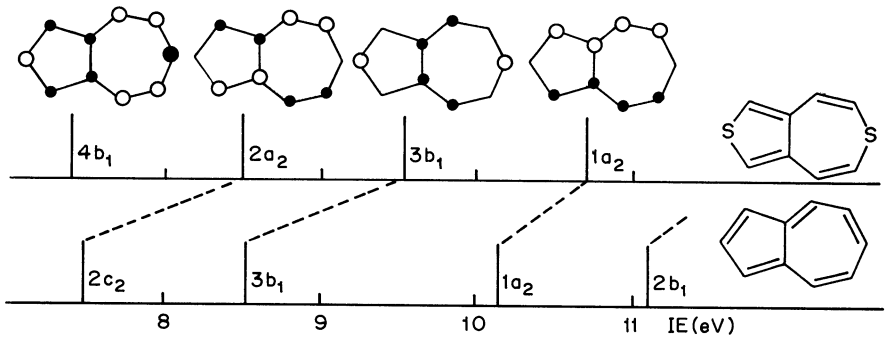
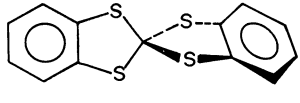


FIGURE 17. Correlation of low IE bands of **43** and of azulene. Reprinted with permission from Reference 39. Copyright (1985) American Chemical Society

Gleiter and Uschmann[42] have synthesized and recorded the PE spectra of nine heterospirenes including the three tetrasulfide derivatives 2,2′-spirobi[1,3-benzodithiole] (**48**), 2,2′-spirobi[naphtho[2,3-*d*]-1,3-dithiole] (**49**) and 2,2′-spirobi[naphtho[1,8-*de*]-1,3-dithiin] (**50**). Their spectra are compared with those of the related fragment molecules, 2,2-dimethyl-1,3-benzodithiole (**51**), 2,2-dimethylnaphtho[2,3-d]-1,3-dithiole (**52**) and 2,2-dimethylnaphtho[1,8-*de*]-1,3-dithiin (**53**). For **51** the lowest four ionization bands are assigned as $b_1(n_S^+) < a_2(n_S^-) < a_2(\pi_A) < b_1(\pi_S)$ though recognizing that these designations do not accurately represent the considerable n_S–π mixing which occurs. Joining two π fragments of **51** together via a sp^3 carbon center yields **48**. However, in the resulting spiro-compound, the D_{2d} symmetry ensures that only the $a_2(C_{2v})$ MOs interact, with the $b_1(C_{2v})$ MOs remaining unchanged. The former produce b_1 and a_2 orbitals, and the latter e orbitals, within the D_{2d} symmetry. The PE bands of **48** are hence assigned as $10e(n_S^+) < 2a_2(n_S^-) < 2b_1(n_S^-) < 1a_2(\pi_A) < 9e(\pi_S) \sim 1b_1(\pi_A)$, and its spectrum is compared with that of **51** in Figure 18.

For **49**, considered as the symmetric spiro-combination of two fragments of **52**, the strongly overlapped PE bands are interpreted in a similar manner with the broad first



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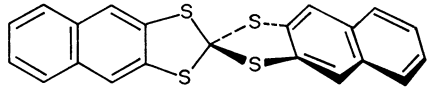
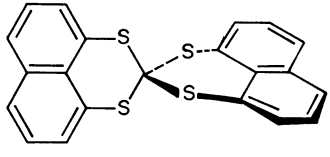
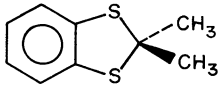


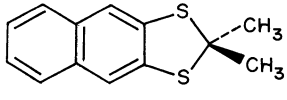
(49)



(50)



(51)



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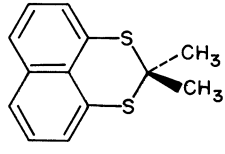

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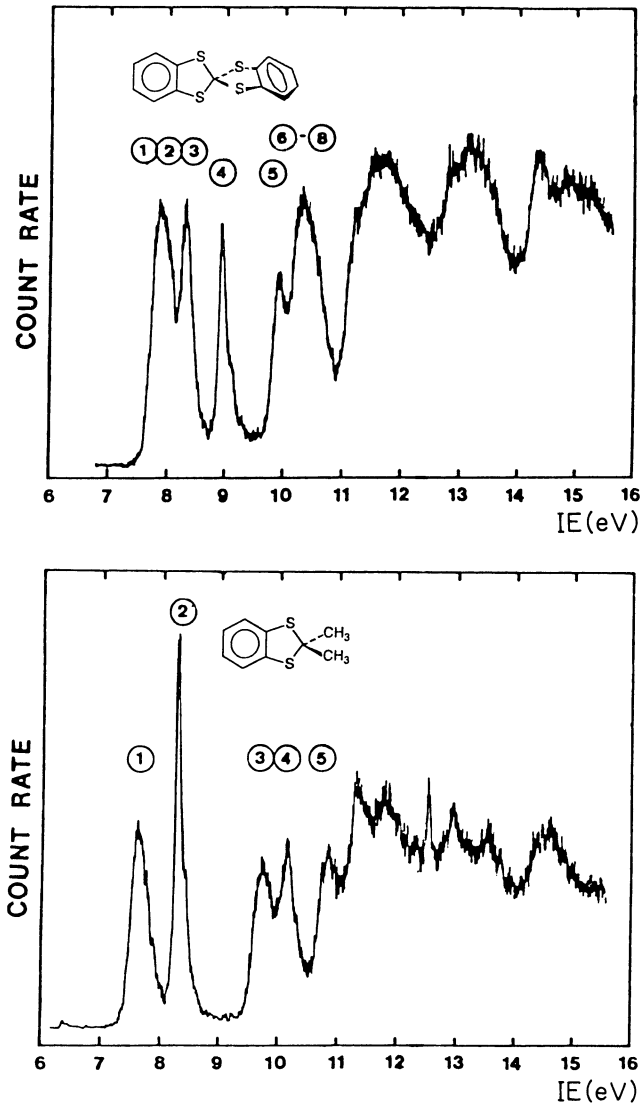


FIGURE 18. Photoelectron spectra of **48** and **51**. Reprinted with permission from Reference 42. Copyright (1986) American Chemical Society

band of 7.5–8.0 eV being assigned to three ionizations $3a_2 \sim 4e \sim 3b_1$, as indicated in Table 1, which also includes a comparison with the results of semiempirical PPP and MINDO/3 calculations. For **50**, considered as the symmetric spiro-combination of two fragments of **53**, the analysis of the PE spectrum is complicated by the S atoms being involved in six-membered rings which are likely to be nonplanar. The spectrum of **50** is very similar to that of **53** indicating that the major effect of this nonplanarity is to reduce

TABLE 1. Measured vertical ionization energies, I_V, and calculated orbital energies, ε (in eV) of **48**, **49** and **50**[a]

Compound	Band	I_V	$-\varepsilon$ assignment	$-\varepsilon$ PPP	$-\varepsilon$ MINDO/3
48	1	7.85	$10e$[b]	7.50	8.00
	2				
	3	8.29	$2a_2$	7.94	8.48
	4	8.92	$2b_1$	8.56	9.15
	5	9.92	$1a_2$	9.57	10.02
	6	10.3	$9e$	9.88	11.08
	7				
	8		$1b_1$	10.17	11.47
49	1		$3a_2$[c]	7.50	7.99
	2				
	3	7.5–8.0	$4e$	7.68	8.00
	4		$3b_1$	7.76	8.27
	5	9.0	$2a_2$	8.89	9.23
	6	9.5	$2b_1$	9.54	10.03
	7				
	8		$3e$	9.57	9.27
	9	10.15	$1a_2$	10.17	10.56
	10		$1b_1$	10.44	11.21
50	1	7.3	$3a_2$[b]	7.21	7.50
	2	7.5	$3b_1$	7.42	7.99
	3	8.5	$15e$	8.39	8.21
	4				
	5	8.9	$14e$	8.97	8.96
	6				
	7		$2a_2$	9.44	9.44
	8	9.3	$2b_1$	9.82	10.75
	9	10.5	$13e$	10.61	11.42
	10				

[a]Reprinted with permission from Reference 42. Copyright (1986) American Chemical Society.
[b]Numbering refers to valence orbitals only.
[c]Numbering refers to π orbitals only.

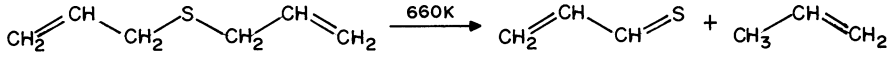
the spiro-resonance integral. Consequently, the first two bands of **50** show a splitting of only 0.2 eV with $3a_2 < 3b_1$. Using comparisons with related molecules to accommodate the effects of these steric factors, together with the MO calculations, the authors derive the assignments given in Table 1. In summary, the spiro-conjugative interactions between the two fragments is considerably reduced in the 1,8 disulfur-substituted naphthalene represented by **50**, compared with the 2,3 disulfur-substituted naphthalene represented by **49**, which shows strong spiro-conjugation.

III. THIOCARBONYLS

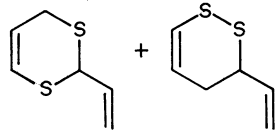
Many of the smaller organic sulfur compounds surveyed so far in this review have been synthesized using high-temperature pyrolysis of suitable precursors. This technique is of even more importance in the case of the thiocarbonyls, many of which are short-lived molecules. The prototype thiocarbonyl, thioformaldehyde, $CH_2{=}S$, was first identified by

PE spectroscopy by Bock and coworkers[43] as the gas-phase pyrolysis product of CH_3SCl. The history of this important technique and its use in real-time gas analysis of flow systems, including the optimization of gas-phase reactions and heterogeneously catalyzed processes, has been reviewed by Bock and coworkers[7].

A recent illustrative example is that of thioacrolein (**54**) which Bock and coworkers obtained by the thermal decomposition of diallyl sulfide[44]. At 600 K this yields propene and thioacrolein, which can be cool-trapped as a mixture of Diels–Alder dimers (**55**). Heating of the isomeric dimers at 670 K leads to retrodiene splitting to pure thioacrolein, which is identified by its PE spectrum as this can be correlated with that of its analogue acrolein, as shown in Figure 19. The assignment is easily accomplished using the Koopmans IEs from MNDO calculations where the first band at 8.87 eV involves the n_S lone-pair orbital, and the second ionization at 9.88 eV is associated with the outermost π MO, which includes both π_{CC} and π_{CS} character.

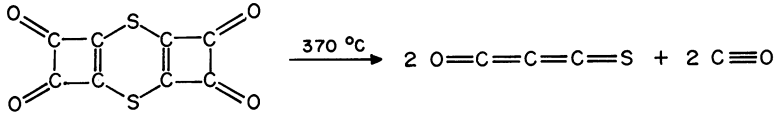


(**54**)



(**55**)

The synthesis of O=C=C=C=S, 3-thioxo-1,2-propadien-1-one, was achieved by Bock and coworkers[45] via the specially prepared precursor 4,5,9,10-tetraoxo-2,7-dithia[6.2.0.0^{3,6}]deca-1(8),3(6)-diene (**56**) which, after evaporation at 200 °C, eliminates CO at 370 °C allowing the liquid nitrogen trapping of the OC_3S. The first two ionization bands at 9.73 and 12.44 eV are both assigned to π states, while the third and fourth ionizations are strongly overlapped with a broad band onsetting at 14.5 eV underlying a narrow band with a maximum at 14.89 eV. The former is associated with the n_S lone-pair, which is of σ symmetry, while the latter is assigned to a third π state.



(**56**)

Schweig and coworkers have also exploited the flow pyrolysis technique in the study of reaction intermediates. A recent example is that of dicyanothioketene (**57**) which, though previously formulated as an intermediate, had defied all attempts at isolation. Flash

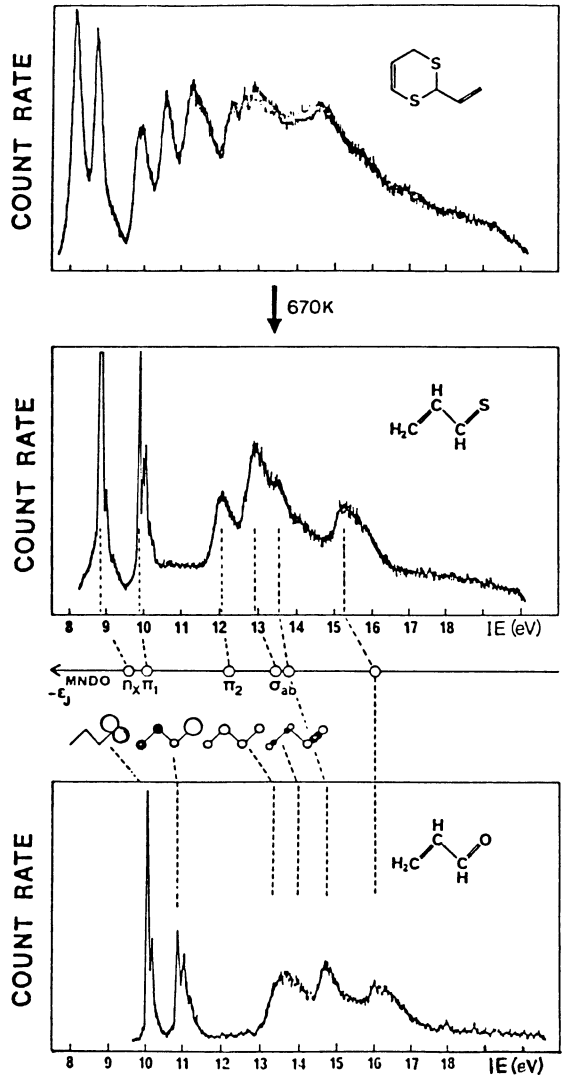
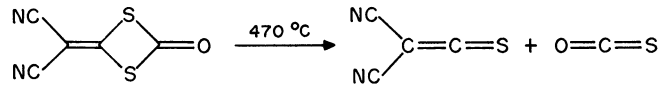


FIGURE 19. Photoelectron spectra illustrating the synthesis of thioacrolein (**54**) from its Diels–Alder dimer **55**. Correlation of the IEs of **54** with calculated values and with the IEs of acrolein. Reprinted with permission from Reference 44a. Copyright (1982) American Chemical Society

pyrolysis of 2-(4-oxo-1,3-dithietan-2-ylidene)malononitrile (**58**) directly above the ionization region in the PE spectrometer allowed the identification of **57** in a mixture with the coproduct OCS[46]. The first IE of **57** at 9.94 eV is separated by nearly 3 eV from the second band and, showing the same fine structure as the energetically lowest-lying $^2B_1(\pi)$ band in the PE spectrum of thioketene[47], is assigned equivalently.



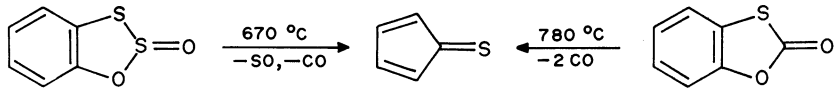
(58) (57)

By comparison, bis(trifluoromethyl)thioketene (**59**) is a stable compound, and its PE spectrum, measured by Gleiter and coworkers[48], shows a first band at 9.96 eV, very close to that in ketene, and is assigned to the analogous $^2B_1(\pi)$ state. The PE spectrum of cyclopentylidene thioketene (**60**), prepared by Schulz and Schweig[49] using pyrolysis of the precursor cyclohexene-1,2,3-thiadiazole, also shows an isolated first band, at 7.95 eV, assigned as the $^2B_1(\pi)$ level. A combination of differing inductive and hyperconjugative effects is responsible for this IE being 2 eV lower than the corresponding first IEs of **59** and ketene.

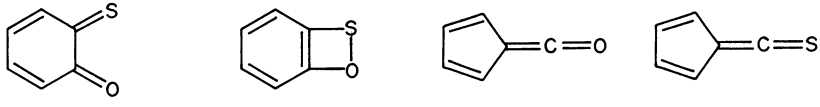
(59) (60)

The first synthesis of cyclopentadienethione (**61**) and its unambiguous characterization from its PE spectrum was performed by Schulz and Schweig[50] using gas-phase pyrolysis of two isomeric precursors, 1,2,3-benzoxadithiol-2-oxide (**62**) and 1,3-benzoxathiol-2-one (**63**). The first band at 8.87 eV, due to its shape, position and energy-dependence of the intensity, is unequivocally the $^2B_2(n_S)$ band, while the close second band at 9.18 eV is assigned to $^2A_2(\pi)$ because of its position relative to the corresponding band in cyclopentadienone[51]. Thermal fragmentation of **62** and **63** probably proceeds via the monothio-*ortho*-benzoquinone intermediate **64**. When **62** is pyrolyzed at 550–600 °C, a compound with bands at 8.85, 9.45 (high intensity) and 11.6 eV, consistent with the results of MNDO- and CNDO/S-PERTCI calculations on **64**, is revealed. The isomeric benzoxathiete **65** is calculated as being considerably more energy-rich than **64**, so is unlikely to be observed. Other possible products, fulven-6-one (**66**) and fulven-6-thione (**67**), with known PE spectra, are also not observed.

The structure of the intramolecularly hydrogen-bonded enolic form of β-dicarbonyl compounds and their monosulfur analogues, the β-thioxoketones, have been the subject of numerous experimental and theoretical investigations. A number of β-thioxoketones that are not unsuitably substituted in the α-position are known to exist as rapidly

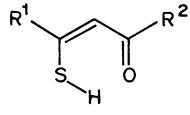


(62) (61) (63)

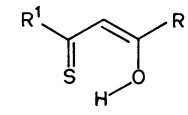


(64) (65) (66) (67)

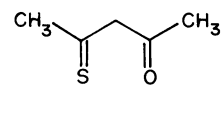
interconverting, equilibrated tautomeric forms **68** and **69**. As a contribution to these investigations, Jorgensen and coworkers[52] have measured the PE spectra of four compounds, thioacetylacetone (**70**), 2-acetylcyclohexanethione (**71**), 2-thioacetylcyclohexanone (**72**) and 4-(methylthio)pent-3-en-2-one (**73**) (the S-methyl derivative of thioacetylacetone). These were chosen because **70** has comparable concentrations of both the enethiol and enol forms, **71** has a predominant concentration of the enethiol form and **72** has a predominant concentration of the enol form. By contrast **73** exists exclusively in the 'ene thiolic' form. Using group IE data obtained for simple compounds, qualitative MO pictures were constructed comparing the essential enol and enethiol forms represented by the parent systems S=CH—CH=CH—OH and HS—CH=CH—CH=O, respectively. In the effectively planar geometry this description gives rise to three π orbitals and one n orbital, either n_O or n_S, orthogonal to these. In the IE region below 11 eV each PE spectrum can be seen to consist of three bands, well-resolved for **71** and **73**, but showing strong overlap in **72**. Four bands are revealed for **70**, though the first three bands are strongly overlapped. The general assignment is derived as $n_S \sim \pi_3 < \pi_2$ for the enol form, and $\pi_3 < n_O < \pi_2$ for the enethiol form, though both n_S and n_O appear in the spectrum of **70**, as shown in Figure 20. The spectra of **71** and **72** also show the presence of small amounts of the minor isomer in each case.



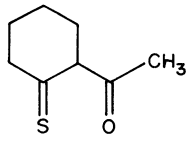
(**68**)



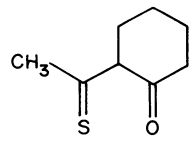
(**69**)



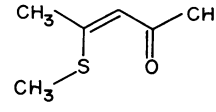
(**70**)



(**71**)

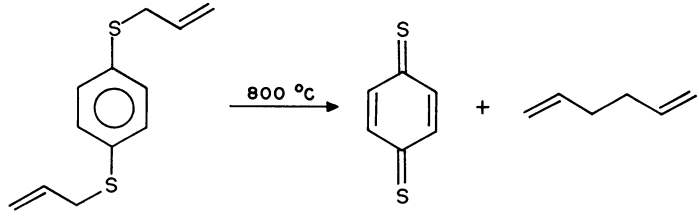


(**72**)



(**73**)

An unusual high-temperature gas-phase synthesis is illustrated by the identification of dithio-*para*-benzoquinone (2,5-cyclohexadiene-1,4-dithione) (**74**) by Bock and coworkers[53] using PE spectroscopy in combination with Ar matrix isolation and UV and IR spectroscopy. The thermal decomposition of 1,4-bis(allylthioxy)benzene (**75**) takes place at 800 °C producing 1,5-hexadiene as the leaving molecule. In combination with the Koopmans IEs obtained using MNDO calculations, the lowest IEs of **74** are identified in



(**75**) (**74**)

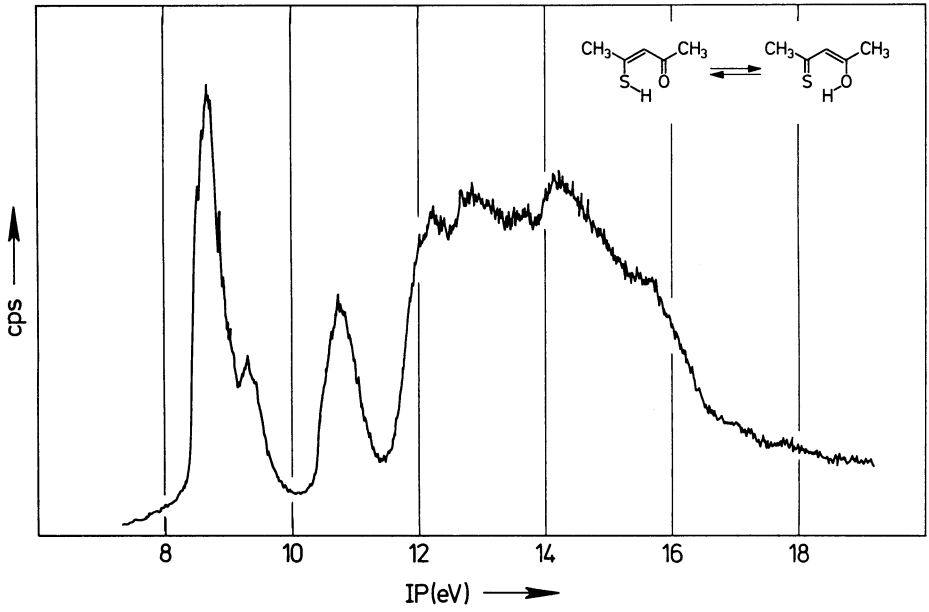


FIGURE 20. Photoelectron spectrum of thioacetylacetone (**70**). Reprinted with permission from Reference 52. Copyright (1981) American Chemical Society

the PE spectrum at 8.4 and 9.10 eV. These are assigned as the outermost π MO (b_{2u}) followed by the strongly overlapped n_S^- (b_{2g}) and n_S^+ (b_{3u}) combinations. The calculation gives a n_S^-/n_S^+ splitting of only 0.1 eV which indicates that there is no through-bond effect acting on these states, and explaining their complete overlap as observed in the PE spectrum. An additional feature of these experiments is that a measurement made with the pyrolysis source close to the photoionization region shows the presence of the allyl radical ($I_1 = 8.13$ eV) as a further product.

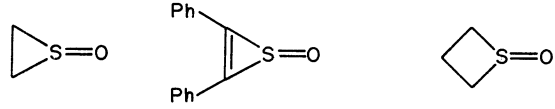
IV. SULFUR–OXYGEN COMPOUNDS

A. Sulfoxides

As described earlier the PE spectrum of dimethyl sulfoxide, $(CH_3)_2SO$, (**6**), is characterized by two low IE bands which are assigned to a $n_S - n_O$ orbital ($I_1 = 9.01$ eV) and a π_{SO} orbital ($I_2 = 10.17$ eV). With symmetric substitution by larger alkyl groups, these bands retain their identity as shown in the spectra measured by Bock and Solouki[54]. Increasing CH hyperconjugative interaction reduces their IEs systematically leading, for di-*t*-butyl sulfoxide, $[(CH_3)_3C]_2SO$, to values of 8.18 eV ($n_S - n_O$) and 9.20 eV (π_{SO}). The separation of 1.02 eV is only slightly less than that of 1.16 eV in dimethyl sulfoxide. In diphenyl sulfoxide, $(C_6H_5)_2SO$, the outer $\pi(e_{1g})$ levels of benzene interpose themselves between the $n_S - n_O$ and π_{SO} bands, though showing an increase in mean IE to 9.5 eV from the benzene values due to conjugative interaction with the n_S orbital. The $n_S - n_O$ band moves correspondingly to lower IE ($I_1 = 8.58$ eV) while the π_{SO} band is relatively unchanged ($I_5 = 10.1$ eV) compared to its value in dimethyl sulfoxide. The substitution by the vinyl group in methyl vinyl sulfoxide, $CH_2{=}CHSOCH_3$, shows no change in

the $n_S - n_O$ ($I_1 = 9.02$ eV) and π_{SO} ($I_2 = 10.22$ eV) bands, though the π_{CC} ionization ($I_3 = 10.80$ eV) is clearly higher than its value of 10.51 eV in ethylene, due to the inductive effect of the SO group as well as some conjugative interaction with the n_S orbital. The $n_S - n_O$ IE should be decreased correspondingly, but this is compensated by a reduced CH hyperconjugative interaction of the CH_2=CH group in comparison with CH_3. In methyl phenyl sulfoxide, $C_6H_5SOCH_3$, the first band at 8.79 eV is intermediate between the dimethyl and diphenyl values showing that the conjugative n_S–π_{CC} interaction is additive in the case of the latter molecule.

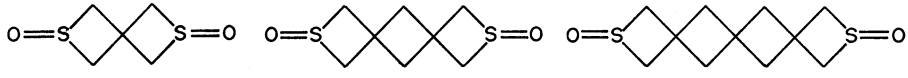
The prototype cyclic sulfoxide represented by ethylene sulfoxide (**76**) exhibits a completely different PE spectrum from that of dimethyl sulfoxide (**6**). The first and second bands are strongly overlapped with vertical IEs at 9.66 eV (n_S) and 9.78 eV (π_{SO}). Bock and Solouki[11] show, using CNDO calculations, that these differences are explained in terms of the reduced CSC and CSO bond angles in ethylene sulfoxide, which move the n_S and π_{SO} orbitals closer in energy, due to reduced n_S/n_O conjugation and increased π_{SO}/σ_{CS} conjugation, relative to their description in dimethyl sulfoxide.



(76) **(77)** **(78)**

Another three-membered ring sulfoxide is 2,3-diphenylthiirene-1-oxide (**77**), which has been studied using UPS by Schweig and coworkers[55] in the absence of the prototype thiirene-1-oxide, which is not known. The low IE region of **77** is very crowded, with six strongly overlapped bands between 8 and 10 eV. On the basis of CNDO/S calculations, the π_{SO} and n_S bands are assigned to the second ($I_2 = 8.89$ eV) and third ($I_3 = 9.07$ eV) bands, respectively, showing relatively little interaction with the π MOs of the PhCH=CHPh moiety, for which the uppermost are well-separated, being assigned as π_1 ($I_1 = 8.29$ eV) and $\pi_2 \sim \pi_3$ ($I_{4,5} = 9.38$ eV), similar to their relative locations in the PE spectrum of *cis*-stilbene.

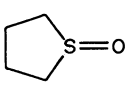
The smallest four-membered ring sulfoxide is thietane-1-oxide (**78**), for which the PE spectrum, measured by Jorgensen and Carlsen[15], shows the same low IE bands as dimethyl sulfoxide, with $n_S - n_O$ ($I_1 = 8.96$ eV) and π_{SO} ($I_2 = 10.14$ eV) being slightly lower than in the latter. An interesting extension of this study is that by Baker and coworkers[56] who considered a series of dithiaspirane sulfoxides as models for the study of the electron transfer mechanism when used as bridging ligands in the Ru(II,III) complexes. The PE spectra of 2,6-dithiaspiro[3.3]heptane disulfoxide (**79**), 2,8-dithiaspiro[3.1.3.1]decane disulfoxide (**80**) and 2,10-dithiaspiro[3.1.1.3.1.1]tridecane disulfoxide (**81**) showed n_S/n_S splittings, represented by $\Delta E(I_2 - I_1)$ of 0.85, 0.38 and 0.25 eV, respectively. This is rather different from the case of the corresponding dithiaspirocyclobutanes, where no clear splitting of the n_S bands is observed in the PE spectra. So the disulfoxides are clearly indicating through-bond interactions of their sulfur lone-pairs, which in the case of **81** occurs over eight bonds, the longest range interaction of its type known at the time.



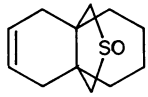
(79) **(80)** **(81)**

The explanation for these observations is demonstrated in detailed calculations by Hush and coworkers[57]. They verified that d orbital participation in S—O bonding is quite minor and the bond is best described as semipolar ($> S^{\delta+} - O^{\delta-}$), rather than as one involving hypervalent sulfur ($> S{=}O$). A crucial finding is that long-range n_S/n_S coupling in the dithiaspiroalkane disulfoxides requires SO bonds oriented out of the plane of their respective alkane rings. For the pyramidally bonded thietane-1-oxide (**78**), the principal components of the HOMO are the out-of-plane combination of O and S p orbitals whose axes lie in the plane containing the S—O bond and the CSC angle bisector, together with minor contributions from carbon orbitals, specifically that carbon which forms the link in the combined ring systems. This contribution, though small, is crucial for through-bond interaction. The HOMOs for the thiaspiroalkanes by comparison are of pure n_S character with no carbon contributions, essentially because the localized n_S orbitals are each oriented perpendicular to the plane of the alkane rings. A further finding is that the n_S/n_S splitting of 0.85 eV in the double-ring disulfoxides is comprised of approximately equal through-space and through-bond contributions, but in the larger systems there is no through-space contribution.

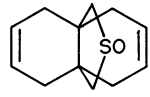
The simplest five-membered ring sulfoxide is tetramethylene sulfoxide (**82**) which, as measured by Bock and Solouki[54], has the expected low IE photoelectron bands attributed to $n_S - n_O$ ($I_1 = 8.77$ eV) and π_{SO} ($I_2 = 9.75$ eV). This saturated ring appears as one of the three fused rings which comprise the sulfoxides of the thia[4.4.3]propellanes. The PE spectra of 12-thia[4.4.3]propella-3-ene-12-oxide (**83**), 12-thia[4.4.3]propella-3,8-diene-12-oxide (**84**), 12-thia[4.4.3]propella-2,4-diene-12-oxide (**85**) and 12-thia[4.4.3]propella-2,4,7,9-tetraene-12-oxide (**86**) were measured by Bohm and Gleiter[58]. In **83** and **84** the first band is easily assigned to the $n_S - n_O$ band at 8.50 and 8.52 eV, respectively. In **83** the single ethylenic moiety provides a π_{CC} band which overlaps the π_{SO} band, these being identified at 9.35 and 9.5 eV, respectively. In **84** by contrast, the two ethylenic moieties interact strongly to provide well-separated π bands, which fall to either side of the π_{SO} band, these appearing at π^- ($I_2 = 9.1$ eV) $< \pi_{SO}$ ($I_3 = 9.5$ eV) $< \pi^+$ ($I_4 = 9.70$ eV). In **85**, which includes a butadiene unit, and **86**, which includes two butadiene units, the strongly overlapped low IE bands below 10 eV are described in terms of a $n_S - n_O$ band followed by one and two π_{CC} bands, respectively.



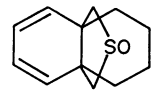
(**82**)



(**83**)



(**84**)



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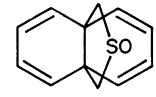
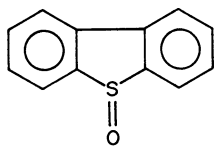


(**86**)

In 2,2′-biphenylene sulfoxide (**87**), the five-membered sulfoxide ring is formed when the SO group makes a second bridge between the phenyl units. This is the analogue of the planar fluorene system which provides four well-spaced low-energy PE bands. The PE spectrum of **87** measured by Bock and Solouki[54] is interpreted as showing these bands as I_2 to I_5 intervening between the $n_S - n_O$ ($I_1 = 8.43$ eV) and π_{SO} ($I_6 = 10.29$ eV) bands, with these orbitals retaining their localized character, because their orientation excludes any significant interaction with the π_{CC} orbitals.



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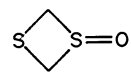

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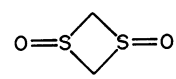


(**89**)

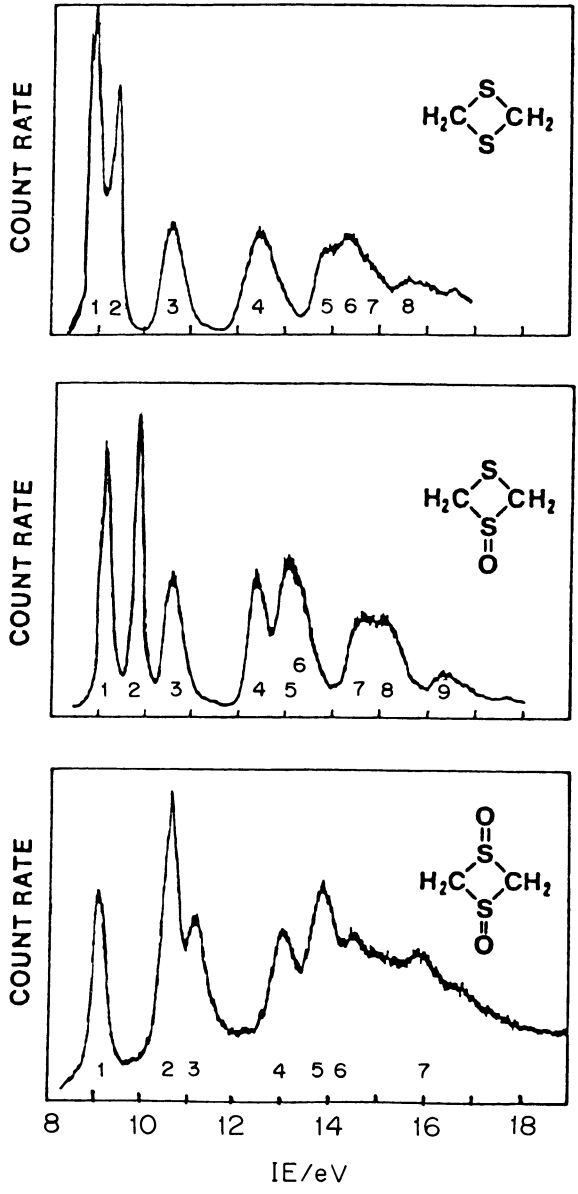


FIGURE 21. Photoelectron spectra of 1,3-dithietane (**13**), 1,3-dithietane-1-oxide (**88**) and 1,3-dithietane-1,3-dioxide (**89**). Reprinted with permission from Reference 21. Copyright (1982) American Chemical Society

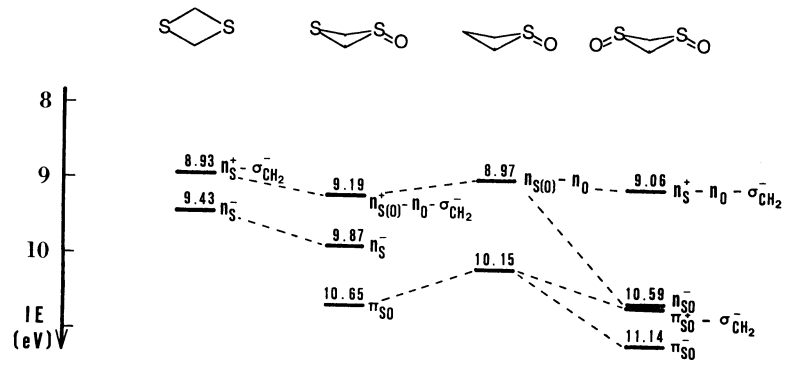


FIGURE 22. Correlation of n_S and π_{SO} IEs of four-membered ring sulfides and sulfoxides. Reprinted with permission from Reference 21. Copyright (1982) American Chemical Society

The two S-oxides of 1,3-dithietane (**13**), i.e. 1,3-dithietane-1-oxide (**88**) and 1,3-dithietane-1,3-dioxide (**89**), were synthesized by Block and coworkers[21] and studied by various spectroscopic techniques. The oxide **88** was synthesized by a reaction involving bis(chloromethyl) sulfoxide with sodium sulfide, and microwave spectroscopy showed it to have a puckered geometry. Oxidation of **88** with either iodobenzene dichloride in aqueous pyridine at −30 °C or *m*-chloroperbenzoic acid in methylene chloride at 0 °C produced respectively a 3:1 or 2:3 mixture of the *cis* and *trans* forms of **89**. These isomers were readily separable by fractional crystallization from dimethylformamide and were clearly distinguished by NMR spectroscopy. The PE spectra of **88** and **89** are compared with that of the parent 1,3-dithietane (**13**) in Figure 21, and the low IE bands correlated with those of **13** and thietane-S-oxide (**78**) in Figure 22. The first and second ionizations of **13** show a through-bond crossover resulting in the order $n_S^+ - \sigma_{CH_2} < n_S^-$. In **88** the additional oxygen atom inductively increases the IEs of these n_S-based orbitals, with antibonding admixture of n_O character being greater in the HOMO according to semiempirical calculations. This considerably increases the splitting between these bands to 0.68 eV. The π_{SO} ionization is well-separated as the third band, giving the sequence of vertical IEs, $n_S^+ - n_O - \sigma_{CH_2}$ ($I_1 = 9.19$ eV) < n_S^- ($I_2 = 9.87$ eV) < π_{SO} ($I_3 = 10.65$ eV). In **89** a considerable hyperconjugation with the σ_{CH_2} orbital is calculated to affect both the n_S^+ and π_{SO}^+ combinations, which are shifted to lower IEs than their conjugates, the n_S^- and π_{SO}^- combinations. The first band ($I_1 = 9.06$ eV) assigned as $n_S^+ - n_O^+ - \sigma_{CH_2}$ is well-separated from the strongly-overlapped second and third bands ($I_2 = I_3 = 10.59$ eV) assigned as $n_{SO} \sim \pi_{SO}^+ - \sigma_{CH_2}$. The fourth band ($I_4 = 11.14$ eV) is assigned as π_{SO}^-.

B. Sulfones

The PE spectrum of the basic organic sulfone, dimethyl sulfone, $(CH_3)_2SO_2$ (**7**), as described earlier, comprises four low IE bands, which are assigned as $I_1(b_1) = 10.7$ eV ($\pi_O^+ - \sigma_{CS}^-$), $I_2(b_2) = 11.1$ eV (n_O^-), $I_3(a_1) = 11.7$ eV ($n_O^+ - \sigma_{CS}^+$) and $I_4(a_2) = 12.0$ eV (π_O^-) involving the appropriate ± combinations of the oxygen nonbonding orbitals. These four bands are strongly overlapped, so the spectra of the organic sulfones with larger organic substituents are characterized by an increased density of ion states in the region below 12 eV.

For methyl vinyl sulfone, $CH_2{=}CHSO_2CH_3$, an additional band, arising from the ethylene π_{CC}, is expected in this region. The first IE at 10.7 eV is the same as that of **7**, but the location of the extra band relies on calculations for its identification. Muller and

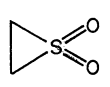
Schweig[13] proposed that interaction occurs between n_O and π_{CC} to give the separated second and third bands $I_2 = 11.0$ eV ($n_O^- - \pi_{CC}$) and $I_3 = 11.5$ eV ($\pi_{CC} + n_O^-$), whereas Bock and coworkers[12] identify the fourth band, $I_4 = 12.0$ eV, as of relatively localized π_{CC} type.

For divinyl sulfone, $(CH_2{=}CH)_2SO_2$, a lower first IE of 10.6 eV is measured, but this is still assigned as the through-bond shifted $\pi_O^+ - \sigma_{CS}^-$ orbital. The second band at 10.8 eV is also lowered in IE relative to that in methyl vinyl sulfone, which Muller and Schweig[13] interpret as due to increased π_{CC} mixing of antibonding character in $n_O^- - \pi_{CC}^+(b_2)$. The conjugate $\pi_{CC}^+ + n_O^-(b_2)$ band is located at $I_4 = 11.7$ eV. The $\pi_{CC}^-(a_2)$ band is assignd to $I_3 = 11.4$ eV. By contrast Bock and coworkers[12] assign the π_{CC} contribution to the fourth and fifth bands, $I_4 = 11.7$ eV as $\pi_{CC}^-(a_2)$ and $I_5 = 12.0$ eV as $\pi_{CC}^+(b_2)$. The calculations relevant to these assignments have assumed C_{2v} symmetry for the molecule.

The PE spectra of the phenyl sulfones, methyl phenyl sulfone and diphenyl sulfone, measured by Bock and coworkers[12] show strong interaction of the $\pi(e_{1g})$ outer orbitals of the benzene moiety with the SO_2 group orbitals. However, the low first IEs of 9.74 eV and 9.37 eV, respectively, suggest that the HOMOs are dominated by benzene π contributions, correlating with the benzene e_{1g} IE of 9.26 eV. The constrained geometry of the related 2,2′-biphenylene sulfone is responsible for its lower first IE of 8.90 eV as this is associated with strong phenyl–phenyl π conjugation.

The PE spectrum of styryl methyl sulfone measured by Cauletti and coworkers[59] is of similar complexity with its first and second bands assigned to ring π orbitals, namely $I_1 = 9.08$ eV (π_3, b_1) and $I_2 = 9.66$ eV (π_2, a_2). Colonna and coworkers[60] also measured the PE spectrum of diphenyl sulfone and made comparative observations for the pyridyl derivatives, 2-pyridyl phenyl sulfone and di-2-pyridyl sulfone. In these latter molecules, while the two lowest ionizations retain their ring π character, nitrogen lone-pair n_N contributions are suggested for the fourth and sixth ionizations.

The parent cyclic sulfone represented by ethylene sulfone (thiirane sulfone) **90**, studied by Bock and coworkers[12], has a first PE band at 10.20 eV, considerably lower than that of dimethyl sulfone, **7**, at 10.65 eV. It is assigned to the same $\pi_O^+ - \sigma_{CS}^-(b_1)$ orbital, but with increased σ_{CS}^- conjugation influenced by the strain introduced with the small CSC bond angle of 55°. By contrast the higher ionizations $I_2 = 11.57$ eV, $n_O^-(b_2)$ and $I_3 = 11.98$ eV, $n_O^+ - \sigma_{CS}^+(a_1)$, are stabilized by 0.3–0.4 eV relative to their analogues in **7**. The dimethyl-substituted analogue of **90**, *cis*-2,3-dimethylthiirane-1,1-dioxide (**91**), measured by Schweig and coworkers[61] shows the expected reduction in IEs to $I_1(b_1) = 9.82$ eV, $I_2(a_1) = 11.10$ eV and $I_3(b_2) = 11.3$ eV, with CH hyperconjugation resulting in shifts of 0.4–0.6 eV. (These authors use the opposite convention to that used here. For C_{2v} symmetry, this involves interchange of the b_1 and b_2 species.) The related spectra of 2-methylthiirene-1,1-dioxide (**92**) and 2,3-dimethylthiirene-1,1-dioxide (**93**), measured by these authors, reveal strong ethylene π_{CC} interactions within the b_2 orbitals. The observation that **92** and **93** have strongly overlapped first and second bands, well-separated from higher ionizations, leads to an assignment of $\pi_{CC}(b_2) \sim \pi_O^+ - \sigma_{CS}^-(b_1)$ with the very close vertical IEs of 10.40 and 10.63 eV for **92** and 9.89 and 10.14 eV for **93**, but not allowing for an exact ordering of these states. A further consideration in this study concerns the 'aromatic' properties exhibited by the thiirene



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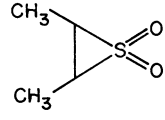

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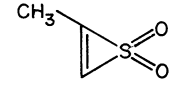

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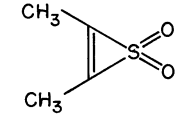


(93)

dioxides, in comparison with the analogous cyclopropenones. The authors conclude that the major interactions between the ethylene and sulfonyl moieties are analogous to those between the ethylene and carbonyl groups, differing only in degree.

The smallest four-membered ring sulfone, thietane-1,1-dioxide (**94**) and the related thiete-1,1-dioxide (**95**), were studied using PE and electron transmission (ET) spectroscopies by Gleiter and coworkers[62]. A comparison with the spectra of halogenated derivatives allows unambiguous assignment of the π ionization and the π^* attachment

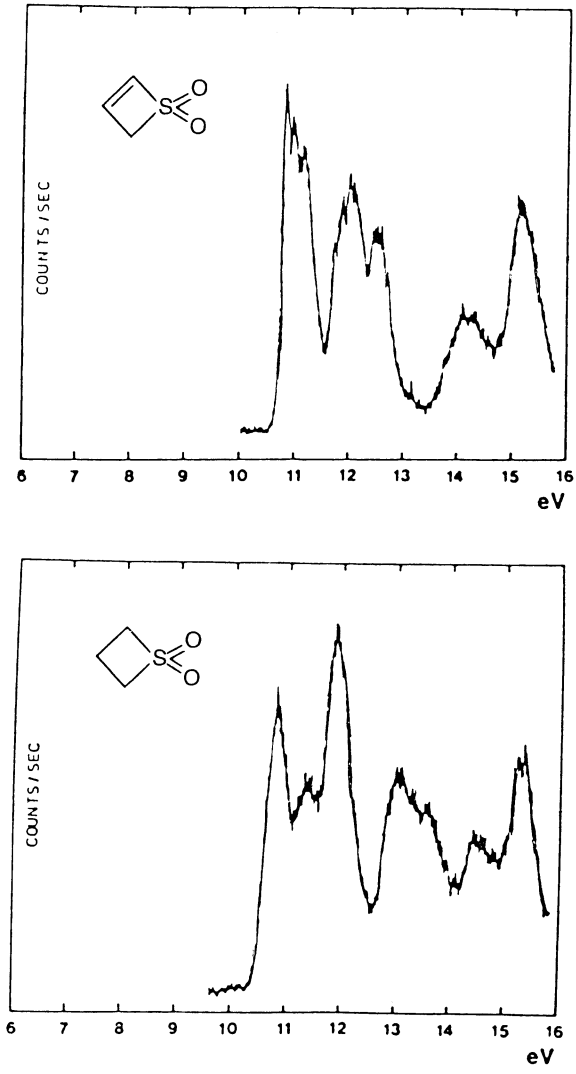


FIGURE 23. Photoelectron spectra of thiete-1,1-dioxide (**95**) and thietane-1,1-dioxide (**94**). Reproduced by permission of Elsevier Science Publishers from Reference 62

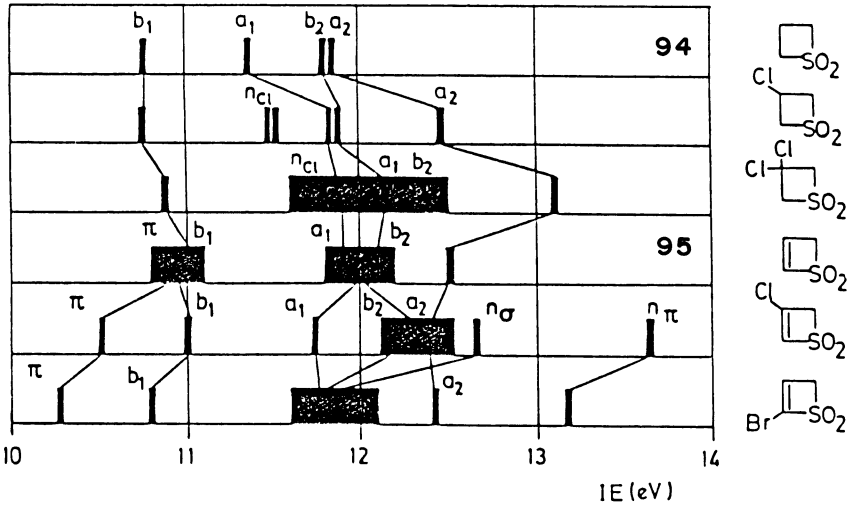
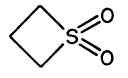


FIGURE 24. Correlation of experimental IEs of thietane dioxides and thiete dioxides. Reproduced by permission of Elsevier Science Publishers from Reference 62

process in **95**. The strongly stabilizing inductive effect of the sulfone group, which is the origin of the high reactivity of **95**, is clearly disclosed in both PE and ET spectra. The spectra of **94** and **95** shown in Figure 23 provide the band maxima displayed in Figure 24, where they are correlated with the IEs of the halogenated derivatives. The PE spectrum of **94** shows considerable differences in its low IE region from that of dimethyl sulfone. The changes in orbital energies seen for the ring closure to ethylene sulfone involve a separation of the outermost $\pi_O^+ - \sigma_{CS}^-(b_1)$ and $n_O^-(b_2)$ orbitals, which also occurs in **94**. However, the insertion of a CH_2 group into the three-membered ring results in increased CH hyperconjugation which destabilizes the $n_O^+ - \sigma_{CS}^+(a_1)$ orbital, causing a crossover with the $n_O^-(b_2)$ orbital. So the assigned band sequence in **94** is $I_1(b_1) = 10.76\,eV$, $I_2(a_1) = 11.36\,eV$ and $I_3(b_2) = I_4(a_2) = 11.82\,eV$, in good agreement with the results of MNDO calculations.



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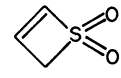
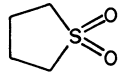


(95)

The presence of an ethylenic π_{CC} bond in **95** reduces the symmetry to C_s which allows $\pi_{CC}(a'')$ orbital mixing with both the $n_O^-(b_2)$ and $\pi_O^-(a_2)$ orbitals of the SO_2 moiety. Relative band intensities indicate a 2:2:1 sequence of overlapped bands below 13 eV. The fine structure in the first PE band, $I_1 = 10.80\,eV$, suggests that this is associated with a relatively localized $\pi_{CC}(a'')$ orbital. The corresponding stabilized SO_2 ionization is seen at $I_5 = 12.50\,eV$, which is then assigned as $\pi_O + \pi_{CC}(a_2, a'')$. The remaining outer SO_2 orbitals retain their order as in **94**, with the third and fourth ionizations coinciding at 12.00 eV and resulting in the assignment of IEs as $I_1(a'', \pi_{CC}) \sim I_2(a', \pi_O^+ - \sigma_{CS}^-) < I_3(a', n_O^+ - \sigma_{CS}^+) \sim I_4(a'', n_O^-) < I_5(a'', \pi_O^- + \pi_{CC})$. By relating the first IE of **95** to that

of related ethylenic molecules, the inductive and mesomeric influence of the SO_2 group can be estimated. Relative to the π_{CC} ionization of propene at 10.0 eV, the π_{CC} IE of 10.80 eV in **95** is shown to comprise 1.3 eV inductive stabilization, partly offset by a resonance contribution of −0.5 eV.

The five-membered ring sulfone, tetrahydrothiophene-1,1-dioxide (**96**), as measured by Schweig and coworkers[63] has a PE spectrum which correlates with that of its four-membered ring analogue, **94**, with the expected marginally lower IEs, except for an interchange of n_O^- and n_O^+ due to CH hyperconjugative destabilization of the former. The outermost four MOs are assigned as $I_1 = 10.24$ eV ($\pi_O^+ - \sigma_{CS}^-$), $I_2 = 11.01$ eV ($n_O^- - \sigma_{CH}^-$), $I_3 = 11.36$ eV ($n_O^+ - \sigma_{CS}^+$) and $I_4 = 11.50$ eV (π_O^-) showing reductions of 0.3–0.5 eV relative to **94**. With the incorporation of an ethylenic π_{CC} bond in 2,5-dihydrothiophene-1,1-dioxide (**97**), the PE spectrum of Bock and coworkers[12] shows the expected additional ionization among the strongly overlapped bands below 13 eV. The π_{CC} ionization is assigned as the first band, $I_1 = 10.44$ eV, and the SO_2-based ionizations follow in the same order as in **96**, namely $I_2 = 10.60$ eV ($\pi_O^+ - \sigma_{CS}^-, b_1$), $I_3 = 11.25$ eV ($n_O^- - \sigma_{CH}^-, b_2$), $I_4 = 11.63$ eV ($n_O^+ - \sigma_{CS}^+, a_1$) and $I_5 = 11.99$ eV (π_O^-, a_2).



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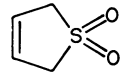

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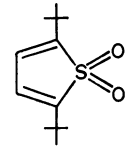
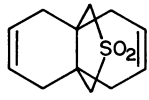


(98)

For 2,5-di-*t*-butylthiophene-1,1-dioxide (**98**), the PE spectrum measured by Schweig and coworkers[63] shows three well-resolved low IE bands, with the first band being associated with the localized π_{CC}^- orbital of thiophene. The n_O^- orbital of the SO_2 group is considerably destabilized by significant interaction with the π_{CC}^+ orbital of thiophene. So the assignment obtained is $I_1 = 8.64$ eV (π_{CC}^-, a_2), $I_2 = 9.70$ eV ($n_O^- - \pi_{CC}^+, b_2$) and $I_3 = 10.57$ eV ($\pi_O^+ - \sigma_{CS}^-, b_1$).

In 12-thia[4.4.3]propella-3,8-diene-12-dioxide (**99**) and 12-thia[4.4.3]propella-2,4,7,9-tetraene-12-dioxide (**100**), the five-membered sulfone ring is associated with coupled ethylenic units and coupled butadiene units, respectively, in which the C_{2v} symmetry is maintained. The PE spectra measured by Bohm and Gleiter[58] are shown to have low IEs dominated by π_{CC} ionizations with first IEs assigned as $I_1 = 9.2$ eV (π_{CC}^-, b_1) for **99** and $I_1 = 8.7$ eV (π_{CC}^-, a_2) for **100**.



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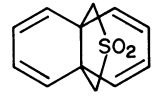

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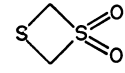

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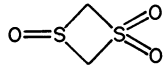

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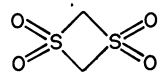


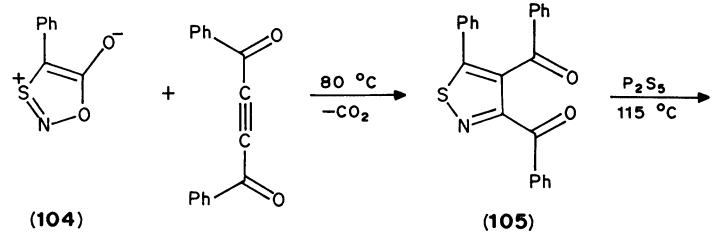
(103)

Three sulfones of 1,3-dithietane were synthesized and studied using various spectroscopies by Block and coworkers[21]. The geometry of 1,3-dithietane-1,1,3,3-tetraoxide (**103**) was shown by X-ray crystallography to have a nearly square four-atom ring with the SO_2 and CH_2 groups essentially perpendicular to it. It is likely that 1,3-dithietane-1,1-dioxide (**101**) and 1,3-dithietane-1,1,3-trioxide (**102**) are also of this geometric form, and hence of C_{2v} symmetry. The PE spectrum of **101** shows an isolated first band at $I_1 = 9.71$ eV, which is assigned as the sulfide lone-pair, n_S, subject to some conjugative interaction represented by its orbital description as $n_S - \pi_O^+(b_1)$. The four SO_2 ionizations are clearly bunched but are identified by vertical IEs of 11.18, 11.57, 11.72 and 11.94 eV. Semiempirical calculations provide an assignment for these as $\pi_O^+ - \sigma_{CS}^-(b_1) < n_O^-(b_2) < n_O^+ - \sigma_{CS}^+(a_1) < \pi_O^-(a_2)$. The PE spectra of **102** and **103** have not been satisfactorily assigned. For **102** the two well-defined low IE bands at 10.2 and 11.0 eV can perhaps be assigned to $n_S - n_O(b_2)$ of SO and $\pi_O^+ - \sigma_{CS}^-(b_1)$ of SO_2. For **103** the low-energy region between 10.5 and 14 eV reveals three bands in the approximate intensity ratio of 1:6:1. The eight orbitals dominated by oxygen lone-pair character are obviously involved, but an exact sequence cannot be prescribed because the results of semiempirical calculations are not convincing.

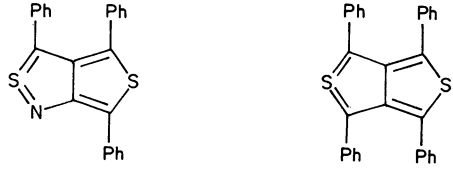
V. SULFUR–HETEROATOM COMPOUNDS

Organic sulfur compounds in which sulfur is bonded to a heteroatom other than oxygen have not been widely studied by photoelectron spectroscopy. Those studies which have been reported mostly involve either nitrogen or a halogen as the heteroatom.

Gleiter and coworkers[64] have studied a number of planar heteroaromatic systems involving S—N bonds within the ring structure. Thieno[3,4-*c*]isothiazole is a nonclassical condensed thiophene, and its triphenyl derivative, triphenylthieno[3,4-c]isothiazole (**106**), is a 10π system containing two different masked 1,3-dipolar systems. It was synthesized from 4-phenyl-1,3,2-oxathiazolylium-5-olate (**104**) and dibenzoylacetylene via the direct precursor isothiazole (**105**) and its photoelectron spectrum compared with that of the related thieno[3,4-*c*]thiophene (**107**)[34]. The spectrum is characterized by an isolated first band at 6.9 eV which is verified by PPP–CI calculations to involve the $\pi(a_u')$ orbital confined to the thienothiophene ring.

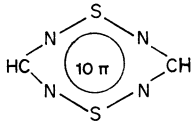


(104) (105)

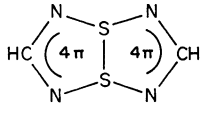


(106) (107)

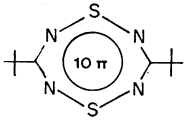
The photoelectron spectra obtained by Gleiter and coworkers[65] for 3,7-di-*t*-butyl-1,5-dithia-2,4,6,8-tetrazocine (**109**), 3,7-diphenyl-1,5-dithia-2,4,6,8-tetrazocine (**110**) and 3,7-bis(dimethylamino)-1,5-dithia-2,4,6,8-tetrazocine (**111**) were interpreted with the aid of model (*ab initio* and MNDO) calculations on the parent 1,5-dithia-2,4,6,8-tetrazocine (**108**). These show that the electron-rich 10π system prefers a planar monocyclic structure, **108a**, though π-donor substituents can induce a pseudo-Jahn–Teller distortion leading to a bicyclic 8π system with a transannular S—S bond, **108b**. A qualitative correlation diagram of the outermost π orbitals of the 10π and 8π structures shows that a shortened S—S bond stabilizes the $2b_{1u}$ HOMO of **108a** and correlates with the $7a_1$ orbital, which corresponds to the S—S bond. Parallel to this stabilization is the anticipated destabilization of the $1b_{2g}(\pi)$ orbital which is antibonding with respect to a S—S bond. The PE spectrum of **109** is characterized by an isolated first band at 8.39 eV which is assigned to the $b_{1u}(\pi)$ MO in the monocyclic 10π structure. By contrast **110** has strongly overlapped bands in the low IE region. The calculations suggest that a total of five π levels, the $b_{1u}(\pi)$ orbital of the 10π structure and the four phenyl orbitals b_{2g}, b_{3g}, a_u and b_{1u} derived from the degenerate e_{1g} MOs of benzene, appear in this structure. It is not possible to assign a specific order for these ion states. A similar situation is encountered with the PE spectrum of **111**. The broad peak observed at 7.5–9.5 eV is likely to correspond to five or six transitions according to the calculations, but the absence of comparative spectra of related molecules means that a definitive assignment cannot be made.



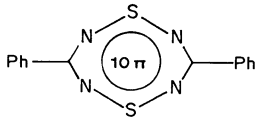
(108a)



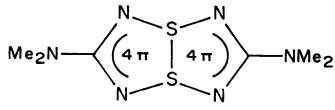
(108b)



(109)



(110)



(111)

A unique study by UPS is represented in the data obtained by Westwood and coworkers[66] on the gas-phase radicals 1,2,4,6-thiatriazinyl, $R_2C_2N_3S^{\bullet}$ (**112**) and 1,2,3,5-dithiadiazolyl, $RCN_2S_2^{\bullet}$ (**113**) with R = CF_3, Cl and Ph. The study of radical species by PE spectroscopy has been limited to short-lived diatomic and triatomic radicals and the smaller alkyl radicals, but it is suitable for any radical which can be produced in comparable concentration to its precursor molecule. This is the case for the more stable radicals investigated in this study. The thiatriazinyls were prepared in two ways, by on-line reduction of the corresponding 1-chlorothiatriazines over heated silver wool (for R = Ph or Cl), or at ambient temperature over triphenylantimony (for R = CF_3 or Cl), and by direct sampling of the vapor over the radical dimer (for R = Ph). This latter technique was used exclusively for the dithiadiazolyls. The reduction over Ag wool is exemplified by the He(I) PE spectra, in Figure 25, showing 1,3,5-trichloro-1,2,4,6-thiatriazine and its reduction product 3,5-dichloro-1,2,4,6-thiatriazinyl, where the radical species is identified by its isolated low IE band at 8.57 eV. By comparison the bis(trifluoromethyl) analogue has $I_1 = 9.1$ eV and the biphenyl analogue has $I_1 = 7.35$ eV. The variations are in line with

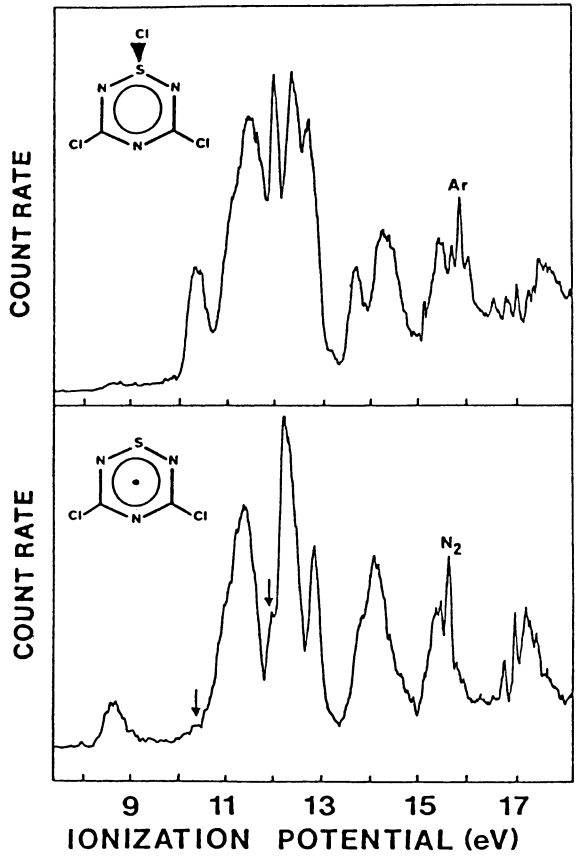
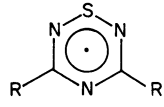


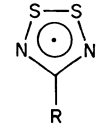
FIGURE 25. Photoelectron spectra of 1,3,5-trichloro-1,2,4,6-thiatriazine and its reduction product 3,5-dichloro-1,2,4,6-thiatriazinyl. Reprinted with permission from Reference 66. Copyright (1989) American Chemical Society

the relative inductive influence of the substituent groups involved, and semiempirical calculations indicate that the HOMO in each radical includes n_S character and is of $\pi(b_1)$ designation. The PE spectra of the dithiadiazolyls similarly show isolated first IEs at 8.25 eV (R = CF_3), 8.00 eV (R = Cl) and 7.40 eV (R = Ph). In these cases the HOMO is of $\pi(a_2)$ type based on the antibonding n_S^- combination orbital.



R=CF_3, Cl, Ph

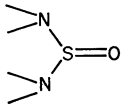
(112)



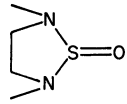
R=CF_3, Cl, Ph

(113)

The higher formal valence of sulfur involved in the sulfoxide group appears in the diamine systems of bis(dimethylamino) sulfoxide (**114**) and its cyclic analogue *N,N'*-ethylene-*N,N'*-dimethylthionyl diamide (**115**). The PE spectra obtained by Bock and Solouki[54] are compared with their oxygen analogues dimethyl sulfite (**116**) and ethylene sulfite (**117**). All spectra are shown to feature the low IE n_S and π_{SO} bands characteristic of the sulfoxide group, followed by the n_N^-/n_N^+ (for **114** and **115**) and the n_O^-/n_O^+ (for **116** and **117**) combination bands. The PE spectra of **114** and **115** in Figure 26 show the variation in the distribution of these first four bands, which is verified by CNDO calculations to be determined by the directionality of the localized n_N orbitals as influenced by the molecular conformation in each case.



(114)



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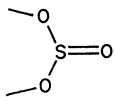
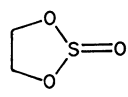
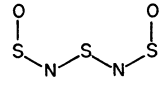


(116)

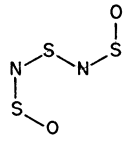


(117)

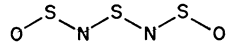
The PE spectrum of the chain molecule $S_3N_2O_2$ (**118**) was measured and interpreted by Gleiter and Bartetzko[67] as part of a study on the structures of the 8π systems S_4N^-, $S_3N_2O_2$ and $S_4N_3^-$. The most likely planar arrangements for **118** number five, **118a–118e**, and MNDO calculations suggest that the minimum energy conformation is a structure with two sickle-like arrangements, either **118a** or **118b**. The PE spectrum is simulated with good accuracy by the Koopmans values obtained in the calculations on these two conformers. For the C_{2v} geometry of **118a** the HOMO is assigned as $\pi(b_1)$, corresponding to the isolated band with $I_1 = 9.25$ eV. The next three bands at 11.08, 11.38 and 11.60 eV are strongly overlapped and are assigned as $\pi(a_2) < n(a_1) < n(b_2)$. The fifth band at $I_5 = 12.51$ eV is also well-resolved and is assigned to another $n(a_1)$ orbital.



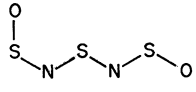
(118a)



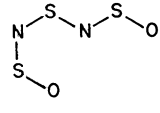
(118b)



(118c)



(118d)



(118e)

The highest formal sulfur valence is exemplified in the dimethyl sulfone analogues *S,S*-dimethyl sulfoximide (**119**) and *S,S*-dimethyl sulfodiimide (**120**) for which the PE spectra were measured by Bock and coworkers[12]. As expected the first IE of **119** ($I_1 = 9.50$ eV) and **120** ($I_1 = 8.87$ eV) are lower than that of dimethyl sulfone **7** ($I_1 = 10.65$ eV). The four well-resolved low IE bands observed in each case correlate with the dimethyl

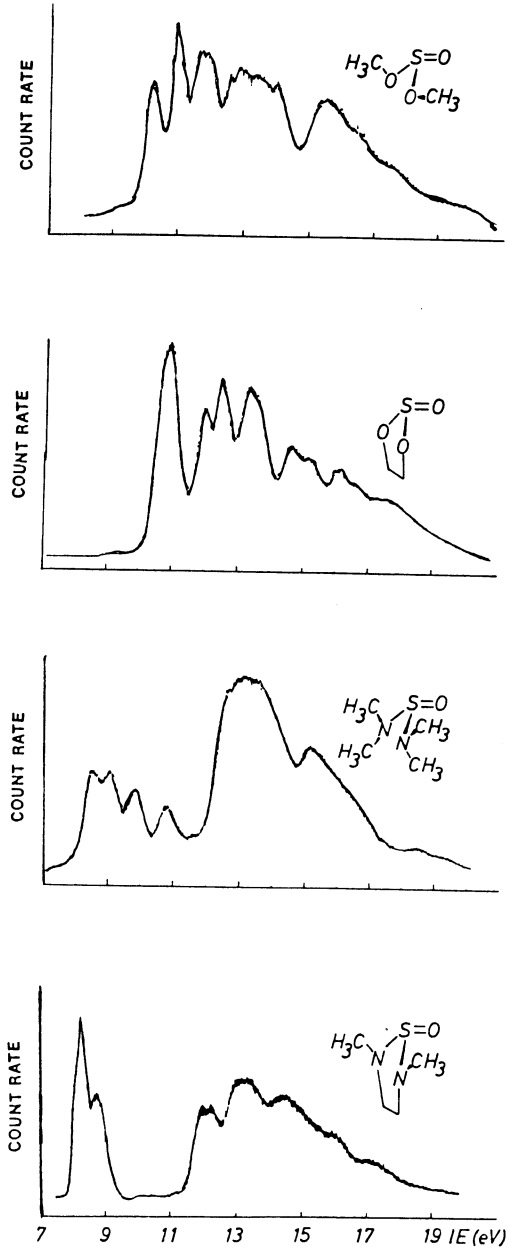
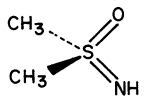
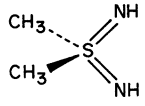


FIGURE 26. Photoelectron spectra of dimethyl sulfite, ethylene sulfite, bis(dimethylamino) sulfoxide and *N,N'* ethylene-*N,N'*-dimethylthionyl diamide. Reproduced by permission of VCH Verlagsgesellschaft from Reference 54

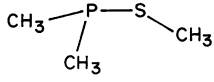
sulfone bands $\pi_O^+ < n_O^- < n_O^+ < \pi_O^-$ except that the third and fourth are interchanged in the assignments derived for **119** and **120**.



(119)



(120)



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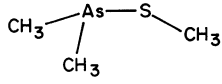


(122)

The PE spectra of $(CH_3)_2PSCH_3$ (**121**) and $(CH_3)_2AsSCH_3$ (**122**), measured by Gleiter and coworkers[68], were interpreted by reference to their S—S analogue, dimethyl disulfide, CH_3SSCH_3, where the first and second bands, associated with the n_S^- ($I_1 = 8.97$ eV) and n_S^+ ($I_2 = 9.21$ eV) orbital combinations, are separated by 0.24 eV. The corresponding bands of **121** and **122** are assigned to the analogous asymmetric lone-pair orbital combinations. For **121**, $I_1 = 8.6$ eV ($n_p - n_S$) and $I_2 = 9.2$ eV ($n_S + n_P$) separated by 0.6 eV, and for **122**, $I_1 = 8.5$ eV ($n_{As} - n_S$) and $I_2 = 9.2$ eV ($n_S + n_{As}$) separated by 0.7 eV.

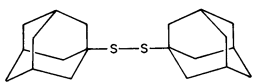
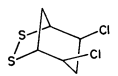
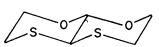
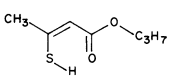
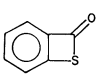
Organic molecules containing a sulfur–halogen bond have been little studied by photoelectron spectroscopy. Divalent sulfur compounds such as methanesulfenyl chloride, CH_3SCl, and methanesulfenyl bromide, CH_3SBr, are relatively reactive, but are suitably prepared by the low-pressure gas-phase reaction of methanethiol, CH_3SH, with Cl_2 and Br_2, respectively. The PE spectra measured by Nagy-Felsobuki and Peel[69] were obtained by spectrum subtraction of the appropriate reactant spectra from the spectra of these reaction mixtures. The first and second bands of CH_3SCl are well-separated at 9.21 and 11.37 eV respectively, and, as verified by an *ab initio* calculation, are assigned to the lone-pair combination orbitals $n_S - n_{Cl}(a'')$ and $n_{Cl} - \bar{n}_S(a')$, respectively. The analogous bands of CH_3SBr at 9.05 and 10.74 eV are also well-spaced. While the HOMO is assigned as the antibonding $n_S - n_{Br}(a'')$ combination consistent with the broadened appearance of the first PE band, the second band is observed to be narrow, so its assignment to a localized $n_{Br}(a')$ orbital is consistent with the calculation which determines it to be of 86% Br character.

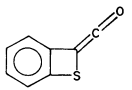
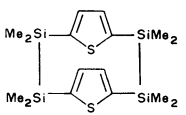
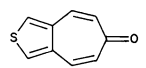
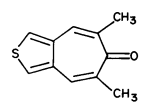
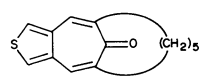
The PE spectra of the methanesulfonyl halides, CH_3SO_2F and CH_3SO_2Cl, studied by Bock and coworkers[12] were compared with those of their inorganic analogues F_2SO_2 and Cl_2SO_2. The strongly overlapped four low IE bands of $(CH_3)_2SO_2$, π_O^+, n_O^-, n_O^+ and π_O^-, are inductively increased in IE by halogen replacement of CH_3. An interchange of n_O^+ and π_O^- results in the fourth IE being associated with a $n_O^+ + n_X$ orbital containing halogen character. In F_2SO_2 the lowest IE bands remain essentially of oxygen character, but in Cl_2SO_2 they become essentially of chlorine character.

VI. TABLE OF IONIZATION ENERGIES

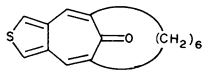
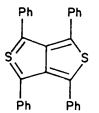
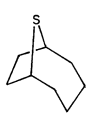
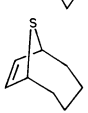
A compilation of the IEs for 129 of the compounds discussed in this review is given below. It is organized in the same style as the earlier compilation of Gleiter and Spanget-Larsen[6] and excludes compounds included in their table. The data tabulated includes (1) the structural formula of each molecule, (2) the molecular point group to which the molecule belongs with an asterisk indicating an idealized geometry, (3) the vertical ionization energies, in eV, and their orbital assignments, and (4) literature references. The IEs are normally the respective band maxima but are limited to the lowest five observed bands. The assignments are normally those given by the original authors, but some have been adjusted or extended by the reviewer to fit the general formalism adopted in the review.

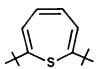
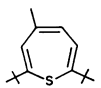
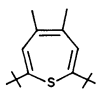
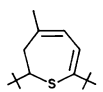
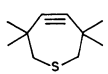
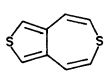
Compilation of ionization energies (in eV) of organic sulfur compounds

Molecule	Symmetry	Ionization energies and assignment					References
	C_2	7.86 n_S^-	8.37 n_S^+	9.8 σ	11.4 σ	13.5 σ	19
	C_s	8.20 $n_S^-(a'')$	10.31 $n_S^+(a'),\sigma_{CS}^-(a'')$				20
	D_{2h}	8.95 $n_S^+(b_{2u})$	9.43 $n_S^-(b_{3g})$	10.60 $\sigma(b_{1u})$	12.53 $\sigma(b_{3u})$	13.87	21
	C_1	8.62 n_S	8.91 n_S	9.79 n_O^+	10.44 n_O^-		22
$HC{\equiv}CSCH_3$	C_s	8.81 $n_S - \pi_{CC}(a'')$	10.34 $\pi_{CC}(a')$	11.62 $\pi_{CC} + n_S(a'')$	12.59 $n_S\sigma$		24
$CH_3SC{\equiv}CSCH_3$	C_2	8.25 n_S^-	8.55 n_S^+	10.80 π_{CC}^-	11.12 π_{CC}^+		24
	C_1	8.81 $n_S - \pi_{CC}$	10.05 n_O^σ	10.58 π_O^-	10.96 $\pi_{CC} + n_S$		25
	C_s	9.45 $n_S(a'')$	10.28 $n_O(a')$	11.8 σ			26
	C_s	8.24 $\pi(a'')$	9.32 $\pi(a'')$	10.31 $\pi(a'')$	10.84 $\sigma(a')$		28
	C_s	8.56 $\pi(a'')$	9.94 $\sigma(a'),\pi(a'')$	10.87 $\pi(a'')$	11.76 $\sigma(a')$		27

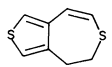
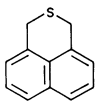
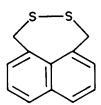
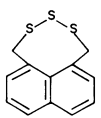
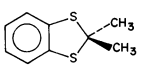
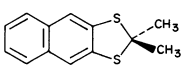
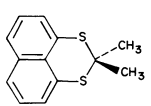
	C_s	8.35 $\pi(a'')$	8.56 $\pi(a'')$	10.01 $\pi(a'')$	11.2 $\pi(a'')$	12.3 $\sigma(a')$	28
	C_{2v}	8.46 $n_S^- - \pi(a_2)$	8.77 $n_S^+ - \pi(b_1)$	10.17 $\pi + n_S^-(a_2)$	11.2 $\pi + n_S^+(b_1)$		29, 30
	C_{2v}	9.05 $n_S^+ - \pi(b_1)$	9.36 $n_S^-(a_2)$	11.83 $n_S^\sigma(b_2)$	12.31 $n_S^\sigma(a_1)$	12.61 $\pi + n_S^+(b_1)$	31
	C_{2v}	8.36 $n_S^+ - \pi(b_1)$	8.77 $n_S^-(a_2)$	11.32 $n_S^\sigma(b_2)$	11.83 $n_S^\sigma(a_1)$		31
	C_{2v}	10.2 $n_S^+ - \pi(b_1), n_S^-(a_2)$	12.95 $n_S^\sigma(b_2)$	13.45 $n_s^\sigma(a_1)$			31
	C_{2h}	7.4 $\pi^+(a_u)$	8.0 $\pi^+(a_g)$	8.4 $\pi^-(b_g)$	8.7 $\pi^-(b_u)$	9.4 $\sigma(a_g)$	32
	C_{2v}	8.62 $\pi(a_2)$	8.77 $\pi(b_1)$	9.07 $n(b_2)$	10.68 $\pi(b_1)$	10.84 $\pi(a_2)$	33
	C_{2v}	8.40 $\pi(a_2)$	8.59 $\pi(b_1)$	9.09 $n(b_2)$	10.48 $\pi(b_1)$	10.61 $\pi(a_2)$	33
	C_{2v}*	8.25 $\pi(a_2)$	8.57 $\pi(b_1)$	9.15 $n(b_2)$	10.01 $\pi(b_1)$	10.43 $\pi(a_2)$	33

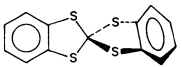
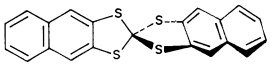
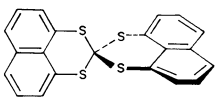
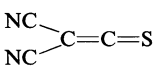
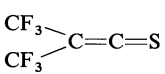
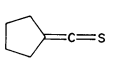
(continued)

Molecule	Symmetry	Ionization energies and assignment					References
	C_{2v}*	8.22 $\pi(a_2)$	8.38 $\pi(b_1)$	9.14 n(b_2)	10.11 $\pi(b_1)$	10.48 $\pi(a_2)$	33
	D_{2h}	6.19 $\pi(a_u)$	7.85 $n_S{}^+(b_{2u})$	8.35–9.35 $\pi(b_{1g})$	10.75		34
	C_s	7.91 $\pi(a'')$	8.60 $\pi(a'')$	9.85 $\pi(a'')$	10.8 $\pi(a'')$		35
	C_s	7.76 $\pi(a'')$	8.64 $\pi(a'')$	9.72 $\pi(a'')$	11.5 $\pi(a'')$		35
	C_{2v}	8.54 $n_S - \pi(b_1)$	9.86 $\pi + n_S(b_1)$	11.24 $n_\sigma(a_1)$			36
	C_{2v}	8.40 $n_S(b_1)$	10.92 $n_\sigma(a_1)$				36
	C_s	8.39 $n_S(a')$	8.65 $\pi_{4,a}(a'')$	9.33 $\pi_{2,s}(a')$	10.66 $\pi_{4,s}(a')$		37
	C_s	8.16 $n_S(a')$					37
	C_s	8.20 $n_S(a')$	9.28 $\pi_{2,s}(a')$				37

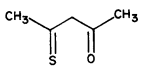
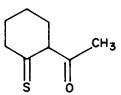
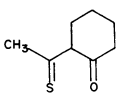
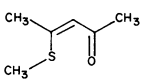
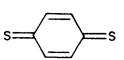
	C_s	8.26 $n_S(a')$	8.59 $\pi_{4,a}(a'')$	10.51 $\pi_{4,s}(a')$		37
	C_s	7.74 $\pi(a'')$	10.04 $\pi(a'')$	11.50 $\sigma(a')$	12.12 $\sigma(a')$	38
	C_s	7.7 $\pi_4(a')$	(9.0) $\pi_3(a')$	9.3 $\pi_2(a'')$	10.2 $\pi_1(a'), n_S(a')$	39
	C_1	7.6 π_4	8.9 π_3	9.2 π_2	10.0 π_1, n_s	39
	C_s	7.5 $\pi_4(a')$	8.6 $\pi_3(a')$	8.9 $\pi_2(a'')$	9.7 $\pi_1(a'), n_S(a')$	39
	C_1	7.7 π	8.9 n_S	10.1 π		39
	C_1	8.19 n_S	9.05 π_y	9.36 π_z		40
	C_{2v}	7.42 $\pi(b_1)$	8.52 $\pi(a_2)$	9.75 $\pi(b_1)$	10.7 $\pi(a_2)$	39

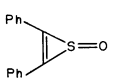
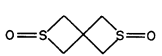
(*continued*)

Molecule	Symmetry	Ionization energies and assignment					References
	C_s	7.67 $\pi(a'')$	8.73 $\pi(a'')$	9.38 $\pi(a'')$	11.0 $\pi(a'')$		39
	C_s	7.91 π	8.42 $n_S(\pi)$	8.84 π	9.59 π	9.9	41
	C_1	7.78 π	8.14 n_S^-	8.90 π	9.67 π	9.89 n_S^+	41
	C_s	7.9 π	8.3 n_S	8.95 π	9.7 π	10.1 n_S, n_S	41
	C_{2v}	7.66 $n_S^+(b_1)$	8.33 $n_S^-(a_2)$	9.77 $\pi_a(a_2)$	10.18 $\pi_s(b_1)$	10.9 $\sigma(b_2)$	42
	C_{2v}	7.63 $n_S^+(b_1),\pi_a(a_2)$	9.15 $n_S^-(a_2)$	9.55 $\pi_s(b_1)$	10.10 $\pi_a(a_2)$	10.9 $\sigma(b_2)$	42
	C_{2v}	7.33 $n_S^-(a_2)$	8.46 $n_S^+(b_1)$	8.86 $\pi_s(b_1)$	9.2 $\pi_a(a_2)$	10.6 $\pi_s(b_1),\sigma(b_2)$	42

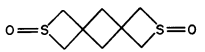
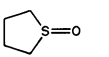
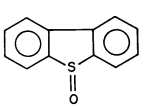
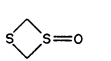
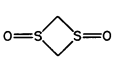
	D_{2d}	7.85 $n_S^+(e)$	8.29 $n_S^-(a_2)$	8.92 $n_S^-(b_1)$	9.92 $\pi_a(a_2)$	10.3 $\pi_s(e),\pi_a(b_1)$	42
	D_{2d}	7.5–8.0 $\pi_a(a_2),n_S^+(e),\pi_a(b_1)$	9.0 $n_S^-(a_2)$	9.5 $n_S^-(b_1),\pi_s(e)$	10.15 $\pi_a(a_2).\pi_a(b_1)$		42
	D_{2d}	7.3 $n_S^-(a_2)$	7.5 $n_s^-(b_1)$	8.5 $n_S^+(e)$	8.9 $\pi_s(e),\pi_a(a_2)$	9.3 $\pi_a(b_1)$	42
$CH_2{=}CHCH{=}S$	C_s	8.87 $n_S(a')$	9.88 $\pi(a'')$	12.0 $\pi(a'')$	12.9 $\sigma(a')$		44
$O{=}C{=}C{=}C{=}S$	$C_{\infty v}$	9.73 π_3	12.44 π_2	14.89 $n_S(\pi),\pi_1$	16.7 σ		45
	C_{2v}	9.94 $\pi(b_1)$	12.79 $\sigma(b_2)$	13.0–13.8 $\pi(b_1),\sigma(b_2),\sigma(a_1),\pi(a_2)$			46
	C_{2v}	9.96 $\pi(b_1)$	12.53 $\pi(b_2)$	13.16 $\pi(b_1)$	14.38 $\sigma(a_1)$		48
	C_{2v}	7.95 $\pi(b_1)$	10.50 $\pi(b_2)$				49
	C_{2v}	8.87 $n_S(b_2)$	9.18 $\pi(a_2)$	10.35 $\pi(b_1)$			50

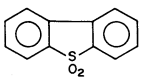
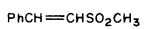
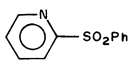
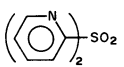
(*continued*)

Molecule	Symmetry	Ionization energies and assignment			References
	C_s	8.85 $n_S(a')$	9.45 $n_O(a'),\pi(a'')$	11.6 $\pi(a'')$	50
	C_s	8.73 $n_S(a'),\pi_3(a'')$	9.29 $n_O(a')$	10.77 $\pi_2(a'')$	52
	C_s	8.34 $\pi_3(a'')$	9.16 $n_O(a')$	10.34 $\pi_2(a'')$	52
	C_s	8.30 $n_S(a'),\pi_3(a'')$	10.24 $\pi_2(a'')$		52
	C_s	8.54 $\pi_3(a'')$	9.03 $n_O(a')$	10.57 $\pi_2(a'')$	52
	D_{2h}	8.4 $\pi(b_{2u})$	9.10 $n_S^-(b_{2g}),n_S^+(b_{3u})$		53
	C_1	8.51 $n_S - n_O$	10.89 $n_O + n_S$	11.8	15

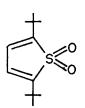
$CH_2{=}S{=}O$	C_s	10.31 $\pi(a'')$	10.7 $n_S - n_O(a')$	13.4 $\sigma(a')$	13.7 $\pi(a'')$		16
$(CH_3)_2SO$	C_s	9.01 $n_S - n_O(a')$	10.17 $\pi_{SO}(a'')$	12.57 $n_O(a')$	13.40	13.9	54
$(C_2H_5)_2SO$	C_s	8.76 $n_S - n_O(a')$	9.83 $\pi_{SO}(a'')$	12.18 $n_O(a')$	12.5	14.2	54
$(C_3H_7)_2SO$	C_s	8.60 $n_S - n_O(a')$	9.69 $\pi_{SO}(a'')$	11.9 $n_O(a')$	13.55	15.6	54
$(Me_2CH)_2SO$	C_s	8.46 $n_S - n_O(a')$	9.52 $\pi_{SO}(a'')$	11.80 $n_O(a')$	12.4	13.9	54
$(Me_3C)_2SO$	C_s	8.18 $n_S - n_O(a')$	9.20 $\pi_{SO}(a'')$	11.20 $n_O(a')$	12.80	15.0	54
Ph_2SO	C_1	8.58 $n_S - n_O$	9.54 $\pi_3, \pi_3', \pi_2, \pi_2'$	10.1 π_{SO}	12.1		54
$CH_2{=}CHSOCH_3$	C_1	9.02 $n_S - n_O$	10.22 π_{SO}	10.80 π_{CC}	12.99	13.0	54
$PhSOCH_3$	C_1	8.79 $n_S - n_O$	9.7–10.1 π_{SO}, π_3, π_2	12.3			54
	C_s	9.66 $n_S - n_O(a')$	9.78 $\pi_{SO}(a'')$	12.91 $n_O(a')$	13.30	15.9	11,54
	C_s	8.29 π_1	8.89 $\pi_{SO}(a'')$	9.07 $n_S(a')$	9.38 π_2, π_3	9.92 π_4	55
	C_s	8.96 $n_S - n_O(a')$	10.14 $\pi_{SO}(a'')$	12.00			15
	C_2	8.75 $n_S^- - n_O^-$	9.60 $n_S^+ - n_O^+$	10.45 π_{SO}			56, 57

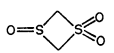
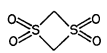
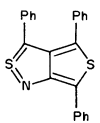
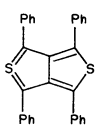
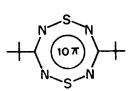
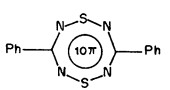
(*continued*)

Molecule	Symmetry	Ionization energies and assignment					References
	C_{2v}/C_{2h}	8.78 $n_S^- - n_O^-$	9.16 $n_S^+ - n_O^+$	10.10 π_{SO}			56, 57
	C_2	8.75 $n_S^- - n_O^-$	9.00 $n_S^+ - n_O^+$	10.15 π_{SO}			56, 57
	C_s	8.77 $n_S - n_O(a')$	9.75 $\pi_{SO}(a'')$	11.99 $n_O(a')$			54
	C_s	8.50 $n_S - n_O(a')$	9.35 $\pi_{CC}(a')$	9.5 $\pi_S^O(a'')$			58
	C_s	8.52 $n_S - n_O(a')$	9.1 $\pi_{CC}^-(a')$	9.5 $\pi_{SO}(a'')$	9.7 $\pi_{CC}^+(a')$		58
	C_s	8.71 $n_S - n_O(a'),\pi(a'')$	10.06 $\pi_{SO}(a'')$	10.64 σ_{SO}			58
	C_s	8.44 $n_S - n_O(a')$	8.56 $\pi^-(a'')$	8.9 $\pi^+(a'')$	9.9 $\pi_{SO}(a'')$		58
	C_s	8.43 $n_S - n_O(a')$	8.59–10.09 $\pi_{CC},\pi_{CC},\pi_{CC},\pi_{CC}$	10.29 $\pi_{SO}(a'')$			54
	C_s	9.19 $n_S^+ - n_O(a')$	9.87 $n_S^-(a')$	10.65 $\pi_{SO}(a'')$	12.49	13.21	21
	C_{2v}	9.06 $n_S^+ - n_O^+(a_1)$	10.59 $n_{SO}(b_2),\pi_{SO}^+(b_1)$	11.14 $\pi_{SO}^-(a_2)$	13.0		21

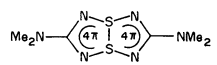
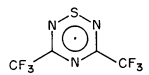
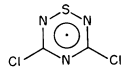
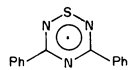
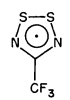
$(CH_3)_2SO_2$	C_{2v}	10.65 $\pi_O^+(b_1)$	11.18 $n_O^-(b_2)$	11.65 $n_O^+(a_1)$	12.00 $\pi_O^-(a_2)$	14.52	12, 13
$CH_2{=}CHSO_2CH_3$	C_s	10.65 $\pi_O^+(a')$	11.00 $n_O^-(a'')$	11.50 $n_O^+(a')$	11.95 $\pi_{CC}(a'')$	12.15	12, 13
$(CH_2{=}CH)_2SO_2$	C_{2v}	10.56 $\pi_O^+(b_1)$	10.78 $n_O^-(b_2)$	11.30 $n_O^+(a_1)$	11.59 $\pi_{CC}(a_2)$	11.99 $\pi_{CC}(b_2)$	12, 13
$PhSO_2CH_3$	C_s	9.74 $\pi(a'),\pi(a'')$	10.45 $\pi_O^+(a')$	10.95 $n_O^-(a'')$	11.80 $n_O^+(a')$		12
Ph_2SO_2	C_{2v}	9.37 $\pi(b_1)$	9.82 $\pi(a_2),\pi(b_2)$	10.30 $\pi(a_1),\pi_O^+(b_1)$	11.87 $n_O^-(b_2)$		12, 60
	C_{2v}	8.90 $\pi(a_2)$	9.85 $\pi(a_2),\pi_O^+(b_1)$	10.40 $\pi(b_2)$	10.63 $\pi(b_2)$	11.30 $n_O^+(a_1)$	12
	C_{2v}*	9.08 $\pi_3(b_1)$	9.66 $\pi_2(a_2)$	10.44 $\pi_O^+(b_1)$	10.85 $n_O^-(b_2)$	11.13 $n_O^+(a_1)$	59
	C_{2v}*	9.57 π_{CC}	9.76 π_{CC}	9.99 σ_{SO},n_N	10.81 π_{SO},π_{CC}	11.76 σ_{SO}	60
	C_{2v}*	9.56 π_{CC}	9.76 σ_{SO}	10.15 π_{CC},n_N	10.87 π_{SO},π_{CC}	11.76 σ_{SO}	60
	C_{2v}	10.20 $\pi_O^+(b_1)$	11.57 $n_O^-(b_2)$	11.98 $n_O^+(a_1)$	12.03	13.92	12
	C_{2v}	9.82 $\pi_O^+(b_1)$	11.1–11.3 $n_O^+(a_1),n_O^-(b_2),\pi_O^-(a_2)$				61

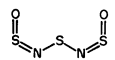
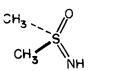
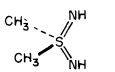
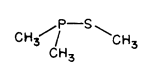
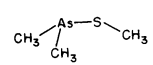
(*continued*)

Molecule	Symmetry	Ionization energies and assignment					References
	C_{2v}*	10.40 $\pi_{CC}(b_2)$	10.63 $\pi_O^+(b_1)$	11.88 $n_O^+(a_1)$	12.17 $n_O^-(b_2)$	12.43 $\pi_O^-(a_2)$	61
	C_{2v}	9.89 $\pi_{CC}(b_2)$	10.14 $\pi_O^+(b_1)$	11.57 $n_O^+(a_1)$	11.76 $n_O^-(b_2)$	11.94 $\pi_O^-(a_2)$	61
	C_{2v}	10.76 $\pi_O^+(b_1)$	11.36 $n_O^+(a_1)$	11.82 $n_O^-(b_2), \pi_O^-(a_2)$			62
	C_s	10.80 $\pi_{CC}(a''), \pi_O^+(a')$	12.00 $n_O^+(a'), n_O^-(a'')$	12.50 $\pi_O^-(a'')$			62
	C_{2v}	10.24 $\pi_O^+(b_1)$	11.01 $n_O^-(b_2)$	11.36 $n_O^+(a_1)$	11.50 $\pi_O^-(a_2)$		63
	C_{2v}	10.44 $\pi_{CC}(b_2)$	10.60 $\pi_O^+(b_1)$	11.25 $n_O^-(b_2)$	11.63 $n_O^+(a_1)$	11.99 $\pi_O^-(a_2)$	12
	C_{2v}	8.64 $\pi_{CC}(a_2)$	9.70 $n_O^-(b_2)$	10.57 $\pi_O^+(b_1)$			63

	C_{2v}	9.2 $\pi_{CC}^{-}(b_1)$	9.75 $\pi_{CC}^{+}(a_1)$	10.0 $\pi_{SO}(b_1)$	10.7 $\sigma_{SO}(a_1)$		58
	C_{2v}	8.7 $\pi_{CC}(a_2)$	8.9 $\pi_{CC}(b_2)$	10.5 $\pi_{SO}(b_1)$	11.0 $\sigma_{SO}(a_1)$		58
	C_{2v}	9.71 $n_S(b_1)$	11.18 $\pi_O^{+}(b_1)$	11.57 $n_O^{-}(b_2)$	11.72 $n_O^{+}(a_1)$	11.94 $\pi_O^{-}(a_2)$	21
	C_{2v}	10.2 $n_S - n_O(b_2)$	11.0 $\pi_O^{+}(b_1)$				21
	D_{2h}	11.00	12.55	13.51			21
	D_{2h}*	6.9 $\pi(a_u)$	8.8 $\pi(b_{1g})$	9.0 $n_N(b_{2u})$	9.3		64
	D_{2h}	6.2 $\pi(a_u)$	7.9 $\pi(b_{1g})$				64
	D_{2h}	8.39 $\pi_S(b_{1u})$	9.2 $\pi(a_u)$	9.68 $n_N(b_{1g}), n_N(b_{3u})$	10.25 $n_N(b_{2u})$		65
	D_{2h}	9.0–9.9 $\pi(b_{1u}), \pi(a_u), \pi(b_{2g}), \pi(b_{3g}), \pi(a_u), \pi(b_{1u}), \pi(b_{1g})$					65

(*continued*)

Molecule	Symmetry	Ionization energies and assignment					References
	C_{2v}	8.15–8.8 $\pi(a_2),\sigma(a_1),\pi(b_1),n(a_2),n_N^-(b_2)$		10.6 $n_N^+(a_1)$	10.95 $\sigma(b_1),n(b_2)$		65
	C_{2v}	9.1 $n_S-\pi_N^+(b_1)$	11.5	12.2	12.7	13.7	66
	C_{2v}	8.57 $n_S-\pi_N^+(b_1)$	11.0	11.29	12.22 n_{Cl}	12.79	66
	C_{2v}	7.35 $n_S-\pi_N^+(b_1)$	8.9 π_{CC}	9.2 π_{CC}	9.4	10.9	66
	C_{2v}	8.25 $n_S^- - \pi_N^-(a_2)$	11.1	11.65	12.0	13.23	66
	C_{2v}	8.00 $n_S^- - \pi_N(a_2)$	10.27 $\pi(b_1)$	11.0	11.33	11.80	66
	C_{2v}	7.40 $n_S^- - \pi_N^-(a_2)$	8.9 π_{CC}	9.4 π_{CC}	10.2	10.6	66
	C_s	8.53 $n_S(a')$	9.06 $\pi_{SO}(a'')$	9.82 $n_N^- + \pi_{SO}(a'')$	10.82 $n_O - n_N^+(a')$	13.1 $\sigma_{SO}(a')$	54

	C_s	8.2 $n_S(a'),\pi_{SO}(a'')$	8.77 $n_O - n_N{}^+(a')$	12.01 $n_N{}^- + \pi_{SO}(a'')$	12.27 $\sigma_{SO}(a')$	13.25	54
	C_s	10.25 $n_S(a')$	10.95 $\pi_{SO}(a'')$	11.60	11.90	12.80	54
	C_s	10.93 $n_S(a'),\pi_{SO}(a'')$	11.96	12.48	13.33	14.6	54
	C_{2v}	9.25 $\pi(b_1)$	11.08 $\pi(a_2)$	11.38 $n(a_1)$	11.60 $n(b_2)$	12.51 $n(a_1)$	67
	C_s	9.50 $\pi_{NO}{}^+(a')$	10.29 $n_{NO}{}^-(a'')$	10.94 $\pi_{NO}{}^-(a'')$	12.00 $n_{NO}{}^+(a')$		12
	C_{2v}	8.87 $\pi_N{}^+(b_1)$	9.43 $n_N{}^-(b_2)$	10.11 $\pi_N{}^-(a_2)$	12.05 $n_N{}^+(a_1)$		12
	C_1	8.6 $n_P - n_S$	9.2 $n_S + n_P$	11.1 σ_{PS}	11.7 σ_{CP}	12.3 σ_{CS}	68
	C_1	8.5 $n_{As} - n_S$	9.2 $n_S + n_{As}$	10.7 σ_{AsS}	11.3 σ_{CAs}	12.2 σ_{CS}	68
CH_3SCl	C_s	9.21 $n_S - n_{Cl}(a'')$	11.37 $n_{Cl} - \bar{n}_S(a')$	12.55	12.93	14.39	69
CH_3SBr	C_s	9.05 $n_S - n_{Br}(a'')$	10.74 $n_{Br}(a')$	11.66	12.35	13.70	69
CH_3SO_2F	C_s	12.53 $\pi_O{}^+(a'),n_O{}^-(a''),\pi_O{}^+(a')$		13.91 $n_O{}^+$	15.57		12
CH_3SO_2Cl	C_s	11.6 $\pi_O{}^+(a')$	11.94 $n_O{}^-(a'')$	12.36 $\pi_O{}^+(a')$	12.6 $n_O{}^+ + n_{Cl}(a'')$	13.32 $\pi_{SO}{}^+(a')$	12

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CHAPTER 5

The NMR and ESR spectra of sulphonic acids and their derivatives

ALAN R. BASSINDALE and JAMES N. ILEY

POCRG, Department of Chemistry, The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK

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I. INTRODUCTION

The sulphonic acids and their derivatives comprise a very large number of compounds, many of which have been studied by NMR spectroscopy and ESR studies have been attempted. The ESR data on sulphonic acids and derivatives are limited for a number of reasons discussed in detail in Section II. The only radicals for which extensive ESR data are available are the sulphonamide derivatives $RSO_2\dot{N}R$. The related radicals $RSO_3^{\bullet}$ have not been observed. There are only one or two examples of radical cations, $RSO_2\overset{+}{\dot{N}}R_2$, and radical anions $RSO_2NR_2^{-\bullet}$ and $RSO_3R^{-\bullet}$. The radical cation is difficult to form and the radical anions decompose readily. The NMR spectra of sulphonic acids and derivatives have been well-studied and multinuclear studies have been popular in recent years. Results are available for ^{33}S, ^{15}N and ^{17}O NMR. In general the NMR investigations have concentrated on chemical shift correlations and some comparisons with other sulphur acids. The widespread use of sulphonic acids and derivatives, such as tosylates, in organic chemistry and the many medicinal uses of sulphonamides means that much NMR data are contained in synthetic, mechanistic and analytical papers. We have not exhaustively searched for NMR data of individual compounds, but the tables give a good coverage of representatives of each subgroup and each nucleus.

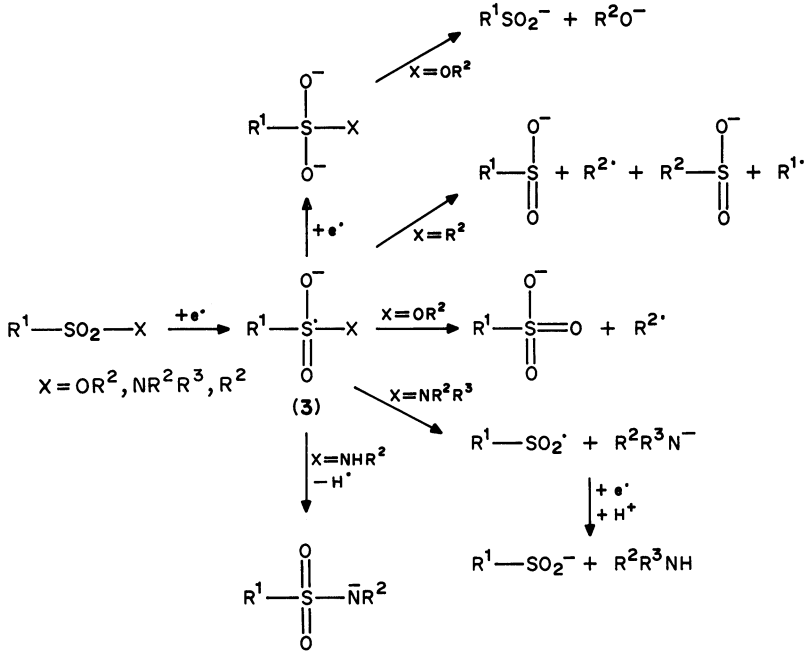
II. ELECTRON SPIN RESONANCE STUDIES

A. Introduction

Compared to both sulphenic and sulphinic acids and their derivatives, the sulphonic acids and related compounds have not been extensively investigated by ESR methods. Sulphonamides alone have been subjected to most detailed study; the largest body of work relates to the sulphonamidyl radical **1**, and a couple of papers report on the nature of the sulphonamide radical cation **2**. Radicals derived from sulphonic acids and their acid chlorides are the subject of only a handful of reports. The reasons for this paucity of information are not hard to find. First, the sulphonyloxy radicals, $RSO_3^{\bullet}$, which is the oxygen analogue of **1**, is, for symmetry reasons, not expected to be observed[1,2]. This is because such radicals are thirty-one electron species in which the unpaired electron is associated with the triply degenerate ligand oxygen non-bonding orbitals. These species are subject to very rapid spin–lattice relaxation times which render them undetectable by ESR spectroscopy. Second, the powerful electron-withdrawing properties of the sulphonyl group results in compounds containing such a group being good electron acceptors. In turn, processes involving the loss of an electron to form a radical cation, such as **2**, are less common. To our knowledge, only two cations of structure **2** have been reported[3–6]. However, the electron-accepting properties of sulphonyl compounds are well-known, and both one- and two-electron processes have been observed. The one-electron reduction of sulphonyl compounds, which can be effected electrochemically or by electron transfer from sodium or the naphthalene radical anion, yields radical anions (**3**) that, in principle, can be detected by ESR (Scheme 1)[7–9]. In practice, however, only a few such radicals have

$R^1SO_2\dot{N}R^2$ (**1**) $\quad$ $R^1SO_2\overset{+}{\dot{N}}R^2R^3$ (**2**)

been studied because there are several pathways by which the radical anion can rapidly fragment with cleavage of the S—X bond (Scheme 1)[7–10].



SCHEME 1

B. Radical Anions of Sulphonic Acids and their Derivatives

1. $MeSO_3H^{-\cdot}$[11]

γ-Irradiation of methanesulphonic acid using a ^{60}Co source at 77 K generates a radical that can be assigned the structure $MeSO_3H^{-\cdot}$. The ESR spectrum of irradiated $MeSO_3H$ consists of a central triplet, assigned to the $\dot{C}H_2SO_3H$ radical (Section II.E), that lies on top of the spectrum due to $MeSO_3H^{-\cdot}$. However, the spectrum also displays weak-intensity outer lines due to a ^{33}S-containing radical and these are quintets rather than triplets (Figure 1). The ^{33}S spectrum is consistent with $MeSO_3H^{-\cdot}$ if the hyperfine coupling of the methyl and hydroxyl protons are identical. The value of the ^{33}S hyperfine coupling, $a(^{33}S)$, is 93.6 G and is almost isotropic; the value of $a(H)$ is 13 G. Thus, the spin density on the sulphur 3s orbital is calculated to be 0.096 (using a value of 975 G for the coupling to a pure sulphur 3s orbital[2]), and since the ^{33}S coupling is essentially isotropic there is little spin density on the sulphur 3p orbitals. Similarly, the spin density on the carbon $2p_z$ orbital of the methyl group is 0.57 (assuming a spin density of 1 corresponds to a value of 23 G for $a(H)$, i.e. the value for Me·), and that on the $2p_z$ orbital of the oxygen of the OH group is 0.29 (assuming that the maximum coupling is 44.4 G). The most likely molecular orbital to contain the unpaired spin density is a three-centre σ antibonding orbital, as depicted in **4**, in which the radical adopts a trigonal bipyramidal structure. This is similar to that proposed for the isoelectronic phosphoranyl radicals[12]. There is no

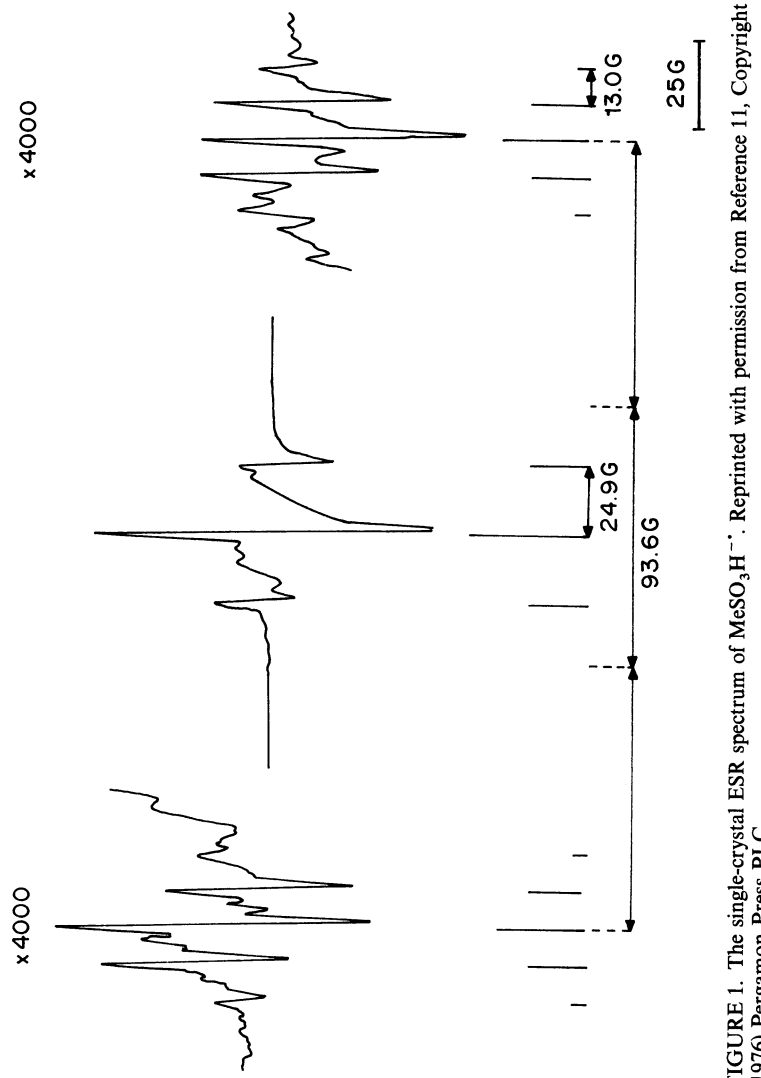
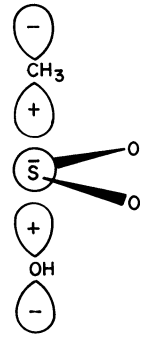


FIGURE 1. The single-crystal ESR spectrum of $MeSO_3H^{-\cdot}$. Reprinted with permission from Reference 11, Copyright (1976) Pergamon Press PLC

evidence from the ESR spectrum of the unpaired electron residing in a non-bonding sulphur sp^2 or spd hybridized orbital as might be expected from VSEPR considerations.



(4)

Radical anion structures of related sulphonic acids have been tentatively assigned to the species giving rise to the ESR spectra of γ-irradiated cysteic acid[13] and sodium isethionate[14]. Thus, the spectrum observed from irradiation of an alkaline glass of $^{-}OSO_2CH_2CH(NH_2)CO_2^{-}$ at 77 K, in which a triplet hyperfine splitting of 12 G is apparent and thought to be that of $^{-}O_2CCH(NH_2)CH_2SO_3^{2-\bullet}$. The magnitude of this proton coupling is remarkably similar to that of $MeSO_3H^{-\bullet}$. Similarly, irradiation of $HOCH_2CH_2SO_3^{-}$ may yield $HOCH_2CH_2SO_3^{2-\bullet}$, though the spectrum obtained is not sufficiently resolved for anything but the most speculative of assignments.

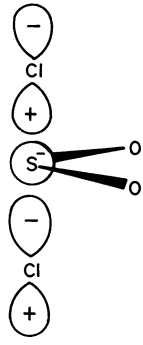
2. $SO_2Cl_2^{-\bullet}$ [15]

Sulphuryl chloride is the dichloride of sulphuric acid and, because the results obtained for its radical anion are similar to those for $MeSO_3H$, we include here a discussion of $SO_2Cl_2^{-\bullet}$ for comparative purposes.

The radical anion $SO_2Cl_2^{-\bullet}$ can be generated by γ-irradiation of a single crystal of sulphuryl chloride at 77 K. The g-tensor for the ^{32}S radical yields $g_{\parallel} = 2.0055$ and $g_{\perp} \approx 2.029$, from which $g_{iso} \approx 2.021$. The ^{32}S spectrum exhibits hyperfine coupling to two equivalent chlorine atoms for which $a_{\parallel}(^{35}Cl) = 63.8$ G and $a_{\perp}(^{35}Cl) = 15(\pm 2)$ G (the latter value being obtained by calculation because of practical problems in obtaining the minimum value of the chlorine hyperfine coupling). Thus, $a_{iso}(^{35}Cl) = 31.3$ G and $a_{aniso}(^{35}Cl) = 32.5$ G and, by comparison with the values expected for coupling to an electron in pure s and p orbitals[2], the spin densities in the 3s and 3p orbitals of each chlorine atom are 0.02 and 0.33, respectively. The ^{32}S spectrum was observed to be 544 times the intensity of one of the outer sets of lines of the ^{33}S spectrum as expected from the natural abundance of ^{33}S (0.74%). Unfortunately, exact values of a_{iso} and $a_{aniso}(^{33}S)$ were not forthcoming, though $a_{iso}(^{33}S)$ lies in the range 200–230 G and $a_{aniso}(^{33}S) < 20$ G. Thus, the unpaired spin density in the sulphur 3s orbital is 0.22 ($\pm$ 0.015), while that in the sulphur 3p orbital lies between 0 and 0.36. However, the combined spin density of the two chlorine atoms plus that in the sulphur 3s orbital is 0.92, a result that suggests the unpaired spin density in the sulphur 3p orbital is no more than 0.08.

The results support the concept of $SO_2Cl_2^{-\bullet}$ existing as a trigonal bipyramid (**5**) in which the two chlorine atoms occupy apical positions, as required by the anisotropic chlorine couplings being equivalent for both atoms, and having cylindrical symmetry. The

unpaired electron appears to occupy an anti-bonding orbital that primarily comprises the sulphur 3s and chlorine 3p atomic orbitals. The similarity with $MeSO_3H^{-\bullet}$ is apparent.



(5)

3. 4-$O_2NC_6H_4SO_2NMe^{2-\bullet}$[8]

Electrochemical reduction of sulphonamides involves the series of reactions 1–5[8]. Primary and secondary sulphonamides can undergo all five reactions and exhibit three reduction processes corresponding to equations 1,3 and 4. Tertiary sulphonamides are unable to undergo reactions 2 and 5 and therefore display only two reduction processes (equation 1 and 4). Since primary and secondary sulphonamide radical anions are unstable and lose H$^\bullet$ (equation 2), it is not surprising that ESR reports of such species are lacking. It is somewhat surprising that the equivalent radical anions of tertiary sulphonamides have yet to be investigated by ESR, especially since the cathodic peaks corresponding to equations 1 and 4 are well separated, e.g. for 4-$NO_2C_6H_4SO_2NMe_2$ $E_{p.c}{}^1 \approx 0.9$ V and $E_{p.c}{}^4 \approx 1.65$ V, and reversible[8]. Clearly, this is a potential area of future research.

$$R^1SO_2NR^2R^3 + e^\bullet \rightleftharpoons R^1SO_2NR^2R^{3-\bullet} \quad (1)$$

$$R^1SO_2NR^2R^{3-\bullet} \xrightarrow[\text{slow}]{R^2=H} R^1SO_2NR^{3-} + H^\bullet \quad (2)$$

$$R^1SO_2NR^{3-} + e^\bullet \rightleftharpoons R^1SO_2NR^{3\,2-\bullet} \quad (3)$$

$$R^1SO_2NR^2R^{3-\bullet} + e^\bullet \rightleftharpoons R^1SO_2NR^2R^{3\,2-} \quad (4)$$

$$R^1SO_2NR^2R^{3\,2-} \xrightarrow[\text{fast}]{R^2=H} R^1SO_2NR^{3\,2-\bullet} + H^\bullet \quad (5)$$

In the one report of sulphonamide radical anion[8], the anion of *N*-methyl-4-nitrobenzenesulphonamide was reduced at a potential (-1.4 V) that gives rise to the dianion radical, 4-$NO_2C_6H_4SO_2NMe^{2-\bullet}$ (equation 3). This species had a hyperfine coupling to *one* nitrogen, $a(^{14}N)$, of 9.41 G, and also displayed hyperfine coupling to two pairs of equivalent protons, a(H, *ortho*) 3.33 G and a(H, *meta*) 1.08 G. In the absence of other sulphonamide radical dianions the assignment of the proton hyperfine couplings must remain tentative at this stage. Indeed, although the order of the hyperfine couplings to the aryl protons in $PhSO_2Me^{-\bullet}$ has been assigned *para* > *ortho* > *meta*, those for the corresponding 4-$NO_2C_6H_4SO_2Me^{-\bullet}$ are *meta* > *ortho*[16] (see Section II.B.4). Further-

more, it is unclear which nitrogen, the sulphonamide or nitro, gives rise to the observed hyperfine coupling, especially since 4-$NO_2C_6H_4SO_2Me^{-\bullet}$ displays nitrogen coupling, $a(^{14}N)$, of 7.84 G[16]. If the assignment of a(H, *ortho*) > a(H, *meta*) for 4-$NO_2C_6H_4SO_2NMe^{2-\bullet}$ is correct, it would suggest that this may be a π-radical with some involvement of sulphur 3d orbitals, as discussed by Koch and Moffitt for sulphones many years ago[17]. If so, this would mean that there is a significant difference in structure between radical anions of sulphonic acids and those of their corresponding sulphonamides. However, in the absence of more extensive data, further speculation is unwarranted, but this area clearly would benefit from more careful investigation.

4. $R^1SO_2R^{2-\bullet}$

Although sulphones are not formally derivatives of sulphonic acids, it is worthwhile to describe the radical ions derived from them for comparative purposes. A molecular orbital description of the sulphone group has the LUMO (equivalent to the SOMO of the radical anion) containing contributions from the p_π molecular orbitals of the R^1 and R^2 groups and an empty sulphur 3d orbital[17,18]. The ESR spectra of diphenyl sulphone[18], methyl phenyl sulphone[16] and methyl 4-nitrophenyl sulphone[16] appear to bear out such a

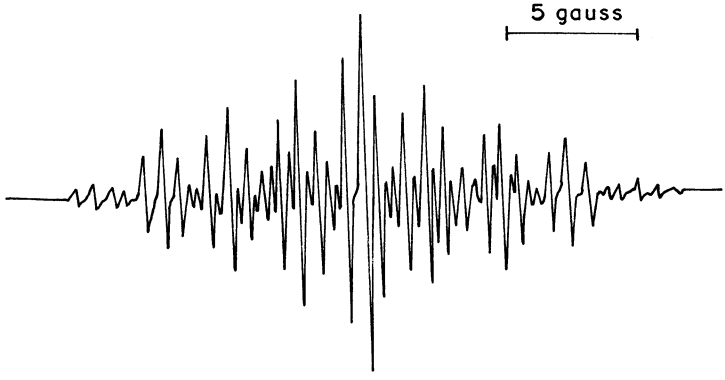


FIGURE 2. The ESR spectrum of $Ph_2SO_2^{-\bullet}$ at 200 K. Reproduced by permission of Taylor & Francis Ltd from Reference 18

TABLE 1. ESR parameters for representative sulphone radical anions

Radical anion	Hyperfine coupling (G)			Ref.
	a(H)	$a(^{14}N)$	$a(^{33}S)$	
$Ph_2SO_2^{-\bullet}$	2.41(*ortho*), 0.65(*meta*), 4.64(*para*)			18
$(m\text{-Tol})_2SO_2$	2.10(*ortho* 2-H), 0.59(*meta* CH_3), 4.89(*para*), 0.59(*meta* 5-H), 2.24(*ortho* 6-H)			18
$MePhSO_2^{-\bullet}$	3.84(*ortho*) < 0.9(*meta*), 8.96(*para*), 1.96(3H)			16
$Me(4\text{-}O_2NC_6H_4)SO_2^{-\bullet}$	< 0.24(*ortho*), 3.81(*meta*), 0.78(3H)	7.84		16
$Me_2SO_2^{-\bullet}$	*ca* 3		129[a]	19

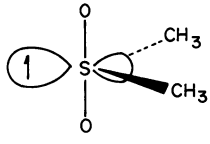
[a] $a_\parallel(^{33}S)$ 143 G, $a_\perp(^{33}S)$ 122 G.

description; coupling is observed to the *ortho*, *meta* and *para* protons of the aryl ring (and to the *para* nitrogen too), as well as to the protons of the methyl group of the alkyl aryl sulphones (Table 1). Indeed, the spectrum of $Ph_2SO_2^{-\bullet}$ (Figure 2) conclusively demonstrates that the unpaired spin couples to *all* four *ortho*-, *all* four *meta*- and *both para*-hydrogen atoms. Thus, there is extensive delocalization of the unpaired spin density throughout the molecule. Using equation 6, with $Q = 25$ G[18], it is possible to calculate the spin densities associated with the ring carbon atoms (Table 2). The agreement between these values and those obtained from MO calculations[16,18] is reasonably satisfactory. Interestingly, the MO calculations for $MeSO_2Ph$ indicate a sulphur 3d spin density of 0.118.

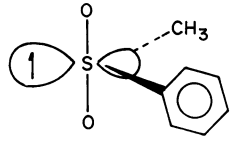
$$a(H) = Q\rho_c^{\pi} \tag{6}$$

Radical anions of aryl sulphones therefore appear to adopt a different set of molecular orbitals and possibly a different geometry to radical anions of sulphonic acid derivatives. Consistent with this view, the coupling to the protons of the methyl group in $MePhSO_2^{-\bullet}$, a(H) 1.96 G, is almost an order of magnitude smaller than the analogous coupling to the methyl group of $MeSO_3H^{-\bullet}$, a(H) 13 G (Section II.B.1). Moreover, for $MeSO_3H^{-\bullet}$, the methyl hyperfine coupling can be interpreted by comparison between the contribution of the carbon $2p_z$ orbital with that of the methyl radical (as discussed earlier). In contrast, for $MePhSO_2^{-\bullet}$, the coupling to the ring protons is quite different from the coupling observed in the phenyl radical [for which a(H, *ortho*) 17.4 G; a(H, *meta*) 5.9 G; a(H, *para*) 1.9 G][20]. Thus, neither the Me nor Ph proton hyperfine coupling are consistent with a radical anion in which the unpaired electron resides in an antibonding σ orbital.

It is, therefore, instructive to examine this point further with $Me_2SO_2^{-\bullet}$. This radical anion has $g_{\perp}$ 2.012 and $g_{\parallel}$ 2.003, from which $g_{iso} = 2.009$[19]. The magnitude of g_{iso} is indicative of a significant spin density at sulphur, which has large spin–orbit coupling[2]. Much more convincing evidence for spin density residing at sulphur comes from ^{33}S hyperfine coupling. In a CD_3OD glass at 77 K, $a_{\parallel} = 143$ G and $a_{\perp} = 122$ G. In turn these yield values of a_{iso} and a_{aniso} of 129 G and 14 G, respectively, from which unpaired spin densities in the sulphur 3s and 3p orbitals of 0.13 and 0.25 can be calculated. This corresponds to an orbital of approximately sp^2 hybridization, and the radical is thought to have structure **6** in which the oxygen atoms are apical and the methyl groups equatorial. Significantly, the methyl proton hyperfine couplings of $Me_2SO_2^{-\bullet}$ are *ca* 3 G, the same order of magnitude as those for $MePhSO_2^{-\bullet}$, but much less than those for $MeSO_3H^{-\bullet}$. Therefore it is entirely probable that a similar structure is adopted for $MePhSO_2^{-\bullet}$ and related radicals, in which the Me and Ph (or Ar) groups occupy the equatorial positions of a trigonal bipyramid (**7**). The order of coupling to the aryl ring protons then follows for a π-radical if the aryl ring is coplanar with OSO.



(6)



(7)

Now, if we assume that the proton hyperfine coupling of the methyl group can be expressed by equation 7, then it can be calculated from $Me_2SO_2^{-\bullet}$ (for which $\cos^2\theta = 0.5$) that $B = 24$ G. Thus, from the observed value of a(H) for a freely rotating methyl group in, say, $MePhSO_2^{-\bullet}$, it is possible to calculate the sulphur π-spin density using the relationship $a(H) = 12\rho_s$: for $MePhSO_2^{-\bullet}$, $\rho_s^{\pi} = 0.16$; for $Me(4\text{-}O_2NC_6H_4)SO_2^{-\bullet}$,

TABLE 2. Experimental and theoretical spin densities for selected sulphone radical anions

Radical anion	Experimental spin density					Theoretical spin density				
	ortho	*meta*	*para*	Me	*S*	*ortho*	*meta*	*para*	Me	*S*
$Ph_2SO_2^{-\bullet}$	0.096	0.026	0.186	—		0.087	−0.022	0.179	—	
$MePhSO_2^{-\bullet}$	0.153	< 0.05	0.359	0.012		0.122	−0.016	0.399	0.057	0.118[a]
$Me_2SO_2^{-\bullet}$					0.13[b] 0.25[c]					

[a]Sulphur 3d.
[b]Sulphur 3s.
[c]Sulphur 3p.

$\rho_s^\pi = 0.065$. This reduction in unpaired π-spin density at the sulphur atom along the series $Me_2SO_2^{-\bullet}$, $MePhSO_2^{-\bullet}$, $Me(4\text{-}O_2NC_6H_4)SO_2^{-\bullet}$ is understandable in terms of delocalization of the unpaired electron onto the aryl ring. It remains to be explained, firstly, why the methyl groups in $Me_2SO_2^{-\bullet}$ appear to adopt equatorial positions whereas the Me group in $MeSO_3H^{-\bullet}$ appears to adopt an apical position, and, secondly, why the unpaired electron occupies a non-bonding sp^2 orbital on sulphur in $Me_2SO_2^{-\bullet}$ but an antibonding σ orbital in $MeSO_3H^{-\bullet}$.

$$a(\mathrm{H}) = B\rho_s^\pi \cos^2\theta \tag{7}$$

C. Sulphonamidyl Radicals, $R^1SO_2NR^{2\bullet}$

1. Formation

The most useful method for generating sulphonamidyl radicals (**8**) for ESR studies is the photolytic cleavage of an N—X bond in *N*-bromo, *N*-chloro and *N*-arylthiosulphonamides (equation 8)[21–27]. The procedure is compatible with R^1 = aryl and alkyl, R^2 = alkyl, alkoxyl, arylthio, and also with sultams, i.e. where R^1,R^2 are linked to form part of a ring. Rigorous exclusion of oxygen is required, as it is for all methods, otherwise the corresponding nitroxides (**9**) are formed (equation 9). Another reagent, other than oxygen, for accomplishing this latter reaction is NO_2, and this has been deliberately used in some instances to generate the sulphonyl nitroxide radicals for the purposes of comparison[28]. We have discussed sulphonyl nitroxide radicals in the corresponding chapter to this in *Chemistry of Sulphinic Acids and their Derivatives* and shall not discuss them further here, other than to mention that their ESR parameters are significantly different from those of sulphonamidyls. For example, when R^1 = Me and R^2 = Bu^t, **8** has g 2.0044, $a(^{14}N)$ 12.9 G and a(H) 0.68 G (Bu^t) whereas **9** has g 2.0060, $a(^{14}N)$ 12.6 G with no observable coupling to the Bu^t group.

$$R^1SO_2N(X)R^2 \xrightarrow{h\nu} R^1SO_2NR^{2\bullet} + X^\bullet \tag{8}$$

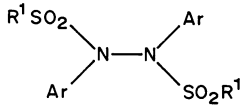
(**8**) X = Cl, Br, ArS

$$R^1SO_2NR^{2\bullet} + \tfrac{1}{2}O_2 \longrightarrow R^1SO_2N(O)R^{2\bullet} \tag{9}$$

(**9**)

Other, less common methods that have been used to generate sulphonamidyls include direct hydrogen atom abstraction from the parent sulphonamide using $Pb(OAc)_4$ or *t*-BuO$^\bullet$ (equation 10)[28–30], which has the advantage that it does not require an extra synthetic step to synthesize the *N*-halo substituted compound, thermal dissociation of a 1,2-bis(sulphonyl)hydrazine (equation 11)[31] and, for one solid state study, γ-irradiation of the sulphonamide (equation 12)[32].

$$R^1SO_2NHR^2 \xrightarrow[\text{or } Pb(OAc)_4]{t\text{-BuO}^\bullet} R^1SO_2NR^{2\bullet} \tag{10}$$



(11)

$$^-O_3S\overset{+}{N}H_3 \xrightarrow{\gamma} {}^-O_3SNH^\bullet \tag{12}$$

2. g-Values and hyperfine coupling constants

The spectra of some representative sulphonamidyl radicals are shown in Figure 3. Notable features of the spectra are (a) the coupling to the ^{14}N nucleus, which gives rise to the 1:1:1 triplet pattern most obvious in Figure 3a, b, (b) the coupling to the β-CH protons in the *N*-alkyl and *N*-alkoxy radicals (Figure 3a, b, c), (c) the coupling to the *N*-aryl but not

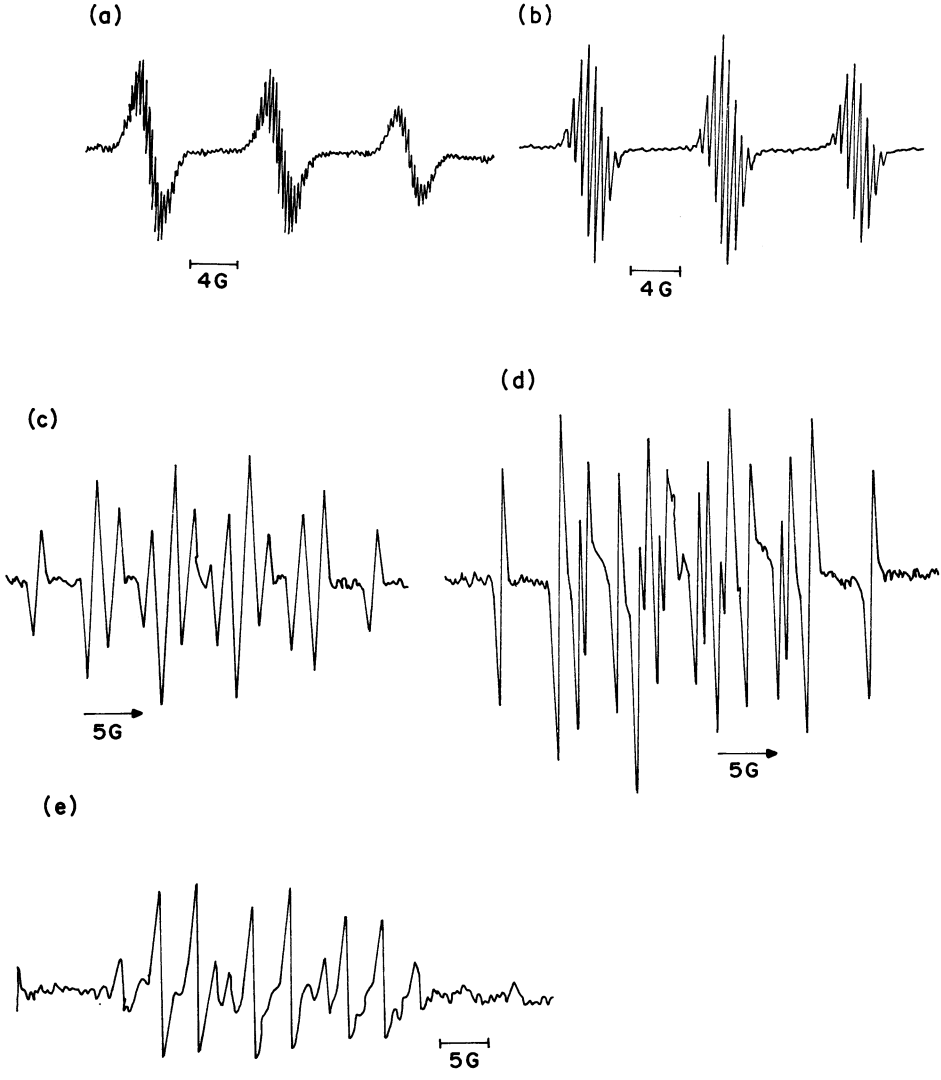
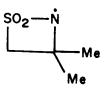
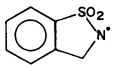
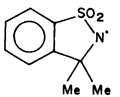
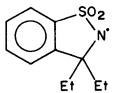


FIGURE 3. ESR spectra of some sulphonamidyl radicals: (a) $MeSO_2NBu^t$•, (b) $CD_3SO_2NBu^t$•, (c) $MeSO_2N(3,5\text{-}Bu^t{}_2C_6H_3)$•, (d) $PhSO_2N(3,5\text{-}Bu^t{}_2C_6H_3)$•, (e) $(2,6\text{-}Me_2\text{-}4\text{-}Bu^tC_6H_2)SO_2NOMe$•. Reproduced by permission from References 21, 24, 28 and 31

TABLE 3. ESR parameters for sulphonamidyl radicals

Radical	Solvent	Temp. (K)	g-Value	Hyperfine coupling (G) a(N)	Hyperfine coupling (G) a(H)	References
$MeSO_2\dot{N}Me$	Cyclopropane	303	2.0041	13.4	29.7 (3H)	23, 25, 26
$MeSO_2\dot{N}Et$	Cyclopropane	303	2.0041	13.2	35.7 (2H)	25, 26
$MeSO_2\dot{N}Pr^i$	Cyclopropane	273	2.0041	13.09	8.70 (1H), 0.92 (6H)	25, 26
$MeSO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223	2.0044	12.9	0.68 (9H), 0.34 (3H, Me)	21, 26
$CD_3SO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223	2.0044	12.9	0.68 (9H)	21
$MeSO_2\dot{N}(3,5\text{-}Bu^t{}_2C_6H_3)$	Benzene	293	2.0033	7.79	5.59 (2H, *ortho*-), 7.57 (1H, *para*-)	28, 31
$MeSO_2\dot{N}OBu^t$	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0052	11.8		22
$Pr^iSO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223	2.0042	13.0		21
	CH_2Cl_2–CCl_4 (3:2)	233	2.0050	12.4	44.5 (2H), 1.4 (2H)	23
	CH_2Cl_2–CCl_4 (3:2)	253	2.0043	12.1	1.03 (8H)	23
	Cyclopropane	303	2.0042	13.3	43.4 (2H)	25
	$CFCl_3$–CH_2Cl_2 (2:1)	256	2.0045	13.3	46.5 (1H), 45.6 (1H), 0.86 (2H)	23
	$CFCl_3$–CH_2Cl_2 (2:1)	242	2.0045	13.3	46.6 (1H), 45.9 (1H)	23
$PhSO_2\dot{N}Pr^i$	Cyclopropane	273	2.0042	13.07	8.82 (1H), 0.98 (6H)	25
$PhSO_2\dot{N}(C_6H_4NMe_2-4)$	CH_2Cl_2	233	2.0031	6.2 4.2 (NMe_2)	6.2 (2H, *ortho*-), 4.2 (6H, NMe_2) 2.1 (2H, *meta*-)	30
$PhSO_2\dot{N}(3,5\text{-}Bu^tC_6H_3)$	Benzene	298	2.0033	7.75	5.63 (2H, *ortho*-), 7.56 (1H, *para*-)	28

$PhSO_2\dot{N}NPh_2$	Dioxan		2.0033	9.4 (2N)	2.1 (2H, *ortho*-), 1.0 (2H, *meta*-), 4.2 (1H, *para*-), 1.0 (2H, *ortho*-), 1.0 (1H, *para*-)	33
	$CFCl_3$–CH_2Cl_2 (4:1)	233	2.0044	13.3	45.4 (1H), 44.8 (1H)	23
	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0040	13.2	1.3 (6H)	22
	$CFCl_3$–CH_2Cl_2 (2:1)	193	2.0042	13.1	3.88 (β-2H), 0.60 (β-2H)	22
2-$TolSO_2\dot{N}Me$	$CFCl_3$–CH_2Cl_2 (3:1)	193–263	2.0044	13.52	30.2 (3H)	23
4-$TolSO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223	2.0044	13.0	0.62 (9H)	21
4-$TolSO_2\dot{N}(4\text{-}Me_2NC_6H_4)$	CH_2Cl_2	233	2.0031	6.2 4.2 (NMe_2)	6.2 (2H, *ortho*-), 4.2 (6H, NMe_2) 2.1 (2H, *meta*-)	30
4-$TolSO_2\dot{N}(3,5\text{-}Bu_2{}^tC_6H_3)$	Benzene	293	2.0033	7.79	5.64 (2H, *ortho*-), 7.62 (1H, *para*-)	28, 31
4-$TolSO_2\dot{N}NPh_2$	Dioxan		2.0033	9.4 (2N)	2.1 (2H, *ortho*-), 1.0 (2H, *meta*-), 4.2 (1H, *para*-), 1.0 (2H, *ortho*-) 1.0 (1H, *para*-)	33
4-$TolSO_2\dot{N}OMe$	$CFCl_3$	213–243	2.0050	11.4	4.5 (3H)	24
4-$TolSO_2\dot{N}OEt$	$CFCl_3$	213–243	2.0050	11.6	3.8 (2H)	24
4-$TolSO_2\dot{N}OPr^i$	$CFCl_3$	213–243	2.0050	11.6	3.2 (1H)	24
4-$TolSO_2\dot{N}OBu^t$	$CFCl_3$	213–243	2.0050	11.5		24
4-$TolSO_2\dot{N}OCH_2Ph$	$CFCl_3$	213–243	2.0050	11.5	3.7 (2H)	24
4-$TolSO_2\dot{N}SPh$	Benzene	288	2.0074	8.47	1.82 (3H,*S*-Ph)	27
4-$TolSO_2\dot{N}SC_6D_5$	Benzene	288	2.0074	8.45	11.9($a(^{33}S)$)	27
4-$TolSO_2\dot{N}S$(4-Tol)	Benzene	288	2.0074	8.27	1.9 (2H,*S*-Ar), 2.1(3H, *S*ArMe) 12.0($a(^{33}S)$)	27
4.$TolSO_2\dot{N}S(4\text{-}MeOC_6H_4)$	Benzene	288	2.0074	7.90	1.81 (2H, *S*-Ar) 12.3($a(^{33}S)$)	27

(*continued*)

TABLE 3. (*continued*)

Radical	Solvent	Temp. (*K*)	*g*-Value	Hyperfine Coupling (G) *a*(N)	*a*(H)	References
4-$TolSO_2\dot{N}S(4\text{-}ClC_6H_4)$	Benzene	288	2.0075	8.50	1.8 (2H, *S*-Ar)	27
4-$TolSO_2\dot{N}S(4\text{-}NO_2C_6H_4)$	Benzene	288	2.0073	8.94	1.8 (2H, *S*-Ar)	27
2-$PhC_6H_4SO_2\dot{N}OMe$	Benzene	343	2.0049	11.9	4.5 (3H, OMe)	29
4-$NO_2C_6H_4SO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223	2.0046	12.9	0.68 (9H)	21
4-$NO_2C_6H_4SO_2\dot{N}$ (4-$Me_2NC_6H_4$)	CH_2Cl_2	233	2.0031	6.2 4.2 (Me_2N)	6.2 (2H, *ortho*-), 4.2 (6H, NMe_2) 2.1 (2H, *meta*-)	30
4-$NO_2C_6H_4SO_2\dot{N}OBu^t$	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0048	11.3		22
4-$MeOC_6H_4SO_2\dot{N}Bu^t$	$CFCl_3$–n-pentane (1:1)	223		12.8	0.59 (9H)	21
4-$BrC_6H_4SO_2\dot{N}NPh_2$	Dioxan		2.0034	10.5 9.4	2.1 (2H, *ortho*-), 1.0 (2H, *meta*-), 4.2 (1H, *para*-), 1.0 (2H, *ortho*-) 1.0 (1H, *para*-)	33
2,6-Me_2-4-$Bu^tC_6H_2SO_2NOMe$	$CFCl_3$	213–243	2.0048	11.5	4.5 (3H)	24
2,6-Me_2-4-$Bu^tC_6H_2SO_2\dot{N}OBu^t$	$CFCl_3$	213–243	2.0048	11.6		24
2,6-Me_2-4-$Bu^tC_6H_2SO_2\dot{N}OCH_2Ph$	$CFCl_3$	213–243	2.0048	11.5	3.3 (2H)	24
$^-OSO_2\dot{N}H$	$H_2NSO_3{}^-K^+$ crystal	298	2.0051	13.5	22.7 (1H)	32
$MeOSO_2\dot{N}Bu^t$	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0044	13.0	0.62 (9H), 0.31 (3H)	22
$Me_2NSO_2\dot{N}Bu^t$	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0043	13.0	0.6 (9H), 0.3 (6H)	22
$Me_2NSO_2\dot{N}OBu^t$	$CFCl_3$–CH_2Cl_2 (2:1)	223	2.0052	11.8 0.23 (NMe_2)	0.7 (6H)	22

to the *S*-aryl ring protons (Figure 3c,d) and (d) the coupling to the *S*-alkyl group (Figure 3a, b). A more complete analysis of these spectra is contained in Table 3, together with the corresponding data for all other reported sulphonamidyl radicals. Inspection of Table 3 enables the following general observations to be made:

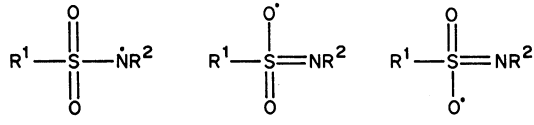
(i) No matter what the *S* substituent (alkyl, aryl, alkoxy, dialkylamino) the *g*-values of *N*-alkylsulphonamidyl radicals lie in the range 2.0043 ($\pm$0.0003); the corresponding *N*-aryl radicals lie in the range 2.0032 ($\pm$0.0001).

(ii) Heteroatom substituents at nitrogen increase the *g*-value in the order S > O > N (indeed, radicals with a sulphur substituent are best considered as sulphenamide radicals, and these have been discussed in detail elsewhere[34]).

(iii) Nitrogen hyperfine coupling constants, $a(^{14}N)$, are largest for *N*-alkylsulphonamidyls, *ca* 13 G, and smallest for *N*-arylsulphonamidyls, *ca* 8 G. Those for *N*-alkoxysulphonamidyls are *ca* 11.5 G, and for *N*-alkylthiosulphonamidyls, *ca* 8.5 G. The magnitude of the hyperfine coupling constants for *N*-alkylsulphonamidyls are somewhat smaller than those for the corresponding carboxamidyls. This point will be discussed further below.

3. Structure

The nature of the electronic configuration of sulphonamidyl radicals has been the subject of several investigations[21–26,28,35]. In principle, sulphonamidyls may be oxygen- or nitrogen-centred radicals, as expressed by the resonance forms **10a–c**. Little, if any, spin density thus resides at the central sulphur atom. Further, both types of radical may involve σ- or π-electronic ground states (designated Σ_O, Σ_N and π_O, π_N respectively). *Ab initio* MO calculations indicate that the Σ_O and π_O states are of much higher energy than the corresponding Σ_N and π_N states[35]. For example, π_N is some 250 kJ mol^{-1} more stable than π_O for $MeSO_2NMe^{\bullet}$. Moreover, the π_N state is *ca* 100 kJ mol^{-1} more stable than the Σ_N state. From this, and the experimental observations discussed below, it has been generally concluded that sulphonamidyls are nitrogen-centred π-radicals. In fact, this conclusion could well have been reached more directly from a consideration of the solid state ESR spectra obtained for the overlooked, but structurally related, radical $^{-}OSO_2\dot{N}H$[32]. This is the only radical containing a sulphonylamino unit that has been observed in a solid matrix, and is formed by γ-irradiation of a single crystal of potassium sulphamide, $KOSO_2NH_2$. ESR data measured for this radical at room temperature are contained in Table 4. From these it can be seen that the nitrogen hyperfine couplings are almost cylindrically symmetric, with the large, unique coupling along the direction of the orbital containing the unpaired electron. This direction is coincident with one of the smaller principal values of the *g*-tensor, and also the intermediate value of the hydrogen hyperfine coupling, $a(^1H)$. The smallest principal value of $a(^1H)$ lies in the direction of the N—H bond, which subtends an angle of 118° ($\pm$4°) with the S—N bond. Thus, it would appear that the radical has structure **11**. The spin population in the hydrogen 1s orbital, calculated from the isotropic coupling (Table 3), is 0.045, and the unpaired spin densities in the nitrogen 2s and 2p orbitals are 0.02 and 0.63, respectively. This confirms that the radical has a π_N configuration. At 77 K, the nitrogen coupling tensor is nearer to cylindrical

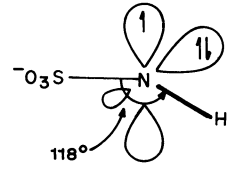


(10a) **(10b)** **(10c)**

TABLE 4. Principal values and directions of the hyperfine coupling and g-tensors for $^{-}O_3SNH^{\bullet}$ at room temperature (adapted from Reference 32)

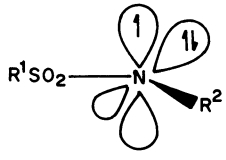
Nucleus	Principal values (G)	Direction cosines in a,b,c axes		
H	−38.2	(−0.625	0	±0.781)
	−21.3	(0	1	0)
	−8.8	(0.781	0	±0.635)
^{14}N	+34.8	(0	1	0)
	+3.7	(−0.584	0	±0.811)
	+2.0	(0.811	0	±0.584)
g	2.0078	(−0.993	0	±0.120)
	2.0038	(0	1	0)
	2.0037	(0.120	0	±0.993)

symmetry, and the calculated nitrogen 2p spin density is 0.73. These differences are attributed to rotation about the S—N bond.

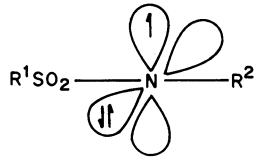


(11)

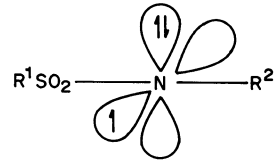
A corresponding solid-state study for a sulphonamidyl radical would be appropriate, but it seems reasonable to assume that such radicals adopt a structure not too dissimilar from $^{-}O_3SNH^{\bullet}$. Certainly, the *ab initio* calculations for $MeSO_2NHMe^{\bullet}$ indicate that a π_N configuration in which the N—C bond subtends an angle of *ca* 120° to the S—N bond is the most stable. This corresponds nicely with the structure **11**. Experimentally, the question as to whether sulphonamidyl radicals adopt the 'bent' structure **12** or the linear structure **13** and **14** is resolved by comparison of the data for acyclic and cyclic radicals. The nitrogen hyperfine couplings for these types of radical are so similar that it can be concluded that both adopt the 'bent' structure **12**.



(12)



(13)



(14)

Delocalization of the spin density onto the R^2 group is particularly efficient if R^2 = aryl, alkoxy or alkylthio. Delocalization of the unpaired spin to an aryl ring is consistent with the lower g-values and $a(^{14}N)$ hyperfine couplings observed for *N*-arylsulphonamidyls. Moreover, the interpolated order for the proton hyperfine couplings, viz. *para* > *ortho*

> *meta* (Table 3), is indicative of a π- rather than a σ-type structure[36]. Delocalization onto an adjacent oxygen (X = O), or sulphur (X = S) atom, as in **15**, raises the g-value but lowers a(N). The contribution of structures such as **15b** is clear from the observed coupling to the α-CH protons when R^2 = alkyl and the ring protons when R^2 = aryl (Table 3).

$$R^1SO_2\dot{N}-\ddot{X}R^2 \longleftrightarrow R^1SO_2\ddot{N}-Xr^2$$

(15a) **(15b)**

In contrast to the delocalization observed for nitrogen substitution, little or no delocalization occurs across the sulphonyl group. Thus, a comparison of the nitrogen hyperfine couplings and g-values for the series of radicals **16**, where R^1 = Me, Pr^i, 4-Tol, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, MeO and Me_2N, reveals that there is negligible variation due to the effect of the substituent. Further, g-values and nitrogen hyperfine coupling constants are quite similar to those for the parent alkylaminyl radicals, $R^1R^2N^{\bullet}$, which themselves are π-radicals[37]. Thus, the presence of the sulphonyl group appears to have little influence on these ESR parameters. The inability of the sulphonyl group to delocalize the unpaired spin of the sulphonamidyl radical is paralleled by similar observations for carbon-centred α-sulphonyl radicals (see Section II.E). The one observation of coupling to the S—R^1 group, i.e. in $MeSO_2NBu^t$, is probably simply due to long-range coupling to the β-CH protons of the *S*-methyl group, since it is of similar magnitude (though smaller) to the coupling to the β-CH protons of the *C*-methyl group.

$$R^1SO_2NBu^{t\bullet}$$

(16)

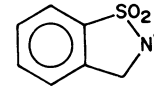
The corresponding carboxamidyl radicals may be expected to display greater delocalization of the unpaired electron into the carbonyl group than is observed with the sulphonamidyls. Certainly the higher g-value is consistent with this. However, the *higher* $a(^{14}N)$ hyperfine coupling observed for carboxamidyls as compared with sulphonamidyls might suggest greater spin density at nitrogen in carboxamidyls than in sulphonamidyls. An alternative explanation, based on *ab initio* calculations, is that the π_N and Σ_N states of carboxamidyls (but not for sulphonamidyls) are sufficiently close in energy for mixing to occur. Thus, the unpaired electron will have a higher s character in carboxamidyl radicals and therefore a larger nitrogen hyperfine coupling constant[35].

Since sulphonamidyl radicals have a π_N-structure, the coupling to the α-CH protons of the NR^2 group can be expressed by equation 13, where ρ_N^{π} is the π-spin density at the nitrogen atom, B is a constant and θ is the torsional angle between the C—H bond and the orbital containing the unpaired electron. For a freely rotating methyl group $<\cos^2\theta> = \frac{1}{2}$. Taking the average value of the hyperfine coupling of an *N*-methyl group to be 30 G (cf. Table 3 for $MeSO_2NMe^{\bullet}$), then $\rho_N^{\pi} B = 60$ G. This value may be used to calculate the torsional angle for the α-CH protons of the relatively rigid cyclic sulphonamidyl radicals **17a**. **17b** and **18**. Using the proton hyperfine coupling data in Table 3, the following values of θ emerge: for **17a**, 30.5°; for **17b**, 28.3° and 29.3°; for **18**, 29.6° and 30.2°. These are precisely the values expected for a radical of structure **19**.

$$a(H) = \rho_N^{\pi} B \cos^2\theta \qquad (13)$$

(17a)

(17b)



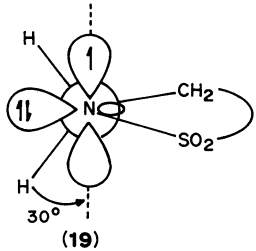
(18)

Significantly, the corresponding Σ_N radical **20** would give rise to proton hyperfine couplings of *ca* 15 G (rather than the 45 G observed), thus providing further evidence for a

TABLE 5. Temperature dependence of the α-CH proton hyperfine couplings in $RSO_2NPr^{i\bullet}$

Radical	Temp. (K)	a(H) (G)
$MeSO_2NPr^{i\bullet}$	293	9.6
	268	8.8
	248	8.1
	233	7.4
	213	6.8
	203	6.5
	166	5.9
$PhSO_2NPr^{i\bullet}$	333	10.9
	313	10.0
	293	9.4
	273	8.8
	253	8.5
	233	8.0
	213	7.4
	193	7.4

π-structure for sulphonamidyl radicals. Similarly, the temperature dependence of the hyperfine coupling to the α-CH of the Pr^i group in the less rigid radicals $PhSO_2NPr^{i\bullet}$[25] and $MeSO_2NPr^{i\bullet}$[26] (Table 5) suggests that these radicals adopt similar conformations in which the α-CH proton lies close to the nodal plane of the orbital containing the unpaired electron, i.e. structure **21** (making the unproven assumption that the methyl groups lie on the opposite side of the π-orbital to the sulphonyl group due to steric interactions).



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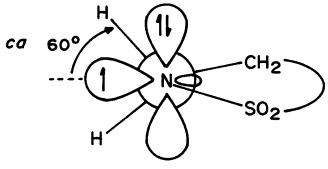

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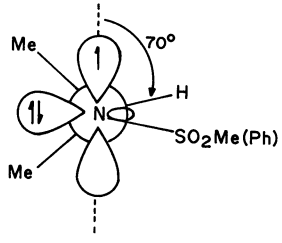


(21)

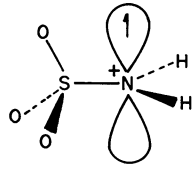
TABLE 6. ESR data for $^{-}O_3SNH_2^{+\cdot}$

Matrix	Temp. (K)	Principal values (G) and direction cosines of the hyperfine coupling tensors			Ref.
		$a(^{14}N)$	$a(^{15}N)$	$a(^{1}H)$	
Sulphamic acid crystal	300	36.8 6.1 11.8		−23.2 −29.7 −15.7	4
Sulphamic acid crystal	77	43.6 3.6 0.4			32
Sulphamic[a] acid crystal	300		52.4(0.631, 0.727, 0.269) 17.3(0.525, 0.146, 0.839) 0(0.571, −0.671, 0.474)	−22.4(0.667, 0.715, 0.210) −14.0(−0.489, 0.207, 0.847) −30.4(0.562, −0.668, 0.488)	3
Potassium[b] sulphamate crystal	77		45.0(0.507, 0.000, ± 0.862) 6.9(0.000, 1.000, 0.000) 2.9(0.862, 0.000, ± 0.507)	26.5(0.899, 0.000, ± 0.437) 18.1(0.437, 0.000, ± 0.899) 9.8(0.000, 1.000, 0.000)	5

[a]Direction cosines for the S—N bond are (0.537, −0.743, 0.399).
[b]Direction cosines for the S—N bond are (0.920, 0.000, ± 0.392).

D. Sulphonamide Radical Cations, $R^1SO_2NR^2R^{3+\cdot}$

The most extensively studied radical cation of a sulphonyl amine is that of sulphamic acid, $^-O_3SNH_2{}^{+\cdot}$. Though not strictly a sulphonamide radical cation, it provides useful information against which sulphonamide radical cations may be compared. The radical is generated by γ-irradiation of potassium sulphamate or sulphamic acid. It is characterized by coupling to one nitrogen and two hydrogen atoms. The data are summarized in Table 6. The principal directions of the proton and nitrogen hyperfine coupling tensors are nearly parallel, and the largest proton and smallest nitrogen coupling tensors lie close to the direction of the S—N bond. The largest principal value of the nitrogen tensor is nearly perpendicular to the S—N bond, and the nitrogen hyperfine couplings approach cylindrical symmetry, particularly at lower temperatures. These observations are consistent with $^-O_3SNH_2{}^{+\cdot}$ having a π-structure **22**, and calculations derived from the principle values of the nitrogen couplings (Table 7) verify that the unpaired electron occupies an essentially 2p nitrogen orbital. The variation seen in the calculated p electron density has been ascribed to the effects of rotational motion[32].



(22)

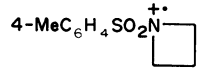
The radical cation of *N*-(4-toluenesulphonyl)azetidine (**23**) is the only sulphonamide radical cation so far studied[6]. It is generated by γ-irradiation of a frozen solution of the parent sulphonamide in $CFCl_3$ at 77 K. The isotropic *g*-value for **23** is 2.0041, which is similar to that for *N*-alkylsulphonamidyl radicals. The components of the nitrogen hyperfine coupling can be resolved into $a_{\parallel}(^{14}N)$ 38 G and $a_{\perp}(^{14}N)$ *ca* 0 G (i.e. within the linewidth). Thus $a_{iso}(^{14}N)$ is 13 G and $a_{aniso}(^{14}N)$ is *ca* 25 G. In turn, these lead to values for the unpaired spin density in the nitrogen 2s and 2p orbitals of 0.02 and 0.74, respectively. These are of similar magnitude to those for the sulphamate radical cation discussed above, and clearly the sulphonamide radical cation has a π-structure. This being so, then equation 13 should hold for the proton hyperfine coupling to the α-CH hydrogen atoms. The observed value for $a(^1H)$ is 41 G. If we assume that, because of the rigid nature of the azetidine ring, the α-CH bonds subtend angles of 30° to the nitrogen 2p orbital containing the unpaired spin density, then $\rho_N^{\pi} B$ for sulphonamide radical cations is *ca* 55 G. This

TABLE 7. Isotropic and anisotropic components of the nitrogen hyperfine coupling, and the derived 2s and 2p orbital spin densities for $^-O_3SNH_2{}^{+\cdot}$[a,b]

$a_{iso}(^{14}N)$	$a_{aniso}(^{14}N)$	$a_{iso}(^{15}N)$	$a_{aniso}(^{15}N)$	*s*	*p*	$\frac{p}{s+p}$	Ref.
18.2	18.6	—	—	0.03	0.55	0.95	4
15.9	27.7	—	—	0.03	0.81	0.96	32
—	—	23.2	29.2	0.03	0.61	0.95	3
—	—	17.9	27.1	0.02	0.56	0.97	5

[a]Couplings in G.
[b]Calculated from the original data.

value is almost identical to that calculated for sulphonamidyl radicals (60 G, see Section II.C.3). Thus, it would appear that sulphonamidyls and sulphonamide radical cations have very similar parameters—g_{iso}, $a_{iso}(^{14}N)$, ρ_N^{π}, $\rho_N^{\pi}B$—and are therefore of similar structure.



(23)

E. α-Sulphonyl Radicals, $R^1\dot{C}HSO_2R^2$

1. Formation

α-Sulphonyl radicals derived from sulphones and sulphonic acids may be generated in aqueous solutions by a hydrogen-atom abstraction reaction involving the phenyl [generated from PhN_2^+/Ti(III) at pH 8] or hydroxyl (equation 14) radicals[38,39]. The phenyl radical appears to be the more efficient of the two.

$$R^1CH_2SO_2R^2 \xrightarrow[HO^{\bullet}\ (pH\ 1.5)]{Ph^{\bullet}\ (pH\ 8)} R^1\dot{C}HSO_2R^2 \qquad (14)$$

An alternative process involves the trapping of radical species, generated by pulse radiolysis, by sodium vinyl sulphonate (equation 15)[39].

$$X^{\bullet} + CH_2CHSO_3^- \longrightarrow XCH_2\dot{C}HSO_3^- \qquad (15)$$

$$X = H, OH, CO_2^-, SO_3^-, SO_4^-$$

γ-Irradiation of methanesulphonic acid also produces the α-methanesulphonic acid radical (equation 16)[11].

$$CH_3SO_3H \xrightarrow{\gamma\text{-irradiation}} \dot{C}H_2SO_3H \qquad (16)$$

A different type of α-sulphonyl radical is obtained when arenesulphonic acids or their sulphonyl fluorides are reacted with PbO_2 in HSO_3F at *ca* 200 K. Under these conditions, electron transfer takes place to generate the radical cations of the parent compound (equation 17)[40].

$$ArSO_2X \xrightarrow[200\,K]{PbO_2/HSO_3F} ArSO_2X^{+\bullet} \qquad (17)$$

$$X = OH, F$$

2. g-Values and hyperfine coupling constants

Table 8 contains the ESR spectral data for α-radicals of both sulphones and sulphonic acids. The *g*-values of these radicals are remarkably constant throughout the series and are almost of the same magnitude as the free-spin value. Moreover, they have the same *g*-values as the corresponding alkyl radicals, e.g. for Me$^{\bullet}$ and Et$^{\bullet}$, $g = 2.0025$, and slightly smaller ones than the analogous α-radicals of carboxylic acids, e.g. $Me\dot{C}HCO_2^-$ has $g = 2.00323$[38,39]. Similarly, the magnitude of the proton hyperfine couplings of α-sulphonyl radicals is much the same as those observed for alkyl radicals. Compare, for example, those of $^{\bullet}CH_2SO_2Me$ and $^{\bullet}CH_2SO_3^-$ with Me$^{\bullet}$ which has a(3H) 22.9 G, and those of $^{\bullet}CH(Me)SO_2Et$ and $^{\bullet}CH(Me)SO_3^-$ with Et$^{\bullet}$ which has a(2H) 22.2 G and a(3H) 27.1 G.

Table 9 contains the data for radical cations of arenesulphonic acids and arenesulphonyl fluorides[40,41].

TABLE 8. ESR spectral parameters for α-sulphonyl radicals of sulphones and sulphonic acids

Radical	Solvent	g	a(H) (G)	Ref.
$^{\bullet}CH_2SO_2Me$	H_2O, pH 8	2.0025	22.3 (2H), 2.1 (3H)	38
$^{\bullet}CH(Me)SO_2Et$	H_2O, pH 8 and 1.5	2.0025	21.6 (1H), 27.3 (3H), 2.1 (2H)	38
	H_2O, pH 8 and 1.5	2.0025	21.0 (1H), 38.8 (2H), 1.8 (2H)	38
$^{\bullet}CH_2SO_3^-$	H_2O, pH 11	2.00238	22.26 (2H)	39
	CH_3SO_3H crystal		24.9 (2H)	11
$^{\bullet}CH(Me)SO_3^-$	H_2O, pH 2.6 and 7	2.00246	21.73 (1H), 25.96 (3H)	39
	H_2O, pH 1.5	2.0025	21.7 (1H), 25.9 (3H)	38
$^{\bullet}CH(CH_2OH)SO_3^-$	H_2O, pH 7	2.00233	21.55 (1H), 23.73 (2H), 0.34 (1H)[a]	39
$^{\bullet}CH(CH_2CO_2^-)SO_3^-$	H_2O, pH 7.4	2.00247	21.75 (1H), 24.75 (2H)	39
$^{\bullet}CH(CH_2SO_3^-)SO_3^-$	H_2O, pH 6.4 and 12	2.00255	21.52 (1H), 19.55 (2H)	39
$^{\bullet}CH(CH_2OSO_3^-)SO_3^-$	H_2O, pH 7	2.0024	21.77 (1H), 20.77 (2H)	39

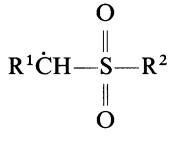
[a]Disappears at pH 12.

TABLE 9. ESR spectral data for α-sulphonyl radical cations[40,41]

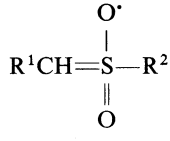
Radical	Hyperfine coupling constants (G) a(H)	a(F)
2,3,4,6-$Me_4C_6HSO_2F^{+\cdot}$	3.30(1H), 8.40(Me), 13.80(Me), 16.68(Me)	0.80
2,4,5-$Me_3C_6H_2SO_2F^{+\cdot}$	2.90(1H), 0.85(1H), 3.15(Me), 15.05(Me), 19.50(Me)	0.85
2,5-$Me_2C_6H_3SO_2F^{+\cdot}$	3.0(1H), 4.45(1H), 17.0(Me), 18.60(Me)	0.67
2,3,5,6-Me_4-4-$FSO_3C_6SO_2F^{+\cdot}$	11.4(3-Me), 11.65(2-Me)	0.95
2,3,4,5-$Me_4C_6HSO_3H^{+\cdot}$	5.4(1H),6.35(Me), 14.55(Me), 15.45(Me)	
2,3,4,6-$Me_4C_6HSO_3H^{+\cdot}$	3.2(1H), 8.15(Me), 13.75(Me), 16.66(Me)	
2,4,5-$Me_3C_6H_2SO_3H^{+\cdot}$	0.75(1H), 2.3(1H), 3.65(Me), 14.75(Me), 19.17(Me)	
2,5-$Me_2C_6H_3SO_3H^{+\cdot}$	0.75(1H), 2.85(1H), 4.0(1H), 17.1(Me), 18.5(Me)	

3. Structure

In principle, the unpaired electron in α-sulphonyl radicals may be delocalized onto the adjacent sulphonyl group **24a–c**. However, the close similarity of the g-values and proton hyperfine coupling constants with those of simple alkyl radicals implies that the sulphonyl group does not remove any spin density from the carbon radical centre and that α-sulphonyl radicals have structure **24a**[38,39]. On the basis of the ratio of the proton hyperfine coupling of the R^1 group to that of the CH proton, which varies between 0.95 and 1.26, it has been deduced that the tervalent carbon is planar[38]. These observations parallel those made for the corresponding sulphonamidyl radicals (Section II.C). Thus, α-sulphonyl radicals have structure **24d**.



(24a)



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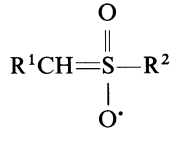

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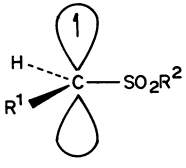

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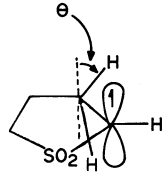
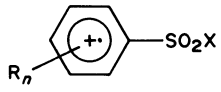


(25)

The large coupling of 38.8 G observed for the CH_2 protons adjacent to the radical centre in the cyclic radical **25** is nicely accommodated by this planar structure. Assuming that equation 13 (replacing ρ_N^π with ρ_C^π) holds for the coupling of such protons to the unpaired spin, then, from the value of 27.3 G observed for the coupling to the methyl group in $MeCHSO_2Et$, a value of 54.6 G can be calculated for $\rho_C^\pi B$. From the observed value of 38.8 G it follows that for the cyclic radical, $\theta = 32.5°$, which is close to the anticipated value of 30°.

In sulphones, coupling is observed across the sulphonyl group to the α'-CH protons. This is considered to arise from spin polarization and to have a negative sign[38]. It is larger than the corresponding coupling in sulphonamidyls (see Table 3). Interestingly, coupling across the sulphonyl group of the radical cations of arenesulphonyl fluorides is detectable, as observed in the small coupling to the ^{19}F nucleus[40]. Such radical cations appear to have structure **26** as judged by the large proton hyperfine couplings to the groups attached to the aryl ring.



(26) X=F,OH

III. THE NMR SPECTRA OF SULPHONIC ACIDS AND THEIR DERIVATIVES

A. Proton and ^{13}C NMR Chemical Shifts and Coupling Constants

1. Introduction

Sulphonyl groups are particularly strongly electron-withdrawing groups as shown by the substituent constant data in Table 10. They are therefore expected to deshield strongly adjacent alkyl groups. An indication of how strongly electron-withdrawing sulphonyl groups is given by the similarity of the σ constants to those of the nitro group. Like the nitro group the SO_2X groups are resonance electron-withdrawing with σ_p^- values of 0.99 for SO_2NH_2[49] and 1.06 for SO_2OR[43], compared with 1.23[50] for NO_2. The sulphonic acid groups and their derivatives are the most strongly electron-withdrawing of the sulphur acids and the order falls as $SO_2X > SOX > SX$.

It is generally true that the various σ constants give information on NMR shielding patterns, but often only in a qualitative manner. There is some evidence, discussed in later sections, that the SO_2X groups show significant chemical shift variations, in detail, from those suggested by single substituent constants. However, chemical shifts, both ^1H and ^{13}C, of RSO_2X compounds are particularly influenced by the strong electron-withdrawal by SO_2X.

Although there do not appear to have been any recent reviews on the ^1H or ^{13}C NMR spectra of sulphonic acids and derivatives, most compilations of spectra and spectral data contain a range of relevent data. *The Aldrich Library of N.M.R. spectra*[51] has a wide selection of proton NMR spectra of sulphonic acids and their derivatives. Some

TABLE 10. Some substituent constants for $—SO_2X$ and related groups

Group	σ_m	σ_p	Reference	σ_I	σ_R°	Reference
SO_2OH	0.55		42			
$SO_2O^-M^+$	0.26	0.30	46	0.23	0.07	46
SO_2OCH_3	0.71	0.90	43, 44	0.50	0.09	48
SO_2NH_2	0.53	0.60	45	0.44	0.12	46
SO_2Cl	0.92	1.04	46	0.80	0.11	46
SO_2F	0.79	0.91	47	0.75	0.26	46
NO_2	0.70	0.80	45	0.72	0.0	45

TABLE 11 ^{1}H NMR chemical shifts for some sulphonic acids and their derivatives[51]

Compound	δ(ppm)[a]
CH_3SO_3H[b]	2.9(s)
$CH_3CH_2SO_3H$	3.24(q)CH_2; 1.42(t)CH_3
$CH_3SO_2OCH_3$	3.91(s)OCH_3; 3.0(s)CH_3SO_2
FSO_2OCH_3	4.22(s)
$CH_3SO_2SCH_3$	3.27(s)CH_3SO_2; 2.65(s)SCH_3
CH_3SO_2Cl	3.7(s)
$CH_3CH_2SO_2Cl$	3.68(q)CH_2; 1.62(t)CH_3
$ClSO_2N(CH_3)_2$	3.0(s)
$CH_3SO_2N(CH_3)_2$[52]	2.81(s)NCH_3; 2.76(s)CH_3SO_2

[a]Solvent $CDCl_3$ unless stated otherwise.
[b]DMSO-d_6–$CDCl_3$ mixture.

TABLE 12. ^{13}C NMR chemical shifts for some sulphonic acids and their derivatives[54]

Compound	δ(ppm)	Solvent
$CH_3SO_2OC_4H_9$	37.0(CH_3SO_2)	$CDCl_3$
$CH_3SO_2NH_2$	43.1	Polysol
CH_3SO_2Cl	52.6	$CDCl_3$
CH_3SO_2F	37.5	$CDCl_3$
$CH_3CH_2SO_2OH$	46.7(CH_2); 8.1(CH_3)	$CDCl_3$
$CH_3CH_2SO_2NH_2$	49.1(CH_2); 8.4(CH_3)	Polysol
$CH_3CH_2SO_2Cl$	60.3(CH_2); 9.2(CH_3)	$CDCl_3$

representative examples are given in Table 11, and the deshielding order from these limited data is

$$-SO_2Cl > SO_2OR > -SO_2OH > SO_2NR_2 > -SO_2SR$$

which is approximately as expected from the σ-values.

The ^{13}C chemical shifts are not so straightforward, as shown in Table 12, where the deshielding order for the aliphatic carbon nuclei is

$$-SO_2Cl > -SO_2NH_2 > -SO_2OH > -SO_2F > -SO_2OR$$

The *ispo* aromatic carbon-13 nuclei follow a slightly different order[53]:

$$-SO_2Cl > SO_2OH, -SO_2O^-Na^+ > -SO_2NH_2 > SO_2OR > -SO_2F$$

2. *Sulphonic acids*

Sulphonic acids are very strong acids with pK_a values of -6.5 ± 1[54]; accordingly the spectrum observed may be either that of the acid or of the anion, depending on the solvent. In some cases no distinction is made in the original report and the data are recorded according to the compound added to the solvent rather than the species in solution.

Wherever possible we report on the species being observed. Koeberg-Telder and Cerfontain[54] observed the transition from RSO_3^- (in 10% H_2SO_4) to RSO_3H (in 90% H_2SO_4) and plotted the ^1H NMR chemical shift change against the acidity function H_o^a. For methanesulphonic acid there was a 0.6 ppm deshielding as the anion was converted to acid. It was found for a range of aliphatic acids that the protons α to the acid ($—CH_nSO_3H$) were consistently 0.4 to 0.6 ppm deshielded compared with the anion. The β-protons were generally deshielded in the acid by 0.2 to 0.3 ppm. It has also been reported[55] that neopentyl sulphonic acid has proton NMR resonances of δ 2.98 and 1.12 ppm in $CDCl_3$ and sodium neopentane sulphonate has proton NMR resonances at δ 2.94 and 1.12 ppm in the same solvent.

In ^{13}C NMR, deprotonation of acids is generally accompanied by deshielding (i.e. a high-frequency shift). Aliphatic carboxylic acids usually have α-carbon resonances shielded by about 3.6 ppm compared with their alkali metal salts[56]. Alkyl sulphonic acid ^{13}C NMR resonances for α-carbons are usually slightly *deshielded* relative to their sodium salts[57], as shown in Table 13. The titration shifts for alkyl sulphonic acids are [57]α-C, -0.7 ± 0.5; β-C, 1.6 ± 0.3; δ-C, 1.0 ± 0.3 ppm, where a positive sign represents a high-frequency shift on deprotonation.

The aromatic sulphonic acids behave more like other organic acids and the titration shifts for benzenesulphonic acid are[57]: *ipso*-C, 6.8; *ortho*-C, −0.8; *meta*-C, −1.4 and *para*-C, −2.6 ppm.

Empirical equations have been developed for the ^{13}C chemical shifts of alkanesulphonic acids, and the substituent effects of SO_3^- on alkane chemical shifts, relative to H, have been calculated[58] to be: α-C, 39.7; β-C, 3.7 and γ-C, −0.2 to −2.1 ppm. These effects are quite small in relation to the electron-withdrawing effect; the NO_2 group deshields an α-carbon nucleus by 64 ppm[59].

Freeman and Angeletakis[60] carried out a more detailed examination of the substituent effect in sulphonic acids, and calculated the α,β,γ and δ carbon additivity parameters[59,62] relative to both thiols and the corresponding alkane. The values relative to the alkanes are given in Table 14. As with the sulphinic acids the α-deshielding is not constant, decreasing by about 5 ppm with each α-methyl substitution. The explanation advanced was that the C—S bond becomes more polarized as the α-carbon is more substituted, but why this should lead to a decrease in electron density at the α-substituted carbon was not understood[60]. It was also noted that sulphonic acids were *more* shielded by −8.63 to −0.68 ppm at C-α than the sulphinic acids, which runs against the trend in electronegativity. The increase in shielding for sulphonic acids may be attributed to bond-angle widening, caused by increased steric compression on the α-carbon by the sulphonic acid

TABLE 13. ^{13}C NMR chemical shifts of some alkanesulphonic acids and their sodium salts[57]

Compound	δ (ppm)				Solvent
	C-1	C-2	C-3	C-4	
CH_3SO_2OH	39.06				97% H_2SO_4
CH_3SO_2ONa	41.1				D_2O
$CH_3CH_2SO_2OH$	49.0	9.2			97% H_2SO_4
$CH_3CH_2SO_2ONa$	47.8	11.0			D_2O
$CH_3CH_2CH_2SO_2OH$	55.4	18.8	13.7		97% H_2SO_4
$CH_3CH_2CH_2SO_2ONa$	55.2	20.2	14.9		D_2O
$CH_3CH_2CH_2CH_2SO_2OH$	54.0	26.9	22.9	14.7	97% H_2SO_4
$CH_3CH_2CH_2CH_2SO_2ONa$	53.4	28.7	23.7	15.5	D_2O

TABLE 14. ^{13}C NMR chemical shifts[a] and substituent constants[b] for some sulphonic acids, RSO_2OH[60]

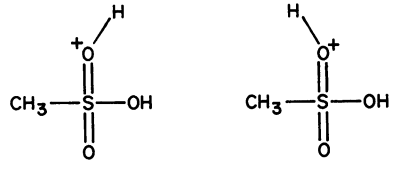
R	C-α		C-β		C-γ		C-δ	
	δ_c[a]	α[b]	δ_c	β[b]	δ_c	γ[b]	δ_c	δ[b]
CH_3	39.06	41.16						
CH_3CH_2	46.62	40.52	9.2	3.3				
$CH_3CH_2CH_2$	53.73	38.13	18.8	2.7	13.7	−1.9		
$CH_3(CH_2)_2CH_2$	52.09	38.9	25.47	0.5	21.32	−3.7	13.41	0.2
$(CH_3)_2CH$	52.85	36.8	16.76	1.2				
$(CH_3)_3C$	55.91	31.6	24.97	−0.2				
$(CH_3)_3CCH_2$	63.39	35.5	30.89	−0.6	29.42	1.7		
$C_6H_5CH_2$	58.36	37.1						

[a] ^{13}C chemical shifts (ppm) in $CDCl_3$ with internal TMS standard, at 62.89 MHz, except for $(CH_3)_3CCH_2$ which was measured at 22.63MHz.
[b] Chemical shift differences from the same carbon of the corresponding alkane[62].

group relative to the sulphinic acid group[60]. In contrast to the sulphinic acids, the β-carbons are mostly deshielded relative to their alkane equivalents[60].

The ^{13}C NMR shifts of a series of RCH_2SO_3Na compounds are shown graphically, together with many other sulphur compounds, in a paper in Japanese[61]. The δCH_2 values range from about 43 ppm for R = C≡CH to about 63 ppm for R = $(CH_3)_3C$. Rather curiously the δCH_2 values for R = CH_3, OH and Cl all appear to be 53 ppm; not all of the data appears to agree with other published ^{13}C NMR chemical shifts for sulphonic acid derivatives. The carbon-13 spectra of a number of benzenesulphonic acids in NaOH solutions were measured and additivity correlations attempted[63]. The ^{13}C shifts of sodium benzenesulphonate, relative to benzene, are: *ipso*-C, 16.7; *ortho*-C, 3.3; *meta*-C, 0.3; *para*-C, 5.9 ppm. When these values were used in an additive manner with other substituents in $XC_6H_4SO_3^-$, very poor correlations (deviations of 2.7 to −7.7 ppm.) were obtained for any possibly interacting group X (e.g. $—O^-$, NH_2, Cl). Correlations of $\delta^{13}C$ with σ_m or σ_p for X were non-existent[63], but correlations with σ_p^- values were not attempted. It was suggested that the electronic nature of the sulphonate group varies according to the nature of X[63].

Alkene- and arenesulphonic acids have been studied in strong or super acid media by ^1H NMR spectroscopy. Olah and coworkers[64] in 1970 examined sulphonic acids in fluorosulphuric acid–antimony pentafluoride–sulphuryl chloride fluoride solution at low temperature (−60 °C). In SO_2 solution methanesulphonic acid has a ^1H chemical shift of δ 3.1 ppm for the methyl group. In the superacid medium there are two singlets at δ 4.15 and 4.07, with ratio 60:40, for the methyl protons. It was suggested that this indicated the presence of two isomers, possibly **27** and **28**, due to restricted rotation about the SO bond.



(27) **(28)**

As no coupling was observed between the methyl protons and the OH proton, no structural assignments could be made. Protonation of ethane, propane and butanesulphonic acids also resulted in a deshielding of C-α by about 1 ppm, but in those cases only one resonance was observed for the α-CH_2 group, and it was suggested that in those cases only one favoured isomer was formed. No evidence for RSO_2^+ was observed. As the solutions warmed to −10 °C the sulphonyl fluorides were formed as their antimony pentafluoride complexes, which on standing gave carbocations. Arenesulphonic acids under all conditions only gave the SbF_5 complex of $ArSO_2F$. Koeberg-Telder and Cerfontain[54] also measured the spectra of alkanesulphonic acids in 100–115% sulphuric acid. The methanesulphonic acid resonance was a singlet shielded by 0.4 ppm relative to CH_3SO_3H and attributed to $CH_3SO_3H_2^+$ and the pyrosulphonic acid, RSO_3SO_3H (equations 18a and 18b). This equilibrium was suggested[54] because protonation only, by comparision with Olah's results[64], would be expected to lead to a 1 ppm deshielding in total, and calculations suggested that the acid should be at least 75% protonated in the 115% H_2SO_4 medium. Also pyrosulphonic acid formation would be expected to give a 0.21 ppm shift[65].

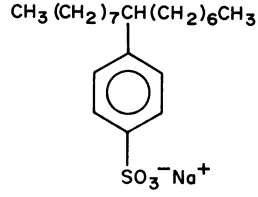
$$CH_3SO_3H + H^+ \rightleftharpoons CH_3SO_3H_2^+ \quad (18a)$$

$$CH_3SO_3H + SO_3 \rightleftharpoons CH_3SO_3SO_3H \quad (18b)$$

There are many uses in chemistry for sulphonic acids and their anions and NMR studies have been carried out in relation to some of these uses.

Bisulphite addition to aldehydes is common, but in some cases, such as α,β-unsaturated aldehydes, there are a number of different possible products. Johnson and Jones[66] used ^1H NMR to elucidate the bisulphite addition products to citral and citronellal. Model compounds were prepared and it was shown that $—CH_2SO_3^-$ appeared at *ca* δ 2.85 ppm and $—CH(OH)SO_3^-$ at δ 4.4 ppm. Hence the different addition models could be differentiated.

The surfactant properties of alkali metal sulphonates lead to interesting motional properties in solution that can be studied by ^1H and ^{13}C relaxation times. Franses and Miller[67] observed segmental motion and phase transitions by ^{13}C NMR in chloroform/water solutions when studying the surfactant SHBS **29**. For the lamellar liquid-crystalline phase formed by SHBS and water, T_1 and linewidth measurements indicated a pronounced motional gradient, resulting from anisotropic motion, as the head group is approached.



(29)

Bacaloglu, Bunton and coworkers[68] used ^1H and ^{13}C chemical shift measurements to locate naphthalenesulphonate anions in a micellar system. In a carefully argued paper the effect of the naphthalene ring on the chain carbon nuclei and protons of cetyltrialkylammonium bromides was evaluated. Similarly the effect of the environment on the naphthalene ring protons and carbon nulei was discussed. It was concluded that the naphthalenesulphonate anions are located at the micellar interface in aqueous cetyltrialkylammonium bromides, as has been postulated for other aromatic systems[68].

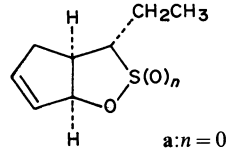
TABLE 15. ^{1}H NMR chemical shifts for some sulphonate esters

Compound	δ ppm (Hz)	Solvent	Reference
$CH_3SO_2OCH_3$	3.91(s)OCH_3; 3.0(s)CH_3SO_2	$CDCl_3$	51
	3.96(s)OCH_3; 3.03(s)CH_3SO_2	SO_2ClF	64
$CH_3SO_2OCH_2CH_3$	4.36(q)OCH_2; 3.08(s)CH_3S; 1.42(t)CH_3	$CDCl_3$	51
	4.47(q 7.5)OCH_2; 3.11(s)CH_3S; 1.55(t, 7.5)CH_3	SO_2ClF	64
$CH_3SO_2OCH_2CH_2CH_3$	4.10(t)OCH_2; 2.96(s)CH_3S; 1.76(m)CH_2; 1.0(t)CH_3S	$CDCl_3$	51
$CH_3SO_2OCH_2CH_2Cl$	4.45(m)OCH_2; 3.72(m)CH_2Cl; 3.1(s)CH_3S	$CDCl_3$	51
$C_6H_5SO_2OCH_3$	7.90(m)Ar; 3.80(s)CH_3	SO_2ClF	64
p-$CH_3C_6H_4SO_2OCH_2CH_3$	7.6(m)Ar; 4.1(q)OCH_2; 2.45(s)Ar-CH_3; 1.3(t)CH_3	$CDCl_3$	51
p-$CH_3C_6H_4SO_2OCH_2CH_2Cl$	7.6(m)Ar, 4.2(m) OCH_2; 3.7(m)CH_2Cl; 2.48(s)Ar-CH_3	$CDCl_3$	51
$CF_3SO_2OCH_3$	4.29(s)	$CDCl_3$	51
FSO_2OCH_3	4.21(s)	$CDCl_3$	51
$FSO_2OCH_2CH_3$	4.65(q)OCH_2; 1.55(t)CH_3	$CDCl_3$	51
$CF_3SO_2OCH_2CH_3$	4.55(q)OCH_2; 1.50(t)CH_3	$CDCl_3$	51
	4.50(t)OCH_2; 3.25(m)CH_2S; 2.65(m)CH_2	$CDCl_3$	51

Ion exchange resins containing aromatic sulphonic acid groups are used to separate individual lanthanide ions (Ln^{3+}). Complexes of lanthanides with *p*-toluenesulphonic acid (ptsa) were shown[69] to have the general formula $Ln(ptsa)_3$, and their ^1H NMR spectra were recorded. Analysis of the lanthanide induced shifts, by the method of Reilley and coworkers[70], suggested a change in coordination of ptsa around Ln^{3+}, across the lanthanide series.

3. *Sulphonate esters, anhydrides and thioesters*

Sulphonate esters have not been extensively and systematically studied by ^{13}C or ^1H spectroscopy although there are large numbers of such compounds recorded. Much of the chemical shift data are to be found in isolated reports, not primarily concerned with NMR spectroscopy. The ^1H NMR chemical shifts of some simple sulphonate esters are given in Table 15, and the ^{13}C NMR shifts of some sulphonate esters are given in Table 16. In RSO_2OR^1 both α-C_R and α-C_{R_1} are reasonably deshielded, as expected, although the α-C_R is considerably more deshielded in thiosulphonates RSO_2SR^1. Direct comparison is not possible but, for example in CH_3SO_2OR ($R = CH_2CH_2$), α-CH_3 appears at δ 37.2 ppm[53], whereas in CH_3SO_2SR ($R = CH_3$), α-CH_3 appears at δ 48.74 ppm[71]. No explanation appears to have been advanced for this phenomenon, but it may be related to the relative shielding effects of β-oxygen[72] and sulphur or a bond-angle effect[60]. Another, perhaps related, discrepancy between expectation and observation can be found in a report[73] on some bicyclic 1,2-oxathiolanes, **30**. The ^{13}C NMR spectra of three compounds **30a,b,c**, where $n = 0$, 1 and 2 respectively, are given in Table 17. As the electron-withdrawing properties of the groups fall in the order $—SO_3— > —SO_2— > —SO—$ it would be expected on electronic grounds that C-1 and C-4 in **30**, $n = 2$ would be more deshhielded than in **30**, $n = 0$ and 1. In thiosulphonates the α-C($—CHSO_2—$) is deshielded relative to the equivalent carbon in the thiosulphinates and disulphides[71,74,75], but the α^1-C ($—SO_2SCH—$) is very similar in chemical shift to the equivalent carbon nucleus in the disulphide. However, the thiosulphinate α^1-C is generally *shielded* by up to about 8 ppm relative to that in the thiosulphonate[71,74,75] (see later). By analogy, **30**, $n = 2$ should show a significantly deshielded C-4 relative to **30**, $n = 1$ and 0. That is clearly not the case as C-4 with δ 63.3 ppm is the *most* shielded in the series. The same

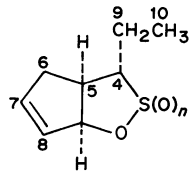


(30) **a**: $n = 0$
b: $n = 1$
c: $n = 2$

TABLE 16. ^{13}C chemical shifts for some sulphonate esters in $CDCl_3$[53]

Compound	δ(ppm)
$CH_3SO_2OCH_2CH_3$	67.0, OCH_2; 37.2, SCH_3; 15.0, CH_3
$CH_3SO_2O(CH_2)_3CH_3$	70.4, OCH_2 C-1; 37.0, SCH_3; 31.2 C-2 18.8, C-3; 13.5, C-1
$C_6H_5SO_2OCH_3$	135.2 *ipso*-C; 134.1 *para*-C; 129.5 *ortho*-C; 128.0 *meta*-C
p-$CH_3C_6H_4SO_2O(CH_2)_9CH_3$	144.6, *para*-C; 133.8, *ipso*-C; 129.9, *meta*-C; 127.9, *ortho*-C; 70.7, C-1; 32.0, C-8; 29.5, C-5,6,7; 29.1, C-2,4; 25.5, C-3; 22.8, C-9; 21.5, CH_3-*p*; 14.2, C-10

TABLE 17. ^{13}C NMR chemical shifts for the 1,2 oxathiolanes **30** in $CDCl_3$[73]



(30)

	δ(ppm)							
n	C-1	C-4	C-5	C-6	C-7	C-8	C-9	C-10
0	95.0	64.8	51.0	39.3	136.7	128.1	27.2	12.8
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
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.

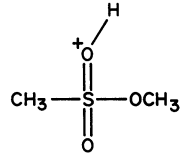
is also true for C-1 where the α^1-C for **30**, $n = 2$ is the most shielded. We have no explanation for these observations, which are similar to those for sulphonic acids[60]. It does seem as if the ^{13}C NMR chemical shifts of sulphonate esters are worth a more detailed examination as there are interesting and seemingly anomalous trends to explore.

In one series, at least, the proton chemical shifts are more well-behaved. The ^1H chemical shifts of the aromatic ring protons, the methylene protons and the acetylenic proton for p-$XC_6H_4SO_2OCH_2C{\equiv}CH$ are recorded in Table 18[76]. Electron withdrawal by X deshielded both the aromatic protons and the methylene protons. The propargyl hydrogen chemical shift was essentially independent of X. A plot of δ_{Ar} against σ_p for X gave a good straight line ($r = 0.984$). Similarly δ_{CH_2} against σ_p for X gave another line ($r = 0.982$). For δ_{CH_2} a similarly good line was obtained by plotting it against σ_o. In part this was attributed to the 'steric peculiarity' of sulphonate esters whereby R and R^1 in RSO_2R^1 were said to be gauche[76].

TABLE 18. ^1H chemical shifts for the series p-$XC_6H_4SO_2OCH_2C{\equiv}CH$ at 60 MHz in CCl_4[76]

		δ(ppm)	
X	C_6H_4	CH_2	CH
CH_3O	7.36	4.61	2.56
PrO	7.38	4.61	2.56
CH_3	7.50	4.62	2.56
Bu	7.49	4.62	2.56
CH_3CH_2	7.49	4.62	2.56
H	7.60	4.65	2.57
Cl	7.70	4.68	2.57
Br	7.71	4.68	2.57
CN	8.10	4.74	2.58
NO_2	8.20	4.76	2.58

Olah and coworkers[64] studied some sulphonate esters in super acid media by ^1H NMR spectroscopy. At $-60\,°C$ in $FSO_3H—SbF_5—SO_2ClF$, $CH_3SO_2OCH_3$ showed two major peaks at δ 4.8 and 4.03 ppm for the OCH_3 and CH_3S protons. Each of these had a shoulder which disappeared at $-30\,°C$ but reappeared on cooling. The approximately 1 ppm deshielding and the presence of two sets of resonances strongly suggested that two isomers of protonated sulphonate ester, **31** and **32** (as with CH_3SO_3H), were being observed. At higher temperatures than 20 °C, **31** and **32** break down by alkoxy–sulphur cleavage to form the CH_3SO_2F complex[64]. Ethyl methanesulphonate also protonated below 10 °C, although only one isomer was observed. Above 10 °C alkyl–oxygen cleavage occurred, by contrast, to give carbocations[64].



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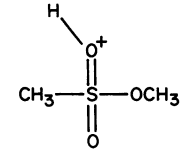


(32)

Very little is known of the ^{13}C NMR of sulphonic anhydrides[60]. What data are available, together with their substituent constants, are given in Table 19.

Thiosulphonate esters have received attention by several groups[55,71,74,75,77–79]. The ^1H NMR chemical shifts of some thiosulphinate esters are given in Table 20. Much of the published work on thiosulphonates has been concerned with the comparison between disulphides[33] **33**, thiosulphinates[35] **34** and thiosulphonates **35**. The thiosulphinate esters have received most attention[35] as the α^1-protons in **34** have anomalous high-frequency shifts and the α^1-carbon nuclei have anomalously low-frequency chemical shifts. It is generally assumed that it is the thiosulphinates that deviate from expected patterns, but there is also reason to believe that shielding patterns in thiosulphonates are not entirely simple and regular[55].

The available[13] information on ^{13}C NMR shifts for thiosulphonates is summarized in Table 21. The ^{13}C substituent effects relative to the parent disulphides for the thiosulphonates and, for comparison, the thiosulphinates are given in Table 22. Oxidation of a disulphide to a thiosulphonate results in an α-carbon deshielding of about + 22 ppm and a β-carbon shielding of about − 6 ppm. The α^1-carbon nuclei of thiosulphonates are, perhaps surprisingly, almost unaffected, being shielded by about 3 ppm relative to the disulphides. One notable exception appears to be $(CH_3)_3CSO_2SC(CH_3)_3$ where the α^1-carbon is 10.66 ppm deshielded[71], and for which no explanation has been attempted.

TABLE 19. ^{13}C NMR chemical shifts[a] and substituent constants[b] for some sulphonic anhydrides, $(RSO_2)_2O$[60]

	C-α		C-β		C-δ	
R	δ_C^a	α^b	δ_C	β^b	δ_C	δ^b
CH_3	41.46	43.56				
$(CH_3)_3CCH_2$	66.93	39.0	31.96	0.5	29.35	1.5
$C_6H_5CH_2$[c]	60.46	39.2				

[a] ^{13}C chemical shifts, ppm in $CDCl_3$ with internal TMS standard, at 62.89 MHz except for R = $(CH_3)_3CCH_2$ which was measured at 22.63 MHz.
[b] Chemical shift differences from the same carbon of the alkane RH[62].
[c] δ Ar, 125.7–131.1 ppm.

TABLE 20. ^{1}H NMR chemical shifts (δ, ppm) of some thiosulphonates, RSO_2SR^1

R	R^1	H-α	H-β	H-γ	H-δ	H-α^1	H-β^1	H-γ^1	H-δ^1	Ref.
CH_3	CH_3	3.17				2.60				79
C_6H_5	CH_3					2.48				74
C_6H_5	CH_2CH_3					3.00	1.28			74
C_6H_5	$CH_2CH_2CH_3$					2.97	1.62	0.90		74
C_6H_5	$CH_2CH_2CH_2CH_3$					2.99			0.83	74
CH_3	C_6H_5	3.12								74
CH_3CH_2	C_6H_5	3.16	1.41							74
$CH_3CH_2CH_2$	C_6H_5	3.14	1.91	1.01						74
$CH_3CH_2CH_2CH_2$	C_6H_5	3.18		0.92						74
$C_6H_5CH_2$	$C_6H_5CH_2$	4.21				4.01				55
$C_6H_5CH_2$	C_6H_5	4.43								55
C_6H_5	$C_6H_5CH_2$					4.27				55
$(CH_3)_3CCH_2$	$(CH_3)_3CCH_2$	3.35			1.21	3.1			1.04	55
$(CH_3)_3CCH_2$	C_6H_5	3.27			1.14					55
C_6H_5	$(CH_3)_3CCH_2$					2.96			0.92	55

TABLE 21. ^{13}C NMR shifts for some thiosulphonates RSO_2SR^1

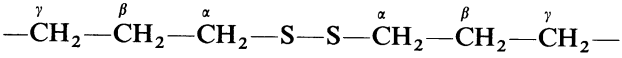
R	R^1	δ (ppm)[a] C-α	C-β	C-γ	C-α^1	C-β^1	C-γ^1	Ref.
CH_3	CH_3	49.2 ($J_{^{13}C=H}$ 141 Hz)			18.3 ($J_{^{13}C=H}$ 143 Hz)			79
		48.74			18.23			
CH_3CH_2	CH_2CH_3	56.94	8.31		30.54	15.12		71
$CH_3CH_2CH_2$	$CH_2CH_2CH_3$	64.68	17.63	13.36	38.36	23.45	12.89	75
$CH_3CH_2CH_2CH_2$[b]	$CH_2CH_2CH_2CH_3$	62.53	25.53	21.76	35.97	31.71	21.32	75
$(CH_3)_2CH$	$CH(CH_3)_2$	63.35	16.26		42.70	24.22		71
$(CH_3)_3CCH_2$	$CH_2C(CH_3)_3$	74.95	32.12	29.76	49.92	33.47	28.86	55
$C_6H_5CH_2$	$CH_2C_6H_5$	69.01			40.85			75
$C_6H_5CH_2$	C_6H_5	66.08						75
C_6H_5	$CH_2C_6H_5$				40.4			75
$(CH_3)_3C$	$C(CH_3)_3$	68.02	23.74		56.29	31.52		71
C_6H_5	CH_2CH_3				30.5	14.1		74
CH_3CH_2	C_6H_5	53.9	5.3					74
$CH_3CH_2CH_2$	C_6H_5	61.2	17.3	12.6				74
C_6H_5	$CH_2CH_2CH_3$				38.0	22.2	13.0	74

[a] In $CDCl_3$ on a variety of spectrometers.
[b] C-δ 13.44ppm; C-δ^1 13.56 ppm.

TABLE 22. ^{13}C NMR substituent effects for thiosulphonates, RSO_2SR^1 (and thiosulphinates, $RSOSR^1$)[a] relative to RSSR

R	R^1	α	β	γ	δ	α^1	β^1	γ^1	δ^1	Ref.
CH_3	CH_3	26.70				−3.81				
		(20.75)				(−7.60)				75, 71
CH_3CH_2	CH_2CH_3	24.12	−6.19			−2.28	0.62			71
		(17.06)	(−6.83)			(−6.01)	(1.76)			
$CH_3CH_2CH_2$	$CH_2CH_2CH_3$	23.42	−4.93	0.24		−2.90	0.89	0.23		75
		(16.89)	(−5.33)	(0.09)		(−6.35)	(1.73)	(−0.46)		
$CH_3CH_2CH_2CH_2$	$CH_2CH_2CH_2CH_3$	23.56	−5.84	0.08	−0.23	−3.00	0.34	−0.3	−0.11	75
		(17.12)	(−5.87)	(0.23)	(−0.14)	(−6.06)	(1.25)	(0.08)	(0.01)	
$(CH_3)_2CH$	$CH(CH_3)_2$	22.11	−6.34			1.56	1.62			71
		(14.12)	(−6.43)			(−2.87)	(2.03)			
$(CH_3)_3C$	$C(CH_3)_3$	22.39	−6.77			10.66	1.01			71
		(13.18)	(−6.50)			(2.30)	(1.69)			
$(CH_3)_3CCH_2$	$CH_2C(CH_3)_3$	18.99	1.81	0.93		−6.04	3.16	0.03		75
		(15.69)	(1.95)	0.73)		(−9.03)	(1.76)	(−0.11)		
$(CH_3)_2CHCH_2$	$CH_2CH(CH_3)_2$	21.88	−3.00	0.70		−4.03	0.69	−0.10		75
		(16.58)	(−3.29)	(0.27)		(−7.06)	(−1.52)	(0.12)		
$C_6H_5CH_2$	$CH_2C_6H_5$	25.69				−2.47				75
		(18.98)				(−7.23)				

[a]The substituent effects are calculated as $\Delta\delta = \delta_C(-SO_2S-) - \delta_C(-SS-)$ or $\Delta\delta = \delta_C(-S(O)S-\delta_C(-SS-)$; values for thiosulphinates are given in parentheses.



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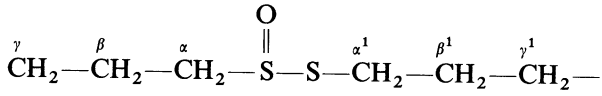

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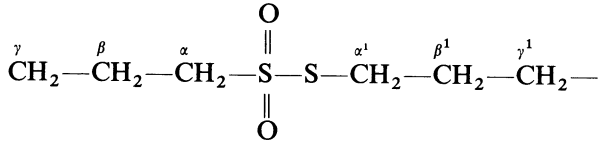
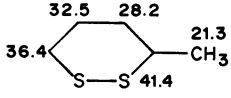


(35)

It is interesting to compare the cyclic series studied by Oae and coworkers[74]. The ^{13}C chemical shifts for compounds **36–40** are shown on the structures. The α and β effects can be seen very clearly in compounds **36–40** (tentative assignments in parentheses). In both **38** and **40** the α-carbons are deshielded by > 22 ppm, and the β-carbons are shielded by 4–7 ppm. The biggest β-shielding is for the methyl group of **38**, where steric crowding may be maximized. The α^1 shifts between **36**, and **38** and **40**, are small and variable, as with other thiosulphonates.



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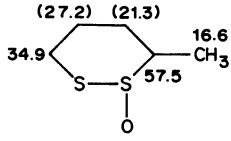

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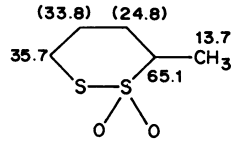

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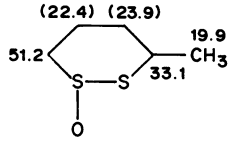

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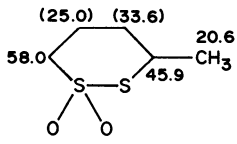


(40)

There is still opportunity for further enlightenment in the interpretation of chemical shifts of thiosulphonates, particularly with reference to sulphonic acids, anhydrides and esters.

4. *Sulphonamides*

The pharmaceutical uses of sulphonamides have ensured that they have been well-studied by NMR spectroscopy. Proton NMR spectra have been reported, but in recent years systematic studies have been particularly evident for ^{13}C and other nucleus NMR (Section III.B).

Proton NMR chemical shifts for some sulphonamides are given in Table 23. Figure 4 shows graphically the ^1H NMR chemical shifts for some sulphonamide drugs[81] (not all

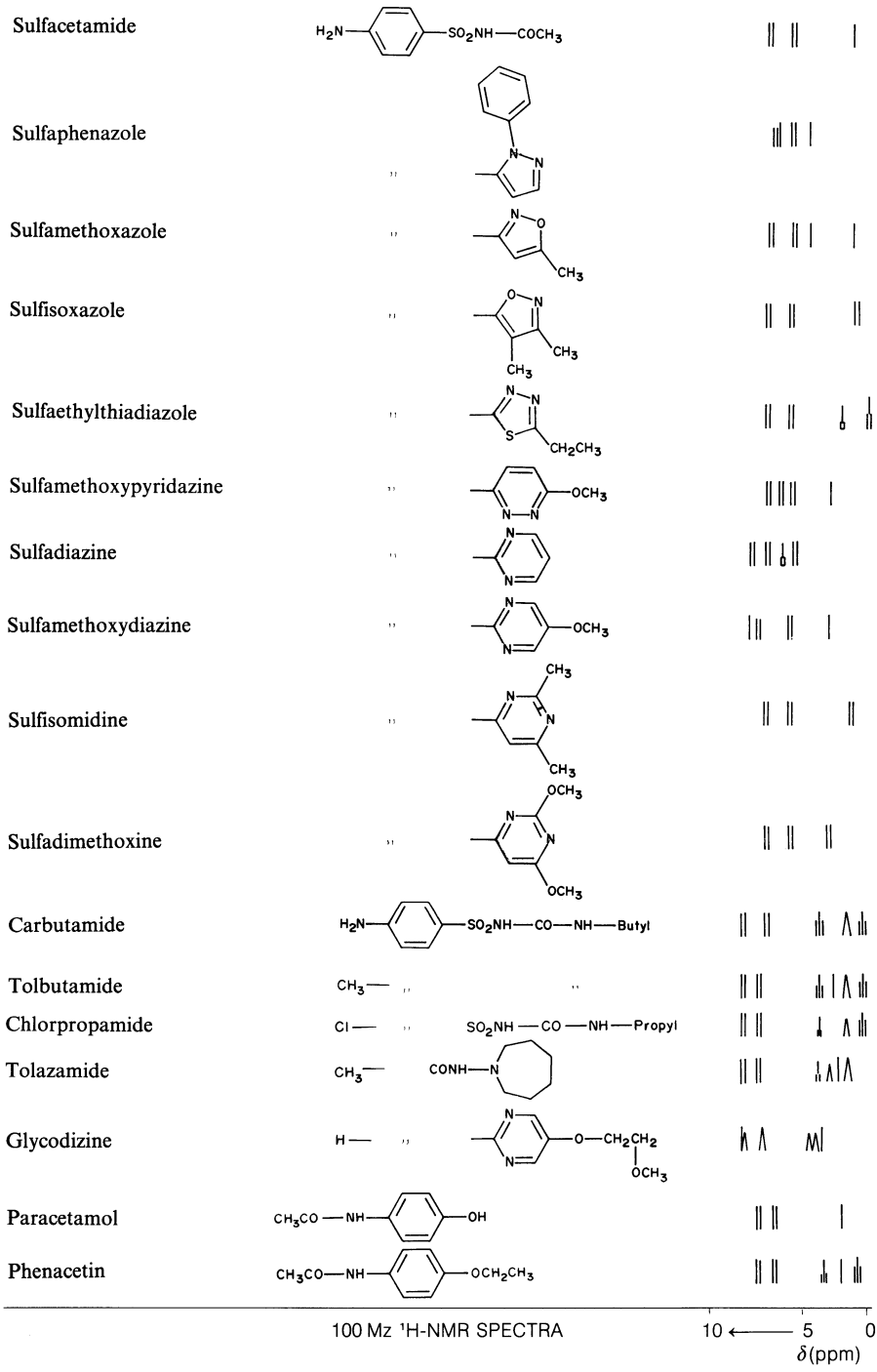


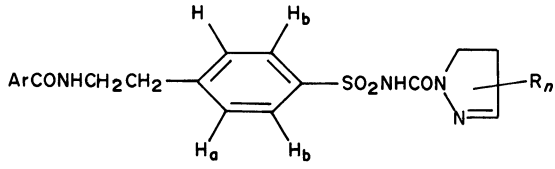
FIGURE 4. Schematic representation of the 100 MHz ^{1}H NMR spectra of some oral antidiabetics. Reproduced by permission of Elsevier Scientific Publishers Ireland Ltd from *Forensic Science*, **4**, 219 (1974)

TABLE 23. ^{1}H NMR chemical shifts for some sulphonamides, $RSO_2NR^1_2$

R	R^1	δ(ppm)	Solvent	Ref.
Cl	CH_3	2.95 (s) ($^1J_{^{13}C-H}$ 141.9 Hz)	CH_2Cl_2	52
CH_3	CH_3	2.81 (s) NCH_3($^1J_{^{13}C-H}$ 139 Hz); 2.76 (s) CH_3S($^1J_{^{13}C-H}$ 137.4 Hz)	$CHCl_2$	52
$ClCH_2$	CH_3	2.33 (s)[a]	CH_2Cl_2	52
C_6H_5	CH_3	2.66 (s) NCH_3($^1J_{^{13}C-H}$ 139.1 Hz)		
C_6H_5	H, $SiMe_3$	7.8–8.0 (m) 2H, 7.45–7.77 (m) 3H Ar; 5.3–5.9 broad (s) NH; 0.18 (s) $SiMe_3$	CD_3CN	80

[a] NCH_3; SCH_2 not recorded.

of which may still be in common use). Another report[82] gives ^{1}H chemical shifts for a series of hypoglycemic agents belonging to the sulphonamide group. The compounds have the general formula **41**. The aromatic protons H_a and H_b appear as a doublet of doublets



(41)

($J = 8$ Hz) at δ7.6–7.7 and 8.12–8.02, respectively. The chemical shifts of the other fragments are also given[82]. The ^{1}H (and ^{31}P) NMR spectra of some arylsulphonamides of some chiral organophosphoric acids have been reported[83].

One-bond ^{13}C—H coupling constants have been measured for numbers of sulphonamides[52,84] and it has been observed[84] that the coupling constants for *S*-methyl groups are similar for all sulphonamides and sulphinamides (137 Hz approximately), but those for *N*-methyl groups are a little larger in sulphonamides (138.9–139.2 Hz) than in sulphinamides (137.2–137.3 Hz).

As with amides, a $^3J_{HH}$ coupling in the HNCH fragment is often observed, for example in *N*-methyl-*p*-toluenesulphonamide the NCH_3 protons appear as a doublet, $J = 5.9$ Hz, in $CDCl_3$[51].

The ^{13}C NMR chemical shifts of some simple sulphonamides are given in Table 24. The α-carbon resonances in sulphonamides, $CH_3SO_2NR_2$, are shielded by about 6 ppm relative to those in the equivalent sulphinamides [$CH_3SO_2N(CH_3)_2$, δ α-C, 32.3 ppm; $CH_3SON(CH_3)_2$, δ α-C, 39.0 ppm and $CH_3SO_2NH_2$, δ α-C 43.5 ppm; CH_3SONH_2, δ α-C, 48.9 ppm]. The trend is the same as in the sulphonic acids[60]. The α^1-carbon nuclei in sulphinamides and sulphonamides have very similar shifts in the limited examples available [$CH_3SO_2N(CH_3)_2$, NCH_3 δ 36.7 ppm; $CH_3SON(CH_3)_2NCH_3$ δ 36.1 ppm and $C_6H_5SO_2N(CH_3)_2$ δ 37.7 ppm; $C_6H_5SON(CH_3)_2$, NCH_3 δ 36.7 ppm]. This is in contrast to the thiosulphonates where the α^1-carbon nucleus is deshielded by up to 8 ppm relative to the thiosulphinate (Section III.A.3). Again, the ^{13}C NMR chemical shift patterns within a particular series, such as the sulphonamides, are internally consistent, but do not relate well to those in other series (such as sulphonic acids or thiosulphonates).

Aromatic sulphonamides have been particularly exhaustively studied. The substituent-

TABLE 24. ^{13}C NMR chemical shifts of some sulphonamides, $RSO_2NR^1_2$

R	R^1	δ (ppm)	Solvent	Ref.
CH_3	H	45.3 (SCH_3)	$(CD_3)_2CO$	84
CH_3	CH_3	37.3 (NCH_3); 32.3 (SCH_3)	$(CD_3)_2SO$	85
		36.7 (NCH_3); 32.2 (SCH_3)	$CDCl_3$	85
CH_3	H, C_6H_5	138.9 (C-1); 129.9 (C-3,5); 125.1 (C-4); 121.2 (C-2,6); 39.3 (SCH_3)	$CDCl_3$	84
CH_3	C_6H_5	142.5 (C-1); 129.9 (C-3,5); 128.5 (C-2,6); 127.7 (C-4); 40.3 (SCH_3)	$(CD_3)_2CO$	84
C_6H_5	H, CH_3	140.2 (C-1); 133.0 (C-4); 129.6 (C-3,5); 127.5 (C-2,6); 29.3 (NCH_3)	$(CD_3)_2CO$	84
C_6H_5	CH_3	135.1 (C-1); 132.7 (C-4); 129.0 (C-3,5); 127.5 (C-2,6)	$(CD_3)_2CO$	84

TABLE 25. Substituent-induced shifts of aromatic carbons of some sulphonamides ($\delta_{C_6H_6} = 128.5$)

Compound	C-1[a]	C-2,6	C-3,5	C-4	Solvent	Ref.
$C_6H_5SO_2NH_2$	+16.1	−1.9	+1.0	+4.1	$(CD_3)_2CO$	86
	+15.5	−3.0	+0.3	+3.2	$(CD_3)_2SO$	87
$C_6H_5SO_2NHCH_3$	+11.7	−1.0	+1.1	+4.5	$(CD_3)_2CO$	84
$C_6H_5SO_2N(CH_3)_2$	+6.7	−1.0	+0.8	+4.4	$(CD_3)_2SO$	86
	+6.7	−0.9	+0.6	+4.3	$CDCl_3$	86
$C_6H_5SO_2N(C_6H_5)_2$						
(C_6H_5S)	+13.0	−0.4	−0.1	+5.1	$(CD_3)_2CO$	84
	+12.8	−0.3	+0.6	+4.2	$CDCl_3$	84
(NC_6H_5)	+14.1	+1.4	+0.7	+1.3	$(CD_3)_2CO$	84
	+11.8	−1.1	+0.3	−1.0	$CDCl_3$	84
$C_6H_5SO_2NHC_6H_5$						
(C_6H_5S)	+12.1	−0.9	+1.0	+4.8	$(CD_3)_2CO$	88
	+11.1	−1.7	+0.8	+4.6	$(CD_3)_2SO$	89
(NC_6H_5)	+9.9	−7.0	+1.2	−3.3	$(CD_3)_2CO$	88
	+9.2	−8.3	+0.8	−4.2	$(CD_3)_2SO$	89

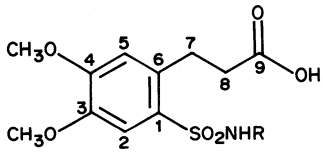
[a]Positive shifts to high frequency of benzene.

induced shifts for the aromatic carbons in several series of sulphonamides are shown in Table 25. The substituent effects are unsurprising, with those on the *S*-phenyl ring appropriate to the electron-withdrawing SO_2NR_2 group and those on the *N*-phenyl ring characteristic of the resonance electron-supplying (albeit weakly) nitrogen atom. It is interesting to note the γ-shielding effect on the *ipso* carbon in the series $C_6H_5SO_2NH_2$, $C_6H_5SO_2NHCH_3$ and $C_6H_5SO_2N(CH_3)_2$ where each additional methyl group shields C-*ipso* by about 5 ppm. There is again a perplexing comparison between sulphonamides and sulphinamides; the substituent constants for $C_6H_5SO_2N(CH_3)_2$ in $CDCl_3$ are: C-1, +6.7; C-2,6, −0.9; C-3,5, +0.6 and C-4, +4.3 ppm[86], while those for $C_6H_5SON(CH_3)_2$ also in $CDCl_3$ are: C-1, +14.7; C-2,6, −2.7; C-3,5, +0.4 and C-4, +2.4 ppm[86]. So the sulphinamide α-carbon is considerably deshielded relative to the sulphonamide, whereas the rest of the carbon atom shifts reflect the greater electron-withdrawing power of SO_2NR_2.

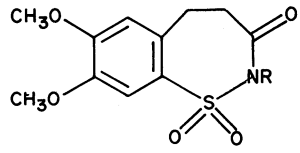
For a series of *para*-substituted sulphonamides, $p\text{-}XC_6H_4SO_2NH_2$, the sulphonamido *ipso*-carbon chemical shift is strongly affected by the nature of X[87] and a good correlation ($r = 0.998$) between $\delta^{13}C$ and σ_R^+ has been obtained[87]. Electron withdrawal by X deshields C-1 as expected. In the same study[87] other spectral parameters (IR, ^1H and ^{15}N NMR) were also correlated with σ_R^+ and the ^{13}C NMR C-1 chemical shift was clearly related to the computed net-charges (INDO).

The effect of ring formation and ring size on the ^{13}C NMR chemical shifts of some aromatic sulphonamides **42**–**45** has been reported[90]. The ^{13}C NMR chemical shifts of some compounds **42**–**44** are given in Table 26. Two interesting observations can be made about these compounds. The first is that, in contrast to $C_6H_5SO_2NR_2$ (Table 25), there is no measurable 'γ-effect' on C-1. The only possible exception is **42** (R = Ph) where C-1 is reported to be δ 137.96 ppm while C-1 for all other **42** is about δ 133.5 ppm. However, C-6 is recorded as having a chemical shift of 134.02 ppm and an erroneous assignment appears possible. Conformational effects with the substituent, R, in an equatorial position could be responsible for the lack of a γ-effect in **43** and **44**, but cannot be an explanation for the acyclic series **42**.

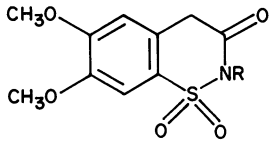
The second observation[90] concerns the effect of ring closure and ring size on the aromatic carbon nuclei in **42**–**44**. Table 27 gives $\Delta\delta$ values corresponding to the difference in



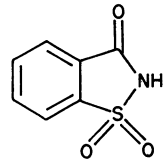
(42)



(43)



(44)



(45)

chemical shift between the acyclic series **42** (R = H) and the cyclic series **43** and **44** (R = H). The ring-closed compounds have C-1, C-2 and C-6 shielded by up to 7.5 ppm relative to the open-chain compound. The effect is strongest for the six-membered rings **44**.

It was found that the ^{13}C NMR chemical shifts of saccharin **45** could be calculated reasonably well by simply adding the substituent parameters for SO_2NH_2 and COOH ($CONHSO_2$— being unavailable) and then adding the corrections for the five-membered ring formation given in Table 27.

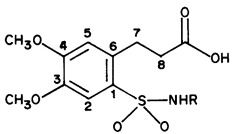
Two studies[91,92] report little or no transmission of substituent effects through the S—N bond in the $ArSO_2N$— system.

The ^{13}C NMR chemical shifts of eight sulphonamide drugs (sulphanilamide, sulphaguanidine, sulphathiazole, sulphasuxidine, sulphadiazine, sulphamerazine, sulphamethiazine and sulphapyridine) have been determined and assigned[93].

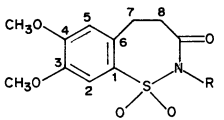
The solid-state ^{13}C c.p.–m.a.s. (cross polarization-magic angle spinning) spectra of some aromatic sulphonamides have been recorded[94]. It had been observed previously that carbon nuclei bonded to nitrogen are characterized by an asymmetric doublet structure in the ^{13}C c.p.–m.a.s. spectra[94,95]. The doublet structure of N—CH_3 resonances was also observed for sulphonamides[94] and attributed, as for other similar systems, to a perturbation of the ^{13}C–^{14}N dipolar interaction by the ^{14}N quadrupolar nucleus. There were some differences in chemical shift between the solid and solution spectra[94], which were said to be greater than could be accounted for by solvent effects. Spin–lattice relaxation times T_1 in both the solid and solution state are recorded in Table 28[94] for some sulphonamides. As expected, motion is slower in the solids resulting in higher T_1 values. In the *N,N*-dimethylsulphonamides, the relaxation time of the N—CH_3 carbons is about half that of the CH_3C carbons and the NCH_3 carbon in *p*-$CH_3C_6H_4SO_2NHCH_3$, possibly because in the solid state nearby protons have the same spin temperature and behave as an assembly[94].

The solid state ^{13}C c.p.–m.a.s. spectra of the 1:1 and 2:1 complexes of benzenesulphonamide with 18-crown-6-ether have been measured as a function of temperature[96]. The dynamics of the crown-ether motion were particularly studied, but motion about the sulphonamide *ipso–para*-carbon axis was also investigated[96]. The effect of 18-crown-6-ether on the proton resonances of some sulphonamides in solution has also been reported[97].

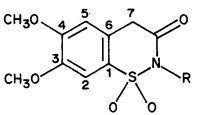
TABLE 26. ^{13}C NMR chemical shifts for compounds **42–44**[90] in $(CD_3)_2SO$



(42)



(43)



(44)

Compound	R	δ(ppm)										
		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C=O	CH_3O	R
42	H	133.82	111.35	146.22	151.11	114.43	132.46	27.63	35.52	174.01	55.87	
42	CH_2CH_3	133.40	112.10	146.37	151.49	114.56	130.05	27.53	35.56	173.87	58.84	37.4 (CH_2); 14.94 (CH_3)
42	$CH(CH_3)_2$	133.22	112.08	146.24	151.36	114.40	131.03	27.36	35.46	173.87	55.77	45.07 (CH); 23.25 (CH_3)
42	C_6H_5	137.96	112.73	146.29	151.93	114.56	134.02	27.34	35.52	173.78	55.83; 55.89	119.36; 123.68; 128.86; 129.20
42	C_5H_4N[a]	133.29	112.5	145.99	151.29	114.38	131.88	27.51	35.49	173.93	55.78; 55.90	114.38; 140.99; 141.75; 153.68
43	H	130.24	108.05	146.69	151.98	114.51	130.24	27.13	34.19	171.75	55.92; 56.02	
43	CH_2CH_3	130.67	108.45	146.94	152.59	114.96	129.83	27.95	34.56	171.40	56.10	41.09 (CH_2); 14.81 (CH_3)
43	$CH(CH_3)_2$	130.19	108.28	146.81	152.26	114.66	130.19	27.71	35.61	172.90	55.32	51.32 (CH); 20.73 (CH_3)
43	C_6H_5	131.16	108.96	147.09	152.94	115.29	129.18	28.13	34.73	172.28	55.36; 55.51	129.75; 135.88
43	C_5H_4N[a]	130.42	108.59	145.95	152.44	114.87	129.17	27.75	34.35	171.83	55.94; 56.07	124.61, 125.06 138.94; 149.42 148.82
44	H	127.19	104.11	148.00	152.49	112.25	124.95	37.34	—	170.61	56.31	
44	*p*-ClC_6H_4	128.27	105.72	148.11	153.10	112.46	124.83	38.39	—	168.25	56.26; 56.33	129.75, 130.59, 131.89, 134.54

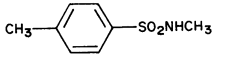
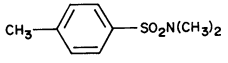
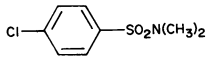
[a]Presumably 2-C_5H_4N.

TABLE 27. ^{13}C NMR chemical shift differences $\Delta\delta^a$ between **43–42** (R = H) and **44–43** (R = H)[90]

Compounds	C-1	C-2	C-3	C-4	C-5	C-6
43–42	−3.58	−3.30	0.47	0.87	0.08	−2.22
44–42	−6.63	−7.24	1.78	1.38	−2.18	−7.51

[a]A negative sign means the ring-closed compound has chemical shift to the low-frequency of the equivalent carbon in **42** (R = H).

TABLE 28. ^{13}C NMR relaxation times T_1 for the methyl carbon nuclei of some sulphonamides in solution and in the solid state[94]

Compound	Solid or solvent	T_1 (s)	
		NCH_3	CH_3C
	$CHCl_3$	2.6	2.6
	Solid	8.3	8.5
	Solid	4.5	8.6
	$CHCl_3$	3.0	
	Solid	3.8	

5. *Sulphonyl chlorides*

The are very limited data available for sulphonyl chlorides[98]. The substituent-induced shifts for SO_2Cl on a benzene ring are; C-*ipso* + 15.6; C-2,6 − 1.7; C-3,5 + 1.2 and C-4 + 6.8 ppm. The ^{13}C NMR resonance for CH_3SO_2Cl appears at δ 52.8 ppm[79] and those for $CH_3CH_2SO_2Cl$ at δ 69.6 and 14.5 ppm[98].

B. Multinuclear Studies of Sulphonic Acids and their Derivatives

1. ^{33}S *NMR*

^{33}S is a quadrupolar nucleus, $I = 3/2$, with a natural abundance of 0.76%. As the ^{33}S nucleus also possesses an electric quadrupole moment, the electric field gradients at the nucleus can lead to short relaxation times and hence broad lines. One advantages of the short relaxation times is that rapid pulsing is possible in FT experiments. The first paper on ^{33}S NMR appeared in 1972[99] using c.w. techniques but it was not until 1981 that the next paper was published[100]. The report by Faure and coworkers[100] using FT NMR showed that certain compounds, particularly sulphonic acids and their derivatives, gave narrow linewidths and were amenable to study by ^{33}S NMR. The ^{33}S NMR chemical shifts of a number of sulphonic acids and their derivatives are given in Table 29. The chemical shifts in Table 29 have SO_4^{2-} as reference; those measured relative to CS_2 have been converted to the SO_4^{2-} scale by subtracting 334.2 ppm[86] although 328 ppm has also been used as the conversion factor elsewhere[104].

There is no clear correlation between ^{33}S NMR chemical shifts and the electronegativity of X and Y in $X—SO_2—Y$[101], but there is a reasonable correlation for closely related groups such as CH_3SO_2Y[101]. In the case of CH_3SO_2Y the more electronegative Y tend to

TABLE 29. ^{33}S NMR chemical shifts of some sulphonic acids and their derivatives

Compound	δ(ppm)[a]	$\Delta\nu_{1/2}$[b]	Solvent	Ref.
CH_3SO_3H	-5 ± 2.5	150	D_2O	100
	-5.2	22	H_2O	103
p-$CH_3C_6H_4SO_3H$	-10 ± 1.5	90	D_2O	100
$H_2NCHCH_2SO_3H$	$+9 \pm 1.5$	80	D_2O	100
COOH				
$CH_2{=}CHSO_3Na$	-11 ± 1.5	70	D_2O	100
$CH_3SO_2N(CH_3)_2$	-10.2		$CDCl_3$	86
$C_6H_5SO_2N(CH_3)_2$	-2.2		$CDCl_3$	86
$CH_3SO_2OCH_3$	$+0.8$	300	$CHCl_3$	101
CH_3SO_2F	-0.2	300	$CHCl_3$	101
CH_3SO_2Cl	$+0.8$	300	$CHCl_3$	101
	$+6.8$		$CHCl_3$	102
CF_3SO_2Cl	-22.2	300	$CHCl_3$	101
$CH_3CH_2SO_2Cl$	$+17.8$	2000	$CHCl_3$	101
$CH_3CH_2SO_2OCH_3$	$+2.8$	1500	$CHCl_3$	101
$CF_3SO_2OCH_3$	No resonance detectable		$CHCl_3$	101
$CH_3SO_2SCH_3$	-6.2	25	H_2O	105

[a] SO_4^{2-} reference, see text.
[b] Half-height width (Hz).

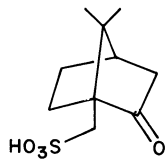
deshield the sulphur nucleus. However, for $ClSO_2Y$ and CH_3OSO_2Y increasing electron withdrawal by Y shields the sulphur nucleus[101].

The sulphonic acids (usually as their salts) have been well-studied by ^{33}S NMR[103,105-108]. A linear relationship between $\delta^{33}S$ and σ_p for p-$XC_6H_4SO_3H$ (1 M in D_2O) was first discovered by Hinton and Buster[106]. Electron-withdrawing X shield the ^{33}S nucleus. An extended study by Crumrine and coworkers[107] showed that ^{33}S NMR chemical shifts could be used to determine the pK_a values for arenesulphonic acids, through equation 19. In another study Crumrine and Gillece-Castro[103] studied the

$$pK_a = 0.0725\delta(^{33}S) - 5.787 \qquad (r = 0.996) \tag{19}$$

concentration dependence of ^{33}S linewidths, and in addition showed that the shielding γ-effect operates in ^{33}S NMR. As an example of this the ^{33}S chemical shift of m-$C_6H_4(SO_3Na)_2$ is δ -14 ppm ($\Delta\nu_{1/2}$ 51 Hz) whereas o-$C_6H_4(SO_3Na)_2$ has $\delta^{33}S$ -19 ppm ($\Delta\nu_{1/2}$ 240 Hz)[103].

Evans[105] explored the analytical possibilities of ^{33}S by examining a known mixture of sulphonic acids in H_2O. Each acid gave rise to a resolved signal: **46**, δ -10.16; **47**, δ -15.9; **48**, δ -18.03 ppm.



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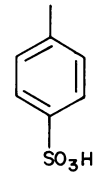

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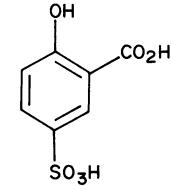


(48)

Cassidei and Sciacovelli[108] measured the ^{33}S chemical shifts of fifteen sulphonates, RSO_3Na, and compared the chemical shift trend with the ^{13}C chemical shift of the

TABLE 30. ^{33}S NMR chemical shifts and linewidths for sodium sulphonates RSO_3Na[108] and ^{13}C NMR chemical shifts for RCOONa

R	$\delta^{33}S^a$	$\Delta\nu_{1/2}$ (Hz)	$\delta^{13}C^a$
CH_3	-5.6 ± 0.1	28	181.7[b]
CH_3CH_2	$+4.2 \pm 0.5$	160	185.1[b]
$CH_3CH_2CH_2$	$+2.2 \pm 0.6$	200	184.3[b]
$CH_3CH_2CH_2CH_2$	$+3.4 \pm 1.0$	350	184.4[b]
$CH_2{=}CH$	-13.4 ± 0.1	35	177.8
C_6H_5	-11.7 ± 0.1	15	177.8
p-$CH_3C_6H_4$	-11.1 ± 0.1	32	177.9
m-$NH_2C_6H_4$	-11.5 ± 0.1	26	178.4
$NaOOCCH_2$	-9.6 ± 0.1	10	178.5[c]
H_2NCH_2	-2.3 ± 0.2	80	182.0[d]
m-$NO_2C_6H_4$	-16.5 ± 0.3	100	175.1
p-$NH_2C_6H_4$	-10.5 ± 0.1	16	178.5
1-naphthyl	-15.2 ± 0.1	12	180.2
2-naphthyl	-11.5 ± 0.1	15	177.8
p-ClC_6H_4	-13.2 ± 0.1	12	176.7

[a]Measured in H_2O solution.
[b]Reference 109.
[c]Reference 110.
[d]Reference 111.

carboxylate carbon in the equivalent compounds RCO_2Na. The results are given in Table 30. A very good correlation was found (with the exception of R = 1-naphthyl) and the following relationship was presented:

$$\delta(^{33}S) = -390.3 + 2.129\delta(^{13}C) \qquad (r = 0.990)$$

The ^{33}S substituent chemical shift can therefore be rationalized in the same way as for the carbonyl carbon in carboxylate groups. When R is unsaturated ($CH{=}CH_2$; C_6H_5, etc.) the ^{33}S resonance is generally shielded relative to $R = CH_3$. This was rationalized[104] in terms of electron release from the conjugated π-system to the sulphur atom. There is still much work to be done in ^{33}S NMR.

2. ^{17}O NMR

Oxygen-17 is quadrupolar, $I = \frac{5}{2}$, and has very low natural abundance (0.037%). Despite these limitations ^{17}O NMR is now a very valuable tool for use in studies on structure and bonding. Table 31 gives some ^{17}O chemical shifts of some sulphonic acid derivatives.

From the limited data available it seems that ^{17}O and ^{33}S follow the same general trend in chemical shift patterns. For CH_3SO_2Y, electron-withdrawing groups deshield the ^{17}O nucleus[101] but the chemical shift change with substituent for ^{17}O is greater than that for ^{33}S as expected (from the presence of oxygen non-bonding electrons). An α-chlorine atom has a very strong deshielding effect on the ^{17}O resonances in $ClSO_2X$ but a smaller and inconsistent effect on ^{33}S shifts. For example, $\delta^{17}O$ is 164, 238 and 296 ppm for $CH_3SO_2CH_3$, CH_3SO_2Cl and $ClSO_2Cl$, respectively, whereas $\delta^{33}S$ is 320, 335 and 287 ppm, respectively. This effect has been attributed[101] to an interaction between the oxygen lone-pairs of electrons and the S—Cl σ^* orbital.

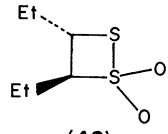
The γ-shielding effect is also observed in the ^{17}O NMR spectra of sulphonic acid derivatives, as in $CH_3SO_2SCH_3$ $\delta^{17}O$ 199 ppm and in $(CH_3)_2CHSO_2SCH(CH_3)_2$ δ ^{17}O 183 ppm[105].

TABLE 31. ^{17}O NMR chemical shifts of some sulphonic acid derivatives[a]

Compound	$\delta^{17}O$ (ppm)[a]	$\Delta\nu_{1/2}$ (Hz)	Solvent	Ref.
$CH_3SO_2SCH_3$	199			105
$CH_3CH_2SO_2CH_2CH_3$	190			105
$(CH_3)_2CHSO_2SCH(CH_3)_2$	183			105
$CH_3SO_2OCH_3$	170	100–300	$CHCl_3$	101
CH_3SO_2F	186	100–300	$CHCl_3$	101
CH_3SO_2Cl	238	100–300	$CHCl_3$	101
$CH_3SO_2N(CH_3)_2$	156		$CHCl_3$	86
CF_3SO_2Cl	211	100–300	$CHCl_3$	101
$CF_3SO_2OCH_3$	147	100–300	$CHCl_3$	101
	147(S=O);	40	C_6D_6	112
	104(SOC)	70		
$CF_3SO_2OSiMe_3$	158	30	C_6D_6	112
CH_3SONH_2	169.7		$(CD_3)_2CO$	84
$CH_3SO_2N(CH_3)_2$	156		$CDCl_3$	86
$CH_3SO_2NHC_6H_5$	169.4		$(CD_3)_2CO$	84
$CH_3SO_2N(C_6H_5)_2$	170.2		$(CD_3)_2CO$	84
$C_6H_5SO_2NH_2$	159.4		$(CD_3)_2CO$	84
$C_6H_5SO_2NHCH_3$	148.2		$(CD_3)_2CO$	84
$C_6H_5SO_2N(CH_3)_2$	139.9		$(CD_3)_2CO$	84
p-$CH_3C_6H_4SO_2NH_2$	160.8		$(CD_3)_2CO$	84
p-$BrC_6H_4SO_2NH_2$	159.6		$(CD_3)_2CO$	84
p-$NO_2C_6H_4SO_2NH_2$	158.7		$(CD_3)_2CO$	84
m-$NO_2C_6H_4SO_2NH_2$	160.1		$(CD_3)_2CO$	84
o-$NO_2C_6H_4SO_2NH_2$	164.4		$(CD_3)_2CO$	84

[a]Referenced to external H_2O. SO_2 oxygen only reported unless otherwise stated.

It has been shown that stereochemically distinct oxygen nuclei (diastereotopic) can be distinguished by ^{17}O NMR. Compound **49** shows two well-separated ^{17}O NMR



(49)

resonances at δ 210 and 243 ppm[113]. It has also been observed[112] that two well-resolved ^{17}O resonances are produced by $CF_3SO_2OCH_3$ whereas $CF_3SO_2OSiMe_3$ has only one averaged ^{17}O resonance. This can be attributed to rapid inter- or intramolecular exchange of $SiMe_3$ groups between bonding sites.

Sulphonamides have received some attention with respect to their ^{17}O chemical shifts[84,86,94]. Each *N*-methyl substituent in $RSO_2NH_{2-n}(CH_3)_n$ has an approximately 10 ppm shielding effect on the oxygen chemical shift[84], but the presence of *N*-phenyl groups does not have a regular or strong effect[84]. Substituents on the benzene ring in $XC_6H_4SO_2NH_2$ have very little effect on the ^{17}O resonances[84].

3. *^{15}N NMR*

^{15}N spectra have been recorded for many sulphonamides, and some ^{15}N NMR chemical shifts are given in Table 32. The aromatic sulphonamides in particular have

TABLE 32. ^{15}N NMR chemical shifts for some sulphonamides

Compound	$-\delta^{15}N^{a}$ (ppm)	$^{1}J_{NH}$ (Hz)	Solvent	Ref.
$C_6H_5SO_2NH_2$	288.0		$(CH_3)_2CO$	84
	285.7[b]		$(CH_3)_2SO$	114
$C_6H_5SO_2NHCH_2CH_3$	281.4[b]		$(CH_3)_2SO$	114
$C_6H_5SO_2NHCH_2C_6H_5$	283.2[b]		$(CH_3)_2SO$	114
p-$H_2NC_6H_4SO_2NH_2$	284.1[b]		$(CH_3)_2SO$	114
$C_6H_5SO_2N(CH_2C_6H_5)_2$	279.1[b]		$(CH_3)_2SO$	114
$C_6H_5SO_2N(CH_3)_2$	299.2		$CHCl_3$	115
	300.7		$(CH_3)_2SO$	84
$C_6H_5SO_2NHCH_3$	296.3		$(CH_3)_2CO$	84
$C_6H_5SO_2NHC_6H_5$	259.4		$(CH_3)_2CO$	84
$C_6H_5SO_2N(C_6H_5)_2$	281.0		$(CH_3)_2CO$	84
$C_6H_5SO_2N(CH_2CH_3)_2$	279.0		None	115
p-$CH_3C_6H_4SO_2NH_2$	287.6		$(CH_3)_2CO$	84
p-$ClC_6H_4SO_2NH_2$	287.8		$(CH_3)_2CO$	84
p-$BrC_6H_4SO_2NH_2$	287.8		$(CH_3)_2CO$	84
p-$NO_2C_6H_4SO_2NH_2$	288.4		$(CH_3)_2CO$	84
m-$NO_2C_6H_4SO_2NH_2$	288.3		$(CH_3)_2CO$	84
o-$NO_2C_6H_4SO_2NH_2$	285.6		$(CH_3)_2CO$	84
p-$NCC_6H_4SO_2NH_2$	286.0	81.9	$(CD_3)_2SO$	87
p-$HOOCC_6H_4SO_2NH_2$	285.9	80.6	$(CD_3)_2SO$	87
p-$NO_2C_6H_4SO_2NH_2$	285.8	83.6	$(CD_3)_2SO$	87
$C_6H_5SO_2NH_2$	285.7	80.8	$(CD_3)_2SO$	87
p-$BrC_6H_4SO_2NH_2$	285.7	79.3	$(CD_3)_2SO$	87
p-$ClC_6H_4SO_2NH_2$	285.6	80.6	$(CD_3)_2SO$	87
p-$CH_3C_6H_4SO_2NH_2$	285.5	80.3	$(CD_3)_2SO$	87
p-$FC_6H_4SO_2NH_2$	285.2	81.6	$(CD_3)_2SO$	87
p-$CH_3CONHC_6H_4SO_2NH_2$	285.1	80.7	$(CD_3)_2SO$	87
p-$CH_3OC_6H_4SO_2NH_2$	284.7	78.2	$(CD_3)_2SO$	87
p-$HOC_6H_4SO_2NH_2$	284.6	79.3	$(CD_3)_2SO$	87
p-$H_2NC_6H_4SO_2NH_2$	284.0	78.7	$(CD_3)_2SO$	87
$C_6H_5SO_2NHC_6H_4OCH_3$-p	262.8[b]	84.2	$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_4F$-p	261.2[b]	84.2	$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_4CH_3$-p	261.0[b]	84.2	$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_4Br$-p	259.5[b]	82.5	$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_5$	259.5[b]	82.5	$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_4CN$-p	254.3[b]		$(CD_3)_2SO$	114
$C_6H_5SO_2NHC_6H_4NO_2$-p	253.1[b]		$(CD_3)_2SO$	114
$CH_3SO_2NH_2$	288.7		$(CD_3)_2CO$	84
$CH_3SO_2NHCH_3$	296.3		$(CD_3)_2CO$	84
$CH_3SO_2N(CH_3)_2$	298.3		$(CD_3)_2CO$	84
$CH_3SO_2NHC_6H_5$	260		$(CD_3)_2CO$	84
$CH_3SO_2N(C_6H_5)_2$	281.5		$(CD_3)_2CO$	84
$CH_3SO_2N(CH_3)_2$	302		$CHCl_3$	115
$CH_3SO_2N(CH_2CH_3)_2$	281		None	115
$CH_3SO_2N(CH(CH_3)_2)_2$	269		None	115

[a]Referenced to nitromethane.
[b]Originally measured relative to $^{15}NO_3^-$; to get the originally reported chemical shift, subtract 6.0 ppm and change the sign.

been thoroughly examined. Roberts and coworkers[114] in the original ^{15}N study of sulphonamides reported that the ^{15}N chemical shifts in sulphonamides and ethanamides followed similar patterns. Increased alkyl substitution on nitrogen was said to result

in downfield shifts[114]. Ruostesuo and coworkers[84,86] by contrast found that in $C_6H_5SO_2NH_{2-n}(CH_3)_n$ increasing alkyl substitution shielded N by about 8 ppm. A close examination of all the available data shows no readily discernable or consistent trends on nitrogen substitution by alkyl or aryl groups.

For the series sulphenamide, sulphinamide and sulphonamide, Häkkinen and Ruostesuo[86] report the order of shielding, sulphenamide > sulphinamide > sulphonamide for alkyl and aryl compounds, whereas Dorie and Gouesnard[115] reported sulphenamide > sulphonamide > sulphinamide for $ClSO_nNR_2$ ($n = 0$–2).

Electron-withdrawing substituents X in $C_6H_5SO_2NHC_6H_4X$ tend to produce downfield shifts in the ^{15}N resonance, but these effects only partially follow trends in pK_a[114].

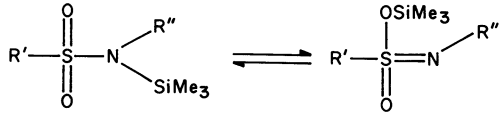
A correlation ($r = 0.976$) between σ_R^+ and δ ^{15}N for $XC_6H_4SO_2NH_2$ has been claimed[87] whereas other similar reports found no correlation between δ ^{15}N and the electronic properties of X[84,116].

In general, ^{15}N and ^{17}O chemical shifts in sulphonamides appear to be influenced by similar factors and follow similar trends[84].

An interesting study by Kricheldorf[117] showed that a methanesulphonamide titration with alkali could be followed by ^{15}N NMR. The ^{15}N chemical shift of $CH_3SO_2NH_2$ in H_2O at pH = 1 is δ − 284.4 and that of the anion $CH_3SO_2NH^-$ in 8 M NaOH solution is − 271.8 ppm. A plot of δ ^{15}N against pH gave a typical titration curve, with the inflexion at pH = 10.4–10.6.

4. ^{29}Si NMR

Bassindale and coworkers[118] used ^{29}Si NMR to determine the structures of N-silylated sulphonamides and derivatives. The ^{29}Si NMR chemical shifts of some silylsulphonamides are given in Table 33. The equilibrium under study is represented by equation 20. The tautomer **50** is the exclusive form when R″ is inductively electron-supplying. However, when R″ was Cl or NMe_2, substantial amounts of **51** were observed



(50) **(51)**

TABLE 33. ^{29}Si NMR chemical shifts of some silylated sulphonamides $R^1SO_2NR^2SiMe_3$ in C_6D_6[118]

R^1	R^2	δ(ppm)[a]
Ph	H	9.82
Ph	CH_3	14.18
Ph	Ph	14.22
Ph	Cl	9.74, 27.51
Ph	NMe_2	13.33, 26.96
Ph	$SiMe_3$	10.26[b] (and 25.89, − 3.24 minor)
p-$CH_3C_6H_4$	Cl	9.38, 27.13
CF_3	Ph	9.34

[a]Relative to internal TMS.
[b]Also reported[119] as δ + 10.0 ppm only in CH_2Cl_2.

with a lesser amount for R″ = $SiMe_3$. The ratio of **50**:**51** was 98:2 for $PhSO_2N(SiMe_3)_2$, 1:25 for $PhSO_2NClSiMe_3$, 1:1.75 for $PhSO_2N(NMe_2)SiMe_3$ and 1:1.3 for *p*-$CH_3C_6H_4SO_2NClSiMe_3$. The assignments of structure were based on a comparison of the ^{29}Si NMR chemical shifts of the sulphonamides compared with those of related model compounds. The equilibrium constants obtained allowed an estimate to be made of the S=N molar bond enthalpy as 325 kJ mol^{-1} [118].

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CHAPTER 6

Acidity

J. F. KING

Department of Chemistry, The University of Western Ontario, London, Ontario N6A 5B7, Canada

I. INTRODUCTION

Sulfonic acids constitute the most strongly acidic class of uncharged organic compounds. One of these, trifluoromethanesulfonic acid, CF_3SO_3H, is the strongest known neutral organic acid and, indeed, one of the strongest neutral monoprotic acids of any kind. Sulfonamides and sulfonimides with at least one hydrogen atom on the nitrogen are also acids in the ordinary sense and, in addition, sulfonamides are also sufficiently basic to be protonated by strong acids. This chapter takes up aspects of the acid–base equilibria of these species.

II. DEFINITIONS AND OTHER PRELIMINARIES

An acid in the Brönsted sense is defined as a species having a tendency to lose a proton. The acid strength or acidity of such an acid is defined in terms of the equilibrium 1 for the dissociation of the acid, most commonly in water. The dissociation, or ionization, constant K_a is defined by equation 2 where the subscripted *a* terms refer to the activities of these species. For some purposes activities may be replaced wholly or in part by concentration, and so we may also have equations 3 and 4. The (a) 'thermodynamic', (b) 'concentration' or 'classical' and (c) 'practical' or 'mixed' values, respectively K_a, K_a^c and K_a', become indistinguishable at zero ionic strength, and for many circumstances the differences between these constants are unimportant, often being less than experimental uncertainty. Provided due prudence is used in comparing results

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obtained by different methods or under different conditions, the 'practical' or 'mixed' constants, for example, are easily determined and can be as useful as the thermodynamic values for most of the purposes of the organic chemist. The term pK will therefore be used for $-\log K_a$, $-\log K_a^c$ or $-\log K_a'$, without distinction in this chapter.

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \tag{1}$$

$$K_a = \frac{a_{H_3O^+} \cdot a_{A^-}}{a_{HA}} \tag{2}$$

$$K_a^c = \frac{[H_3O^+][A^-]}{[HA]} \tag{3}$$

$$K_a' = a_{H_3O^+} \cdot \frac{[A^-]}{[HA]} \tag{4}$$

The strength of a base may be defined in terms of equilibrium 5 and the pK will refer to the acid strength of the conjugate acid, BH^+.

$$BH^+ + H_2P \rightleftharpoons B + H_3O^+ \tag{5}$$

The experimental determination of pK values is well described elsewhere[1,2], and many aspects of acid–base equilibria and their dependence on structure, medium and temperature have been ably presented in other places[3–5], and need not be repeated here.

III. ACIDITIES

A. Sulfonic Acids

The high acidity of sulfonic acids creates a problem in the quantitative determination of their acid strengths in water, the standard medium. Even with some of the weaker sulfonic acids like methanesulfonic acid, a 0.1 M solution of the acid is more than 99.8% ionized, and the precise determination of the components of the equilibrium can be difficult. Media other than water, of course, may be used for the determination of acid strength, and some of these will be discussed in this chapter. The loss of comparability with the vast body of acidity data for aqueous solutions, and the intervention of other problems such as ion pairing, are, however, serious disadvantages to the use of solvent media other than water, and considerable effort has been devoted to finding acceptable pK values for the aqueous system.

Covington and Thompson[6] studied the degree of ionization of some simple alkanesulfonic acids in water by laser Raman and ^1H NMR spectroscopies, and found reasonable agreement between the methods. They then obtained the equilibrium constants by a convergent double extrapolation procedure. The pK values obtained by this route for methanesulfonic, ethanesulfonic and 1-propanesulfonic acids are, respectively, -1.92, -1.68 and -1.53. These and other acids which can be labelled 'moderately strong' acids (pK range $+2$ to -2) are evidently amenable to study by these methods, but with stronger acids direct observation of the unionized forms becomes increasingly difficult, and the extrapolations longer, until ultimately the methods fail to yield useful results. Guthrie[7] has attempted to solve the problem by taking as his starting point the value of -1.92 for methanesulfonic acid and then using two procedures for estimating pK values for the stronger sulfonic and sulfuric acids. These procedures were in reasonable mutual agreement, and the values so obtained were averaged and tabulated by Stewart[3]; these are shown in Table 1. The errors in these values are estimated to be perhaps ± 0.2 pK_a units with the weakest and probably of the order of ± 1 units for the strongest acids.

TABLE 1. Estimated pK values in water of sulfonic and related acids[a]

Acid	pK
$PrSO_3H$	-1.5[b]
$EtSO_3H$	-1.7[b]
$MeSO_3H$	-1.9[b]
$4\text{-}MeC_6H_4SO_3H$	-2.7
$PhSO_3H$	-2.8
$HOSO_3H$	-3.0
CH_3OSO_3H	-3.5
$4\text{-}O_2NC_6H_4SO_3H$	-3.8
CF_3SO_3H	-5.5
FSO_3H	-5.6

[a]Except as otherwise noted, from Stewart (Reference 3, p. 17).
[b]Directly from Reference 6.

A few further points apropos of Table 1 may be noted. (a) The pK value for sulfuric acid so obtained (-3.0) agrees perfectly with Pauling's rule that ratio of first to second dissociation constants should be 10^5; the pK of HSO_4^- is 2.0. (b) The sulfonic acids in Table 1 show an acceptable correlation with the equation $pK = -1.9 - 1.26\sigma^{*}$[7]. (c) Comparison of these sulfonic acid pK values with those of the corresponding sulfinic acids[3] shows that the pK difference, $pK(RSO_2H) - pK(RSO_3H)$, is 4.1 ± 0.3.

Perhaps the best known method for investigating the acid strengths of very strong acids is to use Hammett acidity functions. The most extensive study by this procedure is that of Cerfontain and coworkers[8,9] whose results are summarized in Table 2. With aromatic sulfonic acids these workers looked at the changes in ultraviolet spectra with changes in the concentration of aqueous sulfuric acid, while with alkanesulfonic acids (and two of the arenesulfonic acids) they used ^1H NMR spectra; they also measured ^{13}C NMR spectra of benzenesulfonic acid. The spectroscopic data were plotted against various acidity functions and the correlation with H_0^a and H_A (from benzophenone and primary amides, respectively) deemed better than that with H_0 (from aromatic amines). The H_0^a values at half neutralization are listed in Table 2. The numbers in Table 2, however, are distinctly different from those in Table 1, being three to four units more negative. Kozlov and coworkers[10] have estimated pK values from solubility data and acidity functions and found values for arenesulfonic acids also in the -6 to -7 range. Very recently, however, Benoit and collaborators[11] have reexamined the ^{13}C NMR spectra of benzenesulfonic acid in aqueous sulfuric acid mixtures. They report their spectra to be the same as those of Cerfontain and coworkers[9b] but find that on treating their data using the excess acidity method of Cox and Yates[12] they obtain $pK = -2.53$, a value much closer to that in Table 1.

Whatever the relationship between the pK values in Table 1 and the H_0^a values at half-neutralization in Table 2, it seems likely that the relative values in Table 2 are significant. Hence the effect of substituents in arenesulfonic acids, found by Cerfontain to correspond to $\rho = 0.7$, points to an acid-strengthening effect of electron-withdrawing groups rather less than that in benzoic acids ($\rho = 1.00$). In accord with the picture that the pK values based on acidity functions are mutually consistent, Crumrine and coworkers have reported a correlation between these pK values and ^{33}S chemical shifts of the arenesulfonate anions[13].

As mentioned above, another approach to avoiding some of the difficulties associated with strong acids in aqueous solution, is to use another solvent. Dimethyl sulfoxide (DMSO) is an attractive alternative owing to (a) its good solvent properties, and (b) the

TABLE 2. Acidities of sulfonic acids in aqueous sulfuric acid solutions

Acid	H_0^a at half-neutralization
$MeSO_3H$	-6.2^a
$EtSO_3H$	-5.7^a
$PrSO_3H$	-6.3^a
$3\text{-}MeC_6H_4SO_3H$	-6.56^b
$4\text{-}MeC_6H_4SO_3H$	-6.62^b
$PhSO_3H$	-6.65^b, 6.56^c
$PhCH_2SO_3H$	-6.7^a
$4\text{-}BrC_6H_4SO_3H$	-6.7^a, -6.86^b
$4\text{-}C_6H_4(SO_3H)_2$	-6.8^a
$3\text{-}C_6H_4(SO_3H)_2$	-7.0^b

[a]From ^1H NMR spectra at 31 °C[9a].
[b]From UV spectra[8].
[c]From ^{13}C NMR spectra at 37 °C[9b].

large amount of data on acidities in DMSO, particularly that collected by the monumental efforts of Bordwell and coworkers[14]. Like water, however, DMSO is fairly basic and differences in the acidities of strong acids are not readily determined. Benoit and Buisson[15] reported a pK_{DMSO} of 1.76 for methanesulfonic acid, while McCallum and Pethybridge[16] have found pK_{DMSO} values for trifluoromethanesulfonic acid and methanesulfonic acid of 0.3 and 1.6, respectively.

A brief word may be in order here about the various pK values for aminosulfonic acids quoted in the standard compilations; the value of 3.25 for sulfanilic acid[17] may be taken to be typical. Sulfanilic acid, of course, exists almost entirely in aqueous solution as the zwitterion, $H_3\overset{+}{N}C_6H_4SO_3^-$, and the above p$K$ is that of the anilinium ion, $ArNH_3^+$, and not that of a sulfonic acid, $ArSO_3H$. The zwitterion structures would appear to be the only important forms for all aminosulfonic acids, including sulfamic acid[18] $H_3\overset{+}{N}SO_3^-$ and hydroxysulfamic acid[19] $HO\overset{+}{N}H_2SO_3^-$. This holds not only in water but also in DMSO, for sulfamic acid at least[18].

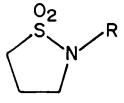
B. Sulfonamides and Sulfonimides

The acidity of sulfonamides is familiar to most organic chemists because it is the basis of the classical Hinsberg test for distinguishing primary from secondary amines. The prototypical sulfonamides, methanesulfonamide, $MeSO_2NH_2$, and benzenesulfonamide, $PhSO_2NH_2$, have pK values of 10.8 and 10.1, respectively, indicating sulfonamides to be weak acids comparable to, or slightly weaker than, phenols (pK of phenol, 10.0). The effect of various structural variations may be gauged from the pK values listed in Table 3. *N*-Alkylation, as in the conversion of $MeSO_2NH_2$ into $MeSO_2NHMe$ or of $PhSO_2NH_2$ into $PhSO_2NHCH_2Ph$, raises the pK in the four examples in Table 3, by 1.0 to 1.2 pK units, perhaps as a result of poorer solvation of $RSO_2\bar{N}R$ as compared to $RSO_2\bar{N}H$. *N*-Phenylation, as in $MeSO_2NH_2 \rightarrow MeSO_2NHPh$, leads to a ΔpK of about -1.7 pK units, as would be expected from the increased delocalization in the aromatic ring available in $RSO_2\bar{N}$—Ph. The effect is not as large as that which occurs on *N*-phenylation of ammonia, which may be estimated to be about 7 units (from the pK values of 27.7 and ~ 35 for aniline and ammonia as acids, given by Stewart[3]). The smaller ΔpK found with sulfonamides is not unreasonable in light of the evidence of N → S electron delocalization

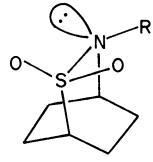
TABLE 3. pK values of sulfonamides in water

Sulfonamide	pK 20 °C	pK 25 °C	Reference
$CH_3SO_2NH_2$		10.80	20
$CH_3SO_2NHCH_3$		11.79	21
$CH_3CH_2SO_2NHCH_3$		11.84	21
$H_2NCOCH_2SO_2NH_2$		9.70	20
$H_2NCOCMe_2SO_2NH_2$		9.92	20
$PhSO_2NH_2$	10.07, 10.00, 10.00	10.11	21, 22, 23, 20
	(11.33)[a]		23
$4\text{-}H_2NC_6H_4SO_2NH_2$	10.51	10.69, 10.43	23, 20, 24
$4\text{-}MeOC_6H_4SO_2NH_2$	10.28		23
$4\text{-}MeC_6H_4SO_2NH_2$	10.21		23
$3,4\text{-}Me_2C_6H_3SO_2NH_2$	10.13		23
$3\text{-}Me\text{-}4\text{-}FC_6H_3SO_2NH_2$	10.06		23
$4\text{-}FC_6H_4SO_2NH_2$	9.99		23
$3\text{-}Cl\text{-}4\text{-}MeC_6H_3SO_2NH_2$	9.84		23
$4\text{-}ClC_6H_4SO_2NH_2$	9.79		23
$4\text{-}BrC_6H_4SO_2NH_2$	9.79		23
$3,4\text{-}Cl_2C_6H_3SO_2NH_2$	9.60		23
$3\text{-}O_2NC_6H_4SO_2NH_2$	9.34		23
$3,5\text{-}(O_2N)_2C_6H_3SO_2NH_2$	8.75		23
$PhSO_2NHCH_3$	11.43		23
	(12.65)[a]		23
1,3-Propane sultam (**1a**)	11.54	11.39	21
2,3-Thiazabicyclo[2.2.2]-octane 2,2-dioxide (**2a**)	11.65		25
1,4-Butane sultam (**3a**)	12.34	12.02	21
$CF_3SO_2NH_2$	6.33[b]		26
$CF_3SO_2NHCH_3$	7.56[b]		26
CF_3SO_2NHPh	4.45[b]		26
$CF_3SO_2NHC_6H_4\text{-}4\text{-}SO_2CH_3$	2.84[b]		26
CH_3SO_2NHPh	8.98		21
$PhSO_2NHPh$	8.40		23
	(9.98)[a]		23
$PhSO_2NHCH_2Ph$	11.25		23
	(12.53)[a]		23
$PhSO_2NHNH_2$	10.96		23

[a]In ethanol–water 50% by weight.
[b]Temperature unspecified.



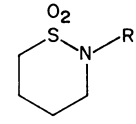
(1)



(2)

(a) R=H

(b) R=Me



(3)

in both sulfonamides and their conjugate bases, since to the extent that electrons are delocalized onto the sulfur the charge on the nitrogen is made more positive, and any tendency for the nitrogen to donate electrons into the phenyl ring accordingly lessened. Perhaps the simplest evidence for N → S delocalization in both a sulfonamide and its conjugate base is that from S—N bond lengths as determined by X-ray crystallography. Cotton and Stokely[27] report the S—N bond lengths of $(PhSO_2)_2NH$ and $(PhSO_2)_2\bar{N}Na^+$ to be, respectively, 1.65 and 1.58 Å, both well below the 1.7 Å (or more) that one may estimate for the S—N single bond from covalent radii or analogous methods.

The acid-strengthening effect of electron-withdrawing substituents in various arenesulfonamides is illustrated in Table 3. These results may be summarized by the expression $pK = 10.00 - 1.06\Sigma\sigma''$ found by Willi[22], and $pK = 10.05 - 0.93\Sigma\sigma$ obtained by Dauphin and Kergomard[23a] for the sulfonamides of general structure $ArSO_2NH_2$ in water at 20 °C. Dauphin, Kergomard and Verschambre[23b] have determined pK values for a large number of sulfonamides with aromatic rings. Because of the low solubility of many of these compounds in water most of the pK determinations were made on ethanol–water solutions. Some of their results are summarized below (all in EtOH–H_2O, 50% by weight).

$$ArSO_2NH_2\text{: } pK = 11.34 - 1.45\Sigma\sigma$$

$$PhSO_2NHAr\text{: } pK = 9.94 - 2.61\sigma$$

TABLE 4. Acidities of *N*-sulfonyl and *N*-acyl sulfonamides in water

Compound	pK 20°C	pK 25°C	References
Benzene-1,2-disulfonimide (**5**)	−4.1[a]		21
Ethane-1,2-disulfonimide (**6**)	−3.1[a]		21
Propane-1,3-disulfonimide (**7**)	−1.7[a]		21
Saccharin (**4**)	1.6, 1.2[a]	1.8	29
$PhSO_2NHSO_2Ph$	1.79, 1.45, −1.8[a]		21, 23, 21
$MeSO_2NHSO_2Ph$	1.76, −1.6[a], −1.7[a]		21
$MeSO_2NHSO_2Me$	2.10[b], −1.3[a], −1.7[c]	1.36	21
$EtSO_2NHSO_2Et$		2.04	21
Compound **8**		2.88	20
		11.00	20
Compound **9**		4.51	20
$MeNHCOCH_2SO_2NHCONH_2$		4.89	20
$MeSO_2NHCOMe$	5.13		21
$H_2NCOCH_2SO_2NHCONH_2$		5.05	20
$MeSO_2NHCONH_2$		5.10	20
$H_2NCOCMe_2SO_2NHCONH_2$		5.15	20
$H_2NCOCHMeSO_2NHCONH_2$		5.21	20

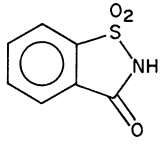
[a] H_0 at half-neutralization determined by UV spectra for **4**, **5**, $(PhSO_2)_2NH$, and $MeSO_2NHSO_2Ph$ (−1.7), and ^1H NMR for **6**, **7**, $(MeSO_2)_2NH$ and $MeSO_2NSO_2Ph$ (−1.6), using the H_0 values of Jorgenson and Hartter[28].
[b] Blaschette[30] reported $pK = 2.85$ for the pH at half-neutralization uncorrected for hydrolysis.
[c] Estimated by the excess acidity method.

$$PhCH_2SO_2NHAr: pK = 10.18 - 2.36\sigma$$

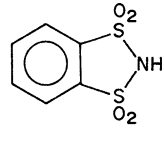
$$ArSO_2NHPh: pK = 9.98 - 1.66\Sigma\sigma$$

Trepka and coworkers[26] found that the trifluoromethyl group attached to the sulfonyl made the sulfonamide more acidic than its methyl-substituted counterpart by about 4 pK units. A series of sulfonamides of general structure CF_3SO_2NHAr showed[26] a good correlation with the expression $pK = 4.42 - 2.15\sigma$ (with $r = 0.994$). Trepka and coworkers also found in their series of sulfonamides that the pK value in water correlated very well with the half-neutralization potential determined in 67% dimethylformamide–water, and from this they calculated pK values for a further eighteen sulfonamides with CFH_2, CF_2H and CF_3 groups[26].

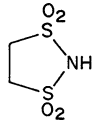
N-Acyl and *N*-sulfonyl sulfonamides also display acid–base chemistry of interest. Saccharin (**4**) is perhaps the best known member of this class of compounds, the pK values of which are summarized in Table 4. The most obvious feature of this list is that, as one would predict, these compounds are generally distinctly more acidic than the sulfonamides in Table 3, and that some are 'strong' acids by just about any measure. Benzene-1,2-disulfonimide (**5**) has been described[31] as 'fully ionized in (and not extractable from) water', and the H_0 value at half-neutralization of -4.1 indicates **5** to be among the strongest neutral nitrogen acids, though bis(tricyanovinyl)amine would appear from its H_0 value at half-neutralization (-6.0) to be stronger[32].



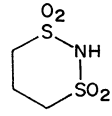
(**4**)



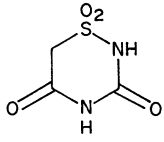
(**5**)



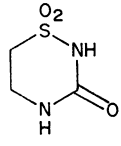
(**6**)



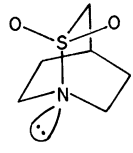
(**7**)



(**8**)



(**9**)



(**10**)

As one might expect from the greater acidity of sulfonamides vs carboxylic amides (pK ~ 15, see Reference 3), the introduction of the second sulfonyl group increases the acidity more than that of an acyl group. This may be seen by comparing **5** with saccharin (**4**), or the sulfonimides, $MeSO_2NHSO_2Me$ (pK 1.36 at 25 °C) and $EtSO_2NHSO_2Et$ (pK 2.04), with $MeSO_2NHCONH_2$ (pK 5.10), or $MeSO_2NHCOMe$ (pK 5.13) (all by titration).

Recalling the hazards of comparing H_0 values at half-neutralization with pK values determined by titration in water, as discussed in the previous section, we determined[21] some of these pKs by both titration and spectrometric methods. Though the values for saccharin obtained by the different methods were of the same order of magnitude, those for the sulfonimides differed typically by about 3 pK units. With $MeSO_2NHSO_2Ph$, for example, titration in our hands gave 1.76, UV spectroscopy −1.7, and ^{1}H NMR −1.6; titration of $(MeSO_2)_2NH$ yielded 2.10, while NMR gave −1.3 as the H_0 at half-protonation, and −1.7 by excess acidity calculations[12]. The discrepancy between titration and spectrometric results may be ascribed[3] to the difference between dissociation constants (measured by the former) and ionization constants (determined by the latter); obviously comparisons among results from different techniques should only be made with great care (if at all).

An interesting result in Table 4 is the acid-strengthening effect of incorporating these functions in a five-membered ring. Both the benz-fused and saturated 5-ring disulfonimides (**5**) and (**6**) with H_0 values at half-protonation of −4.1 and −3.1, are more acidic than either their acyclic counterparts $(PhSO_2)_2NH$ (−1.8) and $(MeSO_2)_2NH$ (−1.3), respectively, or the six-membered cyclic analogue, **7** (−1.7). The pK of saccharin (however measured) is low when compared to that of $MeSO_2NHCONH_2$ (5.10 at 25 °C) or $MeSO_2NHCOMe$ (5.13 at 20 °C); it seems unlikely that the aromatic substituent by itself accounts for the > 3 pK unit difference. It is quite possible that a stereoelectronic factor[35] is involved; the point is under investigation[21].

C. Protonated Sulfonamides

Sulfonamides are well known to be very weak bases, but the amount of quantitative information on the topic is not large. Lemaire and Lucas[33] estimated a pK for *p*-toluenesulfonamide of −3.2 in glacial acetic acid, using spectroscopic measurements and a version of H_0. Laughlin[34] employed ^{1}H NMR spectra and the H_0 scale of Jorgenson and Hartter[28] to find H_0 values at half-neutralization for *N*-methyl-, *N*-ethyl- and *N*,*N*-dimethylmethanesulfonamides. Recently, in connection with an investigation of stereoelectronic factors in sulfonamides and other derivatives of sulfonic acids[35], we have examined some cyclic sulfonamides[25] using Laughlin's method, and our values along with Laughlin's are included in Table 5. There are no aromatic sulfonamides in Table 5; Laughlin was unable to determine the pK of *p*-toluenesulfonamide by his procedure, but concluded that 'protonation appears to be essentially complete by $H_0 = -7$' and

TABLE 5. Acidities of protonated sulfonamides[a]

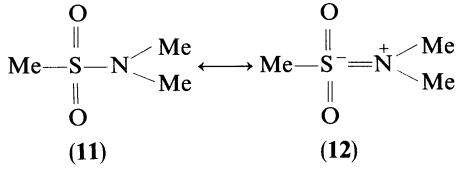
Conjugate base	H_0 at half-neutralization	Reference
$MeSO_2NHMe$	−6.0	34
$MeSO_2NHEt$	−6.0	34
$MeSO_2NMe_2$	−5.5, −5.5	25, 34
N-Methyl-1,3-propane sultam (**1b**)	−4.0	25
N-Methyl-1,4-butane sultam (**3b**)	−4.6	25
N-Methyl-2,3-thiazabicyclo[2.2.2] octane 2,2-dioxide (**2b**)	−3.6	25
2,1-Thiazabicyclo[2.2.2]octane 2,2-dioxide (**10**)	−4.0[b]	25

[a]At 20 °C in aqueous sulfuric acid, determined from ^{1}H NMR spectra, using the H_0 scale of Jorgenson and Hartter[28].

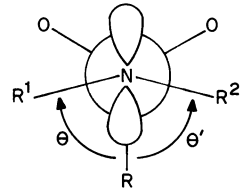
[b]The excess acidity method[12] also gave this value[25].

suggested a pK value between -5 and -6. In our hands N-aryl sulfonamides were clearly much less basic than N-alkyl, and seemed to be significantly protonated only at the highest acidities ($H_0 \leqslant -8$).

It had already been shown[36] from the multiplicity of the ^{1}H NMR signals in fluorosulfuric acid that N-methyl- and N,N-dimethyl-p-toluenesulfonamides were protonated on the *nitrogen* and not the oxygen atoms of the sulfonamide function. Laughlin carried out similar experiments with the N-methyl-, N-ethyl- and N,N-dimethylmethanesulfonamides, and found splitting appropriate to n-protonation; he was careful to note, however, that his results did not exclude the presence of a small amount of the O-protonated tautomer. Laughlin further went on to suggest that the difference in acidity between $RSO_2\overset{+}{N}HR'$ and $R_3\overset{+}{N}H$ (about 16 pK units) was too large to be accounted for on the basis of an inductive effect, and argued that these results indicate that N→S delocalization of electrons (i.e. **11** ⟷ **12**) is important in sulfonamides. Evidence for such a picture had, of course, been presented both before and since[37–39] with some of this[38,39] pointing to the existence of a preferred conformation, shown in **13**, in which the sulfonamide is viewed in a Newman projection along the S—N bond; the key characteristic of this conformation is that the orbital containing the free electron pair on the nitrogen atom is aligned *anti*-periplanar to the C—S bond. Evidence for this picture, which is closely parallel to that for sulfonyl carbanions (see Reference 37 and the numerous papers cited), has been provided by X-ray structural studies by Lipscomb and coworkers[38], and by Jennings and Spratt's observation[39] of an energy barrier to rotation around the S—N bond in Me_2NSO_2Cl. We found[35] from a search of the Cambridge Crystallographic Data Base that for most sulfonamides the dihedral C—S—N—C angle θ (and θ') (defined in **13**) is in the range 60–120°, with none less than 50° (except for some aziridine derivatives in which the *anti*-periplanar alignment of the non-bonded electron pair simply gives a small value of θ). This suggested that if the most favorable arrangement for N→S delocalization occurs when $\theta \sim 80°$, then a sulfonamide in which θ was required to be $\sim 0°$ would have less N→S delocalization and that this might be expected to show itself in increased base strength in the sulfonamide. Accordingly we have synthesized some sultams (**1**–**3**) and compared their H_0 values at half-neutralization with those of some acyclic analogues. The bicyclic sultam **2b** in which $\theta = 0°$ (and $\theta' \sim 170°$) was indeed found to be distinctly more basic than its acyclic counterpart, N,N-dimethylmethanesulfonamide, perhaps by a factor approaching two orders of magnitude.



(**11**) (**12**)



(**13**)

Another bicyclic sultam, **10**, has also been synthesized with an eye to seeing what effect, if any, is produced on the base strength by placing the nitrogen atom at the bridgehead of a

[2.2.2]bicyclic array. The experiment is reminiscent of one reported by Doering and Levy[40] with a [2.2.2]bicyclic trisulfone, which was found to be quite acidic, but not as much so as its acyclic analogue tris(methylsulfonyl)methane. In the case of **10**, its H_0 value at half neutralization (−4.0) points to a distinct but not dramatic difference in base strength when compared, say, to that of $MeSO_2NMe_2$ (−5.5), and that much and perhaps all of this is ascribable to inhibition of N→S delocalization.

IV. ACKNOWLEDGEMENTS

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CHAPTER 7

Acidity, hydrogen bonding and metal complexation of sulfonic acids and derivatives

NAOMICHI FURUKAWA and HISASHI FUJIHARA

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

I. INTRODUCTION

Sulfonic acids represented by the general formula RSO_3H are found in nature. Examples are the amino acids taurine (**1**) and cysteinic acid (**2**)[1].

$^{+}NH_3CH_2CH_2SO_3^{-}$ (**1**)

$^{-}O_3SCH_2CHCO_2H$ with NH_3^{+} on the CH (**2**)

The preparation of aromatic sulfonic acids (R = Aryl) has been studied extensively as one of the main industrial processes like nitration or halogenation. A variety of aromatic

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sulfonic acids has been used as industrially important starting materials for dyes, detergents, surfactants, sweeteners and various ingredients of drugs for more than a century. In particular, most of the modern synthetic surfactants and detergents are derived from the sodium salts of alkylbenzenesulfonic acids or monosulfates bearing alkyl chains longer than ten carbons (ABS). Recently, several ammonium and phosphonium sulfonate salts have been utilized as phase transfer catalysts in synthetic organic chemistry[2] while sodium or potassium salts of sulfonic acids have also been utilized as anionic surfactants which can readily transfer organic substances into an aqueous phase.

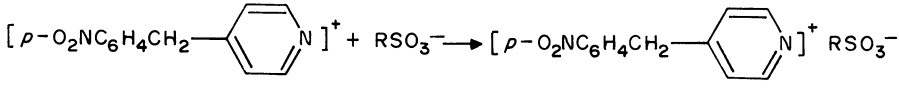
Since the $-SO_3H$ group is extremely hygroscopic (hydrophilic) and, upon dissolution in water, the acid shows strong acidity similar or higher than that of inorganic acids such as HCl or H_2SO_4, sulfonic acids are hardly handled in the presence of air. However, the sodium salts of sulfonic acids are readily prepared and purified. They are quite stable, and consequently the acids are utilized after conversion to their sodium salts. Although most sulfonic acids are very hygroscopic, acidic media decrease their solubility in water and they are crystallized from aqueous acidic media generally as the hydrates. Aminobenzenesulfonic acids, however, are zwitterionic and are slightly soluble in water, serving as exceptions among analogous acids. It is known that the crystallization water is hydrogen-bonded to the SO_3H group and can be removed from the hydrates as an azeotropic mixture upon reflux of the benzene solution of the acids. Hence, they are utilized as effective catalysts for dehydration and condensation reactions such as esterification or acetalization. Alkali metal or ammonium salts of the acids are highly soluble in water and are easily handled for synthetic purposes. In contrast, alkaline earth metal salts or heavy metal salts are hardly soluble in water, giving crystalline precipitates. In order to determine the structures of sulfonic acids, they are usually converted to the stable and easily handled onium sulfonate salts, e.g. benzylthiuronium salts (**3**)[3], *p*-toluidinium salts (**4**) and *N*-*p*-nitrobenzylpyridinium salts (**5**) of various sulfonates[4]. These are readily prepared and have sharp melting points, and are therefore utilized for identification of sulfonic acids.

Thallium salts of sulfonic acids also have sharp melting points and have been utilized for identification of sulfonic acids for a long time[5]. The reactions are illustrated in equations 1–3 and several examples are shown in Table 1.

$$RSO_3Na + [PhCH_2SC(NH_2)_2]^+Cl^- \longrightarrow \underset{\textbf{(3)}}{[PhCH_2SC(NH_2)_2]^+RSO_3^-} + NaCl \qquad (1)^3$$

$$p\text{-}TolNH_3^+ + RSO_3Ag \longrightarrow \underset{\textbf{(4)}}{[p\text{-}TolNH_3^+]RSO_3^-} \qquad (2)$$

p-Tol = p-$CH_3C_6H_4$



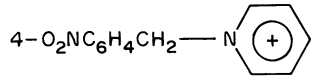
(**5**) $(3)^4$

This chapter describes the acidity and hydrogen-bonding properties of sulfonic acids and their derivatives including metal complexation.

II. ACIDITY OF SULFONIC ACIDS

Sulfonic acids dissociate completely in water, indicating that they are extremely strong acids, as strong as sulfuric acid. The acid dissociation constants or pK_a values of many sulfonic acids were estimated a long time ago. Since they completely dissociate in normal protic solvents, the measurement of their dissociation constants requires special techni-

TABLE 1. Melting points of sulfonates [$RSO_3^-X^+$] used for analysis

R[a]	X^+	mp(°C)	Reference
2-Tol	$[PhCH_2SC(NH_2)_2]^+$	179.5–180.5	3
3-Tol	$[PhCH_2SC(NH_2)_2]^+$	155–156	3
4-Tol	$[PhCH_2SC(NH_2)_2]^+$	182	3
4-$CH_3OC_6H_4$	$[PhCH_2SC(NH_2)_2]^+$	158–160	3
Ph		168	4
2-Tol		170	4
2-NaPh		148.5	4
2-Tol	Tl^+	213–216	5
4-Tol	Tl^+	226–228	5
2,5-$Me_2C_6H_3$	Tl^+	217–219	5
4-ClC_6H_4	Tl^+	258–260	5
4-BrC_6H_4	Tl^+	274–276	5
2-$O_2NC_6H_4$	Tl^+	226–228	5
4-$O_2NC_6H_4$	Tl^+	284–285	5

[a]Tol = MeC_6H_4; Naph = Naphthyl.

ques, such as measuring the acidity in strong acidic media which are protonated by the sulfonic acids.

Earlier, Hantzch and Weissberger[6] and Oswald[7] estimated that *p*-toluenesulfonic acid is more acidic than sulfuric acid but less acidic than perchloric acid. Fiertz and Weissenbach[8] reported that benzenesulfonic and α-naphthalenesulfonic acids have pK_a values of 0.6 and 0.74, respectively. Starting in the 1950s, spectroscopic methods such as IR, UV, NMR and conductivity measurements in solution were applied, and the pK_a values of strong acids could be determined by using a stronger acid, such as sulfuric or perchloric acid as a solvent in order to prevent the leveling effect observed normally in the ordinary basic solvents. By these procedures, Hammett and Dayrup[9] and Bascombe and Bell[10] reported the pK_a values of benzene- and methanesulfonic acids. Gillespie determined the dissociation constant (K_b) of benzenesulfonic acid using freezing point depression of sulfuric acid containing the sulfonic acid and then using the Hammett H_0 function (equation 4)[11].

$$PhSO_3H + H_2SO_4 \overset{K_b}{\rightleftharpoons} [PhSO_3H_2^+][HSO_4^-] \tag{4}$$

$$K_b(PhSO_3H) = \frac{[PhSO_3H_2^+][HSO_4^-]}{[PhSO_3H]}$$

The reported K_b values of benzenesulfonic and *p*-toluenesulfonic acids were 0.011 and 0.026, respectively. However, although sulfonic acids are known to be strong acids, their acidities are not known accurately and the reported pK_a values differ appreciably depending on the methods employed for the measurements. Recently, Cerfontain and coworkers[12] have studied extensively the acidities of strong acids, including various sulfonic acids, using UV, ^1H and ^{13}C NMR spectroscopy in concentrated sulfuric acid by using the $H_0{}^a$ acidity function[13], which is based on benzophenone ($-5.8 < H_0{}^a < -6.8$) rather than the H_0 acidity function applied by Gillespie.[11] Reliable pK_{BH} values were

TABLE 2. pK_{BH} values of sulfonic acids RSO_3H[12a]

R	pK_{BH}[a]
Me	-6.0 ± 0.3
Et	-5.8 ± 0.3
$CH_3(CH_2)_2$	-6.2 ± 0.3
$CH_3(CH_2)_3$	-6.5 ± 0.2[12b]
Ph	-6.65 ± 0.06 (-12.3 ± 0.1, $PhSO_3H_2^+$)
p-BrC_6H_4	-6.5 ± 0.2
p-$C_6H_4(SO_3H)_2$	-6.6 ± 0.2
m-$C_6H_4(SO_3H)_2$	-6.8 ± 0.3

[a]The pK_{BH} value was measured by using the acidity function H_0[a].

determined by using equation 5, and the values obtained are summarized in Table 2.

$$RSO_3H + B \rightleftharpoons RSO_3^- + BH^+; \qquad \log[BH^+]/[B] = -H_0{}^a + pK_{BH} \tag{5}$$

In another approach for measuring the pK values of benzenesulfonic acid, an ^{13}C-NMR method was employed: the difference in the chemical shifts of a given carbon ($\Delta\delta$) in the aromatic ring of the acid (the difference between δ of C_2 or C_4 and δ of C_3) was plotted against $H_0{}^a$ at concentrations of sulfuric acid from 0 to 100%. Similarly, by using $H_0{}^a$ and a UV technique, the ionization of anilinium acids (o-, m-, p-$^-SO_3C_6H_4NH_3^+$) was studied together with the acidity of their oxygen-bound proton. The substituent effect on the ionization was found to be small and the ρ value (using σ constants) is -0.7 ± 0.1[14]. In addition to these values, several other pK_a values are available in the literature, e.g. the pK_a of p-toluenesulfonic acid: -5.4 (in ACOH-H_2O)[15]; -4.1 (by solubility)[16]; -6.2 (using $H_0{}^a$)[12]; -1.3 (by NMR)[17].

Covington and Thompson[18] reported the most reliable pK_a value of methanesulfonic acid in water to be -1.92, which is employed as a standard pK_a value of this acid.

Guthrie[19] assumed that the pK_a values of various sulfonic acids should be correlated with the σ^* values of the substituents R in RSO_3H, provided that both electronic and steric effects are identical in the dissociations of phosphonic (alkyl and aryl phosphates) and sulfonic acids. The acid dissociation of phosphonic acids has been known to correlate with Taft's σ^*[19]. By applying this assumption together with a pK_a of -1.92 for methanesulfonic acid, the linear free-energy relationship of equation 6 was deduced for sulfonic acids and could be used for obtaining pK_a values of sulfonic acids. The pK_a values thus obtained are summarized in Table 3 together with those of several other strong acids. The Taft plot of equation 6 and that for the acid dissociation of phosphonic acids are shown in Figure 1.

$$pK_a(\text{sulfonic acids}) = -1.92 - (1.26 \pm 0.07)\sigma^* \tag{6}$$

As shown in Table 3, sulfonic acids are either identical in strength to, or stronger than, most inorganic acids. Trifluoromethanesulfonic and fluorosulfonic acids are particularly strong acids. Therefore, sulfonic acids have been used in organic chemistry as simple acids whereas the sulfonate groups were used as good leaving groups in both S_N1 and S_N2 substitution[20] and in elimination reactions. For example, trifluoromethanesulfonic acid (triflic acid) is utilized widely in modern organic chemistry since it is quite stable and the triflate anion is a very good leaving group, as shown by the 10^4 times faster elimination of triflate than p-tosylate[21].

The chemical and physical properties of trifluoromethanesulfonic acid and derivatives were thoroughly reviewed[22]. Since triflate has a good leaving ability, alkyl triflates can be used for the determination of nucleophilicities of weak nucleophiles such as arylsulfonate

TABLE 3. pK_a values for sulfonic acids[a]

Acid	pK_a
H_3O^+	−1.74
$CH_3OH_2^+$	−2.18
$CH_3CH_2SO_3H$	−1.68
CH_3SO_3H	−1.92
p-$MeC_6H_4SO_3H$	−5.4[b]
	−4.1[c]
	−6.2[d]
	−1.3[e]
$C_6H_5SO_3H$	−2.8
p-$BrC_6H_4SO_3H$	−3.1
p-$O_2NC_6H_4SO_3H$	−4.0
CF_3SO_3H	−5.9
$ClSO_3H$	−6.0
FSO_3H	−6.4
$HClO_4$	−5.0
H_2SO_4	−2.8
CH_3OSO_3H	−3.4
H_3PO_4	2.12 ($pK_2 = 7.21$)
CH_3COOH	4.76

[a]Reference 19a; pK_a values are all in water at 25 °C.
[b]Reference 15.
[c]Reference 16.
[d]Reference 12.
[e]Reference 17.

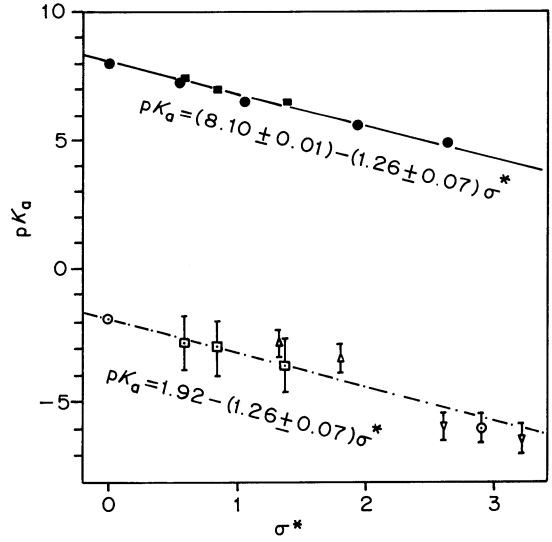


FIGURE 1. pK_a vs σ^* plots for phosphonic and sulfonic acids: (——) least-squares line for alkylphosphonic acid pK_2, (●) alkylphosphonic acids, (■) arylphosphonic acids; (–···–) predicted line for sulfonic acids; (○) alkylsulfonic acids, (□) arylsulfonic acids, (▽) halosulfonic acids, (△) sulfuric acid and monomethyl sulfate

TABLE 4. Substituent effects of $ArSO_3^-$ for the S_N2-type reactions[23]

$$XC_6H_4SO_3^-Bu_4N^+ + MeOSO_2CF_3 \xrightarrow{MeCN} CF_3SO_3^- + MeOSO_2C_6H_4X$$

X	$k_2 \times 10^5$ (l mol^{-1} s^{-1}) (at -23.6 °C)	$\Delta H^{\#}$ (kcal mol^{-1})	$\Delta S^{\#}$ (eu)
p-MeO	1.143	13.9 ± 0.3	-11.5 ± 0.8
p-Me	0.955	14.1 ± 0.2	-10.9 ± 0.6
H	0.681	14.2 ± 0.2	-11.4 ± 0.4
p-F	0.383	14.4 ± 0.1	-11.5 ± 0.4
p-Cl	0.300	14.3 ± 0.2	-12.4 ± 0.6
m-NO_2	0.071	14.9 ± 0.3	-12.8 ± 0.9
p-NO_2	0.081	14.7 ± 0.2	-13.5 ± 0.5

anions in S_N2 reactions. Data on how the substituent affects the nucleophilicity of $ArSO_3^-$ ions in the second-order S_N2-type substitution of methyl triflate with *m*- and *p*-substituted arylsulfonate anions in acetonitrile are given in Table 4. The k_2 values were correlated well with Hammett σ values giving a ρ value of -1.180 ± 0.065 (at -23.6 °C) which resembles the value of -1.09 ± 0.05 obtained in the reaction of the silver sulfonate with MeI in acetonitrile, suggesting that the degree of bonding by sulfonates to the methyl carbon is virtually identical for attack on either Me-I^+-Ag complex or $MeOSO_2CF_3$[23].

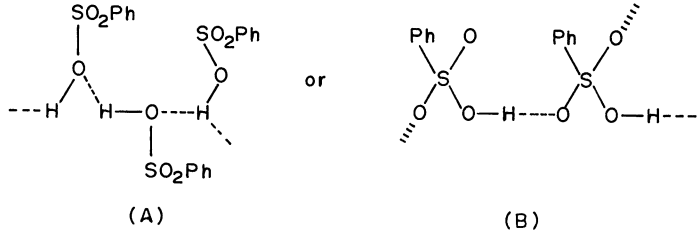
Solvolysis of both 1- and 2-adamantyl arenesulfonates revealed that the arenesulfonates displayed identical nucleofugacities, though the two reactions show enormous rate differences[24].

Other literature data on the usefulness of triflates and related sulfonates for organic synthesis can be found in Reference 25.

III. HYDROGEN BONDING AND COMPLEXATION OF SULFONIC ACIDS AND DERIVATIVES

Hydrogen bonding and metal complexation of organic sulfur compounds have been reported in two former review articles in the Chemistry of Functional Groups series[26]. Sulfonic acids are capable of completely protonating organic substrates in protic media with formation of stable sulfonate anions as shown in the previous section.

However, the strong proton donor ability of the sulfonic acids suggests that the acids will loosely associate by hydrogen bonding with weak basic compounds or with proton



(A) (B)

FIGURE 2. Association of benzenesulfonic acid via intermolecular hydrogen-bonding

acceptors in aprotic media. Observation of inter- or intra molecular association of sulfonic acids and their derivatives has been recognized by freezing point depression or by direct methods such as UV, IR and ^{1}H NMR spectroscopy. X-ray crystallographic analysis or neutron diffraction study reveals more distinctly associations due to hydrogen bonding and to metal complexation of the acids. In an earlier measurement of the freezing point depression of benzene solution, it was suggested that benzenesulfonic acid associates in dilute solution via a polymeric intermolecular hydrogen-bonding net work similarly to phenols or alcohols, but not via dimer formation like carboxylic acids. Two association modes (A and B) including water are possible as shown in Figure 2[27].

A. Detection of Hydrogen Bonding of Sulfonic Acids by Infrared Spectroscopy

IR spectroscopy has been widely utilized as a tool to detect formation of hydrogen bonding or protonation in many compounds bearing acidic protons.

Studies of sulfonic acids by IR spectroscopy were started in the 1950s and have disclosed that sulfonic acids have characteristic absorption bands at regions similar to those of sulfones. They display two characteristic stretching vibration bands due to the SO_2 group, namely $\nu_{asym(SO_2)}$, $\nu_{sym(SO_2)}$ and ν_{SO} in addition to the stretching frequency band of the OH group which represents either a free or an associated form. Baxter and coworkers[28] discussed the formation of an intramolecular hydrogen-bonding between the sulfonyl oxygen atom and the imino nitrogen atom in *N*-*p*-diphenyl-*N*-2′-hydroxyethyltoluene-*p*-sulfonamide. Haszeldine and Kidd[29] discovered the formation of intermolecular hydrogen-bonding of methanesulfonic and trifluoromethanesulfonic acids. Detoni and Hadzi[30a] and Tipson[30b] reported that sulfonic acids display the stretching frequency bands at around 2900 (ν_{OH}, free), 2350 (ν_{OH}, associated); 1350 ($\nu_{asym(SO_2)}$), 1060 ($\nu_{sym(SO_2)}$); 900 (ν_{SO}) cm^{-1}. They also found that the hydrated forms of trifluoromethanesulfonic and *p*-toluenesulfonic acids show $\nu_{asym(SO_2)}$ stretching frequencies at lower wave numbers compared with the corresponding anhydrous acids, due mainly to hydrogen bonding between the SO_3H group and water molecules, i.e. the absorptions of anhydrous CF_3SO_3H at 1471, 1460 ($\nu_{asym(SO_2)}$); 1131 ($\nu_{sym(SO_2)}$) cm^{-1} shift to 1274 ($\nu_{asym(SO_2)}$), 1030 ($\nu_{syml(SO_2)}$) in the hydrate. These ν_{SO_2} stretching bands disappear upon conversion of the acids to the corresponding salts. Generally, the hydrated sulfonic acids display absorption bands at around 2600–2250 cm^{-1} due to $—SO_2—OH———H_2O$ hydrogen bonds and at 1680 cm^{-1} due to the H_3O^+ species.

Extensive IR and Raman spectroscopic investigations on sulfuric and sulfonic acids XSO_2OH (X = F, Cl, OH, Me) have been conducted by Savoie and Giguere[31], Gerding and Maarsen[32], Gillespie and Robinson[33], Simon and coworkers[34], Stafford and coworkers[35] and others[36,37]. These studies have demonstrated clearly that methanesulfonic acid and its derivatives associate strongly via hydrogen bonding at the liquid state and that the strength of the hydrogen bonds decreases or these bonds disappear when the acid is in the gas phase. The extent and strength of the hydrogen bonds depend remarkably on the electronegativity of the substituents attached to the central sulfur atom. These substitutent effects are reflected in the frequency mode of the IR bands. For example, Stafford and coworkers have described the distinct substituent effects on the hydrogen bonding of sulfonic acids[35]. They measured the IR spectra of sulfonic acids (**6a–d**) at the liquid state both at room termperature and at higher temperatures up to 120 °C and for **6d** also in the gaseous state. Typical IR absorptions of acids **6** are summarized in Tables 5 and 6 together with data for several other derivatives and the Raman spectra of **6d**[35,38–41].

$$RSO_2OH$$

(6)

(a) R = F, **(b)** R = Cl, **(c)** R = OH, **(d)** R = CH_3

TABLE 5. IR absorptions (in cm^{-1}) of CH_3SO_3H (**6d**) and related derivatives

Compound	S—(OH)stretch		SO_2 stretch				OH stretch	
	liquid	gas	liquid	$\nu_{asym(SO_2)}$ gas	liquid	$\nu_{sym(SO_2)}$ gas	liquid	gas
FSO_2—OH (**6a**)	956	897	1440	1491	1230	1234	3125	3602
$ClSO_2$—OH (**6b**)	918	852	1400	(1438)[a]	1190	(1218)[a]	—	—
$HOSO_2$—OH (**6c**)	973	883	1368	1450	1170	1224	2970	3610
CH_3SO_2—OH (**6d**)	900	897	1350	1403	1174	1203	2997	3610
HO—ClO_4							3275	3560
FSO_2F				1502		1269		
$ClSO_2Cl$			1410	1434	1182	1205		
$CH_3SO_2CH_3$			1310	1357	1143	1165		

[a]Estimated values.

TABLE 6. Infrared and Raman absorptions of CH_3SO_3H (cm^{-1})

Raman	Infrared		Description[a]
	liquid	gas	
772	767 ms	760 s	S—C str. (assoc.)
		829	S—OH str. (mono.)
904	900 vs	891 s	S—OH str. (assoc.)
1122	1140, 1150	1122 m	S—OH bend
1174	1174 vs		SO_2 sym str. (assoc.)
		1203 s	SO_2 sym str. (mono.)
1350	1350 s		SO_2 asym str. (assoc.)
		1403	SO_2 asym str. (mono.)
2945	2945 w.sh		CH sym str.
	2977 s, vb		—OH str. (assoc.)
3032	3036 w, sh		CH asym str.
		3610	—OH str. (mono.)

[a]Here str. denotes stretching vibration, assoc. denotes associated form and mono. denotes monomeric form.

The wave numbers of the $\nu_{asym(SO_2)}$, $\nu_{sym(SO_2)}$ and ν_{SO} bands were plotted against the average electronegativity (X) of the two substituents A and B in ASO_2B, $X = [x + y]/2$ (x and y are the electronegativities of A and B) proposed by Allred[42] (Figure 3). Three conclusions emerged: (1). Both the OH and SO_2 stretching bands of the acids (**6**) move to higher frequencies while that of SO moves to a lower frequency in passing from the liquid to the gaseous state, indicating that the acids associate by hydrogen bonding in the liquid state. (2) The extent of the frequency shifts depends mainly on the strength of the hydrogen bonding. The higher value of ν_{SO_2} for H_2SO_4 must be due to a higher degree of association compared with that of other acids. (3) The larger frequency shift of methanesulfonic acid in the gas phase as compared with fluorosulfonic acid suggests that the intermolecular hydrogen-bonding ability of the former acid is stronger than that of the latter acid, indicating that less electronegative substituents on sulfur atom increase the basicity of the sulfuryl oxygen atoms and hence lead to stronger hydrogen bonding[43].

In the course of studies intended to elucidate the nature of various hydronium ions, such as H_3O^+, $H_5O_2^+$, and the strength of hydrogen bonding formed between systems composed of strong acids and bases, such as N-oxides, Zundel and his coworkers have disclosed the nature of the hydrogen bonds formed between methane- and substituted arylsulfonic acids with weak bases such as sulfoxides, phoshine oxides and N-oxides by using an IR spectroscopic method[44a]. According to Zundel and coworkers[44], if one draws an energy diagram for hydrogen bonding formed by a combination of strong acids and weak bases and by plotting an appropriate parameter, e.g. the intensity of IR stretching frequency against the O—H----O bonding distance where O—H and O represent the donor (sulfonic acids) and acceptor (bases), respectively, it may take either one of the two states (A and B) shown in equation 7. One (A) is an ideal hydrogen-bonding system where the proton is located between the two oxygen atoms which have a single energy minimum, while in the other (B) two protonated species, the oxonium ions X and X′ are at energy minimum, $A—H^+ \cdots B(X) \rightleftharpoons A^- \cdots H^+—B(X')$, and the hydrogen bond resembles the transition state between these two double-minima proton potentials. In a previous work, these investigators have found that the lower the pK_a values of the acids employed, the closer the system is to the single potential minimum case. For example, in the trifluoroacetic acid–amine oxides system, broad single-minimum potentials were observed, while for a series of various carboxylic acids with $Me_3N \rightarrow O$ the potential

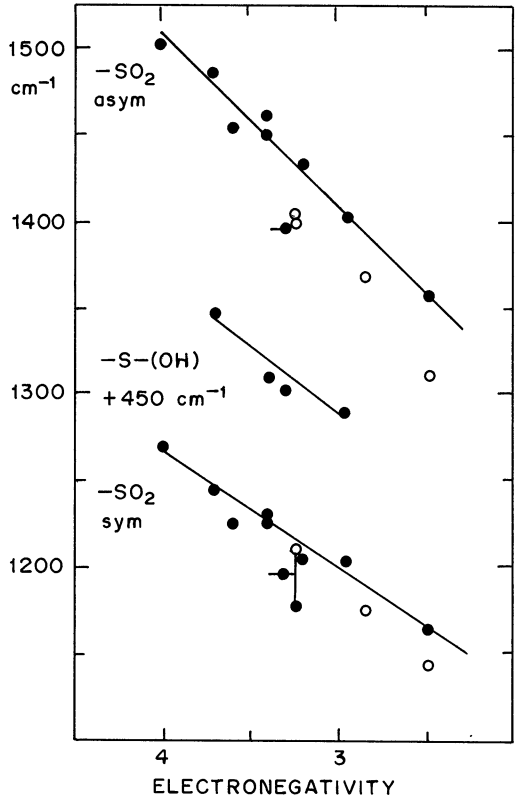


FIGURE 3. Correlations of SO_2 asym, S—OH (displaced vertically by 450 cm^{-1}) and SO_2 sym stretchings with the mean electronegativities [Reference 42, plus OH (= 3.4) and CH_3 (= 2.5)] of X and Y in XSO_2Y. The solid circles refer to gases; the two solid circles with horizontal bar at X = 3.3 refer to associated $ClSO_3H$ vapor; the open circles refer to liquid CH_3SO_2F, CH_3SO_2Cl and $CH_3SO_2CH_3$. Gaseous $(CH_3)_2SO_2$ is also shown and shows the displacement due to change of phase. Reprinted with permission from Chackalackal and Stafford, *J. Am. Chem. Soc.*, **88**, 723. Copyright (1967) American Chemical Society

changes from a single to a double minimum[44b].

$$\underset{\text{(A)}}{OH + O \overset{pK_{ass}}{\rightleftharpoons} O^- \text{------} H^+ \text{------} O} \overset{K_d}{\rightleftharpoons} O^- + H^+O \overset{K_h}{\underset{OH+O}{\rightleftharpoons}} \quad (7)$$

$$[OH\text{------}O^- \rightleftharpoons {}^-O\text{------}HO] + \underset{\text{(B)}}{[O^+H\text{------}O \rightleftharpoons O\text{------}H^+O]}$$

The energy diagram for the hydrogen bonds formed between methanesulfonic and other sulfonic acids and various oxides used as bases could be represented as a plain U-shaped

curve with a broad flat single energy minimum corresponding to the hydrogen bond. This is observed by using the IR frequency shifts of the appropriate absorption bands of methanesulfonic acid.

If the acid is completely protonated, the hydrogen bond formed should be represented by a double-minimum potential diagram. Whether the proton shift takes place via a single or a double minimum depends on the strength of the acid and base employed, i.e. on the difference between the pK_a values of the acid and base. In the reactions of $MeSO_3H$ with various oxygen bases, the IR frequency shifts of ν_{SO_2} and ν_{SO} measured in MeCN solution can rationally explain the formation of the hydrogen bonds and neither $MeSO_3^-$ anion nor $(MeSO_3)_2H^+$ which are formed by complete proton transfer was observed at all in the spectra. Therefore, the proton shift should be only due to hydrogen bonding between $MeSO_3H$ and oxygen bases as represented by intermediate (A) in equation 7. The IR data also demonstrate that the association constant K_{ass} values for the reactions of $MeSO_3H$ and N-oxides, for example, are quite large.

The formation of hydrogen bonding between sulfonic acid and organic oxygen bases can also be deduced by measuring the conductivity of the reaction systems. The results, which are summarized in Table 7, suggest that a charged species such as (B) in equation 7 is present in $< 2\%$. Consequently, in these systems a single-minimum proton potential as shown in (A) seems rational. The bottom of the potential well of the single minimum shifts with either increasing or decreasing ΔpK_a (the difference between pK_a values of the protonated base and -1.92, the pK_a value of $MeSO_3H$[18]). Furthermore, the proton polarizability, represented by the relative position of the proton between the donor and acceptor, was determined by plotting the intensity of the IR absorbance of $MeSO_3H$ at $1400\,cm^{-1}$ in the presence of bases against the ΔpK_a values.

In CD_3CN, the proton potentials are on the average symmetrical and the proton polarizability is largest with a system having a ΔpK_a value of *ca* 0.8, which corresponds to the pair 4-chloropyridine-*N*-oxide and $MeSO_3H$, suggesting that the proton is located

TABLE 7. SO Bands in the IR spectra and specific conductivities I (in $10^{-4}\,\Omega^{-1}\,cm^{-1}$) at 298 K in the systems methanesulfonic acid (MSA)–oxygen bases in CH_3CN[a]. Reprinted with permission from Boner and Zundel, *J. Phys. Chem.*, **89**, 1408. Copyright (1985) American Chemical Society

No.	Oxygen base	$pK_a(BH^+)$	ΔpK_a	I_{AH+B}	I_B	$\bar{\nu}_{SO}(cm^{-1})$		
1.	Ph_2SO	−3.19	−1.27	1.12	0.09			
2.	Ph_3PO	−2.10	−0.18	7.95	0.27	1330	1177	894
3.	Me_2SO	−1.80	0.12	7.80	0.11	1294	1128	956
4.	Bu_2SO	−1.47	0.45	8.45	0.96	1287	1115	980
5.	2-ClPyNO[b]	−0.81	1.11	9.14	0.17	1272	1094	962
6.	4-CO_2CH_3PyNO[b]	−0.41	1.51	6.66	0.16	1293	1112	masked
7.	3-CH_3PyNO[b]	0.92	2.84	6.00	0.14	1258	1122	994
8.	Ph_3AsO	0.99	2.91	8.79	0.33	1251	1136	1008
9.	Me_3NO	4.62	6.57			1245	1154	1023
						1367[c]	1177[c]	882[a,c]
						1204[d]		1034[b,d]
						1274[e]		958[c,e]

[a]Specific conductivity of pure CH_3CN; $0.51 \times 10^{-6}\,\Omega^{-1}\,cm^{-1}$; 0.1 M MSA in CH_3CN: $1.09 \times 10^{-4}\,\Omega^{-1}\,cm^{-1}$.
[b]Py = Pyridine.
[c]Absorptions of CH_3SO_3H.
[d]Absorptions of $Bu_4N^+CH_3SO_3^-$.
[e]Absorption of Bu_4N^+ $[(CH_3SO_3)_2H^-]$.

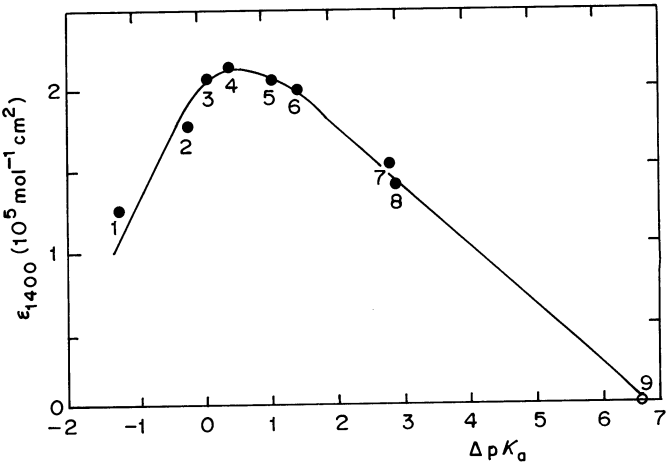


FIGURE 4. Absorptivity of the continuous absorption at 1400 cm^{-1} in the systems methanesulfonic acid + various oxygen bases in CD_3CN, plotted as a function of ΔpK_a. The numbers correspond to the number of the base in Table 7. Reprinted with permission from Boner and Zundel, *J. Phys. Chem.*, **89**, 1408. Copyright (1985) American Chemical Society

near the middle point between the acid and base at this pK_a value. The plot of the absorbance at 1400 cm^{-1} against the ΔpK_a values is shown in Figure 4.

Similarly, the hydrogen bonding between pyridine-*N*-oxides and sulfonic acids was investigated by Kreevoy and Chang using UV spectroscopy[45]. Szafran's group also investigated the hydrogen bonding the sulfonic and carboxylic acids with weak oxygen bases[46]. Whereas in these systems sulfonic acids serve as the proton donors, when the onium salts of sulfonates are employed instead of the acids, they play the role of hydrogen-bond acceptors. Sim and coworkers prepared triethylprop-2-yn-1-yl ammonium *p*-bromobenezenesulfonate in which the sulfonate oxygens interact with the acetylenic hydrogen to form a hydrogen bond as shown in equation 8. This hydrogen bond was recognized by the shift of the IR stretching ≡C—H frequency which normally appeared at 3304 cm^{-1} to 3180 cm^{-1} in dilute Me_2SO–CCl_4 solution, similar to what was observed with carboxylates[47,48]. The formation of the ≡CH ----- OS type hydrogen bond was also detected by X-ray crystallographic analysis of the crystalline sulfonium salt. The analysis shows that the oxygen atoms of the sulfonate not only approach the acetylenic hydrogen atom but also the methylene protons in the Et-N group within intermolecular hydrogen-bond distance of around 2.5 Å. The authors find the IR method which determines the CH stretching to be the more reliable for characterization of the hydrogen bonding in solution than the X-ray analysis.

$$4\text{-}BrC_6H_4—SO_3^- \text{-----} HC \equiv C—CH_2—\overset{+}{N}Et_3 \qquad (8)$$

Other IR studies of hydrogen-bonding effects in sulfonic acids have been presented, including the following topics: association of solvent molecules with polystyrene bearing sulfonic acid moieties[50]; intermolecular hydrogen-bonding between aromatic sulfonates and simple carbohydrates in water[51]; formation of sulfate esters of 8-quinolinol and several of its sulfonated derivatives in oleum[52]; the effect of *o*-substituents on the intramolecular hydrogen-bonding in CH_3SO_3H and its derivatives[53], studies by NMR spectroscopy of intramolecular hydrogen-bonding in sodium alkylsulfonates substituted

with carbonyl, hydroxy or vinyl groups[54]; detection of hydrogen bonding of $Me(CH_2)_{15}SO_3H$ and its Li and Na salts by IR spectra[55]; studies of hydrogen bonding in azo-dye sulfonic acids by UV spectroscopy[56]; intermolecular hydrogen-bonding in aromatic aminomethanesulfonates[57]; spectroscopic study of substituted hydroxymethanesulfonates by IR and mass spectroscopy[58]; complexation of sulfonic acids and *N,N*-dimethylbenzenesulfoneamide by using ^1H and ^{13}C NMR spectroscopy[59]; IR spectroscopic analysis of $MeSO_3H$ and its Na salt by IR spectroscopy[60].

B. Detection of Hydrogen Bonding and Metal Complexation by X-ray Crystallographic Methods

Sulfonic acids are known to absorb different amounts of H_2O molecules and to form crystalline compounds. The crystal structures of various sulfonic acids containing different

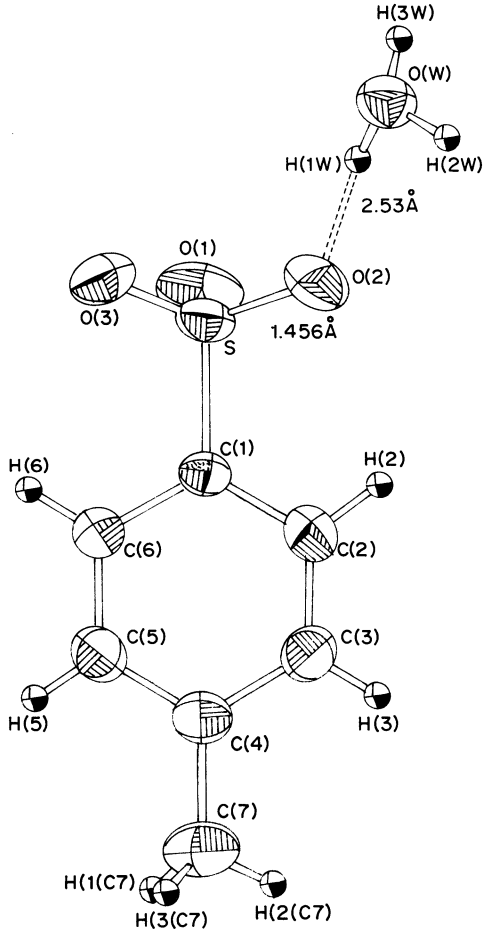


FIGURE 5. Crystal structure of *p*-$TolSO_3^- \cdot H_3O^+$. Reproduced by permission of the International Union of Crystallography from Ref. 68

hydronium ions such as H_3O^+, $H_5O_2^+$ and those of their metal salts have been extensively determined by X-ray crystallographic analysis or by neutron diffraction. Several representative X-ray crystallographic results are summarized below[61–71].

1. Structure of hydrogen bonds determined by X-ray crystallography or neutron diffraction

Since sulfonic acids are quite hydrophilic, it is difficult to crystallize the anhydrous acids which are converted readily to the hydrated forms. There are several reports on the elucidation of the structures of hydrated sulfonic acids by X-ray crystallography or neutron diffraction. Lundgren and coworkers have elucidated the structures of hydrogen-bonded sulfonic acids, particularly the hydrogen-bonding networks formed between the acids, the crystalline water and protons in the case of *p*-toluenesulfonic acid·H_3O^+[61], Picryl sulfonic acid·$H_5O_2^+$·$2H_2O$[62,63], $CF_3SO_3^-$·H_3O^+[64], $CF_3SO_3^-$·$H_9O_4^+$[65] and CF_3SO_3·$^-H_{11}O_5^+$[66].

X-ray crystallographic analysis of *p*-$TolSO_3^-$·H_3O^+ was performed by Dexter[67] and by Arora and Sundaralingham[68] in 1971. They reported that in the crystal structure of the acid, the oxonium ion H_3O^+ is connected to two oxygen atoms of the sulfonate group, giving a hydrogen-bonded network structure to the *ac* direction in the crystals. The discrete structure and the location of the H_3O^+ ion in the crystal were elucidated by Lundgren using neutron diffraction. In *p*-$TolSO_3^-$·H_3O^+, all the hydrogen atoms of the hydronium ion are at nearly equal distances from the central oxygen. The molecular structure of the cation had the O—H distances of 1.011, 1.013 and 1.008 Å with H—O—H angles of 110.7, 109.2 and 111.2°, respectively. The oxygen atom in H_3O^+ is pyramidal and 0.3222 Å out of the plane of the three hydrogen atoms. The crystals have essentially a C_3 symmetry, i.e. the symmetrical OH bonding resembles the structures found in other strongly hydrogen-bounded acids such as $HBr{\cdot}4H_2O$[69]. The crystals are monoclinic, space group P_21/c, with unit cell dimensions of $a = 5.881$ Å, $b = 7.432$ Å, $c = 20.085$ Å and $\beta = 97.95°$.

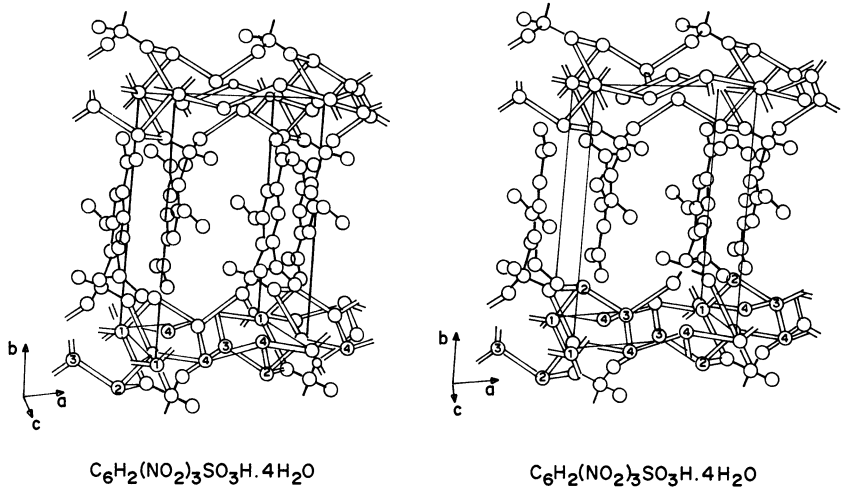


FIGURE 6. Stereoscopic drawing of the crystal structure of $H_5O_2^+C_6H_2(NO_2)_3SO_3^-$·$2H_2O$. The structure is viewed along the *c* axis. Covalent bonds are filled. Hydrogen bonds within $H_5O_2^+$ are half-filled and other hydrogen bonds are open. The water oxygen atoms are denoted by 1,2,3 and 4. Reproduced by permission of the International Union of Crystallography from Ref. 62

A typical crystal structure, that of p-$TolSO_3^- \cdot H_3O^+$ is shown in Figure 5.

Lundgren carried out two additional studies on the hydrogen-bonded structure in sulfonic acids by using both X-ray crystallographic analysis and neutron diffraction[62,63]. One was the determination of the crystal structure of 2,4,6-trinitrobenzene sulfonic acid (picrylsulfonic acid) tetrahydrate, $2,4,6\text{-}(NO_2)_3C_6H_2SO_3H \cdot 4H_2O$. The crystals were triclinic and the cell dimensions were $a = 8.3461$ Å, $b = 11.367(1)$ Å, $c = 8.065(2)$ Å, $\alpha = 97.77(2)$, $\beta = 109.32(1)$, $\gamma = 83.72(1)°$, $v = 713.2$ Å^3 at 22 °C, $Z = 2$, $D_x = 1.0701$ g cm^{-3} and the space group was $P\bar{1}$.

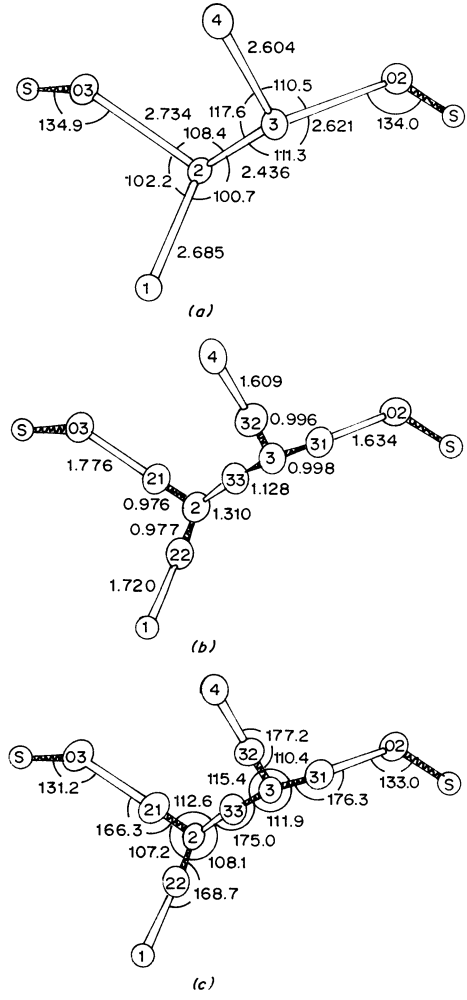


FIGURE 7. Bond distances and angles of 2,4,6-$(O_2N)_3C_6H_2SO_3H \cdot 4H_2O$ in and around the $H_5O_2^+$ ion: (a) distances and angles involving non-hydrogen atoms; (b) distances involving hydrogen atoms; (c) angles involving hydrogen atoms. Reproduced by permission of the International Union of Crystallography from Ref. 63

The stereoscopic view of this acid is illustrated in Figure 6 and the bond distances and angles are given in Figure 7. The hydrogen-bond distance was calculated from the Fourier difference synthesis in the X-ray analysis and determined correctly by neutron diffraction.

The crystals are composed of $H_5O_2^+$ ions, picrylsulfonate anion and water molecules. These three species are hydrogen-bonded together and form layers in the *ab* plane. Carbon rings are located perpendicular to this plane and the distances between carbon rings are 3.83 Å and 4.04 Å. The sulfonate oxygen atoms are nearly equal with S—O distances of 1.432 Å, 1.446 Å and 1.444 Å. This result indicates that the proton in the acid is transferred completely to the water molecule. A short O-----O bond distance (2.427 Å by X-ray) indicates that $H_5O_2^+$ is formed and that the proton is shared by the two water oxygen atoms O(water 2) and O(water 3) to approximately the same degree. The water molecules (W1) and (W4) are bonded together to form chains in the *a* direction, one oxygen (W1) is tetrahedral and the other oxygen (W4) is pyramidal. These results indicate that the diaquahydrogen ion is of asymmetric non-centered type and differ from that found in *p*-TsOH·H_2O. Furthermore, Lundgren carried out the analysis of $CF_3SO_3^-\cdot H_3O^+$ by both X-ray and neutron diffraction. The crystal of the acid, prepared by a known method[70], was monoclinic, of space group $P2_1/c$, and the cell dimensions were $a = 5.9634(3)$ Å, $b = 9.975(3)$ Å, $c = 9.708(1)$ Å, $\beta = 98.661(7)$, $V = 570.9$ Å^3, $Z = 4$, $D_x = 1.956$ g cm^{-1} at 298 K. The bond lengths and angles together with stereoview are shown in Figure 8, and the structure of the oxonium ions is illustrated in Figure 9.

[-----O(W1)-----O(W1)-----O(W4)-----O(W4)-----]

The sulfonate ion is in a staggered conformation with symmetry close to C_{3v}. The average S—O bond distance is 1.444 Å and the O—S—O and C—S—O bond angles are 114.4° and 104.5°, respectively, indicating that the central sulfur is tetrahedral. The oxonium ion is hydrogen-bonded to three water molecules with distances of 2.482 Å, 2.579 Å and 2.639 Å (by neutron diffraction). The O-----O(W)-----O angles are also very different. The hydrated acid should therefore be represented as composed of oxonium ions and water molecules bonded to the trifluoromethanesulfonate ions to form a three-dimensional network. The difference from other hydronium ions derived from strong acids, such as those of *p*-Tol$SO_3^-\cdot H_3O^+$ or HBr·$4H_2O$, is that the hydrogen-bond acceptors are arranged asymmetrically around H_3O^+. Although different bond angles and distances were observed in these investigations, the oxonium ion itself is nearly regular and only its incorporation in the structure results in the distortion of the molecular geometry

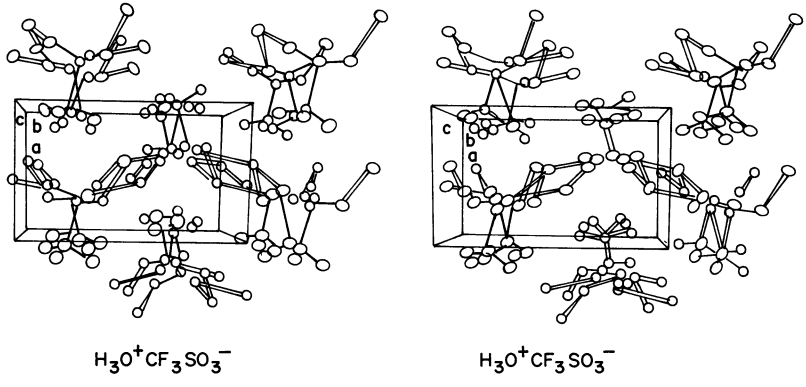


FIGURE 8. Stereoscopic view of the crystal structure of $H_3O^+CF_3SO_3^-$ at 83 K. Reproduced by permission of the International Union of Crystallography from Ref. 64a

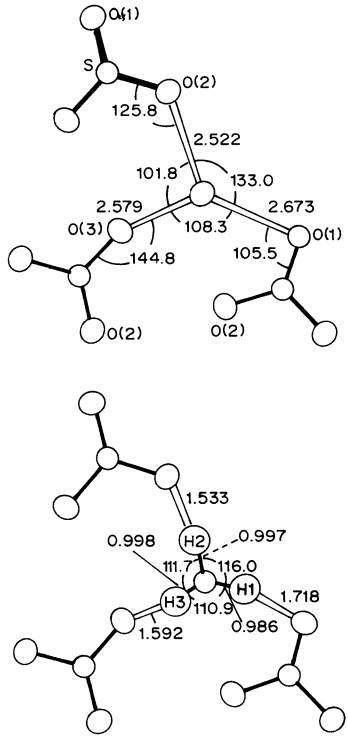


FIGURE 9. The geometry of H_3O^+ and its environment in oxonium trifluoromethanesulfonate. Reproduced by permission of the International Union of Crystallography from Ref. 64b

from the ideal C_{3v} symmetry and in the formation of a bent O----H-----O hydrogen bond. The hydrogen bonding of several other sulfonic acids, appropriately hydrated, has been similarly elucidated by X-ray crystallography[71].

2. *Determination of crystal structures of metal sulfonates by X-ray crystallography*

The hygroscopic sulfonic acids are easily converted to the metal salts, which are easily handled, and the structures of several sulfonic acid salts have been determined by X-ray crystallography. An early X-ray analysis of the Mg and Zn salts of benzenesulfonic acid revealed that the SO_3 group is nearly tetrahedral with S—O bonds of *ca* 1.40 Å, and OSO and CSO bond angles which are nearly tetrahedral. The S—O bond length is shorter than a normal S—O single bond (1.69 Å) and is close to the value of a doubly bonded S=O, suggesting a double bond in the sulfonate ion[72].

Many other results on X-ray crystallographic analysis of salts of sulfonic acids and related derivatives have been summarized by Laur[73]. In the present review, only cesium and ammonium methanesulfonates[74] and related derivatives, i.e. barium sulfate[75], dimethyl sulfone[76] and trimethyloxosulfonium ion[77], are compared. The bond lengths and angles of these compounds, which were determined by X-ray crystallography, are summarized in Table 8.

TABLE 8. Bond length and angles of methanesulfonate salts and related compounds

	SO_4^{-2}	$CH_3SO_3^-$ (Cs^+)	$CH_3SO_3^-$ (NH_4^+)[75]	$(CH_3)_2SO_2$[76]	$(CH_3)_3{}^+SO$[a77]
Band length (Å)					
S—O	1.49	1.47	1.440		
			1.443	1.47	1.45
C—S		1.85	1.750	1.79	1.79
Angles (deg)					
O—S—O	109.5	111.9	113.9	117.9	
			109.8		
O—S—C		106.9	105.7	108.8	112.7
			107.2	103.0	106.1

[a] ClO_4^- salt.

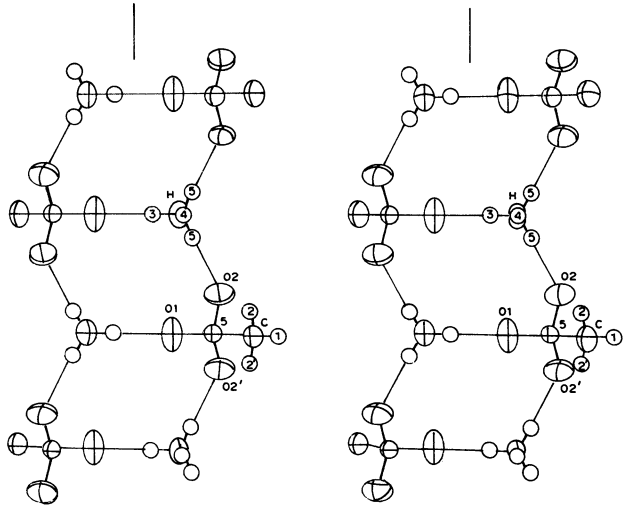


FIGURE 10. Stereoscopic view of interionic hydrogen-bonding scheme around the twofold screw axis ($x = 1/4, z = 0$) in the b direction in ammonium methanesulfonate. Labeled atoms are those of the asymmetric unit. The viewing direction is perpendicular to the b axis. The direction of the screw diad is shown at the top of the figure. Reproduced by permission of the International Union of Crystallography from Ref. 75

The table demonstrates that the central sulfur atom in these compounds is nearly tetrahedral, and that the OSO bond angle increases slightly on increasing the number of the methyl groups, at the expense of a decrease in the OSC angle. In ammonium methanesulfonate, each of three oxygen atoms in the anion is hydrogen-bonded to the neighboring hydrogen atom of the NH_4^+ ion, thus forming an infinite hydrogen-bonding chain. The hydrogen-bonded structure is shown in Figure 10.

IV. EPILOGUE

Sulfonic acids are among the strongest organic acids and they form strong hydrogen bonds with weak bases. Very strong organic acids, such as SbF_5–FSO_3H and SbF_5–CF_3SO_3H which are called 'Magic Acid'[78] and can even protonate methane to CH_5^+, have been introduced recently to organic chemistry. Furthermore, complexes formed between an ion-exchange resin having polysulfonic residues and $AlCl_3$ (So-called 'solid super acids') serve as strong proton donors even for solid-phase reactions and are used widely in organic chemistry[79].

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CHAPTER **8**

Thermochemistry of sulphonic acids and their derivatives

JOEL F. LIEBMAN

Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, MD 21228, USA

The chemistry of sulphonic acids, esters and their derivatives
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I. INTRODUCTION AND ORGANIZATION

Despite the interest in, and importance of, sulphonic acids and their salts, 'osylates' and other sulphonate esters, sulphonamides, sulphonyl halides and miscellaneous derivatives such as disulphones, thermochemical data for this class of compounds are disappointingly sparse and often suspect. Thus the data will not be presented in the form of tables, but rather will be discussed one primary reference at a time per subsection. Because the required gas phase data are almost totally absent, we will also not attempt to generate Benson increments[1] for groups of interest such as $SO_2(C)(O)$, as would be part of a thermochemical study of sulphonic acids and their esters but not the isomeric sulphites that contain the $SO(O)_2$ group. As such, this chapter is unlike so many of the other thermochemical chapters in the other volumes of 'The Chemistry of the Functional Groups' series.

This chapter is organized into ten sections. The first of these introduces the topic of the thermochemistry of sulphonic acids and their derivatives, defines the key concepts of energetics and structure, and acknowledges the seeming paucity of experimental data. The first of a set of fundamental questions and the first of a collection of approximation methods are also presented therein. The second section discusses the multiple experimental difficulties which limit direct measurement of the heat of formation of sulphur-containing organic compounds, the heat of combustion and of solution of 2-aminoethanesulphonic acid, and the solution and solid phase thermochemistry of 'glyoxal sulphites'. Having decided to use an approach characterized by chronology and commentary, the third section discusses the relevant papers published between 1941 and 1950. Sections four through seven likewise present the results from 1951 to 1960, 1961 to 1970, 1971 to 1980 and 1981 to 1990. The text interweaves both the contradictions and patterns explicitly enunciated in the various studies. In the eighth 'epilogue' section we attempt to answer the unsolved questions posed earlier. The final two sections present acknowledgements and references.

We opt to begin this chapter with definitions and explanations. The earlier notation $SO_2(C)(O)$ means a group that is composed of a sulphur atom that is 'inseparably' bonded to two oxygen atoms, a singly bonded carbon atom and another oxygen atom. No prejudice is expressed as to whether the two inseparable oxygen atoms are joined to the sulphur by single or double bonds or even some indeterminate fractional number of bonds because of resonance. Rather 'SO_2' is to be understood much as 'CO' is generally understood, i.e. a carbon inseparably (double) bonded to one oxygen in some carbonyl compound such as the numerous acyl derivatives. Acyl derivatives are almost ubiquitous in discussions of organic chemistry. However, it is not *a priori* obvious what interrelations of energy and of structure, if any, exist between formally similar sulphonyl, acyl and sulphinyl derivatives, RSO_2X, RCOX and RSOX, respectively. It will be seen that, at least from a thermochemical vantage point, too little is known to say anything meaningful—even after writing this review, our knowledge of the chemistry of sulphonyl derivatives remains insufficient.

If bond additivity be valid, the heat of formation associated with the $SO_2(C)(O)$ group would be the average of those for $SO_2(C)_2$ and $SO_2(O)_2$, i.e. the geometric and defining central unit of sulphones and sulphuric acid and its esters. For both of these latter classes of compounds, seemingly reliable thermochemical quantities are available. However, this rather simple assumption that, if true, would be highly useful, has never been tested. The required heats of formation, some measured and others estimated, are found in the various sub-sections of this chapter. The test results will be presented in Section VIII.C.

The first definition is that of 'sulphonic acids and their derivatives', a term that has already appeared several times. For the purpose of this chapter, we take it to mean any compound of the generic type RSO_2X, where R is some group bound by carbon to the sulphur and X is a group that is bound to the sulphur by some hetero atom (N, O, S, halogen). Secondly, the phrase 'thermochemical data' is customarily taken to mean heat of formation. ΔH_f; heat capacity, C_p; and entropy, S, all considered for both gaseous and condensed (liquid and/or solid) phases. However, we are personally interested almost exclusively in the heats of formation. Thus our only reference to heat capacity and entropy data is the compilation of data of these quantities[2]. (See Table 1.)

Our favourite archive and compilation[3] was a starting point for studying the heats of formation. However, so doing almost provided the end point as well—the only qualifying species was diphenyl disulphone, $PhSO_2SO_2Ph$ (**1**). This species qualifies only if one SO_2Ph group is identified as the X, R = Ph according to our definition of the species of interest. While the individual values of the heats of formation of the solid, liquid and gas (-153.6 ± 0.4, -150.5 and -114.9 ± 0.9 kcal mol^{-1}) seem beyond reproach[4], single compounds do not make a review article. However, Benson[5] has made use of the data for

TABLE 1. Heat capacity and entropy data for sulphonic acid derivatives (all data are for solids and are from Reference 2)

Formula	Name	C_p[a]	T[b]	S[a]	T[b]
$C_2H_7NO_3S$	2-Aminoethanesulphonic acid[c], **7**	33.6	300.3	36.8	298.2
$C_6H_7NO_2S$	Benzenesulphonamide	46.2	323		
$C_6H_8N_2O_2S$	4-Aminobenzenesulphonamide	52.8	323		

[a]Both the heat capacity and entropy are given in units of cal mol^{-1} K^{-1}. The reader will note the absence of a superscript on both quantities because the species is not in its standard state.
[b]The temperature is in kelvin, K.
[c]Recall that the trivial name for this zwitterionic species is taurine, and is more properly named 2-ammonioethanesulphonate (**8**).

this one species and the S—S homolysis rate data of Kice and Pawlowski[6] on the bis-4-methylphenyl (di-*p*-tolyl) disulphur polyoxides $ArSO_2SO_xAr$ (Ar = *p*-Tol, $x = 0, 1, 2$ compounds **2**, **3**, **4**) to derive other meaningful heats of formation. More precisely, for gaseous diphenyl disulphide 1,1-dioxide (Ar = Ph, $x = 0$, species **5** also named benzenesulphonyl benzenethiolate) and diphenyl disulphide trioxide (Ar = Ph, $x = 1$, species **6** benzenesulphonyl *S*-benzenesulphinate), Benson derived values of -22 ± 4 and -52 ± 2 kcal mol^{-1}, respectively. These new and relevant heats of formation legitimized an unusual tack for obtaining and presenting thermochemical data, an approach which will be outlined below for use in the current review.

II. DIFFICULTIES AND ARCHIVAL HISTORY

A. Why is the Thermochemistry of Sulphur-containing Species so Difficult?

Why is our conventional archive[3] so devoid of entries on the sulphonic acids and their derivatives? Are there *really* so few pieces of reliable data—those that an organic chemist, if not a thermochemist, could use? For example, lacking heats of formation of the isomeric dimethyl sulphite and methyl methanesulphonate, where is the experiment that tells us their relative stabilities? Apart from idiosyncracies of bonding patterns—e.g. how much $d\pi$–$p\pi$ double bonding is there in a given SO bond—there are other well-defined reasons for our ignorance. In particular, it is well established[7] that heats of combustion (and thus, most heats of formation) studies of sulphur-containing species are fraught by problems not found for those species that contain 'merely' carbon, hydrogen and oxygen. Waddington, Sunner and Hubbard[8] list the following interrelated problems endemic to the thermochemistry of sulphur-containing species.

(1) 'The quantitative conversion of sulfur to sulfate ion'. While both SO_2 and SO_3 are formed upon combustion, the former is also oxidized to the latter after the combustion. This confounds analysis of the products of the combustion process.

(2) 'Inhomogeneity in bomb liquid'. The SO_3, however formed, dissolves in the liquid in the bomb to form sulphuric acid. While this process is highly exothermic, the resulting sulphuric acid solution is not necessarily uniform in concentration. These variations of concentration, associated with large, nonlinearly varying heats of solution, introduce 'significant errors' in determination of the total heat of combustion.

(3) 'Definition of the bomb process'. From the above complications, it is easily discerned that it is not sufficient to look at the empirical formula of the compound and then immediately write down the formal combustion reaction. This is in sharp contrast to the situation for the simpler CHO-containing compounds where equation 1 is generally valid:

$$C_xH_yO_z + (x + y/4 - z/2)O_2 \longrightarrow xCO_2 + y/2\,H_2O \tag{1}$$

(4) 'Correction to standard states'. The fact that oxidized forms of carbon (CO_2) and nitrogen (HNO_2 and HNO_3) accompany the oxidized sulphur (see above) requires knowledge of additional heat of solution data. More precisely, 'the energy evolved when the combustion of a substance takes place in a bomb calorimeter may differ significantly from the decrease in internal energy for the combustion reaction under standard conditions'[9]. For example, the seemingly simple combustion reaction 2 of a CHOS-containing compound, as written by these authors, must be accompanied by numerous correction terms, such as the heat of solution of HNO_3 in H_2SO_4-containing media as a function of the concentration of both acids.

$$\begin{aligned} &C_aH_bO_cS_d\ (\text{c or liq.}) + (a + b/4 + c/2 + 3d/2)O_2(g) + (nd - b/2 + d)H_2O(\text{liq.}) \\ &\quad = aCO_2(g) + d(H_2SO_4 \cdot nH_2O)(\text{liq.}) \end{aligned} \tag{2}$$

(5) 'Cancellation of systematic errors'. The standard material for the calibration of calorimetric experiments is benzoic acid, a well-defined CHO-containing species. Numerous systematic errors may thus be expected to cancel when considering the combustion of other CHO-containing species. However, this cancellation is hardly assured when considering sulphur-containing species. Indeed, the process is exacerbated for sulphonic acid derivatives, if for no other reason than that other hetero atoms are often present. Perusal of the primary papers cited in our organic thermochemical archive (Reference 3) and References 1–14 in Herron's more recent review on sulphoxides, sulphones and their thermochemistry[10] show that Busfield, Mackle and their coworkers studied almost all of them. These authors also studied two other major classes of CHOS-containing species, the organic sulphates and sulphites, but surprisingly not the sulphonates which are isomeric with the latter. We note now, though it will be documented later, that there is no one research group that has dominated the study of the thermochemistry of any of the general class of sulphonic acids and their derivatives, the topic of this current review. As such, there is no reason for confidence that unsuspected and/or unsystematic errors will cancel. Perhaps, the current volume will encourage some thermochemically inclined research group to commence a systematic study of the energetics of sulphonic acids and their derivatives. It is sorely needed.

(6) 'Corrosion'. Said most simply, the final highly acidic combustion products may attack the calorimeter. This results in inaccurate measurements of both the nature of the products and the amount of heat evolved, as well as damaging the apparatus that is to be used for subsequent studies.

(7) 'Determination of the amount of reaction'. That is, one cannot simply determine the amounts of final combustion products and then derive the amount of compound of interest that was burnt.

All of the problems outlined above can, with care and effort, be remediated by methods outlined in Reference 7. For example, quoting from this source (pp. 151–152), 'the amount of reaction is best determined by direct weighing of the sample. This means that the sample must be of known high purity'.

There are additional problems not unique to the thermochemistry of sulphur-containing species such as impure and ill-defined samples and ignorance of the necessary heats of solution, and of the corrections to the results so that they precisely correspond to 25 °C and 1 atmosphere pressure. It was tempting to give up or to write almost nothing. Instead, we opted to take an admittedly atypical approach. We arbitrarily chose to chronologically proceed through salient references on the thermochemistry of sulphonyl derivatives. The data therein and conclusions drawn by the authors will be discussed in terms of their original logic and assumptions. Where appropriate, we will present the just exposed contradictions that arise when these data, or their derived conclusions, are put in juxtaposition with earlier cited papers in our study or results from our archives. We will also present generalizations or unifying principles where we can, even if 'merely' as patterns in the heats of formation of sulphonic acids and some of their derivatives[11].

B. The Thermochemistry of 2-Aminoethanesulphonic Acid (Taurine)

The various authors whose research is chronicled below showed different degrees of sensitivity to the problems outlined above. We will not attempt to appraise these individuals' aptitude, or even orientation, as orthodox thermochemists. Rather, we will simply present the results of the various papers and discuss whatever pattern or discordancy arises. We start with the 'smoothed' results for all the relevant entries of another of our favourite compendia[12]. While this source lacks error bars and primary bibliographic citations, the vast majority of the entries of thermochemical quantities in this

volume are adjusted to be consistent with the total set. As such, any individual result is trustworthy in excess of that from any arbitrary primary source.

The first species from Reference 12 we will adopt is 2-aminoethanesulphonic acid (**7**, taurine). The heat of formation of the solid, ΔH_f (s, **7**), is given therein as $-187.7\,kcal\,mol^{-1}$. From that measurement and heats of solution, the heat of formation of the aqueous solution, $\Delta H_f(aq)$, of the corresponding un-ionized zwitterion[13], $NH_3{}^+(CH_2)_2SO_3{}^-$ (**8**), is $-181.9\,kcal\,mol^{-1}$. Making use of the arbitrary definition[14] $\Delta H_f(aq, H^+) \equiv 0.0\,kcal\,mol^{-1}$, we find the heat of formation of the aqueous taurinate anion **9**, $\Delta H_f(aq, NH_2(CH_2)_2SO_3{}^-) = -171.9\,kcal\,mol^{-1}$. In that anions do not exist alone in solution independent of the existence of cations, the heat of formation of an aqueous salt solution is the sum of the heats of formation for the separate aqueous anion and cation. For example, $\Delta H_f(aq, NH_2(CH_2)_2SO_3Na)$—the heat of formation of an aqueous solution of sodium 2-aminoethanesulphonate (sodium taurinate, **10**)—is found to be $-171.9 + (-57.4) = -229.3\,kcal\,mol^{-1}$.

It would thus appear that we have a handle for calibrating the accuracy of other measurements on sulphonate salt thermochemistry and for estimating heats of formation of aqueous salts of thermochemically uncharacterized sulphonic acids. More precisely, since sulphonic acids are strong, they and their salts are completely dissociated in water. Therefore, the difference in the heats of formation of aqueous RSO_3M and RSO_3M', $\delta\Delta H_f(aq, RSO_3M, RSO_3M')$, is merely the difference of the heats of formation of the aqueous metal ions. Finally, since we recall $\Delta H_f(aq, H^+)$ (the heat of formation of aqueous H^+) is defined[14] as precisely 0.0, the heat of formation of an aqueous sodium sulphonate is always less than that of the aqueous (and tacitly assumed monoprotic) parent acid by a constant $57.3\,kcal\,mol^{-1}$.

C. The Thermochemistry of 'Glyoxal Sulphites': The Energetics of 1,2-Ethanediol-1,2-disulphonic Acid and its Salts

The second thermochemical story is that of 'glyoxal hydrogen sulphite' [$(CHO)_2 \cdot 2H_2SO_3$, **11**], its salts and their aqueous solutions. Recall the long-known addition reaction 3 of bisulphite salts to aldehydes resulting in aqueous α-hydroxysulphonates, i.e.

$$RCHO + NaHSO_3(aq) \longrightarrow Na^+\,RCH(OH)SO_3{}^-(aq) \qquad (3)$$

This reaction tells us how to derive information on the thermochemistry of 1,2-ethanediol-1,2-disulphonic acid (**11**) and its salts, $(M^+)_2\,[O_3SCH(OH)CH(OH)SO_3]^{-2} \cdot nH_2O$ (**12**). Table 2 compiles the data for these species.

We now come to the first of our regularities, although we immediately admit its gross assumptions and only approximate validity. Recall Haberfield's observation[15] that the

TABLE 2. Heats of formation of solid (s) and aqueous solutions (aq) of 1,2-ethanediol-1,2-disulphonic acid (**11**) and its salts (**12a–d**) (all data are in $kcal\,mol^{-1}$ and are from Reference 12)

M	*n*	Compound	ΔH_f(s)	ΔH_f(aq)	(concn)
H	0	**11**		−374.7	
NH_4	1	**12a**	−544.1	−465.6	(1:800)
Na	1	**12b**	−589.8	−512.1	(1:800)
K	0	**12c**	−530.4	−517.3	(1:800)
Ba[a]	2.5	**12d**	−701.6	−522.6	

[a]There is one barium cation for each disulphonate anion.

heat of aqueous solution of substituted acetic acids XCH_2COOH (**13**) approximately equals the sum of the heats of solution of XMe and HCOOH. May we say that the heat of solution of the corresponding substituted sodium acetate salts, XCH_2COONa (**14**), equals the sum of XMe and HCOONa? Equivalently, to the extent that this be true[16], then the difference quantity defined by equation 4 is independent of X. Moreover, if substituent effects on heats of formation are small 'enough', then the difference quantity defined by equation 5 would also result in a constant. Are these conclusions consistent with the data? We examine the case of the sulphonates. That is, let us consider the related equation 6 and sulphur difference quantity

$$\Delta H_{soln}(XCH_2COONa) - \Delta H_{soln}(XMe) \equiv \delta\Delta H_{soln}(XCH_2COONa, XMe) \quad (4)$$

$$\Delta H_f(aq, XCH_2COONa) - \Delta H_f(aq, XMe) \equiv \delta\Delta H_f(aq, XCH_2COONa, XMe) \quad (5)$$

$$\Delta H_f(aq, XCH_2SO_3Na) - \Delta H_f(aq, XMe) \equiv \delta\Delta H_f(aq, XCH_2SO_3Na, XMe) \quad (6)$$

That is, we ask 'How constant is the difference of the heats of formation of aqueous XCH_2SO_3Na (**15**) and XMe'? The reader will note we have heat of formation data for aqueous solutions of $X = NH_2CH_2$— (i.e. sodium 2-aminoethanesulphonate, **10**) and $NH_3{}^+CH_2$— (i.e. an 'artificial' species for which the desired heat of formation of the aqueous solution is the sum of those for the zwitterionic 2-aminoethanesulphonic acid **8**, and Na^+ ion). Our archival Reference 12 also gives us the requisite quantities for the necessary XMe species, which we identify as ethylamine, and ethylammonium ion. There is also the '—CH(OH)CH(OH)—' case, i.e. the above-mentioned sodium salt of 1,2-ethanediol-1,2-disulphonic acid (**12b**) to be compared with 1,2-ethanediol (**16**) for which we also have the needed data. ['Quotes' are used because, strictly, our comparison should have been between disodium butane-2,3-diol-1,4-disulphonate (**17a**) and the parent alcohol (**17b**). However, since we lack the data for this comparison, we have excised two CH_2 groups from **17a** and **17b** to form **12b** and **16**.] Table 3 presents all of the data and the derived thermochemical quantity, $\delta\Delta H_f(aq, XCH_2SO_3Na, XCH_3)$. It is seen that within 'a few' kcal mol^{-1}, $\delta\Delta H_f(aq, XCH_2SO_3Na, XCH_3)$, the difference of the heats of formation of aqueous XCH_2SO_3Na (generic **15**) and aqueous XMe, is a constant, -203 kcal mol^{-1}. So far, the data presented are seemingly consistent.

To some readers, our success may appear as merely an example of additivity relations as suggested by Benson and discussed in the various books and articles cited in References 1. However, it should not be taken for granted because we are taking energy differences as we are comparing:

(a) two pairs of species, one member with a $-CH_2-$ group (**15**) and the other with a —Me group, with another pair of species, one member with a $>CH-$ (**12b**) group and the other with a $-CH_2-$ (**16**);

TABLE 3. Test of equation 5: How constant is the difference of the heats of formation of aqueous XCH_2SO_3Na and XMe?[a]

X	$\Delta H_f(aq, XCH_2SO_3Na)$	$\Delta H_f(aq, XMe)$	δ_3
NH_2CH_2—	−229.3 (**10**)	−24.2	−205.1
$NH_3{}^+CH_2$—	−239.2[b]	−37.3	−201.9
½'—CH(OH)CH(OH)—'[c]	−256.0	−55.0	−201.0

[a] For the purpose of this table we designate this difference by $\delta_3 \equiv \delta\Delta H_f(aq, XCH_2SO_3Na, XMe)$. All data are in kcal mol^{-1}.

[b] Remember, this means the zwitterionic $NH_3{}^+(CH_2)_2SO_3{}^-$ (**8**) with an added Na^+ ion.

[c] Remember, for both of the species in this line, we are to remove two CH_2 groups apiece so that we are actually comparing $NaO_3SCH(OH)CH(OH)SO_3Na$ (**12b**) and $HOCH_2CH_2OH$ (**16**).

(b) species in aqueous solution, not in the gas phase or even in a structureless, or at least non-polar and weakly interacting, solvent at that;

(c) species which are highly and diversely charged—recall our organic species include a cation, a zwitterion, and both a singly and double charged anion.

Should the reader have viewed our 4 kcal mol^{-1} spread as disappointingly large, we now 'replace' the SO_3Na by a Me and consider only gas-phase heats of formation. We thus compare $EtNH_2$ with $PrNH_2$ (−11.3, −16.8, from Reference 3), $EtNH_3^+$ with $PrNH_3^+$ (137.2, 131.0, from Reference 17) and $\frac{1}{2}$(HOCH$_2$CH$_2$OH, **16**) with $\frac{1}{2}$(MeCHOHCHOHMe, **17b**) [$\frac{1}{2}$(−92.6), $\frac{1}{2}$(−115.3), from Reference 3]. The differences of the heats of formation of these pairs of species are 5.5, 6.2 and 11.3 kcal mol^{-1}, which are readily seen to have a comparable degree of constancy as we found for the sulphonate salts.

III. THERMOCHEMICAL MEASUREMENTS FROM 1941 TO 1950

A. The Thermochemistry of n-Dodecane-1-sulphonic Acid and its Derivatives

We now proceed through with our commentary on the thermochemistry of other sulphonic acids and their derivatives. Although we began our literature search with 1941 so as to cover the 50 years before the publication of this volume, the earliest relevant reference is from 1944. In it[18], Roth and Rist-Schumacher determined the heat of combustion, ΔH_c (at constant pressure), of n-dodecane-1-sulphonic acid (**18**) to be 1868.0 ± 3.7 kcal mol^{-1}. These authors related this quantity to the heat of reaction of 69 ± 4 kcal mol^{-1} that would be liberated by the hypothetical reaction 7

$$\text{n-}C_{12}H_{26}(\text{liq}) + H_2SO_4(\text{liq, } 100\%) \longrightarrow \underset{(\mathbf{18})}{\text{n-}C_{12}H_{25}SO_3H(\text{s})} + H_2O(\text{liq}) \qquad (7)$$

We thus deduce ΔH_f(s, **18**) = −141 ± 4 kcal mol^{-1}. The same authors reported the heat of solution of **18** with ethanol to be 1.1 ± 0.7 kcal mol^{-1} and heat of the neutralization reaction of the resulting ethanolic solution with NaOH to be 8.4 ± 0.3 kcal mol^{-1}.

We have little quantitive data with which to compare these figures for the sulphonic acid of interest. However, from the data in Reference 12 we derive that the heat of solution of sulphuric acid with ethanol is at least[19] 17.5 kcal mol^{-1}. Even 4/3 of last quantity (if one were to insist that "n-$C_{12}H_{25}SO_3H$ can only 'indulge' in 3 hydrogen bonds while H_2SO_4 can 'indulge' in 4" is far in excess of that reported for **18**. Something seems wrong here with the heats of solution. Turning to the neutralization reaction 8

$$\text{n-}C_{12}H_{25}SO_3H(\text{in EtOH}) + \text{NaOH(in EtOH)} \longrightarrow \text{n-}C_{12}H_{25}SO_3Na(\text{in EtOH}) + H_2O(\text{in EtOH}) \qquad (8)$$

we lack the corresponding data of sulphuric acid by NaOH in ethanol. Reference 12 shows that the heats of solution of sulphuric acid in ethanol and in water are *not* greatly different, > 17.5 and 22.8 kcal mol^{-1}. Likewise, it shows that the heat of solution of $NaClO_4$ in water increases to 3.3 kcal mol^{-1} at infinite dilution, and (at some undefined concentration) in ethanol is essentially 0. Ethanol is certainly not water, but nonetheless to our perennial 'few' kcal mol^{-1}, it would seem that we can crudely mimic reaction 8 by the aqueous 'semi-neutralization' reaction of H_2SO_4 with NaOH to yield $NaHSO_4$. The heat of this 'semi-neutralization' reaction is 10.9 kcal mol^{-1}, rather close to the measured value of reaction 8, 8.4 kcal mol^{-1}, and so the published neutralization enthalpy for the sulphonic acid **18** looks plausible[20].

These authors[18] also studied n-dodecanesulphonyl chloride (**19**) and additionally presented the value of its heat of solution in ethanol of 12.4 kcal mol^{-1}. This value appears untenable (cf. the discussion for **18**) unless we assume it corresponds to formation of the sulphonate ester (**20**) via the enthanolysis reaction. They also determined that the

reaction 10, of liquid **19** with water to yield the solid **18** is exothermic by only 0.3 ± 2.0 kcal mol^{-1}. Thus reaction 10 does not look thermoneutral in light of knowledge of the high reactivity of, and ease of solvolysis, of sulphonyl chlorides, although the prejudice is no doubt based on reactions in which both the HCl and sulphonic acid **18** are solvated. If, nonetheless, the quoted heat of reaction 10 is accepted, with the archival[12] heats of formation of H_2O(lq) and HCl(q), and solid sulphonic acid **18** from above, we derive ΔH_f(lq, n-$C_{12}H_{25}SO_2Cl$) = -94.5 ± 4.5 kcal mol^{-1}.

$$\underset{\textbf{(19)}}{\text{n-}C_{12}H_{25}SO_2Cl} + C_2H_5OH \longrightarrow \underset{\textbf{(20)}}{\text{n-}C_{12}H_{25}SO_3C_2H_5} + HCl \qquad (9)$$

$$\text{n-}C_{12}H_{25}SO_2Cl + H_2O \longrightarrow \text{n-}C_{12}H_{25}SO_3H + HCl \qquad (10)$$

B. The Thermochemistry of Naphtholsulphonic Acids

In 1946, Badoche[21] directly determined the heat of formation of two solid naphthalenesulphonic acids and their ammonium salts (species **21** and **22**). The data are presented in Table 4.

Are these values self-consistent? We note that the differences of the heats of formation of correspondingly substituted solid naphthalenes and benzenes are really quite constant, i.e. $\delta\Delta H_f$(s, NaphX, PhX) is *ca* 10 kcal mol^{-1} regardless of X (see Table 5). There are no experimental thermochemical data available for the aromatic sulphonic acid archetype,

TABLE 4. Heats of formation of two naphthalenesulphonic acids and their ammonium ion salts (all data are in kcal mol^{-1} and are from Reference 21)

—Sulphonic acid	Counterion	ΔH_f(s)
2-$HOC_{10}H_6$-6-, **21a**	None	−190.0
2-$HOC_{10}H_6$-6-, **21b**	NH_4^+	−212.8
2,4-$(O_2N)_2$-1-*H*$OC_{10}H_4$-7-[a], **22a**	None	−179.2
2,4-$(O_2N)_2$-(1-O^-)$C_{10}H_4$-7-[b], **22b**	$2NH_4^+$	−259.2

[a]This is for anhydrous **22a**. Its dihydrate was reported to have the heat of formation of −323.8 kcal mol^{-1}, and since ΔH_f(lq, H_2O) = −68.3 kcal mol^{-1}, the heat of hydration is 8.0 kcal mol^{-1}.
[b]The *H* italicized in **22a** is absent in this case as the data are for the diammonium salt.

TABLE 5. Heats of formation of a collection of solid substituted naphthalenes and corresponding benzenes[a]

Substituent	ΔH_f(s, NaphX)	ΔH_f(s, PhX)	δ_5
None	18.6	9.3[b]	9.3
1-Me	10.6[b]	1.4	9.2
2-Me	10.7	1.4	9.3
2,3-Me_2	−0.5	9.1[b]	9.6
1-OH	−28.9	−39.5	10.6
2-OH	−29.7	−39.5	9.8
1-COOH	−79.7	−92.1	12.4
2-COOH	−82.7	−92.1	9.4

[a]All unreferenced data are from Reference 3. For the purposes of this table we designate the difference by $\delta_5 \equiv \delta\Delta H_f$(s, NpX, PhX).
[b]These data are from Reference 22.

benzenesulphonic acid (**20**) itself, nor for 2,4-dinitro-1-naphthol **22c**, Badoche's species **22a** *sans* the sulphonic acid group. However, we may estimate the heat of formation of this naphthol by adding 10 kcal mol^{-1} to the value for solid 2,4-dinitrophenol, resulting in a value of -45.6 kcal mol^{-1}. Ideally, sulphonation of an aromatic would result in a constant heat of formation increment. That is, $\delta\Delta H_f$(s, $ArSO_3H$, ArH) would be independent of the choice of arene in ArH. The difference of the heats of formation of 2-naphthol **21c** and its 6-sulphonic acid **21a** is $-179.2-(29.7)=-149.5$ kcal mol^{-1} while that of 2,4-dinitro-1-naphthol **22c** and its 7-sulphonic acid **22a** is $-190.0-(-45.6)=-144.4$ kcal mol^{-1}. Though the two differences are some 5 kcal mol^{-1} apart, given the severity of our assumptions, we view both our assumptions and these data as self-consistent. It would appear that the heat of formation of a sulphonated species is *ca* 146 kcal mol^{-1} lower than its unsulphonated precursor. Equivalently, the sulphonation increment, $\delta\Delta H_f$(s, $ArSO_3H$, ArH), is *ca* -147 kcal mol^{-1}.

However, is this finding consistent with those presented earlier? We cannot compare those for 2-aminoethanesulphonic acid directly with ethylamine because the sulphonic acid is really the zwitterion **8**, nor the 1,2-ethanediol-1,2-disulphonic acid **11** with ethylene glycol **16** because the sulphonic acid exists only in solution. What about the study of Roth and Rist-Schumacher[18]? From ΔH_f(s, n-$C_{12}H_{26}$), -92.7 kcal mol^{-1} taken from Reference 22, we would predict a value of ΔH_f(s, n-$C_{12}H_{25}SO_3H$ (**19**)) $=-240$ kcal mol^{-1} by use of our increment. Even 'forgiving a few' kcal mol^{-1} discrepancy for differences of substitution effects on an aromatic ring as opposed to those on an aliphatic chain, there is still a *ca* 100 kcal mol^{-1} discrepancy between that predicted from our increment and that directly measured. It would appear that the desired consistency between the two sets of direct sulphonic acid calorimetric experiments is lacking.

C. The Heat of Combustion of Benzenesulphonamides

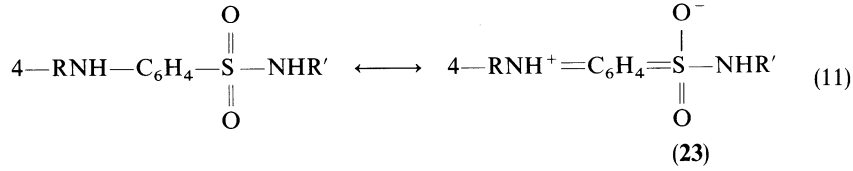
As part of a study that attempted to relate bacteriostatic activity with polarity and other aspects of molecular structure, Pushkareva and Kokosho[23] reported in 1946 the heat of combustion of a series of solid benzenesulphonamides. They were studying some of the 'sulpha' drugs, generically species 4-$RNHC_6H_4SO_2NHR'$ (**23**), and their desamino derivatives. An explicit goal of their study was to investigate the importance of 'p-link' (or now more commonly called quinoidal or quinonoidal) resonance, as shown in equation 11. Table 6 chronicles their findings, expressed solely in terms of heat of

TABLE 6. Heat of combustion (in kcal mol^{-1}) of various solid benzenesulphonamides, *x*-$RC_6H_4SO_2NHR'$(all data are from Reference 23)

x	R	R′	Compound	ΔH_c
	H	H	**24a**	813
3	NH_2	H	**23a**	842.4
4	NH_2	H[a]	**23b**	840
4,2	NH_2,Me	H	**23c**	995.6
	H	Ac	**24b**	1028.7
4	NH_2	Ac	**23d**	1053.0
	H	2-Pyr	**24c**	1413.5
4	NH_2	2-Pyr[b]	**23e**	1428.0

[a]This species is to be recognized as the archetype of the 'sulpha' drugs, sulphanilamide.
[b]This species is also known as 'sulphapyridine'.

combustion since we lack the necessary ancillary thermochemical data that would allow us reliably to convert these values to the more conventional and more desirable quantity, the heat of formation.



(11)

(23)

How self-consistent are these data with other available data? The first comparison is parent benzenesulphonamide (**24a**) and its amino derivatives. By contrasting the solid sulphonamides with liquids that lack the SO_2NHR' group of interest, we may attempt to equate the difference of the heat of combustion of either the 3- or 4-amino species (**23a** and **23b**, respectively) and the unsubstituted benzenesulphonamide (**24a**), directly with the corresponding difference for liquid $PhNH_2$ and PhH. That is, we assume $\delta\Delta H_c(ArNH_2, ArH)$ is a constant[24] equal to *ca* 30 kcal mol^{-1}. For the sulphonamides, the difference $\delta\Delta H_c$(s, **23a** or **23b**, **24a**) equals some 27 kcal mol^{-1}, while for their *N*-acetyl species $\delta\Delta H_c$(s, **24b**, **23d**) the difference is the comparable 24 kcal mol^{-1}. However, we can think of no way of rationalizing why the difference for the corresponding 2-pyridyl derivatives $\delta\Delta H_c$(s, **24c** **23e**) is only somewhat more than 14 kcal mol^{-1}.

The 2.4 kcal mol^{-1} difference between the heats of combustion of the isomeric aminobenzenesulphonamides, **23a**, **23b**, is corroborative of the importance of the quinonoid resonance structure for the latter. Related, but smaller, differences are found for many other isomeric pairs of appropriately 1,3- and 1,4-disubstituted benzenes (e.g. $\delta\Delta H_c[s, H_2NC_6H_4NO_2] = 0.9$ kcal mol^{-1}; $\delta\Delta H_c[s, H_2NC_6H_4COOH] = 0.3$ kcal mol^{-1}). Ring methylation of 4-aminobenzenesulphonamide, as manifested by the transformation of **23b** to **23c**, would be expected to increase the heat of combustion by *ca* 155 kcal mol^{-1} if one equates the change with $\delta\Delta H_c$(lq, PhMe, PhH). We find $\delta\Delta H_c$(s, **23b**, **23c**) = 156 kcal mol^{-1} in good agreement. Acetylation of the sulphonamido group also results in a nearly constant change in the heats of combustion, 314.3 $\pm$ 1.4 kcal mol^{-1}, as shown by comparisons of **24a** with **24b** and **23b** with **23d**. It would appear that consistency is generally found for heats of combustion, and thus for heats of formation, of these numerous derivatives of benzenesulphonamide.

D. The Thermochemistry of Sulphonation Reactions, Part 1: Naphthalene

In Section III.B, we argued that sulphonation is accompanied by a constant change of heat of formation. If we trust Badoche's results[21] on naphthols the value is -147 kcal mol^{-1}, but only *ca* -50 kcal mol^{-1} should we accept those of Roth and Rist-Schumacher[18] on n-dodecane. In 1948 Spyrskev reported[25] that the heat of sulphonation of liquid naphthalene (**25**), reaction 12, was exothermic by 5.1 kcal mol^{-1}, given that the necessary corrections for heats of solution and dilution are made. Additional corrections are required to correspond to the reaction of solid naphthalene by explicitly including ΔH_{fus} (**25**) (4.5 kcal mol^{-1} from Reference 22). Together with the currently recommended values[12] of $\Delta H_f(lq, H_2SO_4)$ and $\Delta H_f(lq, H_2O)$, we find sulphonation affects a change of heat of formation $\delta\Delta H_f(s, RSO_3H, RH)$, of some -127 kcal mol^{-1}. The heat of formation of Spyrskev's mixture of solid naphthalenesulphonic acids (1-, **26a**; 2-, **26b**) is thus -108 kcal mol^{-1}. Spyrskev had earlier shown[26] that the 1-:2-isomer ratio varied from 1:24 to 1:10 to 1:6 as the temperature was increased from 122 °C to 140 °C to 160 °C. By comparison with other naphthalene derivatives (cf. Table 5), it is reasonable to assume that the 2-isomer is but a few kcal mol^{-1} more stable than the 1-isomer. That the product

in reaction 12 is the less stable isomer has but little effect on our thermochemical conclusions[27]. It would seem that Badoche's results are closer to those of Spyrskev[25] than those of Roth's groups[18], but the difference between those of Badoche and Spyrskev's sets of $\delta\Delta H_f$(s, RSO_3H, RH) is still an unacceptable *ca* 20 kcal mol^{-1}.

$$\underset{\textbf{(25)}}{C_{10}H_8(lq)} + H_2SO_4(lq) \longrightarrow \text{mostly } \underset{\textbf{(26a)}}{1\text{-}C_{10}H_7SO_3H(s)} + H_2O(lq) \qquad (12)$$

E. The Heat of Reaction of Acetone and $NaHSO_3$: The Thermochemistry of Sodium 2-Hydroxy-2-propanesulphonate

In 1949/1950 Iliceto and Malatesta[28] reported the heat of reaction 13 of aqueous acetone (**27a**) and $NaHSO_3$ to form sodium 2-hydroxy-2-propanesulphonate (**27b**) as 12.7 kcal mol^{-1}. We have earlier suggested (see Section II.C) that the difference between the heat of formation of an aqueous solution of XCH_2SO_3Na and of XMe is nearly a constant, *ca* 203 ± 2 kcal mol^{-1}. From ΔH_f(lq, *i*-PrOH), we would predict that the heat of formation of the aqueous sulphonate is $-76 + (-203) = -279$ kcal mol^{-1}. From ΔH_f(lq, Me_2CO), ΔH_f(aq, $NaHSO_3$) and the measured heat of reaction 13, we find a value of $-59.3 + (-207.1) + (-12.7) = -279.1$ kcal mol^{-1}.

$$\underset{\textbf{(27a)}}{Me_2CO(aq)} + NaHSO_3\ (aq) \longrightarrow \underset{\textbf{(27b)}}{Me_2C(OH)SO_3Na(aq)} \qquad (13)$$

The agreement is perhaps 'too' good since we have neglected the difference of the heats of solution of both *i*-PrOH and Me_2CO. However, for the related 2-carbon species, EtOH and MeCHO, the heats of solution are 2.6 and 5.7 kcal mol^{-1}. It would appear that, within 'a few' kcal mol^{-1}, our earlier assumptions remain vindicated. (See Section VII.C for more discussion of the thermochemistry of carbonyl addition reactions.)

F. The Heat of Formation of 4-Amino-naphthalenesulphonamides

In 1950, Boldyrev and Postovskii[29] reported the heat of combustion and heat of formation of a series of naphthalenesulphonamides as a sequel to the series of benzenesulphonamides reported earlier by Pushkareva and Kokosho[23]. Table 7 presents the findings on these new species (**28a**–**28c**), 4-$NH_2C_{10}H_6SO_2NHR$. From these data, we find that the comparison of heats of combustion of 4-aminobenzenesulphonamides from Reference 23 and 4-aminonaphthalene-1-sulphonamides from Reference 27 is definitely problematic. In particular, the heats of combustion of the parent species (**23b** and **28a**) differ by 460.6 kcal mol^{-1}, but the *N*-2-pyridyl species (**23e** and **28a**) differ by 474.9 kcal mol^{-1}. We know of no reason why these differences should be so unequal. Furthermore, using heat of combustion data from Reference 3, we find that differences for other corresponding naphthalene and benzene derivatives pairs (cf. Table 5) are *ca*

TABLE 7. Heat of combustion and formation of various solid 4-aminonaphthalenesulphonamides, 4-$NH_2C_{10}H_7SO_2NHR$, from Reference 29 (all data are in kcal mol^{-1})

R	Compound	ΔH_c	ΔH_f	$\Delta H_f\downarrow$[a]
H	**28a**	1300.6	−77.9	− 65
2-Pyr	**28b**	1902.9	−50.3	− 37
4-$NH_2SO_2C_{10}H_6$-1-	**28c**	2492.4	−161.9	−149

[a] This set of numbers denoted by '$\Delta H_f\downarrow$' are those derived from the heats of formation presented in Reference 29 and discussed here in Section III.F, but tentatively re-evaluated in Section VII.A These authors also presented thermochemical data for the desamino analogs of **28a**–**c**. For these three species, we derive $\Delta H_f\downarrow = -60, -22$ and -118 kcal mol^{-1}.

455 kcal mol^{-1}. (Recall that, by definition, a 'constant' heat of combustion difference of corresponding naphthalene and benzene derivatives implies a 'constant' heat of formation difference.)

The above analysis strongly suggests that the data for the pyridyl compounds are suspect. However, for the parent species, the values seem much more credible because their difference of heats of formation is quite close to that of other corresponding naphthalenes and benzenes. As such, if we accept ΔH_f(s, 4-$NH_2C_{10}H_6SO_2NH_2$) = −77.8 kcal mol^{-1} from Reference 23, we conclude that ΔH_f(s, 4-$NH_2C_6H_4SO_2NH_2$) is between −85 and −90 kcal mol^{-1}. In fact, a comparison of this theoretical value with an experimentally measured one for the parent benzenesulphonamide will be made in Section VII.A. It will be seen that the heats of formation of all of the naphthalenesulphonamides discussed in this section should be increased by *ca* 10 kcal mol^{-1}.

IV. THERMOCHEMICAL MEASUREMENTS FROM 1951 TO 1960

A. The Thermochemistry of Sulphonation Reactions, Part 2: Benzene-1,3-diol

Parallelling the earlier studies of the sulphonation of naphthalene (cf. Section III.D and, in particular, Reference 25), the heat of sulphonation of solid benzene-1,3-diol (**29**, resorcinol) to form the 4,6-disulphonic acid (**30**) was reported[30] in 1957. The directly measured value was 3.6 ± 1.1 kcal mol^{-1}. However, to make meaningful comparisons, it is necessary to modify the experimental result by inclusion of ΔH_{fus} (**29**) (the heat of fusion, approximated by the value[2] at the melting point, 383 K, 5.1 kcal mol^{-1} and then halving the sum to correct for disulphonation. These corrections result in a value of 4.4 kcal mol^{-1} for the idealized monosulphonation, a value consonant with the 5.07 kcal mol^{-1} reported for the corresponding monosulphonation of naphthalene. We are thus confident of the derived value, ΔH_f(s, 1,3-$C_6H_2(OH)_2$-4,6-$(SO_3H)_2$) = −346 kcal mol^{-1}.

B. The Thermochemistry of the Chlorosulphonation and Chlorination of n-Dodecane

In 1958, Geiseler and Nagel[31] reported the energetics of the chlorosulphonation reaction of n-dodecane (**31**) with a mixture of SO_2 and Cl_2 (equation 14.) They reported that a mixture of primary and secondary sulphonyl chlorides were formed accompanied by liberation of 39.0 ± 0.5 kcal mol^{-1}. The ratio of primary (**19**) to (the other wise undefined mixture of isomeric) secondary products (**32**) was determined to be *ca* 1:11. However, in the absence of further study, we cannot determine how much this reaction is thermodynamically driven (e.g. sulphonyl chloride and free radical stabilities) versus kinetically driven (e.g. free radical reactivities). We will assume that the difference in heats of formation of all of the secondary sulphonyl chlorides are the same. That the difference of the heats of formation of the primary and secondary products is about 2 kcal mol^{-1} may be derived from values for a set of isomeric primary (n-) and secondary (*i*-) propyl derivatives shown in Table 8. From the long known and highly accurate heats of formation of liquid n-dodecane (**31**, −83.9 kcal mol^{-1}, Reference 3) and of gaseous SO_2 and HCl (−70.9 and −22.1 kcal mol^{-1}, Cl_2 equalling 0 by definition, all from Reference 12), we derive the heat of formation of any of the five different secondary n-dodecanesulphonyl chlorides (**32**) to be −171.9 kcal mol^{-1} and for the primary n-dodecane-1-sulphonyl chloride (**19**) a value of −169.9 kcal mol^{-1}.

$$\underset{(\mathbf{31})}{\text{n-}C_{12}H_{26}} + SO_2 + Cl_2 \longrightarrow [\underset{(\mathbf{19})}{\text{n-}C_{12}H_{25}SO_2Cl} + \underset{(\mathbf{32})}{CH_3(CH_2)_{9-x}CH(SO_2Cl)(CH_2)_xCH_3}] + HCl \qquad (14)$$

TABLE 8. Heats of formation of isomeric liquid n- and *i*-propyl derivatives and the difference for each pair[a]

X	ΔH_g(lq,n-PrX)	ΔH_f(lq,*i*-PrX)	δ_8
Me	−35.0	−36.7	1.7
Et	−41.6	−42.7	1.1
n-Pr	−47.5	−48.9	1.4
i-Pr	−48.9	−49.6	0.7
Ac	−71.1	−71.6	0.5
NH_2	−24.3	−26.8	2.5
NO_2	−40.0	−43.1	3.1
OH	−72.6	−76.0	3.4
ONO_2	−51.3	−54.9	3.6
SH	−23.7	−25.3	1.6
Cl	−38.4	−41.3	2.9
Br	−29.1	−31.2	3.1
I	−15.8	−17.8	2.0

[a]For the purposes of this table we designate the difference by $\delta_8 \equiv \delta\Delta H_f$(g, n-PrX, *i*-PrX). All primary data are taken from Reference 3 and are in kcal mol^{-1}.

These authors[31] also reported that the desulphonylation reaction of the mixture of **19** and **32** was endothermic by 3.6 kcal mol^{-1} and resulted in a mixture of primary and secondary chlorododecanes (**33** and **34**); they could also form by direct chlorination of the hydrocarbon. The heat of formation of 1-chlorododecane (**33**) is well established as −93.8 ± 0.6 kcal mol^{-1}. Let us assume that the difference between heats of formation of isomeric primary and secondary chlorides is a constant, and so $\delta\Delta H_f$(lq, **33**, **34**) = $\delta\Delta H_f$(lq, n-PrCl, *i*-PrCl) = 2.7 ± 0.5 kcal mol^{-1}. [Interestingly, there are no reliable data for any isomeric pair of alkyl chlorides save these propyl chlorides—for 1- and 2-chlorobutane **35a** and **35b**, $\delta\Delta H_f$(lq, **35a**, **35b**) = 1.1 ± 2.0 kcal mol^{-1}.] The heats of formation of any of the various liquid secondary chlorododecanes lumped together here as **34** are all *ca* −96.5 kcal mol^{-1}. If we now assume that the heat of loss of SO_2 is independent of the individual sulphonyl chloride, ΔH_f(lq, n-$C_{12}H_{25}SO_2Cl$) = −167.6 kcal mol^{-1}, and of any of its liquid secondary isomers (**34**), this quantity equals −170.3 kcal mol^{-1}. The agreement is gratifying and we suggest taking the average values of −168.8 ± 1.5 kcal mol^{-1} and −171.2 ± 1.5 kcal mol^{-1} as the heats of formation of the sulphonyl chlorides of interest.

The reader may recall we discussed in Section III.A another (Reference 18, and totally independent) thermochemical study of **19**, in which the heat of formation of this sulphonyl chloride, its heat of solution with ethanol and its reaction with water were all discussed. This earlier value of ΔH_f(lq, **19**) was −94.5 ± 4.5 kcal mol^{-1}, in unequivocal disagreement with one we have just obtained. However, let us assume that the energetics of the reaction with water are correct because it is a simpler measurement than heats of combustion. Let us also assume that the heat of reaction of a sulphonyl chloride is independent of the choice of sulphonyl chloride. We thus derive heats of formation of −215.3 and −217.7 kcal mol^{-1} for the isomeric primary and (the five) secondary n-dodecanesulphonic acids, species **18**, and **36**, respectively. From Reference 22, we find ΔH_f(s, n-$C_{12}H_{26}$) = −92.7 kcal mol^{-1} from which we would derive $\delta\Delta H_f$(s, RSO_3H, RH) = −124 kcal mol^{-1}, comfortably close to the −127 kcal mol^{-1} that we derived earlier using Spyrskev's results[26]. We thus have confidence in the ability to predict the heat of formation of any solid sulphonic acid to within a few kcal mol^{-1} from the corresponding knowledge of the parent hydrocarbon.

C. The Thermochemistry of Sulphonation Reactions, Part 3: The Isomeric Ethyl- and Dimethylbenzenes

In 1959[32], the heats of sulphonation of the isomeric ethylbenzene and the three dimethylbenzenes (xylenes) were reported by Leitman and Pevzner. After correcting for heats of solvation and dilution, these authors found the following exothermicities: for ethylbenzene (**37**), 5.1 ± 0.2; *o*-xylene (**38a**), 5.5 ± 0.2; *m*-xylene (**38b**), 3.9 ± 0.1; *p*-xylene (**38c**), 4.1 ± 0.2 kcal mol^{-1}. No product analysis was reported in this study so that we cannot ascertain the site(s) of sulphonation or even the possibility of rearrangement and/or transalkylation reactions. However, that **37**, **38a**–**38c** have comparable heats of formation [ΔH_f(lq) = -2.9, -5.8, -6.1, -5.8 kcal mol^{-1}], and that their heats of sulphonation are comparable, suggests that all of these results are consistent with each other. The heat of formation of any of the solid isomeric ethyl- or dimethylbenzenesulphonic acids are thus *ca* -136 kcal mol^{-1} with an anticipated 'few' kcal mol^{-1} spread of values[33].

Are these numbers reasonable? First of all, the reported heats of sulphonation are comparable to those earlier chronicled for liquid naphthalene and resorcinol. Second, let us assume that **37**, **38a**–**38c** individually form the most stable sulphonic acid consistent with the *ortho*-/*para*-directing character of alkyl groups and that there was no accompanying isomerization or transalkylation. We may then derive the following heats of formation for four solid sulphonic acids: 4-Et$C_6H_4SO_3H$ (**39**) -133.2; 3,4-XylSO_3H (**40a**), -137.5; 2,4-XylSO_3H (**40b**), -136.2; 2,5-XylSO_3H (**40c**), -136.1 kcal mol^{-1}. Finally, if we set the value of $\delta\Delta H_f$(s, RSO_3H, RH) to be the averaged quantity -126 ± 2 kcal mol^{-1}, and use it with the heats of formation of solid **37** and **38a**–**38c** from Reference 22, we deduce values of -131, -135, -134 and -136 kcal mol^{-1}, respectively, for the heats of formation of solid **39** and **40a**–**40c**. The close agreement between the earlier and current predictions of the heats of formation of these solid sulphonic acids encourages optimism about all of these numbers and, more importantly, also about our heat of formation increment, $\delta\Delta H_f$(s, RSO_3H, RH).

Let us now consider the nearly constant -126 kcal mol^{-1} increment. Recall that in Section II.C we showed $\delta\Delta H_f$(aq, XCH_2SO_3Na, XMe), the related increment for aqueous substituted methanesulphonates, is a nearly constant -203 kcal mol^{-1}. Let us generalize the last result to read the difference of the heats of formation between any aqueous organic species, RH, and its corresponding aqueous sodium sulphonate salt, RSO_3Na, $\delta\Delta H_f$(aq, RSO_3Na, RH). Also recall from Section II.C that the difference of the heats of formation of aqueous sodium salts and the parent acid is 57.3 kcal mol^{-1}. We conclude that the difference of the heats of formation of aqueous RH and aqueous RSO_3H, $\delta\Delta H_f$(aq, RSO_3H, RH), approximately equals -146 kcal mol^{-1}. From the general differences of heats of formation of sulphonic acids and hydrocarbons, first as solids and then in aqueous media, of 126 and 146 kcal mol^{-1}, respectively, we conclude that the heat of solution of a sulphonic acid is increased by *ca* 20 kcal mol^{-1} over that of its parent hydrocarbon. We think this is a reasonable number. In comparison, from Reference 12, we find the heats of solution of some strong, and hence completely dissociated, oxyacids are: H_2SO_4, 20.4; $HClO_4$, 21.4; HNO_3, 7.9; FSO_3H, 18.3 kcal mol^{-1}.

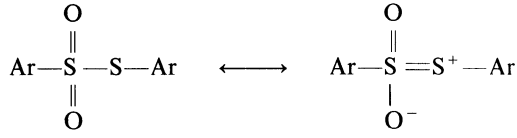
V. THERMOCHEMICAL MEASUREMENTS FROM 1961 TO 1970

A. The Thermochemistry of Diphenyl Disulphone and Related Species

We now turn to the heat of formation of species **1**, diphenyl disulphone. As mentioned early in this chapter, the heats of formation of this species as solid, liquid and gas were directly determined by Mackle and O'Hare[4] in 1964 to be -153.6 ± 0.4, -150.5 and -114.9 ± 0.9 kcal mol^{-1}. In this same year, Kice and Pawlowski[6] determined the

thermochemistry of the S—S bond cleavage of di-*p*-tolyl [bis(4-methylphenyl)]-disulphone and related partially deoxygenated species. Almost 15 years later, Benson[5] unified these data for $ArSO_2SO_xAr$ (Ar = 4-Tol, $x = 0$, 1, 2—species **2**, **3**, **4**) to derive meaningful heats of formation. More precisely, for gaseous diphenyl disulphide *S,S*-dioxide (Ar = Ph, $x = 0$, also named **5**, benzenesulphonyl benzenethiolate and diphenyl sulphone sulphide) and diphenyl disulphide trioxide, (Ar = Ph, $x = 1$, **6**, benzenesulphonyl *S*-benzenesulphinate and diphenyl sulphone sulphoxide), Benson deduced values of -22 ± 4 and -52 ± 2 kcal mol^{-1}, respectively. While these are the only thermochemical data known to the present author for the SO_2S and SO_2SO functionalities, nonetheless we can ask about their plausibility.

In particular, let us look at the differences of the heats of formation of the three $PhSO_2SO_xPh$ species with $x = 0$, 1 and 2, **1**, **5** and **6**, and of the corresponding single sulphur-containing species $PhSO_xPh$, **41**, **42**, and **43**. Table 9 presents the data for the three sets of species. It is seen that the differences in heats of formation of the $x = 0$ and 1 cases, $\delta\Delta H_f$(g, **5**, **41**) and $\delta\Delta H_f$(g, **6**, **42**), are nearly identical, -77 ± 5 and -78 ± 3 kcal mol^{-1}, while the value for $x = 2$, $\delta\Delta H_f$(g, **1**, **43**), equals -88 ± 2 kcal mol^{-1} and thus appears very disparate. Diphenyl disulphone is seemingly stabilized relative to the sulphonylsulphide and sulphonylsulphoxide. This result runs counter to our intuition based on intramolecular Coulombic repulsion, i.e. $S^{\delta+}$–$S^{\delta+}$ repulsion is expected to be maximized in the disulphone. It also argues against the importance of resonance involving octet-expanded ionic structures, e.g.



(15)

that can occur in the sulphonylsulphide and sulphonylsulphoxide, but not the disulphone. We have no explanation for the anomalously high stability of diphenyl disulphone, although we do note that with appropriate 'rigging' (i.e. selective reading) of the error bars, we can arrange the discrepancy change linearly with increasing oxygen count x: -73, -81 and -88 kcal mol^{-1}.

We also note that Kice and Pawlowski[6] described the seemingly facile thermal rearrangement of the sulphone sulphoxide, $ArSO_2S(O)Ar$ (**44**), into the corresponding sulphonyl sulphenate, $ArSO_2$—O—SAr (**45**), when Ar = *p*-Tol. While the rearrangement of sulphoxides to sulphenates is very rare, that the above process occurs readily suggests that ΔH_f (g, $PhSO_2$—O—SPh) $\leqslant -52$ kcal mol^{-1}. This value for benzenesulphonyl benzenesulphenate (**46**) is the sole thermochemical quantity known for any sulphonyl

TABLE 9. Heats of formation of gas-phase diphenyl disulphide polyoxides and diphenyl sulphide polyoxides, and their differences[a]

X	ΔH_f(g, $PhSO_2SO_XPh$)		ΔH_f(g, $PhSO_XPh$)		δ_9
0	-22 ± 4[b]	(**5**)	55.3 ± 0.7	(**41**)	-77 ± 5
1	-52 ± 2[b]	(**6**)	25.5 ± 0.7	(**42**)	-78 ± 3
2	-115 ± 1[c]	(**1**)	-28.5 ± 0.8	(**43**)	-88 ± 2

[a] For the purposes of this table we designate the difference by $\delta_9 \equiv \delta\Delta H_f$(g, $PhSO_2SO_XPh$, $PhSO_XPh$). All data are in kcal mol^{-1}.

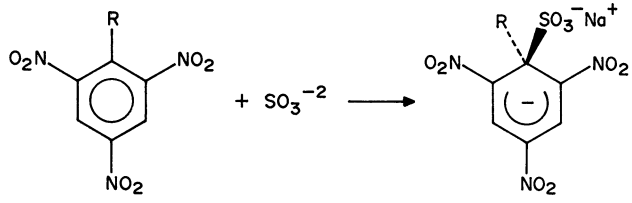
[b] These data are taken from Reference 4.

[c] All of these data are taken from the analysis of Benson[5], who used the primary experimental measurements of Kice and Pawlowski as input numbers.

sulphenate, and one of the very few seemingly available for any sulphenyl derivative[34]. More discussion of this species can be found in Section VIII.A of the current study.

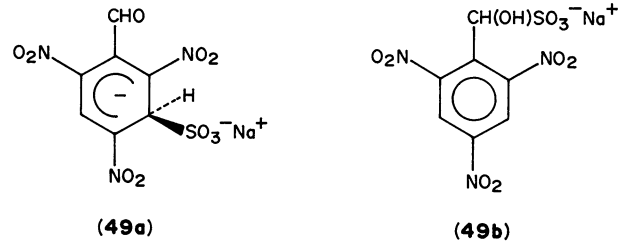
B. The Reaction of Aqueous Sodium Sulphite and 1,3,5-Trinitrobenzene Derivatives

In 1967, Norris[35] reported that 1,3,5-trinitrobenzene (**47**, R = H) reacted with aqueous Na_2SO_3 to form a 1:1 complex. The accompanying exothermicity is 4.00 $\pm$ 0.14 kcal mol^{-1} and the equilibrium constant for its formation is 2.67 $\times$ 10^2 L mol^{-1}. By analogy to the earlier discussed[28] reaction 13 of acetone and $NaHSO_3$ to form the α-hydroxysulphonate **27b** (Section III.E), we assume addition to the benzene ring is via the nucleophilic sulphur. That is, reaction 16 is presumed to result in the dianionic 'Meisenheimer' complex, 48. However, we have insufficient experience with aqueous carbanions to translate Norris' findings into the desired heat of formation, ΔH_f(aq, **48**).



(16)

Relatedly, Norris[35] reported that the heat of complexation of sulphite anion with the 2,4,6-trinitro derivatives of toluene and benzaldehyde (R = Me and CHO in **47**) had equilibrium constants of 5.6 $\times$ 10^0 and 2.15 $\times$ 10^3 L mol^{-1}, respectively. However, in that neither the enthalpy nor entropy of reaction was presented separately for either of these two cases, there is insufficient information to evaluate such issues as whether the latter corresponds to complex **48** with R = CHO, to its non-'*ipso*' Meisenheimer isomer (**49a**) or to the 'normal' carbonyl addition complex **49b**.



C. 2-Oxetanone (β-Propiolactone) and Addition Reactions: The Thermochemistry of Aqueous Disodium 2-Carboxyethanesulphonate

In 1969, Davis, Suba, Klimishin and Carter[36] reported the energetics of the addition reactions of 2-oxetanone (β-propiolactone, **50**) with a large number of different nucleophiles X^- in reaction 17. Of particular relevance to this chapter was the choice of $X^- = SO_3{}^{-2}$ since the product is 2-sulphopropionate (also called 2-carboxyethanesulphonate) dianion, **51**. Rather than probing the question 'What is ΔH_f(aq, **51**)?' we opt to ask and answer instead 'What is ΔH_f(aq, $NaOOC(CH_2)_2SO_3Na$), the heat of formation of its

aqueous disodium salt, **52**?. The answer to this latter question may be derived in several distinct ways. The first is to use directly the observed heat of reaction (-36.9 ± 0.2 kcal mol^{-1}) and the heats of formation of aqueous **50** and aqueous Na_2SO_3[12] (-275.5 kcal mol^{-1}). While the heat of formation of the pure lactone[3] is known accurately (-78.8 ± 0.2 kcal mol^{-1}), we know of no experimental data for its heat of solution. If we approximate ΔH_{soln} (**50**) by ΔH_{soln}(MeOAc), i.e. the measured quantity for the corresponding acyclic ester[37] (namely 1.8 kcal mol^{-1}), ΔH_f(aq, **51**) $= -393$ kcal mol^{-1}.

(aq) + X^-(aq) ⟶ $X(CH_2)_2COO^-$(aq) (17)

(50)

The second approach recalls that we had earlier suggested (see Section II.C) that $\delta\Delta H_f$(aq, XCH_2SO_3Na, XMe) was rather constant at -203 ± 2 kcal mol^{-1}. In the current case, X = $NaOOCCH_2$. While we lack knowledge of the measurements of the heat of formation of aqueous sodium propionate—the XMe species of interest—this quantity is easily estimated. All that need be done is assume the heat of reaction 18 equals 0—after all, the pK_a values of MeCOOH and EtCOOH are very close. From Reference 12 we find that the heat of solution of MeCOOH is negligibly exothermic, -0.3 kcal mol^{-1}. Table 10 documents that the normalized difference of the heats of solution[12] of pairs of other neutral liquid ethyl and methyl species, $\delta\Delta H_{soln}(Et_nX, Me_nX)/n$, is generally quite small. As such, ΔH_{soln}(EtCOOH) is also near 0 and thus ΔH_f(aq, EtCOONa) is *ca* -186 kcal mol^{-1}. Accordingly, ΔH_f(aq, **52**) is found to be -389 kcal mol^{-1}.

$$MeCOONa(aq) + EtCOOH(aq) \longrightarrow MeCOOH(aq) + EtCOONa(aq) \quad (18)$$

We now recall[36] that reaction 17 is exothermic by 36.9 kcal mol^{-1} for X = SO_3^{-2} but by 34.9 kcal mol^{-1} for the 2-hydroxypropionate producing reaction with X = OH^-. Combining these two different anion results, and including enough sodium ions for neutrality, we find reaction 19 is exothermic by 2 kcal mol^{-1}. By analogy to the small differences of the heats of ionization of XCH_2COOH and $X(CH_2)_2COOH$ measured by Avedikian[16] for X = H, Cl, Br and I, let us assume reaction 20 is thermoneutral. From this we derive ΔH_f(aq, $HO(CH_2)_2COONa$) $= -226$ kcal mol^{-1}, and accordingly, ΔH_f(aq, **52**) $= -383$ kcal mol^{-1}.

TABLE 10. Heats of solution of pairs of neutral liquid Et_nX and Me_nX species and their normalized difference[a]

X	$\Delta H_{soln}(Et_nX)$	$\Delta H_{soln}(Me_nX)$	δ_{10}
H	−4.2	−3.4	−0.8
OH	−2.5	−1.7	−0.8
NH_2	−6.5	−5.5	−1.0
>NH	−7.4	−6.8	−0.3
NO_2	+1.4	+0.6	+0.8[b]
>N−	−9.5	−7.6	−0.6

[a] For the purposes of this table we designate the normalized difference by $\delta_{10} \equiv \delta\Delta H_{soln}(Et_nX, Me_nX)/n$. All data are in kcal mol^{-1}.

[b] We have no idea why δ_{10} should be opposite in sign for these nitro compounds to those differences found for the other derivatives of methane and ethane.

$$HO(CH_2)_2COONa(aq) + Na_2SO_3(aq) \longrightarrow NaOOC(CH_2)_2SO_3Na(aq) + NaOH(aq) \quad (19)$$

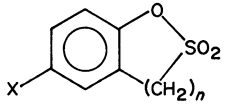
$$HOCH_2COONa(aq) + EtCOONa(aq) \longrightarrow HO(CH_2)_2COONa(aq) + MeCOONa(aq) \quad (20)$$

In summary, we deduce that the heat of formation of aqueous disodium 2-carboxyethanesulphonate is -386 ± 3 kcal mol^{-1}. While the uncertainty is larger than we would have desired, it is encouraging that the results are 'rather' consonant given the ± 2 kcal mol^{-1} uncertainty in the $\delta\Delta H_f$(aq, XCH_2SO_3Na, XCH_3) quantity that was an important input number for one of our estimation approaches. Indeed, we are encouraged by the near constancy of the change in heat of formation accompanying the formal replacement of H by the —SO_3Na group on neutral, cationic and, as we have just found, anionic frameworks.

VI. THERMOCHEMICAL MEASUREMENTS FROM 1971 TO 1980

A. The Energetics of Sultones: The Hydrolysis of Some Benzo[*d*]-1,2-oxathiole and Benzo[*e*]-1,2-oxathiin *S,S*-Dioxides

In 1978, Izbicka and Bolen[38] reported the heats of alkaline aqueous hydrolysis of 2-hydroxybenzenemethanesulphonic acid sultone, **53a** (3*H*-benzo[*d*]-1,2-oxathiole-2,2-dioxide), 2-hydroxybenzeneethanesulphonic acid sultone, **54a**, (3,4-dihydrobenzo[*e*]-1,2-oxathiin-2,2-dioxide) and their nitro derivatives, respectively, **53b** and **54b**. This corresponds to reaction 21. These authors demonstrated that the heats of hydrolysis to the appropriate (2-hydroxybenzene)alkanesulphonate (generically **55**) for the two five-membered ring containing species, the γ-sultones, are identical within the error bars: for **53a**, -43.5 ± 0.2; and for **53b**, -43.8 ± 0.8 kcal mol^{-1}. Likewise, the values for the two six-membered ring species (or δ-sultones) were also the same: for **54a**, -20.0 ± 3.7; and for **54b**, -21.2 ± 0.8 kcal mol^{-1}. What they noted, and left unexplained, is that the dependence on the ring size is 'remarkably large': the heat of hydrolysis of the five-membered ring is some 20 kcal mol^{-1} larger than for the six-membered ring. Their ancillary logic—comparison of the relative rates of hydrolysis, correction for the heats of ionization of the resulting sulphonates (**55**), or estimation of the strain release on hydrolysis of other five-membered heterocycles such as ethylene sulphate (1,3,2-dioxathiolane-2,2-dioxide, **56**)—failed to reconcile more than about half of the observed difference of the heats of hydrolysis. In addition, no products other than the 'acyclic' **55** were observed, corroborative of no particular mechanistic differences between the five- and six-membered ring sultones (e.g. the intermediacy of sulphenes in the former case.)



+ NaOH(aq) ⟶ 5-X C_6H_3—1—OH—2—$(CH_2)_n$ SO_3Na

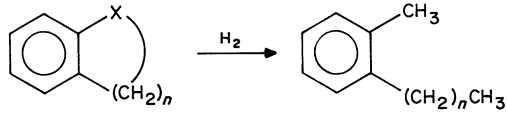
(55) (21)

n=1, X=H, **53a**; n=2, X=H, **54a**

n=1, X=NO_2, **53b**; n=2, X=NO_2, **54b**

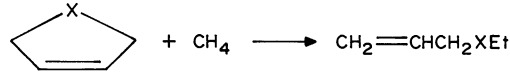
The authors also reported the thermochemistry of the hydrolysis reactions[36] of the related γ- and δ-lactones wherein CO replaces SO_2, i.e. the reaction of **57** and **58** to form the appropriate (2-hydroxybenzene)alkanoate (generically **59**). In this case, the opening of

the five-membered ring compound **57** differed from that of the six-membered ring compound **58** by only slightly more than 1 kcal mol^{-1}. We additionally consider the hypothetical ring-opening hydrogenation reactions 22 of liquid indene and 1,2-dihydronaphthalene (**60a** and **60b**) and of liquid indane and tetralin (**61a** and **61b**) to the saturated products, 2-ethyl- and 2-propyltoluene (**62a** and **62b**). The differences in exothermicities for the five- and six-membered carbocyclic ring cases differ only by *ca* 1 kcal mol^{-1}. Finally, we present documentation that the presence of hexavalent sulphur, i.e. $> SO_2$, in a five-membered ring can even decrease strain energies. Consider the formal reactions of 2,5-dihydrothiophene dioxide (**63a**) with methane to yield allyl ethyl sulphone (**64a**), and of cyclopentene (**63b**) with methane to form 1-hexene (**64b**). (These are reactions 23 with X = SO_2 and CH_2, respectively.) Using data from Reference 3, we find the reaction with X = SO_2 is endothermic by 2.0 kcal mol^{-1}, while with X = CH_2 the reaction is exothermic by 0.7 kcal mol^{-1}. While neither reaction heat directly equals the strain energy[39], we are nonetheless hard pressed to argue the cyclic sulphone is more strained than the carbocycle. We do not know how to reconcile all of these results, but find the discrepancy interesting. Much will be learned about strain energies, hydrolysis reactions and sulphonic acid chemistry when a coherent understanding is finally achieved.



(22)

X=—CH=CH—, n=1, **60a**; X=—$(CH_2)_2$—, n=1, **61a**, n=1, **62a**
X=—CH=CH—, n=2, **60b**; X=—$(CH_2)_2$—, n=2, **61b**, n=2, **62b**



(23)

X=SO_2, (**63a**) (**63b**)
X=CH_2, (**64b**) (**64b**)

B. The Chlorosulphonylation of *N*-Phenylacetamide

In 1978, Cavagna, Grewer, Jaenicke and Zeininger[40] reported reaction 24, the chlorosulphonylation of PhNHAc (**65**, acetanilide), resulted in 4-AcNHC$_6$H$_4$SO$_2$Cl (**66a**) and the liberation of some 27 kcal mol^{-1}. These authors also reported that reaction 25 relating **66a** and its parent sulphonic acid **66b** has an equilibrium constant of approximately 9. To first approximation the entropy of reaction 25, $\Delta S(25)$, should be small. As such, if set arbitrarily to 0, then the standard thermochemical relationships between Gibbs energies, enthalpies, entropies and equilibrium constants (equation 26). allows us to conclude

$$\text{PhNHAc} + 2\text{ClSO}_3\text{H} \longrightarrow \text{4-AcNHC}_6\text{H}_4\text{SO}_2\text{Cl} + \text{H}_2\text{SO}_4 + \text{HCl} \quad (24)$$

$$\text{4-AcNHC}_6\text{H}_4\text{SO}_3\text{H} \rightleftharpoons \text{4-AcNHC}_6\text{H}_4\text{SO}_2\text{Cl} + \text{H}_2\text{SO}_4 \quad (25)$$

$$\Delta G(23) \equiv \Delta H(23) - T\Delta S(23) = \Delta H(23) = -RT\ln(9) = -1.3 \text{ kcal mol}^{-1} \quad (26)$$

The reader may recall that sulphonation of aromatics by H_2SO_4 typically liberates *ca* 5 kcal mol^{-1} (cf. of species **25**, **29**, and **34a–d**, in Sections III.D, IV.A and IV.C,

respectively). Generalizing reaction 12 to all (aromatic and aliphatic) hydrocarbons RH and to any of their substituted derivatives, we deduce reaction 27 is exothermic by 5 kcal mol^{-1}. Likewise generalizing reaction 10 to all sulphonic acids and their chlorides, we conclude reaction 28 is essentially thermoneutral.

$$RH(s) + H_2SO_4(liq) \longrightarrow RSO_3H(s) + H_2O(liq) \quad (27)$$

$$RSO_2Cl(liq) + H_2O(liq) \longrightarrow RSO_3H(s) + HCl(g) \quad (28)$$

Are all of the above findings internally consistent for the R = 4-AcNHC$_6$H$_4$ current case? Neglecting all indications and thermochemical effects of phase and of solution, adding reactions 24 and 25 and substracting this sum from reaction 27 results in reaction 29:

$$ClSO_3H + H_2O \longrightarrow H_2SO_4 + HCl \quad (29)$$

Use of the heats of reactions 24, 25 and 27, namely $\Delta H(24)$, $\Delta H(25)$ and $\Delta H(27)$, would result in an exothermicity of 22 kcal mol^{-1} for reaction 29. By contrast, adding equations 25 and 28 would predict an exothermicity of 1 kcal mol^{-1} for this reaction. Using the heats of formation found in archive 12 for gaseous HCl and liquid H_2O, H_2SO_4 and $ClSO_3H$ we find an exothermicity of 5 kcal mol^{-1}. There appears to be a major discrepancy. However, since we lack heat of solution data for $ClSO_3H$, and for the aniline derivatives **65**, **66a** and **66b**, any further discussion is precluded at this time.

VII. THERMOCHEMICAL MEASUREMENTS FROM 1981 TO 1990

A. The Heats of Combustion and Formation of Benzenesulphonamide and 2- and 4-Toluenesulphonamide

In 1982, Van, Zhang, Jiang and Hu[41] (VZJH) reported the heats of combustion and formation of benzenesulphonamide and two of its methyl (i.e. toluene) derivatives, *x*-RC$_6$H$_4$SO$_2$NH$_2$: R = H, **24a**; *x*-R = 2 and 4-Me, **67a** and **67b**, respectively. These findings are presented in Table 11. The results are internally consistent. The relative isomer stabilities of **67a** and **67b** is qualitatively and quantitatively consistent with that of other substituted benzenes [e.g. $\delta\Delta H_f$(s, **37b**, **37d**) = 0.8 kcal mol^{-1}]. In addition, that either of the isomeric toluenesulphonamides, **67a** and **67b**, is some 9 kcal mol^{-1} lower than that of

TABLE 11. Heats of combustion and of formation of benzenesulphonamide and 2- and 4-toluenesulphonamide[a]

X	R	Compound	ΔH_c	ΔH_f
	H	**24a**	871.7 ± 0.1[b]	−74.6 ± 0.7
2	Me	**67a**	1025.1 ± 0.2	−83.1 ± 0.8
4	Me	**67b**	1024.7 ± 0.1	−83.5 ± 0.8

[a]All data are from Reference 41 and are in kcal mol^{-1}.

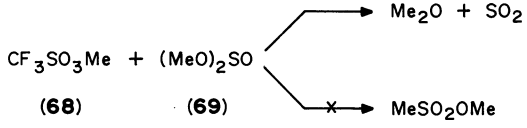
[b]The authors' table reports seven measurements of ΔE_c (the energy of combustion) of *ca* 3650 kJ mol^{-1}, but presents an average value of this quantity of 4647.2 ± 0.4 kJ mol^{-1}. Clearly, whether one 'thinks' in kJ or kcal (or 'merely' remembers that 1 kcal ≡ 4.184 kJ), there is an obvious discrepancy. However, since all seven reported values for each of the two R = Me species and their respective average value are *ca* 4287 kJ mol^{-1}, *and* there is no way that the heat of combustion of a methylated compound can be less than the species without the affixed methyl, we assume there is a typographical error in Reference 41 and that the correct value for species **24a** is 3647.2 kJ mol^{-1}.

parent **24a** parallels $\delta\Delta H_f$(s, PhMe, PhH) = 8 kcal mol^{-1} derived from the hydrocarbon values in Reference 22.

Apparently much more discordant is the nearly 60 kcal mol^{-1} difference in the heat of combustion of **24a** as reported by VZJH and by Pushkareva and Kokosho[23] over thirty years before. However, remember that heat of formation, not combustion, data are more relevant since the products and processes of combustion may differ (e.g. formation of a different quantity of SO_2 vs SO_3 concentration of the resulting H_2SO_4 solution), while the heat of formation is relative to a well-defined state. Recall our estimated value for ΔH_f(s, **24a**) of between −85 and −90 kcal mol^{-1} in Section III.F. That the new value of −74.1 kcal mol^{-1} reported in Reference 41 differs from this estimate of ΔH_f (**24a**) by *only* 10–15 kcal mol^{-1} is reassuring. Should the heats of formation of the naphthalene compounds, **28a**–**28d**, be re-evaluated *de novo* using this approximate 13 kcal mol^{-1} discrepancy? We think not, given ignorance of the precise details of the experiments from which these numbers are derived. On the other hand, the reader may recall we presented an alternative and admittedly tentative set of new heats of formation in Table 5 using this 13 kcal mol^{-1} correction.

B. The Non-interconversion of Dimethyl Sulphite and Methyl Methanesulphonate

In 1983, Christie, Lewis and Casserly[42] reported that the reaction of methyl trifluoromethanesulphonate (**68**) with dimethyl sulphite (**69**) resulted in decomposition (reaction 30) and not rearrangement (reaction 31), that is, methylation of **69** prefers an ester oxygen and not the sulphur. As such, we would seemingly be thwarted from using formally simple reactions on thermochemically sulphites to gain thermochemical information on sulphonates using the same 'methyltropic rearrangement' approach that Beak, Mueller and Lee[43] used for establishing the differences of heat of formation for amides, thioamides, pyridones, 2-pyrones and their respective imidate, thioimidate, pyridinol and 4-pyrone isomers. However, in the current case, reaction 30 with its two moles of product from one of starting material is entropy driven—it is noteworthy that the ether and SO_2 are 10 kcal mol^{-1} less stable than the parent sulphite by heat of formation criteria. We also note that this experiment does not prove that the ester oxygen is the most nucleophilic site. Indeed, our prejudices suggest attack of the 'sulphoxide' oxygen, an alternate reaction 32 of species **68** and **69**, results in what we believe is the most stable intermediate '$Me_3SO_3^+$ cation, $(MeO)_3S^+$ (**70**). However, to the extent that this reaction is reversible and the equilibrium lies on the left, there would have been no way of detecting it by product analysis save isotopic labelling. Of course, our logic also assumes sulphonates are more stable than their isomeric sulphites, a thermochemical comparison that is deferred to Section VIII.B.



(30)

(31)

$$CF_3SO_3Me + (MeO)_2SO \longrightarrow (MeO)_3S^+CF_3SO_3^- \quad (32)$$
(**70**)

C. The Thermochemistry of $NaHSO_3$ Addition to Carbonyl Compounds

The reader may recall (see Section III.E) that in the late 1940s, Illiceto and Malatesta[28] reported that the heat of reaction of aqueous acetone and $NaHSO_3$ was 12.7 kcal mol^{-1}.

In 1986, Olson, Boyce and Hoffman[44] and Deister, Neeb, Helas and Warneck[45] reported, respectively, the related heats of the reactions of aqueous benzaldehyde (**71a**) and formaldehyde (**72a**) with $NaHSO_3$ to be 15.4 and 13.0 kcal mol^{-1}. The reader will note that we do not immediately write these reactions as

$$RR'CO(aq) + NaHSO_3(aq) \longrightarrow RR'C(OH)SO_3Na(aq) \qquad (33)$$

for which R, R′ = Ph, H (**71b**) and H, H (**72b**). These would mimic our earlier reaction 13, in which R, R′ = Me, Me, **27b** is formed. This avoidance is because aqueous **72a** is hydrated to form aqueous methanediol (**73**) (reaction 34) that our thermochemical archives show to be exothermic by some 6.9 kcal mol^{-1}. Putting all of the numbers together, reaction 33 is exothermic by 15.4 and 19.9 kcal mol^{-1} for R = Ph and H, respectively.

$$\underset{\textbf{(72a)}}{CH_2O(aq)} + H_2O(lq) \longrightarrow \underset{\textbf{(73)}}{CH_2(OH)_2(aq)} \qquad (34)$$

Earlier in this chapter (see Section II.C) we suggested that the difference of the heat of formation of an aqueous solution of XCH_2SO_3Na and of XMe was nearly a constant, *ca* -203 ± 2 kcal mol^{-1}. For X = OH, the predicted heat of formation of aqueous $HOCH_2SO_3Na$ is $-58.8 + (-203) = -262$ kcal mol^{-1}. From the heat of formation of aqueous aldehyde **72a** (note, not the diol **73**), aqueous $NaHSO_3$, and the heat of reaction 33 for R = H, we would predict a value of -261 kcal mol^{-1}. This is a wonderful confirmation of that suggestion. This and our earlier successes on comparison of XCH_2SO_3Na and XMe suggests we use the same 203 kcal mol^{-1} correction for the PhCHO and Me_2CO reactions. From the heat of formation of aqueous $NaHSO_3$, heat of formation[3] and of solution in water[46] of the liquid carbonyl compounds, we predict ΔH_f(aq, $PhCH(OH)SO_3Na$) and ΔH_f(aq, $Me_2C(OH)SO_3Na$) = -242 and -282 kcal mol^{-1}, respectively. Encouragingly, the same numbers are found within a kcal mol^{-1}, should we opt to use the heats of formation of liquid $PhCH_2OH$ and Me_2CHOH (Reference 3) and of their heats of solution in water[47]. This suggests that our increment, $\delta\Delta H_f$(aq, SO_3Na, H) = -203 kcal mol^{-1}, provides a simple and reliable method for estimating the heats of formation of aqueous sodium sulphonates.

What else do we learn from these studies? That the heat of reaction of the carbonyl compound increases in the order **27a** < **70a** < **71a** is consistent with our intuition of increasing strain in the product, although it is not really obvious how to compare the steric effect of the two methyl groups with that of the phenyl. Additionally, we do not know how to correct for the differences of the energetics of the tertiary, secondary and primary alcohols (**27b**, **71b** and **72b**) that result from the addition of the $NaHSO_3$ to **27a**, **71a** and **72a**. Table 12 shows that these two effects, the steric vs 'aryl alcohol type', do not parallel. Perhaps surprisingly, reaction 35 is increasingly exothermic as ROH is increasingly hindered. Regretfully, we lack experimental data on any of the various alkanesulphonates in which the α-OH group has been replaced by H to look into the energetics of reaction 35. We also lack data on the α-hydroxysulphones in which some SO_2R' replaces the 'SO_2ONa', a group that would have allowed solvation effects to be probed. However, we do have data on relevant sulphones that lack the α-hydroxy group. Table 13 shows that reaction 36 is also increasingly exothermic as RSO_2Me is increasingly hindered. We lack data on any PhCHOH-containing species with which to directly compare PhCHOH-containing species with which to directly compare $PhCH(OH)SO_3Na$, though we do have data on the energetics of reactions 35 and 36 for R = $PhCH_2$—. (See the last data entry rows in Tables 12 and 13, respectively.) From awareness of the above regularities and paucity of data, we conclude that we have an accurate, yet simple, procedure for estimating the heat of formation of aqueous sodium sulphonates. However, we have no information on the heat of solution of any RSO_3Na species and thus cannot work backwards to derive the

TABLE 12. Heats of gas phase reaction 35, RH + [O] ⟶ ROH[a]

n	$\Delta H_f(g, CMe_nH_{4-n})$	$\Delta H_f(g, CMe_nH_{3-n}OH)$	δ_{12}
0	−17.8	−48.2	30.4
1	−20.0	−56.2	36.2
2	−25.0	−65.2	40.2
3	−30.0	−74.7	44.7
Ph[b]	12.0	−24.0	36.0

[a]All input data are from Reference 3 and are in kcal mol^{-1}. For the purposes of this table, we designate the difference by $\delta_{12} \equiv \Delta H_f(g, CMe_nH_{4-n}) - \Delta H_f(g, CMe_nH_{3-n}OH)$.
[b]This row refers to the heats of formation of gaseous $PhCH_3$ and $PhCH_2OH$, and so should prove relevant to our understanding of the energetics of $PhCH(OH)SO_3Na$.

TABLE 13. Heats of gas phase reaction 36, RH + [$MeSO_2$] ⟶ RSO_2Me + [H][a].

n	$\Delta H_f(g, CMe_nH_{4-n})$	$\Delta H_f(g, CMe_nH_{3-n}SO_2Me)$	δ_{13}
0	−17.8	−89.2	71.4
1	−20.0	−97.7	77.7
2	−25.0	−103.8	78.8
3	−30.0	−113.2	83.2
Ph[b]	12.0	−65.0	77.0

[a]All input data are from Reference 3 and are in kcal mol^{-1}. For the purposes of this table, we designate the difference by $\delta_{13} \equiv \Delta H_f(g, CMe_nH_{4-n}) - \Delta H_f(g, CMe_nH_{3-n}SO_2Me)$.
[b]This row refers to the heats of formation of gaseous $PhCH_3$ and $PhCH_2SO_2Me$, and so should prove relevant to our understanding of the energetics of $PhCH(OH)SO_3Na$.

heat of formation of any solid RSO_3Na salt.

$$RH + [O] \longrightarrow ROH \tag{35}$$

$$RH + [MeSO_2] \longrightarrow RSO_2Me + [H] \tag{36}$$

D. The Heat of Formation of Benzenesulphonic Acid

In 1988, Bennett, Brunton, Gilbert and Whittall[48] (BBGW) examined the association and dissociation reactions of some aromatic and aliphatic oxysulphur radicals, in particular, the multistep process in equation 37. From these experiments, the measured reaction (equations 38 and 39) and derived reaction (equations 40 and 41) heats of hydrolysis of species **1** and **6** of Kice, Margolis, Johnson and Wulff[49] (KMJW), various other measurements and assumptions, and the use of group increments, BBGW derived new 'sulphonyl' and 'sulphinyl' heats of formation. In the name of brevity, only the former will be chronicled here: $PhSO_2$—O—S(O)Ph (**74**), −79.1; $PhSO_2$—O—SO_2Ph (**75**), −129.3; $PhSO_3H$ (**20**), −199.8; $PhSO_2^{\bullet}$ (**76**), −37.0; $PhSO_3^{\bullet}$ (**77**), −175.9 kcal mol^{-1}.

$$2RSO_2^{\bullet} \rightleftharpoons RS(O)—O—SO_2R \longrightarrow RSO^{\bullet} + RSO_3^{\bullet} \tag{37}$$

$$\underset{(\mathbf{1})}{PhSO_2SO_2Ph} + 2OH^- \longrightarrow PhSO_2^- + PhSO_3^- + H_2O \tag{38}$$

$$\underset{(\mathbf{6})}{PhSO_2SOPh} + 2OH^- \longrightarrow 2PhSO_2^- + H_2O \tag{39}$$

$$PhSO_2SO_2Ph + 2H_2O \longrightarrow PhSO_3H + PhSO_2H + H_2O \quad (40)$$

$$PhSO_2SOPh + 2H_2O \longrightarrow 2PhSO_2H \quad (41)$$

However much we would like to use these numbers, we must admit our skepticism. First of all, these values refer to the gas phase when all of the experiments were in solution. Where does the heat of sublimation of $PhSO_2SO_2Ph$ and of the other species appear in the analysis of BBGW for the heats of hydrolysis? One cannot assume such reactions are equally exothermic in the solution and gaseous phases when dealing with ionic and/or hydrogen-bonded species.

Secondly, the earlier assumption of KMJW that the heats of solution of the sulph*i*nic and sulph*o*nic acids **78** and **20** were the same was seemingly accepted uncritically, despite the admission that the former is negligibly dissociated under the reaction conditions (0.3 M $HClO_4$/60% dioxane) while the latter is totally dissociated. This assumption does not affect any of the earlier conclusions[49] about the thermodynamic vs kinetic facility of the hydrolysis reactions. However, while we concur with its usefulness, we wish to point out the contrasting situation of the heat of solution of the 'inorganic sulph*i*nic acid' H_2SO_3 [this species taken by the archivists of Reference 12 to be that of aqueous $SO_2 + H_2O(lq)$], $-3.4\,kcal\,mol^{-1}$, with that of the 'inorganic sulph*o*nic acid' H_2SO_4, $-22.8\,kcal\,mol^{-1}$.

Thirdly, using the new heats of formation suggested by BBGW, one may readily deduce that homolysis reaction 42 is some $115\,kcal\,mol^{-1}$ exothermic. However, given that this reaction is also favourable entropically and requires but the cleavage of a single bond, it is hard to reconcile it with any of the other reactions of sulphonic acid anhydrides known to the current author.

$$PhSO_2—O—SO_2Ph \longrightarrow PhSO_2^{\cdot} + PhSO_3^{\cdot} \quad (42)$$

Fourthly, BBGW assumed the bond to H in $PhSO_3H$ was of comparable strength to that found in $PhSO_2H$, namely *ca* $24\,kcal\,mol^{-1}$. This seems unlikely based on our knowledge of other O—H bond strengths[50] and the apparent lack of radical chemistry associated with most of the reactions of sulphonic acids.

Finally, we recall our earlier derived $\delta\Delta H_f(s, RSO_3H, RH) = -126 \pm 2\,kcal\,mol^{-1}$ from Section IV.C. From this increment and $\Delta H_f(s, PhH)$ [the sum of $\Delta H_{fus}PhH$) (Reference 12) and $\Delta H_f(lq, PhH)$ (Reference 3)], we immediately deduce for $\Delta H_f(s, PhSO_3H)$ a value of $-117\,kcal\,mol^{-1}$. It is hard to reconcile this finding with the $-199.8\,kcal\,mol^{-1}$ of BBGW regardless of phase[48].

E. The Heat of Formation of Benzene- and Methanesulphonyl Chloride

The penultimate article we will chronicle in this chapter is the 1989 gas-phase ion study of Chatgilialoglu, Guerra, Pelli and Trialdi[51] (CGPT). These authors investigated the energetics of sulphonyl chlorides through the use of the electron-impact-induced bond cleavage reaction 43. CGPT chose R to be the archetypical aromatic and aliphatic groups, Ph and Me respectively, for benzene and methanesulphonyl chlorides (**79** and **80**). For reaction 43 with **79** and **80**, they found the appearance energies to be 10.0 ± 0.3 and $11.6 \pm 0.3\,eV$ (231 ± 7 and $265 \pm 7\,kcal\,mol^{-1}$. Quantum chemical (semiempirical 'multiple-scattering Xα') calculations on the radicals $PhSO_2^{\cdot}$ (**76**) and $MeSO_2^{\cdot}$ (**81**) resulted in ionization potentials of 6.9 and 8.5 eV (*ca* 159 and $196\,kcal\,mol^{-1}$). From knowledge of $\Delta H_f(g, \mathbf{76})$, $\Delta H_f(g, Cl)$, and the above appearance and ionization energies, they concluded that $\Delta H_f(g, \mathbf{79}) = -80\,kcal\,mol^{-1}$. No value for methanesulphonyl chloride, $\Delta H_f(g, \mathbf{80})$, was given because CGPT assumed that the observed fragment cation was not the *S*-bonded ion $(MeSO_2)^+$ (**82a**) but the isomeric *O*-bonded ion $(MeOSO)^+$ (**82b**). We recall from Reference 5 that, besides deriving $\Delta H_f(g, \mathbf{76})$, Benson also deduced $\Delta H_f(g, \mathbf{81}) = -55 \pm 1\,kcal\,mol^{-1}$. Despite CGPT's caveats on the R = Me

case, we nonetheless parallel their analysis and derive the heats of formation of the gaseous cation and chloride to be 141 and $-95\,kcal\,mol^{-1}$, respectively.

$$RSO_2Cl + e^- \longrightarrow RSO_2^+ + Cl^\bullet + 2e^- \quad (43)$$

Let us examine these data and assumptions. The easiest assumption to test relates to the energetics of the isomeric cations **82a** and **82b**. The methyl cation affinity of SO_2, i.e. the heat of the gas phase reaction 44, has been experimentally determined by McMahon, Heinis, Nicol, Hovey and Kebarle[52] (MHNHK) to be $60.6\,kcal\,mol^{-1}$. From the highly accurate measurements of the heats of formation of gaseous Me^+ (Reference 53) and SO_2 (Reference 12), we find the heat of formation of the desired ion to be $130\,kcal\,mol^{-1}$. We are very doubtful that the association reaction 44 would not yield the more stable isomer of the cation. If we assume that the fragmentation reaction 43 yields the more stable ion as well, then we have a $10\,kcal\,mol^{-1}$ discrepancy between the two sets of results on methanesulphonyl cation. This is not particularly excessive given the errors reported by CGPT. If, in fact, reaction 43 yields the less stable isomer and this $10\,kcal\,mol^{-1}$ is real, it will then be desirable to compare this difference with the $2\,kcal\,mol^{-1}$ found for MeONO and $MeNO_2$, valence isoelectronic to **82a** and **82b**, respectively.

$$Me^+ + SO_2 \longrightarrow \underset{\textbf{(82b)}}{(MeOSO)^+} \text{ or } \underset{\textbf{(82a)}}{(MeSO_2)^+} \quad (44)$$

Turning now to the neutral benzene and methanesulphonyl chlorides **79** and **80**, Table 14 explores the difference between the heats of formation of gaseous benzene and methane derivatives with other electronegative and π-withdrawing substituents. The desired difference is seen to 'hover' around $31 \pm 2\,kcal\,mol^{-1}$. We cannot think of any way of rationalizing the difference of only $15\,kcal\,mol^{-1}$ for **79** and **80** and do not know which

TABLE 14. The heats of formation of gaseous benzene and methane derivatives with π-withdrawing electronegative substituents (all from Reference 3) and the normalized difference thereof[a]

Group	$\Delta H_f(g, Ph_nX)$	$\Delta H_f(g, Me_nX)$	δ_{14}
CN	51.6	−17.7[b]	33.9
CHO	−8.8	−39.7	29.9
Ac	−20.7	−51.9	31.2
COOH	−70.3	−103.4	30.1
COOMe	−68.8	−98.4	29.6
>CO	13.2	−51.9	32.6
COCl	−24.7	−58.1	33.3
COBr	−11.6	−45.5	33.9
COI	2.5	−30.2	32.7
NO	48.0[c]	16.7[d]	31.3
NO_2	16.1	−17.8	33.9
>SO	25.7	−36.2	30.9
$>SO_2$	−28.4	−89.2	30.4

[a] For the purposes of this table, we designate the normalized difference by $\delta_{14} \equiv \delta\Delta H_f(g, Ph_nX, Me_nX)/n$. All numbers are in $kcal\,mol^{-1}$.
[b] This datum is from X.-W. An and M. Mansson, *J. Chem. Thermodyn.*, **15**, 287 (1983).
[c] This datum is from K. Y. Choo, D. M. Golden and S. W. Benson, *Int. J. Chem. Kinet.*, **7**, 713 (1975).
[d] This datum is from L. Batt and R. T. Milne, *Int. J. Chem. Kinet.* **5**, 1067 (1973).

number, if either, is reliable: the heat of formation of gaseous benzenesulphonyl chloride, $-80\,\text{kcal mol}^{-1}$, or methanesulphonyl chloride, $-95\,\text{kcal mol}^{-1}$?

We opt now to estimate the heats of formation of species **79** and **80**. From the results in Section III.A and our discussion in Section VI.B, we recall that the 'ylchloridation' of sulphonic acids is nearly thermoneutral. That is, reaction 45 (the reverse of equation 28) is essentially thermoneutral. We thus predict $\Delta H_f(\text{lq}, \mathbf{79}) = -71\,\text{kcal mol}^{-1}$. Likewise, if we generalize the findings of Geiseler and Nagel[31] (GN) in Section IV.B, we conclude that the desulphonylation reaction 46 is endothermic by $3.6\,\text{kcal mol}^{-1}$ for R = n-$C_{12}H_{25}$—. Generalizing to other R groups, in particular R = Ph, we derive $\Delta H_f(\text{lq}, \mathbf{79}) = -72\,\text{kcal mol}^{-1}$ in notable agreement with our previous finding. By contrast, CGPT reported $\Delta H_f(\text{g}, \mathbf{79}) = -80\,\text{kcal mol}^{-1}$, a result incompatible with ours since it implies a negative (and thus impossible) heat of vapourization. We may wonder, however, what is the heat of vapourization (ΔH_v) of benzenesulphonyl chloride?

$$RSO_3H(s) + HCl(g) \longrightarrow RSO_2Cl(\text{liq or s}) + H_2O(\text{liq}) \tag{45}$$

$$RSO_2Cl(\text{liq}) \longrightarrow RCl(\text{liq}) + SO_2(g) \tag{46}$$

We now turn to methanesulphonyl chloride, **80**. Recall the above $31\,\text{kcal mol}^{-1}$ difference of heats of formation of comparable PhX and MeX derivatives. This is for gaseous species. For liquid species, we recall the simple but accurate (generally $\pm 1\,\text{kcal mol}^{-1}$) formula derived by Chickos, Hesse, Liebman and Panshin[54]:

$$\Delta H_v = 1.12\tilde{n}_C + 0.31n_Q + b + 0.71 \tag{47}$$

where $\tilde{n}$ is the number of non-quaternary carbons, n_Q is the number of quaternary carbons, and b depends on the substituent. We lack the value of b for sulphonyl chlorides and would like to have it. Nonetheless this knowledge is, in fact, unnecessary now. To the extent that equation 47 is accurate, so is equation 48:

$$\Delta H_v(\text{RX, R'X}) = 1.12\delta\tilde{n}_C + 0.31\delta n_Q \tag{48}$$

where the δn quantities are the differences in the appropriate carbon counts for R and R'. Likewise, equations 48 and 49 'should' be independent of the choice of substituents X and Y for any pair of R and R'. Equivalently, $\delta\Delta H_v(\text{RX, R'X})$ is independent of X. Experience[54,55] has told us that results for 'few-carbon' compounds are less dependable than for 'larger' compounds. Use of equation 47, and thus the use of equations 48 and 49, with methyl species, is thus somewhat precarious. Nonetheless, so doing with R = Ph and R' = Me, equation 48 predicts $\delta\Delta H_v(PhSO_2Cl, MeSO_2Cl) = 5.6\,\text{kcal mol}^{-1}$. Our test of equation 49 is shown in Table 15. We find $\delta\Delta H_v(\text{PhX, MeX})$ should equal $5.6\,\text{kcal mol}^{-1}$ from equation 48, while equation 49 and its implied $\delta\Delta H_v(\text{PhX, MeX})$ for four judiciously chosen X groups is equal to $4.8 \pm 0.7\,\text{kcal mol}^{-1}$. We thus conclude that $\delta\Delta H_f(\text{lq}, PhSO_2X, MeSO_2X) = 31 - 5 = 26\,\text{kcal mol}^{-1}$.

$$\delta\Delta H_v(\text{RX, R'X}) = \delta\Delta H_v(\text{RY, R'Y}) \tag{49}$$

We also recall from GN's study that the heat of formation of liquid n-dodecanesulphonyl chloride (**19**) is $-170\,\text{kcal mol}^{-1}$. Ideally we would like to 'synthesize' methanesulphonyl chloride from **19**. Consider the hypothetical reaction 50:

$$\text{n-}C_{12}H_{25}SO_2Cl(\text{liq}) \longrightarrow CH_3SO_2Cl(\text{liq}) + 11[\text{'—}CH_2\text{—'})(\text{liq})] \tag{50}$$

where '—CH_2—' [or C—$(H)_2(C)_2$ in more orthodox Benson symbolism, cf. Reference 1] refers to an unstrained methylene group. The desired heat of formation, ΔH_f(lq, '—CH_2—') can be obtained in several different ways. We may directly accept the choice of Domalski and Hearing[22], $-6.14\,\text{kcal mol}^{-1}$, or use the 'constant of nature'[1,22] for the gas, -4.93, and add the $\tilde{n}_C = 1$ estimate of heat of liquefaction -1.12, using equation 48 and identity

TABLE 15. The heats of formation of gaseous benzene and methane derivatives[a]

X	ΔH_v(PhX)	ΔH_v(MeX)	δ_{15}
COCl[b]	13.1	7.2	5.9
COBr[c]	14.0	10.3	3.7
NO_2[d]	13.1	9.2	3.9
COOMe[e]	13.7	8.1	5.6

[a]For the purpose of this table, we designate the normalized difference by $\delta_{15} \equiv \delta\Delta H_v$(PhX, MeX). All data are in kcal mol^{-1} and are from Reference 3.
[b]This choice of substituent was motivated because it and SO_2Cl are acid chlorides.
[c]This choice of substituent was motivated because it and SO_2Cl are acid halides and of comparable molecular weight.
[d]This choice of substituent was motivated because it and SO_2Cl are both polar 'dioxygen' groups.
[e]This choice of substituent was motivated because it and SO_2Cl are 'dioxygen' groups of somewhat more comparable mass than is NO_2. (We would have liked to consider the n-butoxycarbonyl or n-pentoxycarbonyl substituents which have even more comparable masses, but almost all of the data needed for this comparison are lacking.)

51, resulting in -6.05 kcal mol^{-1}. Alternatively, one can apply the 'diagonal reference state' reasoning of Van Vechten and Liebman[56] to liquids and set the desired quantity equal to $\frac{1}{6}\Delta H_f$lq, $(CH_2)_6$), namely -6.23 kcal mol^{-1}. Use of any the three nearly identical values for the liquid —CH_2— increment results in a predicted value for ΔH_f(lq, CH_3SO_2Cl) of *ca* -103 kcal mol^{-1}.

$$\Delta H_{liqn} \equiv -\Delta H_v \tag{51}$$

Alternatively, we recall from GN that the desulphonylation reaction of sulphonyl chlorides (our equation 42) is endothermic by some 3.6 kcal mol^{-1}. From this reaction heat, ΔH_f(g, MeCl) (Reference 3), ΔH_{liqn} (MeCl) (Reference 2) and ΔH_f(g, SO_2) (Reference 12), we obtain the desired number to be -99 kcal mol^{-1}. The discrepancy between the two estimates is 4 kcal mol^{-1}. However, recall that it is well established that the -4.93 kcal mol^{-1} increment we used is really not appropriate for the difference of ethyl and methyl derivatives, as opposed to n-dodecyl and n-hendecyl or even the 'smaller' n-propyl and ethyl. The value of $\delta\Delta H_f$(EtX, MeX) relates[57] strongly to the electronegativity of the group X. Let us assume the electronegativity of SO_2Cl and SO_2Me are equal. Then

$$\delta\Delta H_f(\text{g, MeSO}_2\text{Cl, EtSO}_2\text{Cl}) \equiv \delta\Delta H_f(\text{g, MeSO}_2\text{Me, EtSO}_2\text{Me}) = -8.5 \text{ kcal mol}^{-1} \tag{52}$$

Since we have already included the *ca* 1.1 kcal mol^{-1} for $\delta\Delta H_v$(MeX, EtX), the value for ΔH_f(lq, $MeSO_2Cl$) of -103 kcal mol^{-1} should be increased by $8.5 - 4.9 = 3.6$ kcal mol^{-1}. The new value of ΔH_f(lq, $MeSO_2Cl$) equal to *ca* -100 kcal mol^{-1} is in good agreement with our earlier result. Using either of our estimates, we find $\delta\Delta H_f$(lq, $PhSO_2Cl$, $MeSO_2Cl$) is *ca* 27 kcal mol^{-1}, in good agreement with our assumptions.

What can we say about the gaseous methanesulphonyl chloride? Recall that our earlier analysis of the original data gave a value of -95 kcal mol^{-1}, and were we to use the $MeSO_2^+$ data of MHNHK, we would derive a value of -105 kcal mol^{-1}. Considering these results in conjunction with our value for the liquid, we derive ΔH_v($MeSO_2Cl$) equal to either 5 or -5 kcal mol^{-1}. The former value seems too low given that the heat of

sublimation of Me_2SO_2 is 18.4 kcal mol^{-1}. The latter heat of vapourization value is clearly impossible. The only understanding we have is that CGPT underestimated the so-called 'kinetic shift' ($T_{0.5}$) in the electron-impact-induced fragmentation reaction 43. This underestimation is not an uncommon problem (nor, for that matter, is overestimation) and the error is often agonizingly and unpredictably large[58].

F. The Heat of Formation of 2-Chlorobenzenesulphonamide

In 1989, Lyubarskii, Gromova, Smolyanets and Rudakova[59] reported ΔH_f(s, 2-$ClC_6H_4SO_2NH_2$) = -76.1 ± 1.7 kcal mol^{-1}. From our analysis in Section VII.A, we deduce that there are few reliable data for other sulphonamides with which to make any comparison. More precisely, besides this 2-chlorobenzenesulphonamide (**83**) value, the sole thermochemical data on sulphonamides that are seemingly trustworthy are those of Van, Zhang, Jiang and Hu[41] on benzene- and two toluenesulphonamides (**24a**, **67a** and **67b**). It is logical to inquire if there is a constant $\delta\Delta H_f$(s, RSO_3H, RSO_2NH_2) that we can derive from the available data. Given the paucity of measured thermochemical data on sulphonic acids and our success in deriving $\delta\Delta H_f$(s, RSO_3H, RH) = -126 kcal mol^{-1}, it is seen to be more direct to derive $\delta\Delta H_f$(s, RSO_2NH_2, RH). For the case of R = Ph and the isomeric 2- and 4-Tol, this latter increment averages -84 ± 1 kcal mol^{-1}, while we would obtain a value of -76.5 ± 2 for R = 2-ClC_6H_4. The increment we would derive from **24a**, **67a** and **67b** differs by *ca* 7 kcal mol^{-1} from that derived (using data from References 41 and 59 for the sulphonamides and from References 2, 12 and 22 for the non-sulphur-containing species). This is somewhat disconcerting, but we expect some steric [i.e. Cl)···(O] and electronic (i.e. δ^-–δ^-) destabilization in the 2-chloro case. While we cannot quantify this effect for the sulphonamides, we note that for the acyl species $\delta\Delta H_f$(2-ClC_6H_4COX, 3-ClC_6H_4COX) = 4.7 ± 0.5 kcal mol^{-1} for X = OH (s), 4.4 ± 0.5 kcal mol^{-1} for X = Cl (lq), but 1.8 ± 2.0 kcal mol^{-1} for X = H (lq). This suggests that it is the chlorinated sulphonamide that is anomalous and that setting $\delta\Delta H_f$(s, RSO_2NH_2, RH) = -84 ± 1 kcal mol^{-1} is the recommended choice. As such, from the use of identity 53—definitionally true for all species A, B and C—we deduce $\delta\Delta H_f$(s, RSO_3H, RSO_2NH_2) = -42 kcal mol^{-1}.

$$\delta\Delta H_f(A, B) - \delta\Delta H_f(A, C) \equiv \delta\Delta H_f(C, B) \tag{53}$$

VIII. EPILOGUE AND CONCLUSION

A. What Can We Now Say About Sulphonyl Sulphenates?

The reader will have noted that some unanswered questions were left in some of our earlier sections. For example, recall Reference 34 cited in Section V. A; we did not evaluate on which side the equilibrium for reaction 54 lies. Because we subsequently considered the thermochemistry of sulphonyl sulphenates, we can now provide a partial, but admittedly long-winded, answer for the Ar = Ph species (**46**). The reader is reminded that ΔH_f(g, **46**) $\leqslant -52$ kcal mol^{-1} and of the finding of Tureček and coworkers[34] that the heat of formation of *gaseous* benzenesulphenic acid (**84**) is -8 kcal mol^{-1}. Likewise, the reader may recall from Section VII.D our estimation for *solid* benzenesulphonic acid that ΔH_f(s, **20**) = -117 kcal mol^{-1}. These data cannot be immediately combined because of the discrepancy in the state for which the three species other than H_2O are known. Do we wish to consider condensed phase species, in which case we need the sublimation energy of the sulphonyl sulphenate **46** and the sulphenic acid **84**, or to consider gas phase species, in which case we need the sublimation energy of the sulphonic acid **20**?

$$\underset{\textbf{(46)}}{ArSO_2—O—SAr} + H_2O \rightleftharpoons ArSO_3H + ArSOH \tag{54}$$

We consider the latter first since we have more interest, knowledge and experience of the energetics of sulphonic acids and their derivatives than of sulphenic acids and their derivatives. From Chickos' recent and comprehensive review of heats of sublimation[60], we may immediately conclude that insufficient direct measurements exist. The heat of sublimation has been directly reported for one sulphonic acid 4-$NH_2C_6H_4SO_3H$ (**85**); 16.0 kcal mol^{-1}. This seems much too low. It is to be noted, however, that the same paper reported 4-$NH_2C_6H_4COOH$ (**86**) had a heat of sublimation of 33.9 kcal mol^{-1}. Other sources that Chickos considered more reliable gave a value of some 27 ± 1 kcal mol^{-1}. This suggests that we may safely ignore the literature sulphonic acid piece of data.

Instead, we may employ a lower bound using equation 47 to derive a heat of vapourization, in lieu of the heat of sublimation, of benzenesulphonic acid. We have no experimental information as to the appropriate value of *b*. However, it may be simply estimated as the sum of the *b* values for sulphones and alcohols. 'Simple' and 'reliable' are generally not synonymous, although we have earlier found both simple and reliable rules for estimating heats of vapourization of multiply substituted species[61]. From Reference 54 we find that the value of *b* for carboxylic esters and thiolesters is nearly the sum of the *b* values of ketones, and ethers and sulfides, respectively. We also find that the heats of vapourization of MeCOCl and PhCOCl may be estimated within a kcal mol^{-1} of experimental results by approximating the value of *b* for acyl chlorides as the sum of the *b* values for ketones and chlorides. To further calibrate our assumptions, one can calculate the heats both of vapourization and of sublimation of PhCOOH by summing the *b* values for >CO and —OH, ketones and alcohols. The predicted heat of vapourization is 18.1 kcal mol^{-1}, less than the experimental value of ΔH_s(PhCOOH), 21.8 kcal mol^{-1}, and encouragingly close to the value of ΔH_v(PhCOOH), 17.5 kcal mol^{-1} derived by taking the difference between the former quantity and the measured heat of fusion from Reference 2. As such, we opt to estimate the necessary value of *b* by summing those for $>SO_2$ and —OH, sulphones and alcohols. So doing we obtain the inequality $\Delta H_v(PhSO_3H) \approx 27$ kcal mol^{-1} $< \Delta H_s(PhSO_3H)$.

In fact, if we invoke this sulphonic acid/carboxylic acid analogy for heats of sublimation, the following equality looks plausible:

$$\Delta H_s(PhCOOH) - \Delta H_s(Ph_2CO) = \Delta H_s(PhSO_3H) - \Delta H_s(Ph_2SO_2) \qquad (55)$$

The resulting value of $\Delta H_s(PhSO_3H)$ is 25.8 kcal mol^{-1}, somewhat lower than the 27 kcal mol^{-1} just derived before, but still plausible. Finally, combining either value with the earlier value ΔH_f(s,, **20**) = −117 kcal mol^{-1}, we deduce ΔH_f(g, **20**) = -90 ± 3 kcal mol^{-1}. Accordingly, the left-hand side of reaction 50 is at least $[-90 + (-8)] - [-52 + (-58)] = 12$ kcal mol^{-1} more stable than the right-hand side, where we remember that the *value* used for $PhSO_2$—O—S—Ph (**46**) is an upper bound.

We will now assume all of the species in reaction 55 are in their condensed phases and again fail to distinguish heats of vaporization and sublimation. For the sulphonyl sulphenate **46**, we again use equation 47 where the ncessary value of *b* was derived as the sum of those for sulphones, ethers and sulphides, resulting in a predicted ΔH_f(g, **46**) value of −83 kcal mol^{-1}. Relatedly, the value of *b* for sulphenic acids was taken as the sum of those for alcohols and sulphides, and thus ΔH_f(g, **85**) = −26 kcal mol^{-1}. The left-hand side of reaction 39 is $[-117 + (-26)] - [-83 + (-68)] = 8$ kcal mol^{-1} more stable than the right, where we remember that the value for $PhSO_2$—O—S—Ph is an upper bound. The results for the gaseous and condensed phases are thus seen as consonant. It is safe to say that benzenesulphonyl benzenesulfenate is best 'not' viewed as an anhydride since its hydrolysis is endothermic.

B. What Can We Now Say About the Stability of Isomeric Sulphites and Sulphonates?

In Section VII.B we left ambiguous whether dimethyl sulphite (**69**) or methyl methanesulphonate (**87**) was the more stable species. Indeed, the reader may recall this was a rather nagging question even in Section I. To find ΔH_f(lq, **86**), we assume that reaction 56 is thermoneutral. While the thermochemistry of **86** is no more known from direct experiment than the parent acid, we have experience that will allow us to estimate the latter. General reaction 41 in Section VII.E tells us that the particular reaction 57 with R = Me is essentially thermoneutral. From our earlier value of $\Delta H_f(\text{lq}, MeSO_2Cl) = -101\ \text{kcal mol}^{-1}$, we derive $\Delta H_f(\text{s}, MeSO_3H) = -147\ \text{kcal mol}^{-1}$. Is this quantity reasonable? Let us work backwards. From our earlier assumption that $\delta\Delta H_f(\text{s}, RSO_3H, RH) = -126\ \text{kcal mol}^{-1}$, we would deduce $\Delta H_f(\text{s}, CH_4) = -21\ \text{kcal mol}^{-1}$. From Reference 3 we know $\Delta H_f(\text{g}, CH_4) = -18\ \text{kcal mol}^{-1}$, and with the use of equation 36 for hydrocarbons (i.e. the $b = 0$ case, cf. Reference 55), we deduce $\Delta H_f(\text{lq}, CH_4) = -20\ \text{kcal mol}^{-1}$. This would suggest that $\Delta H_{sub}(CH_4) = 1\ \text{kcal mol}^{-1}$, a highly reasonable number.

$$MeSO_3H(\text{lq}) + \tfrac{1}{2}MeOSO_2OMe(\text{lq}) \longrightarrow \underset{(\mathbf{87})}{MeSO_2OMe(\text{lq})} + \tfrac{1}{2}H_2SO_4(\text{lq}) \qquad (56)$$

$$MeSO_3H(\text{s}) + HCl(\text{g}) \longrightarrow MeSO_2Cl(\text{lq}) + H_2O(\text{lq}) \qquad (57)$$

To derive $\Delta H_f(\text{lq}, MeSO_3Me)$, it is still necessary to estimate the heat of formation of liquid methanesulphonic acid (**88**), and not just the number for the solid phase ΔH_f(s, **88**). The first is to assume the validity of the above sulphonic acid/carboxylic acid analogy for heats of fusion, and estimate $\Delta H_{fus}(MeSO_3H)$ using equation 58. The result is an estimate for the heat of fusion of **88** as $6.2\ \text{kcal mol}^{-1}$. Alternatively, we have recently succeeded in estimating entropies of fusion of hydrocarbons[62] and of their substituted derivatives[63] as the sum of entropies of their component groups and some structural features, and the heat of fusion as the product of the estimated entropy of fusion, ΔS_{fus}(est), and the experimentally measured melting point, T_m (in degrees K). Insofar as $T_m \cdot \Delta S_{fus}(\text{est}) \approx \Delta H_{fus}$, equation 59 should be nearly an identity. This results in the heat of fusion of **88** being equal to $4.2\ \text{kcal mol}^{-1}$. Finally, we may bound $\delta\Delta H_{fus}$ by 0, i.e. the heat of formation of the solid and liquid are the same. This results in ΔH_f(lq, **87**) $= -144 \pm 3\ \text{kcal mol}^{-1}$.

$$\Delta H_{fus}(MeCOOH) - \Delta H_{fus}(Me_2CO) = \Delta H_{fus}(MeSO_3H) - \Delta H_{fus}(Me_2SO_2) \qquad (58)$$

$$\Delta H_{fus}(MeCOOH)/T_m(MeCOOH) - \Delta H_{fus}(Me_2CO)/T_m(Me_2CO) = \Delta H_{fus}(MeSO_3H)/T_m(MeSO_3H) - \Delta H_{fus}(Me_2SO_2)/T_m(Me_2SO_2) \qquad (59)$$

Using an averaged value of the heat of fusion for the sulphonic acid **88**, we find the resulting value for the sulphonate ΔH_f(lq, **87**) is $-135 \pm 3\ \text{kcal mol}^{-1}$, while the literature value for the sulphite, **69**, is $-125.1 \pm 0.3\ \text{kcal mol}^{-1}$. This supports our conjecture that reaction 27 is entropy driven. It suggests that, in general, sulphonates with arbitrary R and R′ groups (i.e. both RSO_3R' and $R'SO_3R$) will be more stable than the isomeric sulphites, ROS(O)OR′.

C. What Can We Now Say About Bond Additivity in Sulphonic Acids and Their Derivatives?

The reader may recall that in Section I we asserted that strict bond additivity would result if the heat of formation associated with the $SO_2(C)(O)$ group would equal the average of those for $SO_2(C)_2$ and $SO_2(O)_2$. We are now able finally to test the validity of

that assertion. We do this by making a simple thermochemical comparison. Using the heats of formation of the various RSO_2X species we have either culled from the literature or derived for R = Ph and Me, X = OH, NH_2, Cl and OMe, we answer the question: 'How exothermic or endothermic is the hypothetical "synthetic" (or should we say "metathetic") reaction 60'? Table 16 presents the numerical values for $\Delta H_f(RSO_2X)$ and the deviation from additivity, δ_{16}. The deviation depends on both R and X and is defined by one half of the heat of reaction 60. All of the species are taken in their standard state. While this occasionally 'mixes' phases (e.g. for the R = Me, X = OH case, both the reactant sulphone and product sulphonic acid are solids, but the reactant sulphuric acid is a liquid), this choice corresponds to experimentally realized species under normal conditions.

$$R_2SO_2 + SO_2X_2 \longrightarrow 2RSO_2X \tag{60}$$

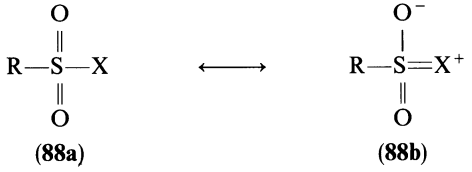
$$\delta_{16} = \Delta H_f(RSO_2X) - \tfrac{1}{2}[\Delta H_f(R_2SO_2) + \Delta H_f(SO_2X_2)] \tag{61}$$

Distressingly, there is no apparent pattern to the stabilization numbers in Table 16 save the absence of group additivity and the general destabilization ($\delta_{16} \geqslant 0$) for sulphonyl derivatives, RSO_2X, when compared with sulphones and sulphuryl derivatives, SO_2X_2. We cannot rationalize any of the individual numbers nor the table as a whole. We do list now some issues that both confound and intrigue us:

(a) For both the X = OH and NH_2 cases, there is no doubt extensive hydrogen bonding between the sulphonyl oxygens and the H on the hydroxy and amino groups.

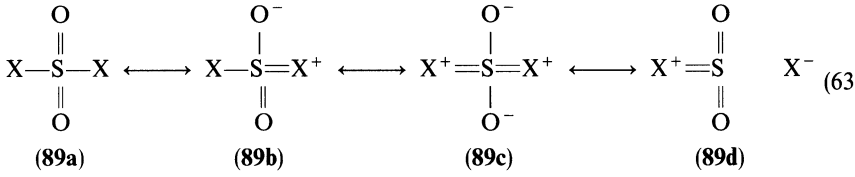
(b) For all X, there is electrostatic repulsion between the negatively changed X and the oxygens on the SO_2 group in both the sulphonyl and sulphuryl species. For the latter there is also repulsion between the two X groups.

(c) For all X in RSO_2X we may invoke resonance structures, such as **88a** and **88b** shown in equation 62, and for the SO_2X_2, we likewise may invoke **89a–89d** as shown in equation 63. However, we do not know enough to quantitate the importance of **88a** vs **88b**, nor **89a** through **89d**.



(62)

(**88a**) (**88b**)



(63)

(**89a**) (**89b**) (**89c**) (**89d**)

D. What Can We Now Say About Sulphonic Acid/Carboxylic Acid/Sulphinic Acid Analogies?

The analogous thermochemical comparison for carboxylic and carbonic acid derivatives can also be made. Using the heats of formation of the various RCOX species we have culled from the literature for R = Ph and Me, X = OH[64,3] NH_2, Cl and OMe[64,3] we answer the question: 'How exothermic or endothermic is the hypothetical "synthetic" (or "metathetic") reaction 64'? Table 17 presents the numerical values for $\Delta H_f(RCOX)$ and the

TABLE 16. Test of bond additivity in the thermochemistry of sulphonyl derivatives, RSO_2X[a].

RSO_2X R =	Me		Ph	
X =	ΔH_f	δ_{16}	ΔH_f	δ_{16}
OH(s)	−147	4	−117	7
NH_2(s)	−105[b]	13	− 75	17
Cl(lq)	−101	0	− 72	2
OMe(lq)	−135	7		

[a]We recall from the text that, for each pair R and X, we define δ_{16} as $\Delta H_f(RSO_2X) - \frac{1}{2}[\Delta H_f(R_2SO_2) + \Delta H_f(SO_2X_2)]$, where we remind the reader that $\delta_{16} > 0$ corresponds to destabilization of the sulphonyl derivative and $\delta_{16} < 0$ corresponds to stabilization. All data are for the 'normal' condensed phase species and are in kcal mol^{-1}.

[b]This value for the heat of formation of solid methanesulphonamide was estimated as $\Delta H_f(s, MeSO_3H) - \delta\Delta H_f(s, RSO_3H, RSO_2NH_2)$, where the increment was obtained from Section VII.F.

TABLE 17. Test of bond additivity in the thermochemistry of acyl derivatives, RCOX[a].

RCOX R =	Me		Ph	
X =	ΔH_f	δ_{17}	ΔH_f	δ_{17}
OH	−103[b]	−4	−70	−3
NH_2	− 57	−2	−24[c]	−1
Cl	− 58	−6	−25	−2
OMe	− 98[b]	−5	−69	−5

[a]We recall from the text that, for each pair R and X, we define δ_{17} as $\Delta H_f(RCOX) - \frac{1}{2}[\Delta H_f(R_2CO) + \Delta H_f(COX_2)]$, where we remind the reader that $\delta_{17} > 0$ corresponds to destabilization of the acyl derivative and $\delta_{17} < 0$ corresponds to stabilization. All data are for gas-phase species and are in kcal mol^{-1}.

[b]See Reference 64.

[c]This datum is from L. A. F. Torres-Gomez and R. Sabbah, *Thermochim. Acta*, **58**, 311 (1982).

deviation from additivity, δ_{17}. The deviation depends on both R and X and is defined by or equivalently one half of the heat of reaction 64. All of the species are taken as gases because (a) this obviates intermolecular phenomena such as hydrogen bonding and (b) we have no thermochemical data for either $CO(OH)_2$ or $COCl_2$ in their condensed phases.

$$R_2CO + COX_2 \longrightarrow 2RCOX \tag{64}$$

$$\delta_{17} = \Delta H_f(RCOX) - \tfrac{1}{2}[\Delta H_f(R_2CO) + \Delta H_f(COX_2)] \tag{65}$$

It is seen that a small degree of stabilization for gas-phase acyl species is the norm, i.e. $\delta_{17} < 0$, while destabilization was generally seen for condensed-phase sulphonyl species. Would stabilization also be seen for sulphonyl derivatives were gas-phase species considered? What does our analysis say about the sulphonic acid/carboxylic acid analogies in Section VIII.A?

What does our analysis say about the sulphonic acid/carboxylic acid/sulphinic acid analogies enunciated in the beginning of this chapter? What does our analysis tell us about the interplay of structure and energetics in the chemistry of sulphonic acids and their derivatives? These questions remain unanswered.

E. Conclusion

This chapter has presented a rather sparse collection of directly measured heats of formation. The data have been supplemented by a significantly larger collection of derived numbers, analogies and estimation principles. The measured and derived values were further combined in a self-consistent manner that allowed for the prediction of the heats of formation of sulphonic acids, sulphonate esters, sulphonamides and sulphonyl chlorides.

Yet, there is the nagging feeling that our presumed knowledge greatly exceeds our true knowledge. More precisely, there are insufficient measurements to test quantitatively many of the assumptions and approaches presented in this chapter. Indeed, as is the case with so much of chemical data and its interpretations, there's more than you think, but less than you need. For example, consider a test to evaluate the validity and utility of the sulphonic acid/carboxylic acid/sulphinic acid thermochemical analogy. Our text reviews all of the salient data on sulphonic acids and derivatives. Bujnicki, Miko/ajczyk and Omenlańczuk in Reference 65 claim to have similarly reviewed sulphinic acids and their derivatives. Our thermochemical archive for organic compounds, Reference 3, cites heat of formation data on a plethora of carboxylic acids and their derivatives in both their gaseous and condensed phases. However, even here, the data are seemingly inadequate for the desired level of comprehension. Numerous carboxylic acids and esters have been studied. Simple amides are thermochemically well-characterized. Yet, there are data on only six gaseous acyl chlorides and a comparable additional number of species for which only the condensed phase has been studied. The heats of formation of only five acyl thiolesters and but two acyl fluorides, bromides and iodides are known. The problems addressed for sulphonic acids and their derivatives seem to reappear for carboxylic acids and their derivatives. It thus appears unequivocally that to investigate further the analogy of interest, we will require further investigation and insight on sulphonic acids, sulphinic acids *and* carboxylic acids[66].

IX. ACKNOWLEDGEMENTS

The author wishes to thank the following people for their helpful comments of science and/or style: Peter Beak, James S. Chickos, Paul E. Dietze, Eugene S. Domalski, Jay M. Freyman, James L. Kice, Edward S. Lewis, Sharon G. Lias, Ralph M. Pollack and Deborah Van Vechten.

X. REFERENCES

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2. E. S. Domalski, W. H. Evans and E. D. Hearing, *Heat Capacities and Entropies of Organic Compounds in the Condensed Phase, J. Phys. Chem. Ref. Data*, **13** (1984), Suppl. 1.
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8. See Reference 7, pp. 149–151.
9. W. N. Hubbard, D. W. Scott and G. Waddington, in *Experimental Thermochemistry: Measurement of Heats of Reaction* (Ed. F. D. Rossini), Interscience, New York, 1956. These additional terms for an *abitrary* organic compound are customarily called 'the Washburn corrections', after E. W. Washburn, *J. Res. Natl. Bur. Stand.*, **10**, 525 (1933).
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11. Quoting from A. Steinsaltz, *The Essential Talmud* (translated from the Herbrew by C. Galai, Weidenfeld & Nicolson, London, 1976, pp. 67–68), '[T]he greatest commentator···R[abbi] Shlomo Yitzhaki of Troyes, known as Rashi···lived in the eleventh century.···[H]is greatest achievement were his great commentaries on the Bible and his monumental work on the Babylonian Talmud,···[that] can serve as the model for all exegesis'—we propose the introduction of the neologism 'Rashimaic' in homage of Rashi, as a term signifying an all-embracing exposition, commentary or initial review.
12. D. D. Wagman, W. H. Evans, V. B. Parker, R. H. Schumm, I. Halow, S. M. Bailey, K. L. Churney and R. L. Nuttall, 'The NBS tables of chemical thermodynamic properties: Selected values for inorganic and C_1 and C_2 organic substances in SI units', *J. Phys. Chem. Ref. Data*, **11** (1982), Suppl. 2. In this chapter, we convert these authors' *proper* thermochemical units $kJ\,mol^{-1}$ into the more commonly used *chemists'* units $kcal\,mol^{-1}$ by the exact conversion factor $4.184\,kJ\,mol^{-1} \equiv 1\,kcal\,mol^{-1}$.
13. Two references that document the 'reasonable' assumption that 2-aminoethanesulphonic acid is a zwitterion are: H. P. Hopkins, Jr., C. H. Wu and L. G. Hepler, *J. Phys. Chem.*, **69**, 2244 (1965) and R. L. Benoit, D. Boulet and M. Fréchette, *Magn. Res. Chem.*, **27**, 233 (1989).
14. The reader should recall in a classical, thermodynamic sense that 'Since···the free energy of formation of an individual ion has no operational meaning, there is no way to determine this quantity. However,···arbitrarily···[we may do so] in a way analogous to that used in tables of standard electrode potentials,···[that is] at every temperature: $\frac{1}{2}H_2(g) = H^+(aq) + e$, $\Delta G_f^\circ = 0$'. (This quote is from I. M. Klotz and R. M. Rosenberg, *Chemical Thermodynamics: Basic Theory and Methods*, 4th ed., Benjamin/Cummings Publ. Co., Inc., Menlo Park, 1986, pp. 461–462.) From this assertion, it is directly derivable that at every temperature $\Delta H_f(H^+) = 0$ as well. This value of precisely $0.0\,kcal\,mol^{-1}$ is not to be taken to mean that the single ion heat of solvation of H^+ is the difference of the reported values for the heat of formation of gaseous and solvated H^+, namely $367.2\,kcal\,mol^{-1}$. In fact, from the proton affinity of H_2O and some extrathermodynamic measurements and assumptions, we find the heat of solvation of H^+ to be $276.8\,kcal\,mol^{-1}$. [See the numbers and analysis of M. Meot-Ner (Mautner), in *Molecular Structure and Energetics: Biophysical Aspects* (Eqs. J. F. Liebman and A. Greenberg), VCH Publ., Inc., New York, 1987.] However, since the energetics of all other aqueous ions—both positive and negative—arithmetically scale with that of aqueous H^+, our original statement stands and our analysis presented in the text remains valid.
When we speak of the thermochemistry of aqueous solutions, whether we mean those of H^+ or of any other species, implicitly we mean at infinite dilution. However, errors are generally small if we equate that value with those obtained at more convenient concentrations. For 2-aminoethanesulphonic acid, from Reference 12 we find at molar ratios of unionized zwitterionic solute to water of 1:50, 1:100, 1:150 and '1:∞' the heats of formation are −182.09, −182.03, −182.00 and $-181.92\,kcal\,mol^{-1}$. The $0.2\,kcal\,mol^{-1}$ spread of values is insignificant compared to the experimental errors of most of the measurements we will cite for organic compounds and of the conceptual errors of many of the assumptions we will employ in their understanding.
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16. We know this must be false in that it assumes that the heat of ionization of any substituted acetic acid is the same. However, it does not appear to be *that* unreasonable or inexact. For example, from L. Avendikian, *Bull. Soc. Chim. Fr.*, 2570 (1966), we find the heats of ionization of XCH_2COOH are X = H, 0.09; F, −0.68; Cl, −0.73; Br, −0.62; I, $-1.16\,kcal\,mol^{-1}$.

17. These values were taken from the evaluated proton affinity compendium, S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, **13**, 695 (1984).
18. W. A. Roth and E. Rist-Schumacher, *Z. Elektrochem.*, **50**, 7 (1944).
19. We have cited the number for H_2SO_4 dissolved in ethanol in a 1:49 ratio from Reference 12. This heat of solution value is probably lower by *ca* 1 kcal mol^{-1} than the value at infinite dilution, noting the heats of solution of H_2SO_4 in ethanol at 1:10, 1:25 and 1:49 ratios are 15.0, 16.8 and 17.5 kcal mol^{-1}
20. From the numbers in References 12, we can derive the heat of neutralization of 2-aminoethanesulphonic acid by NaOH in aqueous medium. This reaction is exothermic by only some 3.3 kcal mol^{-1}, which is far less than either quantity mentioned above. However, 2-aminoethanesulphonic acid is a poor mimic for n-dodecane-1-sulphonic acid because the former exists as the zwitterion, $H_3N^+(CH_2)_2SO_3^-$. As such, we are really talking about the neutralization reaction of a much weaker acid, a substituted ammonium ion, and not a sulphonic acid at all. For comparison, the neutralization of aqueous $C_2H_5NH_3^+$ by aqueous NaOH is essentially thermoneutral.
21. M. Badoche, *Bull. Soc. Chim. Fr.*, 37 (1946).
22. E. S. Domalski and E. D. Hearing, *J. Phys. Chem. Ref. Data*, **17**, 1637 (1988). It should be admitted now that many of the assumptions that fill our chapter assume group additivity works for solids, liquids and solutions. This is a convenient, but generally less legitimate and accurate, assumption than for the gas phase that Benson (Reference 1) and subsequent investigators usually studied. Nonetheless, the success that Domalski and Hearing demonstrate in this paper in developing a set of group increments for predicting the heats of formation of liquid and solid hydrocarbons suggest that group additivity is a generally useful procedure in the organic thermochemistry of condensed phase species as well as for gaseous species. As such, heats of fusion for an arbitrary hydrocarbon can be derived as the difference of the heats of formation of its liquid and solid.
23. V. Pushkareva and Z.Yu. Kokosho, *Zh. Obshch. Khim.*, **16**, 1269 (1946).
24. The purist may argue that this is inexact because all of the sulphonamides are solids while both aniline and benzene are liquids. In fact, using the data from Reference 2, we find at the freezing points aniline and benzene have comparable heats of fusion, and so but a small error is expected to arise at 25 °C: aniline, 2.6 kcal mol^{-1}, 267 K = −6 °C; benzene, 2.4 kcal mol^{-1}, 278 K = −5.0 °C. [For a discussion of some approximations for temperature corrections to heats of fusion, vapourization and sublimation, see J. S. Chickos, in *Molecular Structure and Energetics: Physical Measurements* (Eds. J. F. Liebman and A. Greenberg), VCH Publ., New York, 1987.]
25. A. A. Spyrskev, *Zh. Obshch. Khim.*, **18**, 98 (1948).
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27. Another complication is that the rates of formation of the isomeric napthalenesulphonic acids are not the same. However, to the extent that the heats of formation of the two isomers are comparable, this does not affect any of our conclusions. Interestingly, this result is an undergraduate textbook example of the general phenomenon: 'At low temperatures the controlling factor is *rate of reaction*, at high temperatures, *position of equilibrium*'. (This quote, including italics, is from R. T. Morrison and R. N. Boyd, *Organic Chemistry*, 5th ed., Allyn and Bacon, Inc., Boston, 1987, p. 1181.)
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29. B. G. Boldyrev and I. Ya. Postovskii, *Zh. Obshch. Khim.*, **20**, 936 (1950).
30. V. N. Kisel'nikov, *Russ. J. Gen. Chem.*, **27**, 2914 (1957).
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33. For comparison, from Reference 3 we find that the 'spread' of the heats of formation values from the complete all nine possible solid ethyl and dimethyl substituted benzoic acids is 6.7 kcal mol^{-1}. In this case, 'a few' this means 3.4.
34. The sole thermochemical values known to the author for any sulphenic acid, RSOH, are the ionization and ion fragmentation reaction energetics derived values of R = Me, −45; CH_2=CH—, ⩽4; HC≡C—, 24 and Ph—, −8 kcal mol^{-1}, R. Tureček, L. Brabec, T. Vondrák, V. Hanuš, J. Hájiček and Z. Havlas, *Collect. Czech. Chem. Commun.*, **53**, 2140 (1988). In that we know the heat of formation of no sulphonic acid in the gas phase, we cannot provide an answer to 'Is it better to view the above $ArSO_2$—O—SAr species as an anhydride or an ester'? That is, our

information is seemingly insufficient to deduce on which side the equilibrium lies for the formal hydrolysis reaction

$$ArSO_2—O—SAr + H_2O \rightleftharpoons ArSO_3H + ArSOH$$

We will return to this question in Section VIII, A.

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37. This number is from S.-O. Nilsson and I. Wadsö, *J. Chem. Thermodyn.*, **18**, 673 (1987). Alternatively, we may recall, by definition, the heat of *solution in* H_2O is the difference of the heat of vapourization and heat of *solvation by* H_2O. Using a set of group increments for the latter that Nilsson and Wadsö derived from a set of acyclic esters, we find a value of $-5.3\,kcal\,mol^{-1}$. This quantity seems out of line with those for the other esters that these authors cited—it is not obvious that the anomaly arises from an anomalously low predicted heat of solvation, $5.9\,kcal\,mol^{-1}$, or anomalously high measured heat of vapourization, $11.2\,kcal\,mol^{-1}$, when compared to these quantities for other esters.
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$$(Z)\text{-MeCH}{=}\text{CHEt} + CH_4 \longrightarrow EtCH{=}CH_2 + CH_3CH_3$$

This reaction may be identified as an acyclic counterpart of reaction 23 with $X = CH_2$, and so the difference between the heat of this reaction and that of reaction 23 may be identified as the strain energy of cyclopentene. Using the data in Reference 12, we find the 'acyclic' reaction to be endothermic by $4.4\,kcal\,mol^{-1}$ and so the strain energy of cyclopentene is $4.4-(-0.7) = 5.1\,kcal\,mol^{-1}$ by the definition used in this chapter.
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61. The reader should note that this additivity is related to, but certainly not the same as, our recently published findings of multiple substituent effects on heats of vapourization, J. S. Chickos, D. G. Hesse and J. F. Liebman, *J. Org. Chem.*, **54**, 5250 (1989).
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63. J. S. Chickos, D. G. Hesse and J. F. Liebman, unpublished results.
64. Surprisingly, there are no thermochemical data for $CO(OMe)_2$ although there are some other $CO(OR)_2$ species. In particular, from Reference 3, we find R = Et, Ph, *c*-Hex, 4-$PhC_6H_4CH_2$ and the 'mixed' ester *c*-HexOCOOMe. There are even data for the parent carbonic acid in the gas phase; cf. the analysis of J. F. Liebman, in *Fluorine-Containing Molecules: Structure. Reactivity, Synthesis and Applications* (Eds. J. F. Liebman, A. Greenberg and W. R. Dolbier, Jr.). VCH Publ. Inc., New York, 1988. For our current study, $\Delta H_f(g, CO(OMe)_2)$ was derived to be -135.5 ± 1.5 kcal mol^{-1} by assuming thermoneutrality for the following three reactions:

$$CO(OEt)_2 + 2AcOMe \longrightarrow CO(OMe)_2 + 2AcOEt$$
$$CO(OH)_2 + 2AcOMe \longrightarrow CO(OMe)_2 + 2AcOH$$
$$2(Hex^cOCOOMe) \longrightarrow CO(OHex^c) + CO(OMe)_2$$

65. For individuals interested in the energetics of sulphinic acids and their derivatives, we refer the reader to B. Bujnicki, M. Mikołajczyk and J. Omenlańczuk, 'Thermochemistry and thermolysis of sulphinic acid derivatives', in *The Chemistry of Sulphinic Acids, Esters and their Derivatives* (Ed. S. Patai), Wiley, Chichester, 1989. The comprehensive comparison of the interplay of structure and energetics of sulphinic and sulphonic acid (and, oh yes, sulphenic acid) derivatives is still unwritten and no doubt awaits a chapter in a yet-to-be-organized Supplement volume.
66. We conclude our current chapter with poetry that describes the role of future studies while admitting the current lack of knowledge upon completion of this chapter.

'We shall not cease from exploration
And the end of all of our exploring

Will be to arrive where we started
And know the place for the first time.'

From T. S. Eliot, 'Little Gidding', in *Four Quartets* [reprinted in *The Norton Anthology of English Literature Vol. 2*, 4th ed. (Gen. Ed. M. H. Abrams), W. W. Norton & Co., New York, 1979], (The author wishes to thank Ms. Julia A. Rottman of the Department of English, University of Virginia for finding this reference.)

CHAPTER 9

Analytical methods

M. R. F. ASHWORTH

Organische und Instrumentelle Analytik, Universität des Saarlandes, 6600 Saarbrücken, FRG

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I. SULPHONIC ACIDS AND SULPHONATES

A. Introduction

There is a copious supply of analytical literature on these classes of compound. Anionic detergents, containing usually 12–18 carbon atoms, dominate the examples.

Methods for analysis of the free acids are considered first followed by methods used primarily for sulphonate salts. This distinction is arbitrary but convenient. Clearly, many methods used for free acids can be applied to salts in the presence of added (mineral) acid; and methods used for salts can be applied to acid samples after prior neutralization.

B. Chemical Analytical Methods

1. Analytical methods for the free acids

a. Reaction with bases.

(*i*) *Titration procedures.* Sulphonic acids are strong acids, so that titration is normally straightforward. Many bases have been used as titration agents. These include, in addition to the usual hydroxides (alkali metal, alkaline earth, quaternary), various organic bases, such as guanidines[1–6], ethanolamines[4,7], alkylamines[4,8,9], pyridine[10,11], piperidine[12], morpholine[1,6] and aniline[13]; coulometric titration has also been used[14].

The titration has been performed in both aqueous and non-aqueous solution, with many types of end-point indication, potentiometry and standard colour indicators predominating. Among other end-point determinations, conductometric[5,15–20], 'high

frequency'[8,21] and amperometric[22] techniques may be mentioned. A special case is the determination of sulphonic acids in sulphonation mixtures, e.g. in preparative work or after treatment of petroleum fractions with sulphuric acid. These samples thus contain free sulphuric acid and four techniques have been adopted to deal with this problem:

(1) Prior removal of the sulphuric acid, for instance by precipitation with Ba(II)[23,24] or aniline[25].

(2) Titration to two successive end-points, usually inflections in potentiometric titration but sometimes with two indicator colour changes[1,3,5,11,12,18,26–29]. The first-end-point corresponds to reaction of the sulphonic acid(s) and the first proton of the sulphuric acid, the second to titration of the whole. The titration of the sulphonic acid(s) can then be obtained from the difference.

(3) Separation of the sulphonic acids selectively from the aqueous solution of the sample, using high molecular weight amines[30], e.g. tricaprylamine hydrochloride (Alamine 336) in toluene, which was claimed to remove very little sulphuric acid[31].

(4) Titration with a base giving total acid, and a second titration with Ba(II) to obtain the sulphuric acid value to be subtracted subsequently[5,9,16,20,32–35].

(*ii*) *Preparation of salts for separation, identification or quantitative determination.*

$$RSO_3H + Base \longrightarrow (Base\text{–}H)^+(RSO_3)^-$$

Precipitation of salts with aromatic amines was used in an early attempt to separate sulphonic acids from other material and from each other. Mostly used were aniline, *p*-toluidine, naphthylamines and benzidine[36–43], as well as phenylhydrazine[44,45] and guanidines[46]. These derivatives could be filtered off or extracted by organic solvents and were suitable for identification of the acids. Quantitative determination based on titration with alkali of the strong sulphuric acid moiety of the salt, e.g. by using *p*-toluidine and extracting with ether[47], has been used. The same derivatives are obtained from the (alkali metal) sulphonate salts by reaction with the salts of the amines with strong mineral acids, generally hydrochlorides. This is mentioned in Section II.B.2 below.

(*iii*) *Detection.* A test for residual sulphonic acids in petroleum was based on the turbidity yielded on heating with an equal volume of aniline[48].

b. Pyrolysis with elimination of sulphur dioxide. The simplified equation is

$$RSO_3H \longrightarrow RH + SO_2$$

A product can then be detected or determined. Detection of the SO_2 has been carried out by standard procedures, e.g. with Fe(III)/ferrocyanide[49] or nickel(II) hydroxide[50]. A pyrohydrogenolysis method was developed by Feigl[51] for aliphatic sulphonic acids by heating them with benzoin:

$$RSO_3H + PhCOCH(OH)Ph \longrightarrow RH + PhCOCOPh + H_2O + SO_2$$

The SO_2 was detected with Congo paper/H_2O_2.

Quantitative determination has generally been by pyrolysis–GLC of either the free acids or the salts plus added phosphoric acid[52–54]. Siggia and Whitlock[55] found quantitative evolution of SO_2 from benzene- and *p*-toluenesulphonic acids, but the yields of hydrocarbon were only about 50%. They improved this by adding carbohydrazide to the reaction mixture.

c. Esterification with diazomethane.

$$RSO_3H + CH_2N_2 \longrightarrow RSO_3CH_3 + N_2$$

The product was subjected to GLC for detection, e.g. of methanesulphonic acid in the presence of ethanesulphonic acid[56], or for determination, e.g. of hexadecene-1- and 2-sulphonic acids[57] or of alkylbenzenesulphonic acids[58] or sulphonic acids in aerosols[59].

d. Miscellaneous. Brief mention may be made of classical methods for determining the so-called 'active hydrogen', such as the procedure of Chugaeff/Zerevitinoff with methyl magnesium iodide yielding an equivalent of methane. These methods are not specific for sulphonic acids.

2. *Analytical methods for sulphonate salts*

a. Combination with cations.

$$RSO_3^- + Cat^+ \longrightarrow (Cat)^+(RSO_3)^-$$

This is the main reaction on which analytical work is based. The cation may be organic, inorganic (a metal cation) or the proton.

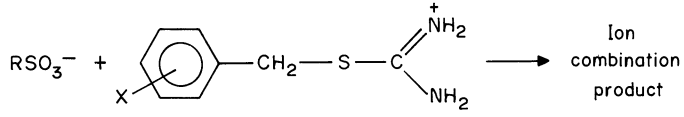
(*i*) *Combination with organic cations.*

(1) Direct titration. This is probably the most widely used method of quantitative determination of surface-active sulphonates where the anion contains 12–18 carbon atoms as a rule. The ion combination product with a large cation is then poorly soluble in water but fairly soluble in organic solvents. Quaternary ammonium cations have been those mostly used, almost always as halides. Examples are cetyl pyridinium[60–62], cetyl trimethylammonium[63–65], benzyl cetyl dimethylammonium[66–69] and benzyl dimethyl-(octaphenoxyethoxyethyl)ammonium(benzethonium, Hyamine 1622)[66,70–74]. Various types of end-point indication have been proposed, some of them most unusual, for example: change in, or maximum, turbidity[62,75,76]; minimum surface tension (when the titrant is a cationic surface-active agent)[77]; stalamometric(maximum mercury drop time)[78]; short foam persistence[79]; use of an electrode sensitive to one of the ions[80–84]; thermometric technique[85]; and use of an indicator with coloured cation or anion, often a triphenylmethane dye, notably methylene blue. A two-phase system, such as water and chloroform, is required. At first, the indicator cation (for example) combines with an equivalent amount of sulphonate sample to give a product soluble in the organic solvent and colouring it. During titration the reagent combines progressively with the sulphonate and, as equivalence is approaching, begins to displace the coloured indicator cation from its product with the sulphonate. The indicator then enters the water layer, colouring it. Visual end-points are based on this movement of colour from the organic solvent into the water, e.g. first appearance of colour in the water or equality of colour intensity in the two layers[86]. Titration in the reverse direction or with a coloured indicator anion likewise gives a movement of colour from one layer into the other. Methylene blue has been the most popular indicator[60,61,65,67,87]; others include bromophenol blue[60,64,65,88], eosin[63] 2,7-dichlorofluorescein[72], phenolphthalein[74] and disulphine blue[89]. Excess cetyl trimethyl-ammonium ion has been back-titrated with tetraphenylborate[68,69], and excess quaternary salt was also back-titrated with a standard anionic reagent, to methyl orange[90]. In a non-titrimetric procedure, Hyamine 1622 was added and the rise in temperature correlated with the sulphonate concentration[91].

(2) Determination of the ion combination product. Another procedure is direct evaluation of the coloured ion combination product with the sulphonate ion. It is extracted into an organic solvent and the colour intensity of the solution related to the sulphonate concentration using a usual calibration curve. Methylene blue has been quoted as pairing ion in some 60 examples. Most methods are modifications of, with reference to, earlier procedures, e.g. of Jones[92], Longwell and Maniece[93] and Abbott[94]. There are sources of error, notably competition reactions with other cations, such as perchlorate or thiocyanate, and also miscellaneous components present in samples and known as methylene blue active substances (MBAS) for which corrections are applied where

possible. Mention may be made of indicator compounds other than methylene blue, such as magenta[95], crystal violet[96,97], rhodamine 6G[98], azure A[99] and methyl green[100].

(3) Identification via the product. The preparation of solid salts by direct reaction of sulphonic acids with organic bases was mentioned above in Section I. B.1.a.ii. The same product is derived from reaction of a sulphonate salt (usually an alkali metal salt) with a salt of the base, most often a hydrochloride[9,36,38,43,46]. Similar are preparations of derivatives by reaction of the sulphonate salts with reagents containing active halogen, such as benzyl-, *p*-nitrophenyl- or 2,4-dinitrobenzylthiouronium chlorides[101–105].



Tabulated melting point data are given in most handbooks.

Other reactive halides employed include butyl iodide to yield butyl esters with, for example, the silver salts of methane- and ethanesulphonic acids[106] or *p*-nitrobenzyl chloride or bromide, reacting in pyridine solution with sulphonates to yield addition product with pyridine molecules[107]. Classifiable here also is conversion to trimethylsilyl derivatives with bis(trimethylsilyl)trifluoroacetamide[108].

An interesting example of analysis based on formation of benzylthiouronium salts is the work of Muramoto and Hirao[109]. It is, in fact, quantitative analysis of binary mixtures of sulphonates, e.g. of *o*- and *p*-toluenesulphonates and other aromatic pairs. They measured the melting points of mixtures of the benzylthiouronium salts prepared from the samples and interpolated the values between those for the pure compounds. Muramoto[110] extended it to further aromatic pairs.

(4) Ion-pair chromatography. This procedure, also termed ion-pair or 'soap' chromatography, has been applied to sulphonates among other classes of compounds. It is based on combination of the sulphonate ion with large cations. In the most usual chromatographic form, reversed-phase ion-pair chromatography, the stationary phase is a non-polar liquid on, for example, silanised silica. The mobile phase is polar, often water plus methanol or acetonitrile, containing the hydrophilic pairing ion. The more stable the ion pairs, the more they are drawn into the non-polar phase, i.e. the stationary phase in this version. Pairing agents used have been aliphatic amines, e.g. tricaprylamine[31], tripentyl- to trioctylamines and also secondary amines[111] or trioctylamine[112]; most used, however, have been quaternary salts[113–121]. Studies have been made of various factors affecting the method, e.g. column packing, temperature, mobile phase composition and pH[122,123]. Crown ethers have been employed, in normal phase HPLC, to form complexes with sulphonates of increased solubility in the organic phase (methanol-chloroform)[124]. Some investigators have improved separation of sulphonates in reversed-phase column chromatography by using mobile phases rich in inorganic salts[125,126]

(*ii*) *Combination with metal cations.*

(1) Quantitative determination. (a) Barium. Titration of sulphate with barium, using certain polyphenols (rhodizonate, tetrahydroxyquinone) or azo dyes, has been known for a long time. In recent years, similar titrations of sulphonate have been carried out, mostly by Russian teams, especially Kuznetsov and coworkers[127–132]. They performed spectrophotometric titration of benzene- and naphthalenesulphonic acids, also containing substituents, such as amino and hydroxyl groups. The reaction medium was acetone-aqueous acetate buffer of pH 3.6 to 4, with Nitchromazo as indicator and light absorption measured at 650 nm.

(b) Copper. Copper(II) reagents complexed with bases have been used in quantitative determination of sulphonates, e.g. with triethylenetetramine followed by spectrophotometry at 435 nm of the reaction product with diethyl dithiocarbamate[133]; with bis(phenanthroline)-erythrosine, extracted into chloroform and evaluated[134]; with bis(ethylenediamine), extracted into chloroform and evaluated colorimetrically[135] or by atomic absorption spectroscopy (AAS)[136]. Franc and Hajková determined alkanesulphonic acids on paper chromatograms by spraying with cupric acetate, then treating with potassium ferrocyanide and finally evaluating the spots with a densitometer[137].

(c) Iron. Taylor and Waters determined traces of anionic surfactants in water by reaction with ferroin containing ^{59}Fe. The ion combination product $[Fe(phen)_3](RSO_3)_2$ was extracted into chloroform and the radioactivity of this solution assayed[138]. Clementz extended and adapted the procedure to determine sulphonate in crude oils[139].

(d) Lead. Franc and Hajková also converted paper chromatography spots of alkanesulphonate into lead salts, cut them out and assayed the lead polarographically[137].

(e) Alkali metals. A recent publication[140] refers to extracting anionic detergents from water with methyl isobutyl ketone in the presence of sodium chloride and determining the sodium by AAS. Kuznetsov and coworkers[141] also spectrophotometrically titrated naphthalene- and anthraquinone sulphonic acids with potassium chloride under conditions similar to those for titration with barium, propossing an analogous mechanism for the reaction.

(2) Detection and identification. Among metal derivatives serving for detection and identification, thallium(I) salts[142] and also cobalt, lead and zinc salts of certain substituted naphthalenesulphonic acids[143,144] may be mentioned.

(*iii*) *Combination with protons, converting to the free acids.* This is practically possible only by using ion exchangers in the H^+ form, often Dowex 50. The free acids in the eluate can then be simply titrated with standard alkali[145–148].

b. Conversion to sulphonyl chlorides. Conversion of free acids or salts to sulphonyl chlorides has generally been performed with PCl_5, but $COCl_2$, $SOCl_2$, SO_2Cl_2 and S_2Cl_2 have also been used. The sulphonyl chloride has most often been assayed by GLC[149–156]. Other methods for determining the sulphonyl chlorides included: conversion to sulphonyl fluorides with KF, followed by GLC[24,157,158]; reduction to thiols with Zn/HCl[159] or $LiAlH_4$[160], then GLC; determination through infrared measurements[161–163]; conversion to the methyl ester, then GLC[164] or HPLC[165]; determination by HPLC[165]; determination of the congealing point of sulphonyl chloride mixtures in analysis of mixtures of the *p*-toluenesulphonates[166]; treatment with hydroxylamine, then conversion with acetaldehyde to yield acetohydroxamic acid, yielding colour with Fe(III) as a test for sulphonic acids[167].

The classical route to derivatives for identifying sulphonic acids/sulphonates is via formation of the sulphonyl chlorides and then converting them to amides with ammonia or a primary or secondary amine.

c. Conversion to phenols. The alkali fusion reaction of arylsulphonic acids, usually performed at 300–400 °C, yields both phenols and sulphite ion for which there are several methods of detection, identification and determination. For phenols, bromination is

$$ArSO_3^- + OH^- \longrightarrow ArOH + SO_3^{2-}$$

employed, followed by iodometric determination of unused reagent[168] or GLC determination of the bromo-products[169], or coupling with a diazonium salt to give a coloured azo compound for detection[170] or for spectrophotometric evaluation[171,172]. The phenol can also be determined by GLC[171,173,174]. Sulphite was determined using an alternative procedure to the determination of phenol by reaction with formaldehyde and titration

of the alkali formed[173]:

$$SO_3^{2-} + HCHO + H_2O \longrightarrow HOCH_2SO_3^- + OH^-$$

d. Conversion to sulphonohydroxamic acids. Aromatic sulphonic acids have been determined on paper or thin-layer chromatograms by spraying first with hydroxylamine and then with cupric acetate to yield zones which were assayed at 480 nm with a densitometer[175].

e. Oxidation. The sulphonic acid/sulphonate group is highly resistant to oxidation. Analytical methods of oxidation thus involve other parts of the molecule. Examples are detection in TLC with $KMnO_4$[176] or oxidation to sulphate, e.g. with $FeCl_3/H_2O_2$[177,178] or with conc. $HNO_3/HClO_4$[179]; the sulphate can then be detected or determined with Ba^{2+}. Such procedures apply to many classes of sulphur-containing compounds and are not presented further here.

f. Reduction, including polarography. Raney nickel alloy/alkali hydroxide[180] and also tin/conc. phosphoric acid[181] have been employed to detect sulphonate by reduction to, and then demonstration of the presence of, sulphide. Other S(VI) and S(IV) compounds react similarly.

Rahn and Siggia[182] reduced benzene- and *p*-toluenesulphonic acids (and also various azo and nitro compounds) with carbohydrazide during 2–4 minutes at 220 °C to the corresponding hydrocarbon, which was determined by GLC. However, conversion was only about 70%.

There appear to be only a few analytical publications on the polarography of sulphonic acids or sulphonates. Most of them concern other groups in the molecule, notably the azo and nitro groups.

C. Physical and Instrumental Methods

1. Spectroscopic methods

a. Ultraviolet. The principal use of ultraviolet measurements in analytical work with sulphonic acids and sulphonates is probably the monitoring of eluates from chromatographic columns. Direct uses in the analysis of mixtures can be divided into two groups:

(i) Aromatic sulphonates, often mixtures of isomers, evaluated at wavelengths between about 200 and 300 nm. Example include evaluation of total toluenesulphonic acids in the presence of sulphuric acid[183]; toluene- and xylenesulphonates[66]; toluenesulphonic acid isomers[184]; benzenesulphonic acid in spent acid[185]; and sulphonated products of phenols[186], aniline[187], chlorobenzene[188], bromobenzene[189], nitrobenzenes[190] and *N*-dimethylaniline[191].

(ii) Alkylarylsulphonate detergents, often evaluated at *ca* 224 nm[192–195], and sulphonates evaluated in the presence of sulphated alcohols[196].

Interesting is the development of IPC-indirect photometric LC for UV-transparent ions, using a UV-absorbing counter ion such as sulphosalicylic or *m*-sulphobenzoic acid or potassium biphthalate[197].

b. Infrared. The examples of the use of IR measurements can also be conveniently divided into two categories:

(i) Aromatic sulphonates (non-detergent), e.g. toluene- and xylenesulphonates[198], aminobenzenesulphonates[199], naphthalenesulphonic acid[200] and aminonaphthalenesulphonic acid[201].

(ii) Alkylarylsulphonates[202–205] and sulphonate oil adducts[206].

An example of a different sort is the determination of oxidized keratin sulphonates[207].

Dlinski and Stein[208] proposed solubilization of sulphonic acids by dissolving them in the liquid ion exchanger 5% Amberlite in CS_2.

Muntean and Halus[209] identified sulphonates in commercial lubricating oil additives through IR absorption at 1420 cm^{-1}.

2. *Chromatographic methods*

Only some of the very large number of publications can be mentioned here. Classification is according to technique.

a. Column chromatography (CC). Examples of use include separation of anionic detergents[210], substituted aromatic sulphonates[211], alkenesulphonates[212] and petroleum sulphonates[213].

b. Paper chromatography (PC). Numerous separations of colouring materials containing the sulphonate group have been described[214–217]. Also reported are separations of aromatic sulphonic acids and sulphonates, frequently with substituents[188,218–223], and of carbohydrate sulphonic acids[224].

c. Thin-layer chromatography (TLC). A similar spectrum of compounds has been subjected to TLC as to PC. Examples include alkanesulphonates[176,225–229] and studies of detergent additives to oil[230,231].

d. High performance liquid chromatography (HPLC). This tool has been employed to separate detergent sulphonates (LAS, ABS)[54,232–235], sulphonic acids of the aliphatic series[197,236] and of the aromatic series, e.g. of toluene and naphthalene[236–243].

e. Electrophoresis. This procedure has not been used often. An example is the separation of substituted benzene- and naphthalenesulphonic acids[244].

II. SULPHONYL HALIDES

A. Introduction

Analytical information has been found practically only for the sulphonyl chlorides. These are also intermediates in identification and determination of sulphonic acids/sulphonates. Although this has been mentioned above in Section I, it nevertheless belongs to the present section.

B. Chemical Analytical Methods

1. *Reaction with water*

$$RSO_2Cl + H_2O \longrightarrow RSO_3H + HCl$$

Carboxylic acid anhydrides have been determined via estimation of the water consumed in an analogous reaction but only two examples could be found for a sulphonyl halide, namely *p*-acetylaminobenzenesulphonyl chloride, where excess water was back-titrated with the Karl Fischer reagent[245,246].

a. Reaction with 'combined' water. Some compounds act as water-suppliers in the

determination of sulphonyl chlorides, e.g. *N*-alkylformamides ($HCONHCH_3$, $HCONHC_4H_9$), giving isocyanides which could be estimated colorimetrically using benzidine acetate/$CuSO_4$[247]. Sass and collaborators[248] gave a method for determining 'nerve gases' where benzenesulphonyl chloride was quoted among the examples investigated. It depends on the colour reaction with diisonitrosoacetone, HON=CHCOCH=NOH. Dziomka and coworkers[249] determined acylating agents, including benzene- and *p*-toluene-sulphonyl chlorides, also by reaction with an isonitroso compound, 2-carboxyisonitrosoacetanilide, which yields luminescent products. Kramer and coworkers[250] patented colour reactions for 'nerve gases' with 4,4′-bis(dialkylamino)benzophenone oximes; sulphonyl halides would probably react in this reaction as well. In all these cases the first reaction step may be abstraction of water from the reagent. Formic and oxalic acids were used in the 1920s for determining carboxylic acid anhydrides in the presence of tertiary bases as catalysts:

$$HCOOH - H_2O \longrightarrow CO$$

$$(COOH)_2 - H_2O \longrightarrow CO + CO_2$$

A gasometric determination or titration of unused oxalic acid was performed. The author observed gas evolution also with sulphonyl halides, but this was not pursued further.

The products of hydrolysis of sulphonyl halides, i.e. sulphonic and hydrohalic acids, can be easily titrated with bases, which accelerate the hydrolysis as well. Thus Cundiff and Markunas titrated potentiometrically benzenesulphonyl chloride (and sulphuric acid) in pyridine with tetrabutylammonium hydroxide in benzene/methanol[251]. Jansseune and Janssen[252] titrated sulphonyl fluorides in butylamine with potassium methoxide. Krivoruchko[253] estimated 2-chloroethanesulphonyl chloride in air by hydrolysing it with alcoholic potassium hydroxide and determining the chloride ion colorimetrically or nephelometrically. Jansseune and Janssen[252] also hydrolysed sulphonyl fluorides with alkali, acidified the mixture, distilled the HF and titrated it with alkali.

However, free acids are almost inevitably present as impurity products of ready hydrolysis in the sulphonyl halide and falsify the values obtained directly as, probably, in the above examples. Interest has therefore centred often on procedures which also measure the contents of these free acids or which eliminate their influence. Advantage was taken of the relatively slow uncatalysed hydrolysis of sulphonyl halides, which may permit the determination of the free-acid impurities in a prior titration. Thus Neitzel[254] first titrated the free acids with aqueous NaOH before hydrolysing the sulphonyl halide with excess alkali and then back-titrating in order to obtain total acid. Drahowzal and Klamann[255] similarly titrated indirectly benzene- and *p*-toluene-sulphonyl chlorides with $AgNO_3$ to assay free HCl, then hydrolysed a second sample with pyridine/water and titrated the total chloride likewise. Klamann[256] titrated the free HCl with silver nitrate/acetone. Bellen[257] and Bellen and Szelagowska[258] similarly determined free HCl by argentometric titration in ether. Barker and collaborators[259] added water/$CHCl_3$ to aromatic sulphonyl chlorides and titrated free acids in the aqueous layer within several seconds; after pyridine-catalysed hydrolysis, they then titrated total acids. In unpublished work the author titrated free HCl in acid chlorides using $AgClO_4$ in toluene. This could perhaps be used with sulphonyl chlorides. 'Differential' methods for correcting for free acids are mentioned below in Sections II.B.2 and II.B.3.

2. *Reaction with alcohols or phenols*

Esters are formed with alcohols and phenols, but they are mostly of rather low melting point and unsuitable as derivatives for identification.

Alcohols have been used in the 'differential' procedure for determining carboxylic acid

anhydrides. In this method two equal samples are reacted according to the following two reactions:

$$(RCO)_2O + R'OH \longrightarrow RCOOH + RCOOR'$$

$$(RCO)_2O + H_2O \longrightarrow 2\,RCOOH$$

The difference between the alkali titrations in the two cases corresponds to the ester formed and hence to the original anhydride. Free-acid impurities are equal in the two cases and cancel out in the difference. In principle, this method should be applicable to sulphonyl halides and anhydrides but no example could be found in the literature.

Sulphonic acids/sulphonates have been determined via conversion to the corresponding sulphonyl chlorides, then reacting these with methanol to yield the methyl esters; these were determined by GLC[164] or HPLC[165] (see Section II.C.3 below).

3. *Reaction with ammonia or amines*

Ammonia or primary or secondary amines have been used instead of alcohols in the differential procedures. Only two examples of application to a sulphonyl halide could be found: Klamann[256] used aniline to determine *p*-toluenesulphonyl chloride, titrating with NaOH. Recently Spince, Luse and collaborators[260,261] determined aromatic sulphonyl chlorides using aniline or α-naphthylamine in DMF or DMSO, titrating with KOH.

As an alternative to the differential procedure a measured amount of excess amine has been used to determine acid anhydrides, unused amine then being back-titrated. Aniline and nitro- or halogeno-substituted anilines have been used, but only two examples could be found of application to sulphonyl halides: Terent'ev and coworkers used hexamethyleneimine in methanol, then back-titrated with HCl/methanol[262]; and Allan and Sobodacha[263] used 3-chloroaniline in 1-methyl-2-pyrrolidone and back-titrated with standard $NaNO_2$.

Sulphonamides are excellent derivatives for identification of sulphonic acids and are prepared via the sulphonyl chloride using usually ammonia, aniline or *p*-toluidine. Melting point tables are in many reference books.

4. *Reaction with hydroxylamine*

A test for sulphonic acids is based on conversion to the sulphonyl chloride and then reaction with hydroxylamine. The reaction product can be converted with a drop of acetaldehyde to a hydroxamic acid which is detected in the classical way through the brown-violet colour with a drop of a Fe^{3+} reagent[264].

$$RSO_2Cl \xrightarrow{NH_2OH} RSO_2NHOH \xrightarrow{CH_3CHO} CH_3CONHOH + RSO_2H$$

$$\downarrow Fe^{3+}$$

coloured chelate compound

5. *Reaction with thiocyanate*

Formation of a yellow precipitate on cooling, after boiling the sample with solid ammonium thiocyanate, was given as a test for sulphonyl chlorides[265]. The product may be RSO_2SCN.

6. *Reaction with azide*

A recent method for determining carboxylic or sulphonyl halides depends on reaction in acetone/water with excess sodium azide. Unconsumed azide is then determined by

conversion with ferric sulphate to a red complex $[FeN_3]^{3+}$, which is evaluated spectrophotometrically at 458 nm[266].

7. Quaternarization reactions

Active halides, such as methyl iodide and substituted benzyl halides, readily form quaternary ammonium salts. This has been utilized analytically with sulphonyl halides. Earlier examples of pyridine ring fission in this way were, in fact, qualitative tests for this compound, using aromatic sulphonyl chlorides[267] as reagents and then adding alkali to yield purple colours. Saville[268] applied the test in the reverse sense to detect benzenesulphonyl bromide. He added KI/NaCN to yield BrCN. This led to ring fission of added pyridine to give glutaconic dialdehyde which, in turn, reacted with benzidine, also present, to give a coloured product. Saville referred to eventual possibilities for quantitative use of the method. Quantitative spectrophotometric procedures have been developed for determining aromatic sulphonyl chlorides, based on reaction with pyridine/water (at 550 nm) or with acetone/pyridine/water (at 386–397 nm)[269]. A test for sulphonyl chlorides is based on a colour reaction with 2-aminofluorene in pyridine[270]. Here, too, pyridine ring fission probably occurs, followed by a condensation reaction with the amino group.

8. Reaction with peroxides

Aromatic sulphonyl chlorides are among the tested compounds in some colorimetric methods for determining 'nerve gases'. Thus Marsh and Neale[271] used *o*-dianisidine/H_2O_2 and Gehauf and coworkers[272] used benzidine/sodium perborate. A possible initial reaction is

$$\text{X-Hal} + \text{HO-O}^- \longrightarrow \text{X—O—OH} + \text{Hal}^-$$

The peroxide then oxidizes the aromatic amine to coloured products.

9. Reduction, including polarography

Sulphonyl halides (excluding the fluorides) can be reduced to sulphinate:

$$RSO_2Hal + 2\varepsilon \longrightarrow RSO_2^- + Hal^-$$

Gringras and Sjöstedt[273] reduced sulphonyl chlorides on paper chromatograms with a sodium sulphite reagent, then visualizing the sulphinate reaction product with tetrazotized *o*-dianisidine. Direct titrations of sulphonyl chlorides with sodium sulphide have also been performed, with instrumental or visual end-point indication (the latter depending on the formation of yellow polysulphide from the excess reagent and the sulphur produced)[274–276].

$$RSO_2Cl + S^{2-} \longrightarrow RSO_2^- + Cl^- + S$$

A TLC detection depends on spraying with NaI/acetone to give amber-coloured spots[277]. The reaction that occurs is probably

$$ArSO_2Cl + 2I^- \longrightarrow ArSO_2^- + Cl^- + I_2$$

Polarographic reduction of sulphonyl chlorides is evidently also a two-electron process, yielding sulphinate and chloride. Work in this domain has not been analytical, however. An indirect method for determining aromatic sulphonyl chlorides in DMSO has been based on H^+ and/or Cl^- waves[278].

Sulphonic acids/sulphonates have been determined by conversion to the sulphonyl chlorides. One method of determining the latter has been by reduction to thiols, e.g. with Zn/HCl[159] or by $LiAlH_4$[160], followed by GLC.

C. Physical and Instrumental Methods

1. Crystallization and extraction procedures

In most earlier work, partial separation or analysis of mixtures of sulphonic acids, especially aromatic isomers, was attempted after conversion to sulphonyl chlorides, e.g. by fractional crystallization[279] or measurement of the congealing point[166].

A separation of sulphonyl chlorides by selective extraction with a solvent and partial crystallization has been patented[280]. An example is that of hexadecane-mono-, di- and polysulphonyl chlorides, extracted from benzene with nitromethane, followed by cooling to $-30\,^{\circ}C$.

2. Spectroscopic methods

Infrared measurements have been conducted with sulphonyl chlorides obtained from, in determination of, sulphonate surfactants (see Section I.B.2.b above)[161–163]. IR measurements at $1212\,cm^{-1}$ were employed to determine *p*-chlorosulphonyl chloride as impurity in *N,N*-di-n-butyl-*p*-chlorobenzenesulphonamide[281].

3. Chromatographic methods

Various mixtures of sulphonyl chlorides or mixtures containing them have been analysed by GLC. Examples include monoalkylbenzenesulphonyl fluorides[282], mono- and polychloro-substituted methane sulphonyl chlorides[283], mixtures of sulphonyl chlorides and sulphones of aromatic hydrocarbons[284], and benzene sulphonyl chloride in the products from reaction of benzene and chlorosulphonic acid[285]. Further, sulphonate mixtures, including detergents, have been analysed by prior conversion to the sulphonyl chlorides, which were then subjected to GLC[149–156]. In two cases, the sulphonyl chlorides were transformed into the corresponding fluorides by heating with KF and these products then submitted to GLC[157,158].

Imaida and coworkers converted the sulphonyl chlorides from alkylbenzenesulphonates into methyl esters, which they then subjected to GLC[164]. Tsukioka and Murakami likewise prepared methyl esters from sulphonyl chlorides of detergent materials but then employed HPLC for analysis[165].

In addition to sulphonamides, *p*-toluenesulphonyl chloride was subjected to TLC by Ulrich[286].

III. SULPHONATE ESTERS

A. Chemical Analytical Methods

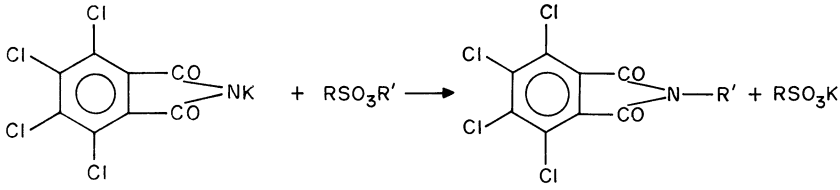
1. Hydrolysis

Hydrolysis as a basis of quantitative determination must be possible for sulphonate esters in general as for the carboxylate esters, for example, by using a measured amount of standard alkali in excess, carrying out hydrolysis and then determining the unused alkali. Very few published examples of this could be found, perhaps because the procedure is so self-evident. Some slightly more elaborate methods may be cited. An East German patent covers alkaline hydrolysis of higher molecular sulphonate esters, with titration of the resulting sulphonate with Hyamine[287]. Brook and Munday[288] analysed mixtures of the ethyl esters of methane- and ethane-sulphonic acids using a reaction rate method and titrating the sulphonic acids formed with sodium butylate. As an alternative to back-titration of unused alkali, Stehlík and Nováčik[289] destroyed the organic matter and

ultimately titrated the residue with acid. *p*-Chlorophenyl *p*-chlorobenzenesulphonate was determined by Kutschinski and Luce[290] by alkaline hydrolysis and colorimetric determination of the *p*-chlorophenol with 4-aminoantipyrine/ferricyanide.

2. Other reactions

Allen and coworkers identified esters through the formation of N-substituted tetrachlorophthalimides by reacting them with potassium tetrachloriophthalimide in DMF or DMSO. Most of their examples were carboxylate esters, but 2-chloroethyl *p*-toluenesulphonate was also tested by them[291].



Sulphonate esters are evidently reduced polarographically to sulphinate[292,293] but no analytical application has been suggested.

B. Physical and Instrumental Methods

1. Spectroscopic methods

In a study of the reactions of methyl *p*-toluenesulphonate Swain and Morgan determined the ester at 261 nm[294]. Katritzky and collaborators[295] determined sulphonate (and sulphate) esters by extraction into CCl_4 and measuring in the IR the intensity of the asymmetric SO_2 stretching mode.

2. Chromatographic methods

a. Thin-layer chromatography. Two examples of the use of TLC can be given: monoalkanesulphonates[296] and esters of acids derived from sulphonation of 1-dodecene[297]. Both were visualized with dichlorofluorescein.

b. High performance liquid chromatography. An example of the employment of HPLC is the last stage in a determination of linear alkyl sulphonates after their conversion into the methyl esters[165].

c. Gas chromatography. GLC has been used to determine *p*-chlorophenyl *p*-chlorobenzenesulphonate[298], alkane monosulphonates[296] and thiosulphonate esters[299]. Esters have also been determined as the final stage in determinations of sulphonates, in two ways: via conversion to sulphonyl chlorides and then reaction with methanol[164], or by direct treatment of the sulphonic acids with diazomethane to give the methyl esters[56–59].

IV. SULPHONAMIDES

A. Introduction

The analytical literature on sulphonamides is vast. Most of it concerns sulphonamides of therapeutic interest, the sulphanilamides, with the basic formula *p*-$H_2NC_6H_4SO_2NH_2$.

The chemical analytical methods considered here are primarily those of the $—SO_2NH_2$ group. Methods in which the *p*-NH_2 group directly reacts, e.g. diazotization, are thus not included. There are, however, many border-line cases, such as halogenation, where the NH_2 or substituted NH_2 group influence the reaction and the reactivity. A compromise has been sought here.

B. Chemical Analytical Methods

1. Reactions as acids

The H atoms of the SO_2NH_2 group are acidic, which opens the way to several procedures.

a. Titration with bases. Only a selection of the many publications on titration with bases can be given, as far as possible those where the sulphonamides formed a major group of the compounds investigated or where there is some special feature of interest. It is not surprising that all the standard bases have found use, e.g. alkali hydroxides[300–303], alkoxides[304–309] and quaternary bases[308,310,311]. Titration, especially of the more weakly acid sulphonamides, has often been in organic, even basic, solvents, of which DMF and DMSO appear to have been the most used, with thymol blue and phenol red as frequent colour indicators, and potentiometric and conductometric titration as the most used instrumental procedures. An interesting end-point indication is thermometric, based on exothermic dimerization, catalysed by the first excess of alkali titrant, of acetone[303] or acrylonitrile[308]. Added cetylpyridinium chloride was found to enhance the end point of potentiometric titration[302]. A Slovak team[312,313] titrated sulphonamides and other weak acids in DMF or DMSO with sodium or potassium borohydride, using visual or potentiometric end-point indication.

b. Reaction with metal cations. Several metal cations have been used for detecting and determining sulphonamides and other weak acids, based on replacement of the acidic hydrogen by the metal cation. Several examples are given below.

(*i*) *Copper.* Copper(II) yields characteristic colours and precipitates, utilized in detection and visualization on chromatograms[314–321]. It has also been employed in direct titration with the help of Cu(II)-sensitive electrodes[322,323], in indirect titration using EDTA to titrate unused reagent[324,325], and through colorimetric assay of the reaction product, e.g. with copper(II)-*p*-chlorophenol[326], copper(II)-phenothiazine[327] or an alkaline copper(II) salt[328]. A recent publication[329] describes a flow injection method with copper(II) [and silver(I)] giving continuous precipitation and evaluation by AAS.

(*ii*) *Silver.* Silver(I) has found use for direct titration of sulphonamides with the aid of silver ion-sensitive electrodes[322,323,330,331], using indicators, such as diphenylcarbazone[300,332], or indirectly[333,334]. Detection with silver(I) depends on formation of a white precipitate. The flow injection method mentioned under 'Copper' was applied also to silver(I)[329].

(*iii*) *Mercury.* Mercury(II) has been used to detect sulphonamides (white precipitate)[316,335,336], for direct(amperometric)titration[337] and using excess with back-titration with ammonium thiocyanate[338] or EDTA[339].

(*iv*) *Cadmium.* Cadmium(II) was among many cations tested for detection of sulphonamides[316,340] and has also been used to determine sulphadiazine by precipitation with excess reagent and determining the unused amount[341]; it has also been added to the mobile phase in HPLC to improve separation of sulphanilamides[342].

(*v*) *Cobalt.* Cobalt(II) has been tested, along with several other cations, for detecting sulphonamides[316,318,320,321].

(*vi*) *Other cations.* Among other cations tested for detection, nickel(II)[320,321] and iron(III)[340] may be mentioned. Zinc was used as ferrocyanide in thin layers for separation of sulphonamides[343].

c. Ion-pair chromatography. Ion-pair chromatography of sulphonamides has been performed in reversed-phase HPLC, with quaternary ammonium as pairing ion and mobile phases often of alcohol–alkane mixtures[344,345].

d. Reactions with large molecules. Large ions have been used to form complexes with sulphonamides, e.g. reineckate, with subsequent gravimetric evaluation[346] or colorimetric determination[347]. Another example is 3-α,β-dicarboxyethylrhodanine, followed by colorimetry of the product[348]. The use of molybdophosphoric acid in detection may be classified here too[349].

A free hydrogen atom of the SO_2NH_2 group condenses with xanthydrols[350,351] and diphenylmethanol[352] to yield products suitable for identification through the melting point.

2. Alkylation and acylation

A hydrogen atom of the sulphonamide group can be alkylated or acylated to yield more volatile products which are then amenable to gas chromatography. Methylation has been carried out with diazomethane[353,354] and with trimethylphenylammonium ions[355]. Derivatives for GLC have been prepared also by using fluorine-substituted reagents, such as trifluoroacetic anhydride[356], pentafluoropropionic anhydride[354], pentafluorobenzyl bromide[356,357], heptafluorobutyric anhydride[356,358], and also methyl iodide[357].

3. Hydrolysis of the C—N bond

Hydrolysis is a standard procedure for determining carboxamides. Alkaline hydrolysis yields ammonia or an amine which can usually be distilled out and easily detected or determined, e.g. by titration with acid. This method can be applied to sulphonamides, usually under rather more vigorous conditions[359,360]. Acid hydrolysis is also possible: the solution can then be made alkaline and the ammonia or amine distilled and determined as after alkaline hydrolysis[361]. In another published work, the sulphonic acid product was isolated, e.g. by using an ion exchanger, and titrated with alkali[362].

The simplicity of the method and the straightforward analogy to carboxamide determination probably explains the small number of publications.

4. Halogenation

Two general reactions are possible in halogenation. One is replacement of the hydrogen atoms in the $—SO_2NH_2$ group. The other, used with sulphanilamides, which form the vast majority of the examples, is nuclear substitution in positions *ortho* to the $—NH_2$ or substituted $—NH_2$ group. In the latter case, this group clearly dominates. However, the analytical procedures are deemed to be important enough for mention here. A classification according to reagent can be made.

a. Halogens. Bromide has been one frequently used, in direct titration[363–366] and also with coulometric titration[367,368]. In an example excess reagent was used and followed by back-titration[369] and in another example coulometric back-titration with Cu(I) was applied[370]. Bromine was also used in detection of sulphanilamide through a white precipitate[363]. The bromate/bromide reagent in acid solution has also been employed in

direct titration[371–375] and back-titration procedures[361,376–378]. It has also found use in a test for various sulphanilamides through colour and precipitate[379]. As alternatives to bromate in analogous methods, iodate[380] and permanganate[381] have been used, the latter in a back-titration procedure.

Chlorine has served in coulometric titration of sulphanilamides[382] and for detection, e.g. in TLC, in which *N*-chloro-substituted products are first formed through the action of the chlorine. These products react successively with the components, cyanide, pyridine and barbituric acid or a pyrazolone, of an added reagent, first to give NCCl, which then effects pyridine ring fission to glutaconic dialdehyde which in turn yields coloured condensation products with the third component[383].

Indirect titration of sulphanilamides, determining unused reagent, has been performed with iodine monochloride[384–386], iodine trichloride[386] and bromine chloride[387].

b. Active halogen on nitrogen. Several reagents with a nitrogen atom carrying an active halogen atom have been used for direct titration of sulphanilamides. They were chloramine T[388–391], dichloramine T[392], *N*-bromo- and chlorosuccinimide (the third procedure quoted was colorimetric, in the presence of phenothiazine)[391,393,394], dibromodimethylhydantoin, also in a method of back-titration[395], *N*-bromophthalimide[396,397] and *N*-bromosaccharin[397].

c. Hypohalites. Colour reactions of sulphonamides with sodium hypobromite[398,399] and hypochlorite[400] are quoted in the literature. Abdine and coworkers determined sulphanilamides quantitatively by assaying the colour formed with a phenothiazine-hypochlorite reagent[327]. A rare example of determination of ordinary sulphonamides, without activating substituents, is the work of Schäfer and Wilde[401]. They carried out thermometric titration in alkaline medium, giving the reaction end-product as $ArSO_2\overset{(-)}{N}—Cl$.

5. Oxidation

Sulphonamides are stable to oxidation and any use of oxidation agents in analysis must be accompanied by a drastic reaction, e.g. oxidation with H_2O_2 gives sulphate, detected by Ba(II)[177] or similar oxidation and then determination of the ammonia moiety of the ammonium sulphate formed[402]. Such methods must apply to many classes of sulphur-containing compounds.

The so-called Roux reagent composed of $KMnO_4$, nitroprusside and alkali, was used in earlier days to detect sulphanilamides through the various colours formed[403,404]. Excess vanadate and back-titrating with Fe(II) has been used to determine sulphanilamides[405]. Cerium(IV) has been used in quantitative determinations of sulphonamides, back-titrating unused reagent[405–408] or evaluating the colour intensity of the products[409]. It has also found use for detection through the various colours given[320,410]. The stoichiometry of the oxidation is unclear.

An unusual oxidation reaction is that of sulphonamides with nitric acid in the presence of concentrated sulphuric or hydrochloric acid to yield an amount of nitrous oxide claimed to be proportional to the amount of sulphonamide[411,412]. Probably, the ammonia formed by hydrolysis reacts to give ammonium nitrate, which is known to yield nitrous oxide on heating:

$$NH_4NO_3 \longrightarrow N_2O + 2H_2O$$

6. Reduction, including polarography

There is little information about analytical reduction of sulphonamides. A test was given

by Burmistrov[413], depending on reduction with Sn/HCl to thiols which were detected with nitroprusside.

Sulphonamides were among examples of weak acids determined polarographically in tetramethylammonium iodide solution[414] and of drugs studied oscillographically in dilute NaOH, HCl and H_2SO_4[415]. Sulpha-diazine, -merazine and -methazine were determined in mixtures by a.c. polarography in dilute perchloric acid solution[416]. Some sulphonamide reductions at the dropping mercury electrode have been studied, but without apparent analytical application[417]. The nature of the reduction in all these cases is unclear and other groups and substituents probably played a part in the reaction.

7. Pyrolysis and thermal analysis

Pyrolysis GLC of sulphanilamides has been studied by Irwin and Slack[418–420]. Coupling with MS enabled the compounds to be identified in various samples, e.g. urine. Evidently aniline and SO_2 are regular products of pyrolysis, together with heterocyclic bases, depending on the particular compound. Cook and Hildebrand[421] presented thermogravimetric curves up to 800 °C for 12 sulphanilamides, suitable for identification purposes. Khattab and coworkers[422,423] also carried out thermal analysis(thermogravimetry, derivative thermogravimetry, differential thermal analysis), on pharmaceuticals, including many sulphanilamides.

Radecki and Wesolowski[424] reviewed the various techniques of thermal decomposition of therapeutic agents, concluding that identification was possible if more than 50% of the tablet consisted of the drug.

C. Physical and Instrumental Methods

1. Crystal structure and appearance

Before the advent of modern instrumental methods, attempts were made to identify drugs, often including sulphanilamides, through the nature and appearance of the crystals obtained on evaporating the solution of a small amount of sample in a drop of solvent, e.g. benzene, acetone, alcohol or water[425–429]. Sometimes the crystals derived from using reagents were inspected, such as with Pd(II)[430], iodine[431], bromine vapour[432], KI[433] or Cu(I) salts[434]. Drugs have also been identified through X-ray powder photography[435].

2. Refractometry

Refractive index values have been used to identify drugs, including sulphanilamides, for example at their melting point[436] or in acetone solution[437]. Rapaport and Solyanik[438] found a linear relationship of refractive index and concentration in NaOH or HCl solutions which they utilized for quantitative determination.

3. Spectroscopic methods

a. Ultraviolet. Sulphanilamides have been identified and also their mixtures analysed with the help of ultraviolet masurements at various wavelengths between about 248 and 288 nm[335,439–447]. The samples were mostly in solution in 96% ethanol, dilute HCl, NaOH or NH_4OH. Two 'non-medical' examples may be given, namely analyses of mixtures of *o*- and *p*-toluenesulphonamides[448,449]. The frequently used monitoring of chromatographic eluates falls under this heading.

b. Infrared. There are some references to the use of infrared data in order to identify and

determine sulphanilamides and other drugs[281,450-453]. The application to detection on paper chromatograms[454,455] is interesting.

4. Chromatographic methods

The literature abounds with references to the use of all forms of chromatography for detecting, identifying and determining sulphanilamides and sulphonamides. As expected, almost all of this work has been devoted to the former compounds. It would swell the contents of this chapter to an unacceptable extent if all of these were cited. Reference is thus made only to the methods for 'non-drug' sulphonamides: PC of *p*-toluene- and *p*-carboxybenzene-sulphonamides[456], and of the isomeric *p*-toluenesulphonamides[457], TLC of *N*-(*p*-tolylsulphonyl) carbamates[458] and of arenesulphonamides (and their isomeric aminosulphones)[459]; GLC of the toluenesulphonamides[460,461]; and HPLC of impurities in commercial saccharin, including toluenesulphonamides[462].

D. Biological Methods

These really fall outside the scope of this chapter but may be mentioned briefly. Antimicrobial materials, including sulphanilamides, have been assayed through their retarding effect on the growth of various organisms, the most frequently used of which appears to be *Bacillus subtilis*. An agar diffusion system at pH *ca* 7.2, containing the sample, is inoculated with the organism and growth usually observed through turbidity. Recently trimethoprim has been added to the medium to increase the sensitivity to sulphanilamides. A selection from many references is given[463-471].

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CHAPTER **10**

Preparation of sulphonic acids, esters, amides and halides

JEFFREY HOYLE

Chemistry and Soil Science Department, Nova Scotia Agricultural College, P.O. Box 550, Truro, Nova Scotia, Canada B2N 5E3

The chemistry of sulphonic acids, esters and their derivatives
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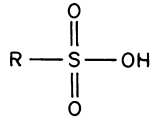
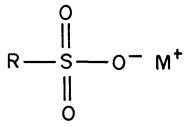
I. INTRODUCTION

Sulphonic acids (**1**) are strong acids, usually comparable with sulphuric acid, that contain a carbon atom bonded to a sulphur(VI) moiety. They are found only rarely in nature.

There have been many different approaches to their synthesis. Sulphonic acid salts (**2**), halides (**3**), esters (**4**) and amides (**5**) may be thought of as derivatives that are formed by reaction of the parent acid with bases, halogens, alcohols and amines respectively, although there are many other routes that have been taken to these compounds.



(**1**)



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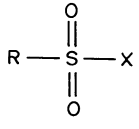
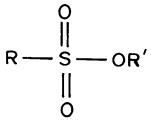


(**3**)

X = F, Cl, Br, I



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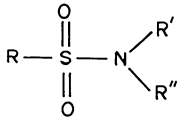


(**5**)

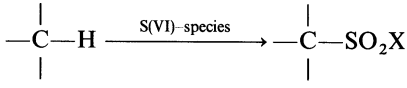
This chapter concerns the preparation of sulphonic acids and their derivatives and considers reactions occurring via one of the following three different methodologies:

(1) By carbon–sulphur(VI) bond formation (equation 1).

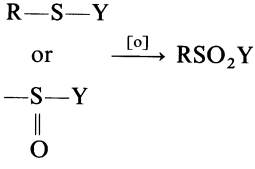
(2) By oxidation of organic compounds that contain a sulphur atom in either the + 2 or + 4 oxidation state (equation 2).

(3) From other sulphur(VI)-containing compounds (equation 3).

In addition, sulphonic acids and their derivatives may be formed by disproportionation reactions of sulphur(IV)-containing compounds. These reactions have been discussed in a previous volume in the Patai series[1] and so will not be covered here.



(1)



(2)

$$RSO_2Z \xrightarrow[\text{interconversion}]{\text{functional group}} RSO_2Y \quad (3)$$

$Y = OH, OR', NR'_2$ or halogen

Sulphonic acids and their derivatives are extremely important compounds and are used industrially in such diverse areas as surfactants, ion-exchange resins, dyes, animal feeds, pesticides and pharmaceuticals. This importance has meant that many hundreds of patents have been obtained concerning the preparation of these compounds. The present review does not cover these publications in any detail, so the reader is directed to the section covering sulphonation in the 'Kirk–Othmer Encyclopedia'[2] for key references in this area.

The present review covers the chemical literature up to the end of 1988, with a few references from early 1989 (added during proofreading).

II. PREPARATION OF SULPHONIC ACIDS AND THEIR SALTS

Sulphonic acids are strong acids that are usually soluble in water and other polar solvents. They are stable compounds that do not decompose readily on heating and are not susceptible to hydrolysis. There have been several reviews concerning the synthesis of sulphonic acids, most notably those of Shultz[3], Andersen[4] and Gilbert[5]. The reader is directed to these for further references to the very extensive literature on this subject.

A. By C—S(VI) Bond Formation

By far the most common method for the industrial preparation of sulphonic acids and their salts is by direct sulphonation. Consequently, there are many hundreds of patents covering the industrial applications of these reactions, especially with reference to aromatic sulphonic acids, and the reader is referred to the reviews of Knaggs, Nunfaum and Schultz[2] and of Gilbert[5] for key references to this patent literature.

In the present section of this chapter the non-patent literature is covered, however, since this literature is so voluminous the reader is referred to the works of Gilbert[5,6] and of Nelson[7] for a more in-depth coverage of this area.

The sulphonation of organic compounds to produce a sulphonic acid or a salt can be performed using a wide variety of reagents, including sulphuric acid and its derivatives, sulphur trioxide, sulphur dioxide, sulphites and hydrogen sulphites. These are all discussed below.

1. Using sulphuric acid and its derivatives

Sulphonation of aromatic compounds with sulphuric acid can take place under a wide variety of conditions depending upon the aromatic compound being used. The reaction is a reversible one, as shown in equation 4, and so either a large excess of mineral acid is required or the water must be removed, either by azeotropic distillation or by another process. One such procedure involves the addition of thionyl chloride to the sulphonating mixture. In this case, any water that is produced reacts with the thionyl chloride to form HCl and sulphur dioxide[6].

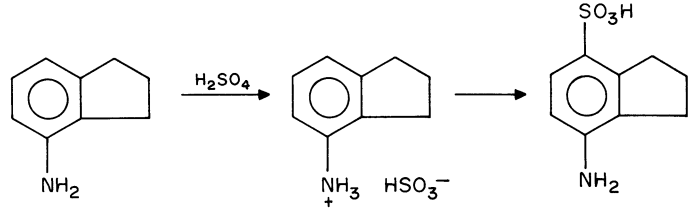
$$ArH + H_2SO_4 \rightleftharpoons ArSO_3H + H_2O \quad (4)$$

For aromatic compounds, that are activated towards electrophilic aromatic substitution, the reaction is easily carried out at room temperature. With highly activated aromatic compounds, di-, tri- or even polysulphonation products may be formed. In such cases, an inert solvent such as chloroform or carbon tetrachloride is used if the monosulphonation product is the one required.

For deactivated aromatic compounds, temperatures of up to 400 °C have been employed and, in this case, extreme caution should be taken since explosions have been reported to occur in some instances[8].

The yields of many of these aromatic sulphonation reactions may be significantly improved by the use of a catalyst. Either metal sulphate salts (such as Hg, Pb and Fe)[9-11], boron trifluoride[12] or hydrofluoric acid[13] may be used to advantage.

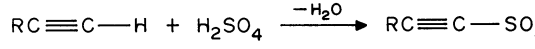
Functional groups such as hydroxyl, alkoxy, carbonyl and halo, attached directly to the aromatic ring, are unaffected even under the forcing conditions of these sulphonation reactions. In the case of amino groups, the reaction either proceeds directly to the amino sulphonic acid[14] or the initially formed ammonium hydrogen sulphate salt undergoes thermal rearrangement to give the required acid[15], as exemplified in equation 5.



(5)

The sulphonation of a wide structural variety of aromatic compounds, with concentrated sulphuric acid, has been extensively studied by Cerfontain and coworkers[16-65] and by others[66-79]. The former group have considered every aspect of the reaction including the isomer distribution, kinetics and mechanisms involved. The group's earlier work resulted in the publication of a book concerning the mechanistic aspects of this and other closely related reactions[80] and a review on acidic sulphonating reagents[81].

Most aliphatic compounds are resistant to sulphonation by reaction with sulphuric acid. However, under forcing conditions some aliphatic compounds react to produce a complex mixture of sulphonic acids, sulphonic anhydrides, alkyl sulphates and sulphones. Therefore this reaction is rarely of any synthetic utility. One exception is the reaction of terminal alkynes with sulphuric acid, which yields the terminal sulphonic acid upon removal of water, as shown in equation 6[82]. Another exception is a rather obscure report that reaction of an alkene and a nitrile with sulphuric acid, in the presence of acetic anhydride, produces 90–100% yield of the 2-amido sulphonic acid, as shown in equation 7[83].



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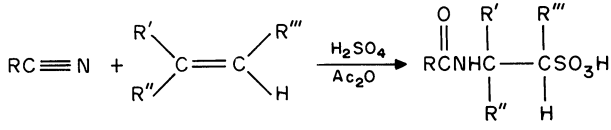


(7)

Chlorosulphonic acid, and other derivatives of sulphuric acid, may also be used for the formation of sulphonic acids by sulphonation of aromatic compounds. These sulphonating reagents are more reactive than sulphuric acid itself[78,84] and so milder conditions (temperatures of 0–25 °C are typical) may be used with them. In addition, water is not normally involved in the reaction and the separation problems, caused by the use of excess reagents, as is the case with sulphuric acid, are significantly reduced.

Sulphonation of aromatic compounds with chlorosulphonic acid proceeds in excellent yields (usually > 75%) if inert solvents are used[85-94]. In this case the use of an inert solvent

is almost mandatory in order to eliminate the production of large quantities of sulphonyl chlorides as unwanted side-products. Fluorosulphonic acid may also be employed for the formation of aromatic sulphonic acids. In this case the unwanted by-products are not formed[95].

Bis(trimethylsilyl)sulphate, formed by reaction of trimethylsilyl chloride with sulphuric acid (equation 8), has also been used for the formation of aromatic sulphonic acids (equation 9). Excellent yields of the required aromatic sulphonic acid, under mild conditions, are usually realized with this reagent after hydrolysis of the initially formed trimethylsilyl ester[96].

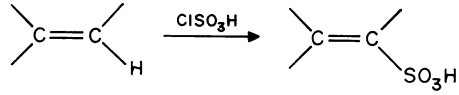
$$2ClSO_2OSiMe_3 + H_2SO_4 \longrightarrow O_2S(OSiMe_3)_2 \quad (8)$$

$$ArH \xrightarrow[2.\ H_2O/H^+]{1.\ SO_2(OSiMe_3)_2} ArSO_3H \quad (9)$$

Alkyl sulphamic acids have also been used for the formation of aromatic sulphonic acids, in excellent yields, by heating this sulphonating reagent with an aromatic compound, as shown in equation 10[97].

$$ArH + alkylNHSO_3H \longrightarrow ArSO_3H \quad (10)$$

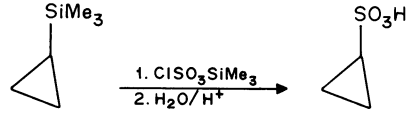
The enhanced sulphonating activity of sulphuric acid derivatives allows them to be used for the sulphonation of alkenes (this reaction is not possible with sulphuric acid). Thus, alkenic sulphonic acids are formed by the replacement of a vinyl hydrogen atom by the sulphonic acid group, as shown in equation 11[98].



(11)

One of the most recent advances in this area is the reaction of organic compounds, containing a trimethylsilyl group, with the trimethylsilyl derivative of chlorosulphonic acid[99–103], as exemplified in equations 12–14. It was by this method that cyclopropane sulphonic acid was first prepared[101].

$$RC{\equiv}C{-}SiMe_3 \xrightarrow[2.\ Na_2CO_3\ H_2O]{1.\ ClSO_3SiMe_3} RC(=O){-}CH_2SO_3^-Na^+ \quad (12)$$



(13)

$$CH_2{=}CHCH_2SiMe_3 \xrightarrow[2.\ H_2O/H^+]{1.\ ClSO_3SiMe_3} CH_2{=}CHCH_2SO_3H \quad (14)$$

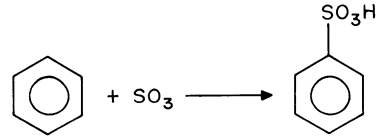
2. *Using sulphur trioxide and SO_3 adducts*

Sulphur trioxide is a much more reactive sulphonating reagent than either sulphuric acid or its derivatives[84]. Oleum, sulphur trioxide in concentrated sulphuric acid, is even

more reactive. Consequently, a much wider range of both aromatic and non-aromatic compounds may be converted to sulphonic acids with these reagents. Indeed, the reactivity with compounds that are activated towards electrophilic attack is so high that this is often moderated by use of sulphur trioxide adducts (most commonly with dioxane or pyridine). These adducts are mostly crystalline solids, which may be readily purified and are much easier to handle than the parent compound. It is important to note that there are some safety concerns when attempting sulphonations with sulphur trioxide, since in some cases it has been noted that explosions may occur[5,104]. In addition, sulphur trioxide has a propensity to trimerize and polymerize and this is averted by the use of adducts.

All these reagents, perhaps with the exception of oleum, have the advantage that no water is involved in the reaction and hence few side-reactions are observed. The one exception is that small quantities of sulphones are formed in some instances, although this does not create much of a separation problem since sulphonic acids and sulphones have such different solubility properties.

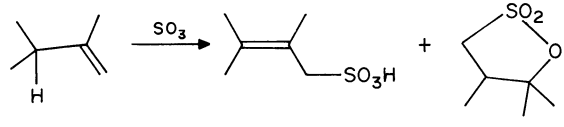
Thus, aromatic sulphonic acids are readily produced. For example, benzenesulphonic acid is formed by reaction of sulphur trioxide in chloroform with benzene (equation 15) in higher yield and at a lower temperature (0–10 °C) compared with sulphonation with concentrated sulphuric acid[105]. The sulphonation of a wide structural variety of aromatic compounds with concentrated sulphur trioxide and its derivatives has been extensively studied by Cerfontain and coworkers[21,23,45,47,52,55,56,58,59,62,64,66,80,81,106–130] and by others[5,105,131–137]. In two rather interesting reports, mono-, di- and trisulphonation of perfluorobenzene was performed by reaction with liquid sulphur dioxide[138,139].



(15)

Sulphur trioxide and its adducts usually react with terminal alkenes to produce quantitative yields of the terminal alkenic sulphonic acid (equation 16)[140–145]. However in a few instances it has been reported that a mixture of products is obtained[146–150], as shown in equation 17, or else addition across the double bond takes place[141,144], as shown in equation 18. Polyfluorovinyl ethers react with sulphur trioxide to give, upon hydrolysis, β-ketosulphonic acids in excellent yield[151].

$$RCH{=}CH_2 + SO_3 \longrightarrow RCH{=}CHSO_3H \qquad (16)$$



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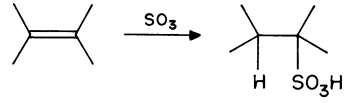


(18)

Alkynes react with either one, two or four moles of sulphur trioxide to give the products as shown in equations 19, 20 and 21, respectively[152,153]. The latter two compounds are

realized only after hydrolysis of the first-formed products.

$$HC{\equiv}CH + SO_3 \longrightarrow HC{\equiv}CSO_3H \tag{19}$$

$$HC{\equiv}CH + 2SO_3 \longrightarrow HC(=O)CH_2SO_3H \tag{20}$$

$$HC{\equiv}CH + 4SO_3 \longrightarrow HC(=O)CH(SO_3H)_2 \tag{21}$$

Aliphatic compounds containing functional groups such as aldehydes, carboxylic acids, esters, ketones, *N*,*N*-dialkylamines and sulphonic acids readily undergo sulphonation in the α-position[5,147,154,155].

3. Using sulphites and hydrogen sulphites

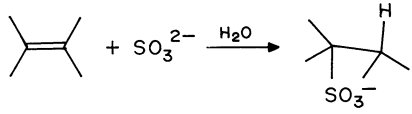
Sulphites and hydrogen sulphites may be used for the preparation of sulphonic acids; however, it is important to note that there is potential biological hazard involved in this process. This danger is discussed briefly below.

Aliphatic sulphonic acids, in particular, may be readily prepared, in good yields, by the reaction of inorganic sulphites with alkyl halides in aqueous media (equation 22). This procedure is generally known as the Strecker synthesis of sulphonic acids, after the scientist who first reported the synthetic use of this reaction[156]. This reaction[5,157–164] or a rather simple modification involving the reaction of an alkyl sulphate in place of the halide[165] has been used to prepare many aliphatic sulphonic acids in good yields. The reaction occurs under mild conditions and thus it can be performed in the presence of functional groups such as esters[166] and ketones[167].

$$RX + SO_3^{2-} \xrightarrow{H_2O} RSO_3H \tag{22}$$

$$X = Cl, Br$$

Some alkenes react with sodium sulphite, in aqueous solution, to give addition across the double bond, forming a sulphonic acid salt[5,168,169], as shown in equation 23.



(23)

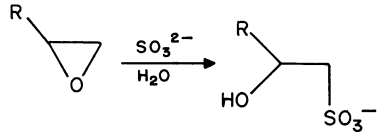
Reaction of hydrogen sulphite ions with alkenes, in the presence of either oxygen or peroxides[170–177], produces a reasonable yield of the sulphonic acid salt (equation 24), formed by anti-Markovnikov addition. Alkynes also undergo a similar reaction[178], except in this case a disulphonate salt is formed (equation 25).

$$RCH{=}CH_2 + HSO_3^- \xrightarrow[\text{peroxide}]{O_2 \text{ or}} RCH_2CH_2SO_3^- \tag{24}$$

$$RC{\equiv}CR' \xrightarrow[\text{peroxide}]{HSO_3^-} RC(SO_3^-)CH_2R' \tag{25}$$

Epoxides also react with sulphite, or hydrogen sulphite, to form hydroxy sulphonate

salts[167,169,179–181], as shown in equation 26.



(26)

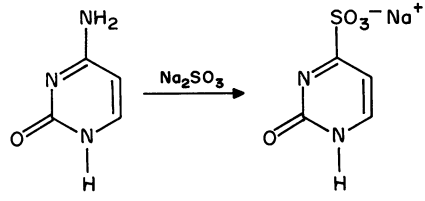
Sulphonic acids are also the products formed on reaction of carbonyl compounds with hydrogen sulphite (bisulphite addition compounds)[182,183]. α-Amino sulphonic acids are produced, albeit in low yield, upon reaction of hydrogen sulphite ions with aldehydes, in the presence of ammonia[184].

Sulphite and hydrogen sulphite ions react with some aromatic compounds to produce aromatic sulphonic acids. In this case reaction occurs by displacement of alkoxy[185,186], chloro[187,188], hydroxyl[5,189], fluoro[5] or amino[190–199] groups that are directly attached to the aromatic nucleus, as depicted in equation 27. Displacement of a chlorine atom is a general reaction for aromatic chlorides that are susceptible to nucleophilic substitution. The reaction has been shown to be catalysed by copper sulphate in one instance[188].

$$ArX + SO_3^{2-} \longrightarrow ArSO_3^- \qquad (27)$$

$$X = NH_2, OH, OR, \text{halogen}$$

The displacement of aromatic amino groups by sulphite, to form a sulphonic acid (or a sulphonate salt), gives rise to the genetic hazard of sulphites. Deamination or dehalogenation of the aromatic rings in nucleosides is a very facile reaction in which sulphonic acid salts are produced, either *in vivo* or *in vitro*[192–199]. For example, cytosine reacts with sodium sulphite to form the 6-sulphonate, by deamination, as shown in equation 28.



(28)

4. Using sulphur dioxide

In a reaction which is a combination of carbon–sulphur bond formation and oxidation, occurring in the same reaction vessel, sulphonic acids may be formed by reaction of various organic substrates with a mixture of sulphur dioxide and oxygen gases. Such a method is used for the preparation of some sulphonate detergents from long-chain alkanes[200,201], as shown in equation 29. Other aliphatic compounds also react in this fashion[202,203].

$$\text{alkyl—H} + SO_2 + O_2 \longrightarrow \text{alkyl—}SO_3H \qquad (29)$$

Aromatic diazonium salts also react with sulphur dioxide, in this case in acetic acid solution, to form sulphonic acids in good yields[204,205], as exemplified in equation 30.

$$ArN_2^+ + SO_2 \xrightarrow[-N_2]{CH_3CO_2H} ArSO_3H \qquad (30)$$

B. By Oxidation

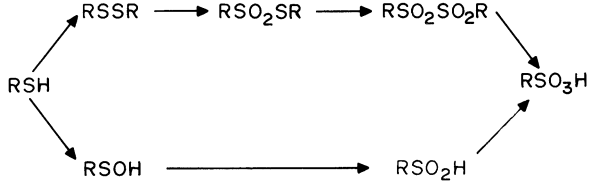
This section covers the preparation of sulphonic acids by the oxidation of three different types of sulphur-containing functionality. Thiols, disulphides and related functional group oxidations are covered in the first part. The oxidation of both thiols and disulphides to sulphonic acids is one of the classical methods for the preparation of aliphatic and aromatic sulphonic acids.

The second part of this section covers the oxidation of sulphides, sulphoxides and sulphones. Although there are fewer examples of this types of reaction, nevertheless, there are some methods by which sulphonic acids, hard to prepare by other routes, can be made.

The final part of this section covers the oxidation of sulphur(IV)-containing moieties to sulphonic acids. The functional groups covered here are sulphinic acids and their derivatives.

1. From thiols, disulphides and related compounds

Thiols are readily oxidized, by many oxidizing agents, to various different sulphur-containing functionalities, depending upon the reaction conditions. These reactions may be thought of as proceeding by one of two distinct routes, both converging at the sulphonic acid level, as shown in equation 31. It should be noted that under extremely forcing conditions, sulphonic acids may themselves be oxidized to sulphate. This latter oxidation has been reviewed previously by the present author[206]. The oxidative reactions of thiols have also been reviewed in an earlier book in the present series[207].



(31)

In the presence of halogens, thiols may be converted to sulphonic acids, as shown in equation 32[208–212].

$$RSH \xrightarrow[H_2O]{X_2} RSO_3H \qquad (32)$$

$$X = Cl, Br$$

Aromatic sulphonic acids and their salts may be produced by potassium permanganate or chromium trioxide oxidation of thiols[213–216]. The reaction probably occurs via the sulphenic acid route (see equation 31). Improved yields are obtained if this reaction is performed in the presence of base[217] or if the reaction is performed under phase-transfer conditions[218].

Oxidation of aromatic thiols with nitrogen dioxide leads to a variety of products, depending on the reaction conditions[5,219,220]. If the reaction is carried out at 25 °C in carbon tetrachloride using six equivalents of the oxidizing agent, then a quantitative yield of the aromatic sulphonic acid is formed, as depicted in equation 33. The reaction proceeds via the disulphide and the thiosulphinate, both of which may be isolated if the reaction is carried out at lower temperatures.

$$ArSH \xrightarrow[CCl_4]{N_2O_4} ArSO_3H \qquad (33)$$

Thiols, thiocyanates or xanthates (the last two functionalities may be considered as masked thiols) are readily oxidized to sulphonic acids, with concentrated nitric acid, in reasonable yields, as indicated by equation 34[221–223]. Lead thiolates are also oxidized by excess nitric acid, to yield the corresponding sulphonic acid after treatment with acid, as shown in equation 35[224].

$$\text{RSH or RSCN} \xrightarrow{HNO_3} RSO_3H \tag{34}$$

$$Pb(SR)_2 \xrightarrow{HNO_3} Pb(O_3SR)_2 \xrightarrow[H_2O]{H^+} RSO_3H \tag{35}$$

Oxygen may be used to oxidize thiols to sulphonic acids upon sensitized irradiation, as shown in equation 36[225,226]. In addition, thiols and disulphides may be quantitatively oxidized to sulphonic acid salts, by oxygen in basic DMF or HMPA solution[227,228]. Thiols may also be converted into sulphonic acids by oxidation with a mixture of potassium persulphate, potassium hydrogen sulphate and potassium sulphate[229]. Thioacetates have been similarly oxidized with persulphate[230].

$$RSH + O_2 \xrightarrow{h\nu} RSO_3H \tag{36}$$

Sulphonic acids are obtained in reasonable yields upon oxidation of disulphides or thiolates with superoxide ions, formed by the reaction of KO_2 with a crown ether[231,232]. Thiols also yield sulphonic acids quantitatively upon oxidation by ozone[233].

Sulphonic acids may normally be obtained in 65–75% yields upon oxidation of thiols, thiolates or disulphides with 30% hydrogen peroxide[234–240]. Higher yields are realized if a tertiary thiol is used. The same products may also be realized by reaction of either thiols or disulphides with aqueous dimethyl sulphoxide (equation 37), in the presence of a catalytic amount of bromine, iodine or a hydrogen halide[241,242]. In this latter oxidation, dimethyl sulphide is formed as a by-product, but is easily removed by aspiration.

$$\text{RSH or RSSR} \xrightarrow[\text{cat.}]{(CH_3)_2SO} RSO_3H \tag{37}$$

Sulphonate salts may be formed by oxidation of aromatic thiocarbamates with hydrogen peroxide, in 50–60% yield[243], as shown in equation 38. The thiocarbamates may be readily formed from phenols by reaction with dimethylthiocarbamyl chlorides[244]. A similar reaction also occurs on oxidation of thioacetates with hydrogen peroxide or peracids[245,246]. Thioacetates are readily prepared by several routes, for example, by reaction of alkenes with thioacetic acid.

$$ArSCNMe_2 \xrightarrow{H_2O_2} ArSO_3^- \tag{38}$$

In a rather novel oxidation process, cysteic acid (a sulphonic acid) was formed in 98% yield by sensitized irradiation of cysteine, in a buffer (pH 3.7), for three hours at 20 °C in the presence of oxygen[247].

Electrochemical oxidation of thiols usually halts at the disulphide level. However, when high potentials are employed, further oxidation may take place to form the sulphonic acid[248]. Thiocyanates may also be electrolytically oxidized to sulphonic acids[221].

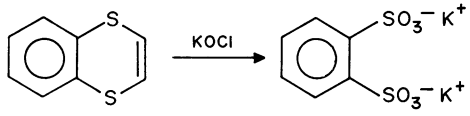
2. *From sulphides, sulphoxides and sulphones*

A few reactions are reported which describe the direct oxidation of sulphides, sulphoxides and sulphones to sulphonic acids. These reactions will be considered in this

section but it should be noted that they are rarely of synthetic utility. One noteworthy exception is the preparation of perfluorosulphonic acids, as detailed below.

Oxidation of some sulphides, with either chromate[249] or permanganate[250–252], leads to low yields of sulphonic acids as exemplified in equation 39. Hypohalite ions or nitric acid may also be used for this transformation[5], as shown in equations 40 and 41. In both cases the yields are rather low.

$$Ph_3CSPh \xrightarrow{CrO_4^-} Ph_3COH + PhSO_3H \tag{39}$$



(40)

$$RSCH_2CH_2OH \xrightarrow{HNO_3} RSO_3H + 2CO_2 \tag{41}$$

The base catalysed autoxidation of dimethyl sulphoxide and methyl phenyl sulphoxide at 80 °C produces low quantities of methanesulphonic acid in both cases and benzenesulphonic acid in the latter case[253,254] (equations 42 and 43). There is, rather surprisingly, no evidence of sulphone formation in either reaction. Dimethyl sulphoxide oxidation to methanesulphonic acid also occurs in the presence of trace quantities of acid and oxygen. Again the reaction would not be synthetically useful[255].

$$(CH_3)_2SO \xrightarrow{base} CH_3SO_3H \tag{42}$$

$$PhSOCH_3 \xrightarrow{base} CH_3SO_3H + PhSO_3H \tag{43}$$

Sulphones are blessed with high thermal and chemical stability and so the oxidation of these species, to form sulphonic acids, requires extreme, forcing conditions in most cases.

The oxidation of sulphones leads to either a sulphonic acid (or a sulphonic acid derivative) or to sulphate. Such reactions have rarely been used for the synthetic preparation of sulphonic acids since these are usually readily available by other well-established routes. However, polyhalogenated sulphones can be oxidized relatively easily to sulphonic acids and these reactions will be discussed here.

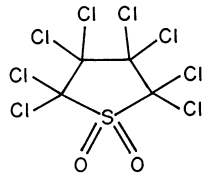
Sulphones containing multiple fluorine or chlorine atoms are very susceptible to hydrolytic cleavage forming sulphonic acids. These reactions may thus be considered as oxidations of sulphones[215]. For example, methyl heptafluoropropyl sulphone is readily cleaved as shown in equation 44 at 100 °C with dilute aqueous sodium hydroxide solution, followed by acid work-up. The reaction occurs by initial nucleophilic attack by hydroxide ion on the sulphone sulphur atom followed by elimination of the more stable $C_3F_7^-$ group. At lower temperatures the sulphone was recovered unchanged whilst prolonged heating at 140 °C (7 days) produced sulphur dioxide and a mixture of organic compounds which did not contain sulphur.

$$CH_3SO_2C_3F_7 \xrightarrow[2.\ H^+]{1,\ OH^-} CH_3SO_3H + C_3F_7H \tag{44}$$

Oxidation of methyl perfluoroalkyl sulphones with refluxing aqueous potassium permanganate produced the perfluorinated alkyl sulphonic acid in 85% yield as the potassium salt (equation 45). Cyclic sulphones containing α,α′-chlorine substituents are also susceptible to easy hydrolysis yielding sulphonic acid salts in good yields (equation 46)[256]. The above-described behaviour should be contrasted with simple dialkyl

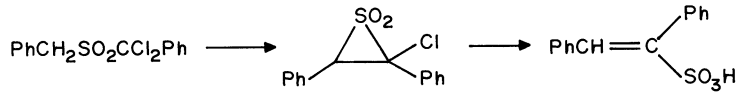
sulphones, which do not normally undergo such reactions[257].

$$C_2F_5SO_2CH_3 \xrightarrow{KMnO_4} C_2F_5SO_3^-K^+ \quad (45)$$



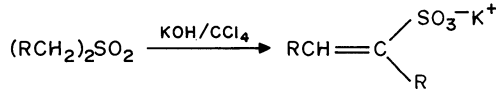
$$\xrightarrow{KOH} CCl_2{=}CCl(CCl_2)_2SO_3^-K^+ \quad (46)$$

Acyclic sulphones with α-chlorine substituents also produce sulphonic acid derivatives in good yields although in these cases rearrangement occurs via a thiirane dioxide intermediate (equation 47)[258].



(47)

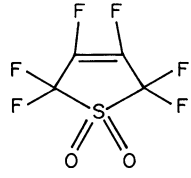
Dialkyl sulphones may be converted to sulphonic acids by reaction with carbon tetrachloride and base at 80 °C[259]. This reaction proceeds by initial formation of α-chloro sulphones that are then converted to a thiirane intermediate, which decomposes to give a sulphonic acid (equation 48).



(48)

The direct fluorination of sulphones has also been studied[260] and this leads to oxidation. At room temperature dimethyl sulphone produced bis (trifluoromethyl)-sulphone and trifluoromethanesulphonyl fluoride in 34% and 15% yields, respectively. The latter was hydrolyzed *in situ* to the corresponding sulphonic acid (equation 49). Electrofluorination of either sulpholene or perfluorosulpholene leads to the formation of a sulphonic acid, after alkaline hydrolysis, as shown in equation 50[261].

$$(CH_3)_2SO_2 \xrightarrow{F_2} (CF_3)_2SO_2 + CF_3SO_2F \quad (49)$$



$$\longrightarrow H(CF_2)_4SO_3H \quad (50)$$

The oxidation of disulphones with iodine in aqueous perchloric acid apparently produces the corresponding sulphonic acid (equation 51)[262].

$$RSO_2SO_2R + I_2 \longrightarrow 2RSO_3H + 2I^- \quad (51)$$

3. *From sulphinic acids and their derivatives*

The preparation of sulphonic acids by the oxidation of sulphinic acids and their derivatives has been studied, by many workers, for at least the last hundred years. Much

of the very early work concentrated on the formation of sulphonic acids from the corresponding sulphinic acid.

a. Using nitric acid and nitrogen oxides. Nitric acid is one of the most common, and cheaper, oxidants used in organic chemistry, and produces few by-products. It is thus not suprising that nitric acid was one of the earliest oxidizing agents used for the preparation of sulphonic acids from their sulphinic acid analogues. Thus benzenesulphonic acid is prepared from benzenesulphinic acid in good yield[263]. Other aromatic sulphinic acids undergo a similar conversion, although ring nitration is prone to occur in the presence of excess oxidant in some cases (equation 52)[264]. Aliphatic sulphinic acids are unstable in the presence of nitric acid and so no synthetically useful reactions have been reported, involving the oxidation of these compounds by nitric acid.

$$ArSO_2H \xrightarrow{HNO_3} ArSO_3H \tag{52}$$

The only oxide of nitrogen that has been reported to oxidize sulphinic acids is dinitrogen tetraoxide. In the presence of dinitrogen tetraoxide, aromatic sulphinic acids are converted to sulphonic acids and novel sulphonyl nitrites[265] (equation 53).

$$ArSO_2H \xrightarrow{N_2O_4} ArSO_3H + ArSO_2NO \tag{53}$$

b. Using oxygen and ozone. Oxygen, in the air, is probably the cheapest, most readily available oxidizing agent and may be used to prepare sulphonic acids from sulphinic acids by an autocatalytic, radical chain mechanism. Such a reaction has been reported[266,267], and a mechanism, based on careful kinetic studies in many solvents, has been proposed as detailed in equation 54. In addition, oxygen has been used to oxidize sulphinate ligands in iron(III) and indium(III) sulphinato porphryns to the sulphonate oxidation level[268,269].

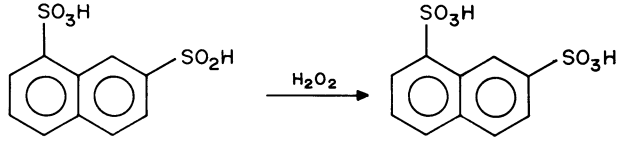
$$\begin{aligned} &RSO_2H + X^{\cdot} \longrightarrow RSO_2^{\cdot} \\ &RSO_2^{\cdot} + O_2 \longrightarrow RSO_2OO^{\cdot} \\ &RSO_2OO^{\cdot} + RSO_2H \longrightarrow RSO_2OOH + RSO_2^{\cdot} \\ &RSO_2OOH + RSO_2H \longrightarrow 2RSO_3H \end{aligned} \tag{54}$$

Superoxide ion, generated *in situ* by the reaction of potassium superoxide with a crown ether, has been sucessfully employed in the oxidative preparation of sulphonic acids from sulphinic acids, under mild, inert conditions[231,232,270]. Using this method of preparation, sodium arenesulphonates are formed in good yields with one equivalent of potassium superoxide at 25 °C in two and a half hours. Aromatic sulphinyl chlorides are oxidized to sulphonic acids in 90 minutes at 20 °C using excess potassium superoxide. In this case, the reaction is initiated by the nucleophilic attack by superoxide on the sulphinyl chloride. Thiosulphinates are even more easily oxidized by superoxide. The reaction occurs even at −40 °C in about 30 minutes using excess superoxide. The products formed are a disulphide, derived from the sulphenyl side of the thiosulphinate, and a sulphonic acid from the sulphinyl side of the thiosulphinate. In this case the difficulties encountered in separating the products from each other probably limit the synthetic utility of the procedures.

c. Using peroxy-containing oxidants. Hydrogen peroxide is used as an oxidant either alone or in the presence of acetic acid. In the latter case, the oxidant is peracetic acid.

Hydrogen peroxide has been used to convert sulphinic acids into the corresponding

sulphonic acids, under a variety of conditions. In 1935, Hann prepared a series of chemotherapeutic agents, one of which was *para*-fluorophenyl sulphonic acid which was prepared from the sulphinic acid using excess hydrogen peroxide at room temperature[271]. Other workers have also oxidized salts of aromatic sulphinic acids to the corresponding sulphonic acids in 30–60% yields using the same methodology[5,224,272–274]. One hydrogen peroxide oxidation of a sulphinic acid (equation 55) has been used in a commercial pilot plant[275]. This procedure is apparently the best method available for this particular synthesis.



(55)

An early study reported the use of barium peroxide for the preparation of 3,4-dimethylbenzene sulphonic acid from the sulphinic acid[276]. However, the synthetic utility of this reaction has not been reported to date.

d. Using other oxidants. The oxidation of a pyrazolophenanthridine sulphinate salt by hypochlorite ion, under basic conditions, yields the corresponding sulphonic acid[277]. In addition, aryl sulphinates also react with hypochlorite to give sulphonate salts, in aqueous solution (equation 56)[278].

$$ArSO_2^- + OCl^- \longrightarrow ArSO_3^- + Cl^- \tag{56}$$

Bromine has been used for the preparation of copper salts of sulphonic acids, by oxidation of the corresponding sulphinic acid salts[279].

In the early 1900s, Borsche and Lange[280,281] prepared cyclic alkanesulphonate salts from the corresponding sulphinic acid salts using aqueous potassium permanganate. These reactions have been pursued by other workers to apparent synthetic advantage[224,282,283]. Further reports, however, have reported that α-disulphones are produced as unfortunate by-products[282–286], or as the only product[275,287,288]. In addition, permanganate oxidation of the sulphinate salts, prepared by reaction of Grignard reagents with sulphur dioxide, proceeds to the sulphonic acid in low yield (equation 57)[289].

$$RSO_2MgX \xrightarrow[2.\ H^+]{1.\ KMnO_4} RSO_3H \tag{57}$$

A review of these reports suggests that either the α-disulphone, or the sulphonic acid, may be produced free of the other if the conditions are carefully controlled. For example, when cold, glacial acetic acid, or a buffered system (pH 7.2–7.5), is used as solvent, then the sulphonic acid is the major product formed (equation 58).

$$RSO_2H \xrightarrow{KMnO_4} RSO_3H + RSO_2SO_2R \tag{58}$$

Tertiary amine oxides have been shown to oxidize arenesulphinyl chlorides to sulphonic acids, albeit in low yields[290,291]. In this reaction other products, such as thiosulphonates, are also produced.

It has been mentioned above that there are few naturally occurring sulphonic acids. One notable exception is taurine (**6**), which is formed biosynthetically in several steps. One of these steps involves the oxidation of either cysteine sulphinic acid or hypotaurine (both of which contain a sulphinic acid group) to sulphonic acids. This reaction is, of course,

catalysed by specific enzymes[292–294].

$$H_2NCH_2CH_2SO_3H$$
(6)

Finally, aromatic sulphonic acids have been readily formed by the reaction of the corresponding sulphinic acid with benzeneseleninic acid (the selenium equivalent of a sulphinic acid) in a range of solvents, at low temperatures (equation 59)[295]. A selenosulphonate is also formed. Benzeneseleninic anhydride [PhSe(O)OSe(O)Ph] may be used in the reaction in place of the seleninic acid.

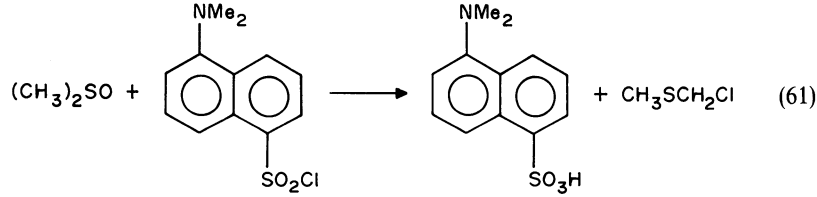
$$ArSO_2H + 2PhSeO_2H \longrightarrow PhSeSO_2Ar + ArSO_3^-(PhSeO_2H_2)^+ \quad (59)$$

C. From Other S(VI)-containing Compounds

Sulphonic acids may be made from several different sulphonic acid derivatives. The synthetic utility of these preparative methods is generally limited (perhaps with the exception of the reactions involving sulphonyl halides) since many sulphonic acid derivatives are prepared starting from the sulphonic acid. Some of the more useful procedures are discussed below.

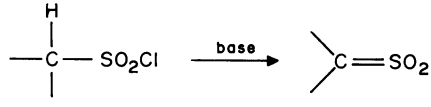
Sulphonyl halides may be hydrolysed in alkaline or acidic solution, and in boiling water, to give good yields of the parent acid[296–303], as shown in equation 60. In addition, a reaction has been reported where a sulphonyl chloride is converted into the corresponding sulphonic acid when the former is dissolved in dimethyl sulphoxide[304]. The solvent takes part in the reaction as shown in equation 61.

$$RSO_2X + H_2O \longrightarrow HX + RSO_3H \quad (60)$$



(61)

Sulphonyl halides, most commonly the chlorides, may also be converted into sulphonic acids via a route involving sulphenes. Normally, sulphene is formed by reaction of a sulphonyl chloride, which possesses an α-hydrogen atom, with a tertiary amine as shown in equation 62. There are, however, many other routes by which sulphenes may be formed and these have been reviewed previously[305]. The intermediate sulphene then reacts with water to give the sulphonic acid. If D_2O is used, then a deuterated sulphonic acid is produced[306–310], as indicated by equation 63.



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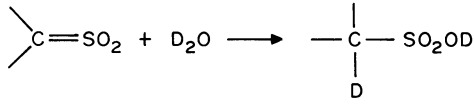
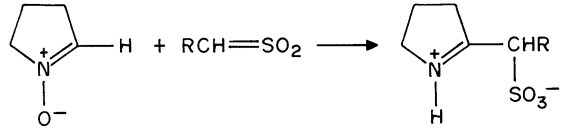


(63)

If no nucleophilic species are present when the sulphene is produced, then it undergoes reaction with itself to form a dimer and a tetramer, which yield sulphonic acids on work-up[311], as shown in equation 64.

$$RCH{=}SO_2 \longrightarrow RCH_2SO_2CH(R)SO_3H \tag{64}$$

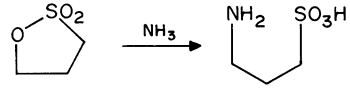
A rather surprising reaction of sulphenes with cyclic nitrones has also been used to prepare a range of sulphonic acid salts (equation 65)[312].



(65)

Sulphonate esters[313,314] and sulphonamides[299,315] are also readily hydrolysed to produce the sulphonic acid. There is evidence to suggest that hydrolysis of some sulphonate esters proceeds via a sulphene intermediate[314]. These reactions are unlikely to have synthetic utility.

Amino sulphonic acids are produced in good yields by reaction of cyclic sulphonate esters with ammonia[316], as exempliied in equation 66.



(66)

Sulphonic acids may also be prepared by the pyrolysis of mixed sulphonic–carboxylic anhydrides above 130 °C. In addition, ketenes are formed which presumably undergo further reaction, depending on the reaction conditions[317]. A series of aromatic sulphonic acids have been prepared by reaction of aromatic sulphonamides with nitrosonium tetrafluoroborate[318], as shown in equation 67.

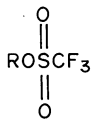
$$ArSO_2NH_2 + NO^+BF_4^- \longrightarrow ArSO_3H \tag{67}$$

Finally, a rather trivial but noteworthy process is the conversion of a sulphonic acid or a salt into a sulphonate salt. This may be accomplished by the use of an ion-exchange resin. For example, sodium sulphonates have been converted into silver sulphonates by first passing them through an ion-exchange resin (in the H^+ form) followed by reaction with silver carbonate[319], as shown in equation 68.

$$RSO_3^-Na^+ \xrightarrow[2.\ Ag_2CO_3]{1.\ \text{ion-exchange}} RSO_3^-Ag^+ \tag{68}$$

III. PREPARATION OF SULPHONATE ESTERS

Sulphonate esters are important compounds in mechanistic studies in organic chemistry and there has thus been much effort expended on the preparation of these compounds. This importance is due to the fact that sulphonate ions are exceptionally good leaving groups, in most instances. This has lead to special names for some sulphonate esters, such



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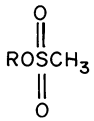

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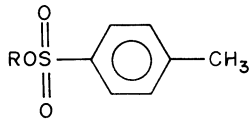

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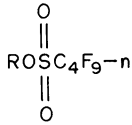
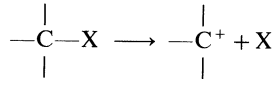


(10)

as triflate (**7**), mesylate (**8**), tosylate (**9**) and nonaflate (**10**). This leaving group ability has been utilized in the formation of a wide range of carbocations, as indicated by equation 69.



(69)

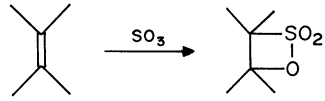
7, **8**, **9** or **10**

By far the most common preparative method has been by the interconversion of other sulphonyl compounds (especially acids and halides) to the ester.

A. By C—S(VI) Bond Formation

The most common method of sulphonate ester production via carbon–sulphur(VI) bond formation is the direct reaction of alkenes with either sulphur trioxide or sulphur trioxide adducts. The product formed in these reactions is usually a four-membered sultone (cyclic sulphonate ester) although in some cases six-membered sultones or more complex products are formed. Sulphonic acids (or their salts) are also produced and this has been covered in an earlier section of the present chapter.

Fluorinated alkenes[320–323] and many simple alkenes[324–327] give β-sultones (equation 70) in reasonable yields, although these sultones are sometimes too unstable to isolate. In the latter case, a carbyl sulphate may be produced[328], as exemplified in equation 71.



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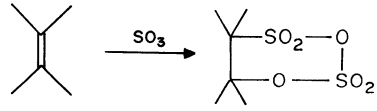
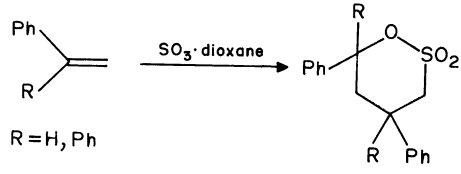


(71)

Cerfontain and coworkers[150,325–327] have shown that both sultone and carbyl sulphate formation are stereospecific reactions. Roberts and coworkers[324] have indicated that the reaction is a [2 + 2] cycloaddition process; however, some earlier workers have argued that the reaction is a step-wise process[321,329].

Reaction of styrene and 1,1-diphenylethene with sulphur trioxide–dioxane complex has been used for the synthesis of six-membered sultones[330,331], as shown in equation 72. A similar product has also been suggested from the reaction of 2-methylpropene with the same sulphonating reagent[332].



(72)

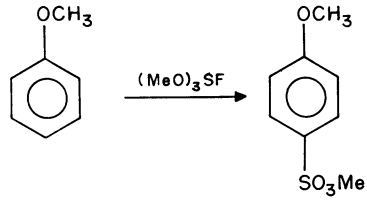
Sulphur trioxide also reacts with fluorovinyl ethers to give sulphonate esters in excellent yields[333,334].

There are other methods that have been reported for the production of sulphonate esters by direct formation of the carbon–sulphur bond and these will now be considered.

The reaction of aromatic compounds with either organic sulphates[335] or alkyl

chlorosulphates[336] produces sulphonate esters in reasonable yields, as depicted in equation 73. Activated aromatic compounds also react with $(MeO)_3SF$ to give high yields of methyl arenesulphonates[337], as shown in equation 74. Sulphonate esters are also produced if alkyl chlorosulphates are heated with a terminal alkene[338]. In this case, the sulphonate ester functionality appears on the terminal carbon atom and the double bond is retained in the product, as shown in equation 75.

$$ArH \xrightarrow[\text{or } SO_2(OR)_2]{ROSO_2Cl} ArSO_3R \tag{73}$$



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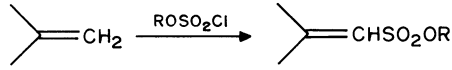
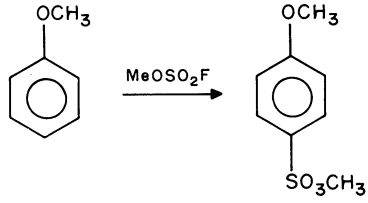


(75)

In some cases, alkyl organic sulphites may be thermally rearranged to give alkyl sulphonate esters, in the presence of an alkyl iodide[339], although unfortunately this reaction does not seem to be generally applicable[340]. This reaction may also be performed by reacting silver sulphite with an alkyl iodide, which then reacts further *in situ*[341], as shown in equation 76.

$$RI + Ag_2SO_3 \longrightarrow [(RO)_2SO] \longrightarrow RSO_3R \tag{76}$$

Reaction of hydroxy- and alkoxy-substituted aromatic compounds with methyl fluorosulphonate leads to the preparation of a sulphonate ester by carbon–sulphur bond formation[342], as shown in equation 77. In the case of the hydroxy-substituted aromatic compounds, the synthetic utility is limited since side-reactions involving O-alkylation readily occur.

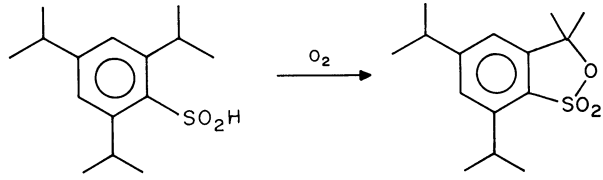


(77)

B. By Oxidation

The preparation of sulphonate esters by oxidation of sulphur(II)- and sulphur(IV)-containing moieties has rarely been reported. This is probably because of the wide range of other synthetic routes that are available (as described in Sections III.A and III.C) and the fact that yields in the oxidative processes so far reported are usually low. There are, however, a few noteworthy attempts at this method of preparation and these are covered below.

Oxygen has been used for the formation of a sultone from a sulphinic acid[343], as shown in equation 78. Sultones have also been produced by the oxidation of cyclic sulphinate esters[344].



(78)

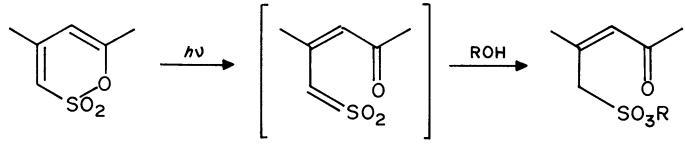
Sulphinic acid esters have also been oxidized, to the sulphonic acid ester, with hydrogen peroxide although the reaction usually proceeds in poor yield[345,346]. This resistance to oxidation is also evident when other oxidants are used[233,347]. A much improved procedure for the oxidation of aromatic sulphinate esters uses potassium permanganate in aqueous solution, as oxidant[345,348,349], as shown in equation 79. *Meta*-chloroperbenzoic acid has also been used with success for the oxidative preparation of sulphonate esters. Indeed, it has resulted in the preparation of unstable sulphonate esters that are hard to form by other means[350].

$$ArSO_2R \xrightarrow{KMnO_4} ArSO_3R \tag{79}$$

C. From Other S(VI)-containing Compounds

This section covers the methods of sulphonate ester preparation that are most often used by chemists. These reactions generally proceed in very good yield and are often applicable to a wide range of structural types of sulphonate esters.

Sulphonate esters may be formed by a transalkylation reaction involving an alcohol and another sulphonate ester. One such reaction of some novelty proceeds in the presence of ultra-violet light via a sulphene as shown in equation 80[351]. Alkyl group exchange may also be accomplished by reaction of alkyl halides with methyl tosylates, by heating in the presence of tetraalkylammonium salts[352].



(80)

Probably the most common preparative method involves the reaction of a sulphonyl chloride with a hydroxyl-containing compound, in the presence of a base. An extremely weak base, like sodium carbonate, may also be used in some instances[353]. The first reported example of this type of reaction being as early as 1860[354]. This reaction occurs with both alcohols and phenols, in the presence of a base[306–308,355–372], as shown in equation 81.

$$RSO_2Cl + R'OH \xrightarrow[-HCl]{base} RSO_3R' \tag{81}$$

Yields are much improved if the reaction is carried out under anhydrous conditions. Yields have also been improved by the use of phase-transfer conditions[373].

Reaction of sulphonyl halides, that contain an α-hydrogen atom, with tertiary amine bases, under anhydrous conditions, usually occurs via a reactive sulphene intermediate.

These reactions have been discussed in the excellent review of King[305]. This reaction proceeds best at temperatures of -20 to $-40\,^{\circ}C$, since oligomerization of sulphene is a problem at higher temperatures. It should be noted that sulphene, generated by methods other than from the sulphonyl chloride, also reacts with alcohols to give sulphonate esters[305,374].

The abnormal behaviour of an α,β-disulphonyl chloride has been reported to lead to an alkene sulphonate ester, as shown in equation 82[375].

$$\begin{array}{l} CH_2SO_2Cl \\ | \\ CH_2SO_2Cl \end{array} \xrightarrow[\begin{array}{c}-SO_2\\-HCl\end{array}]{EtOH} \begin{array}{l} CH_2 \\ \| \\ CHSO_3Et \end{array} \qquad (82)$$

Alkoxide anions also react with sulphonyl halides to produce a good yield of the corresponding sulphonate ester, as shown in equation 83. Both alkali metal[360,376,377] and thallium(I)[378] alkoxides have been employed and the latter reagent produces nearly quantitative yields when mixed with an aromatic sulphonyl chloride. It has been shown that higher yields of the sulphonate ester are realized as the metal counter-ion size increases[379].

$$R'SO_2Cl + RO^-M^+ \longrightarrow R'SO_2OR + MCl \qquad (83)$$

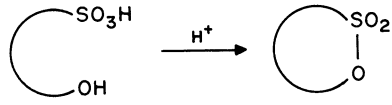
Some functional groups that are sensitive to reaction with strong bases, like alkoxides, undergo reaction under these reaction conditions[380,381]. Thus 2-chloroethanesulphonyl chloride reacts with alkoxides to give the unsaturated sulphonate ester, as indicated in equation 84. Such side-reactions may be averted by reaction of the sulphonyl chloride, or fluoride, with the trimethylsilyl derivative of the alcohol[382], as indicated by equation 85. The derivative may be formed under mild conditions from the alcohol.

$$ClCH_2CH_2SO_2Cl \xrightarrow{OR^-} CH_2{=}CHSO_2OR \qquad (84)$$

$$ClCH_2CH_2SO_2Cl \xrightarrow{ROSiMe_3} ClCH_2CH_2SO_2OR \qquad (85)$$

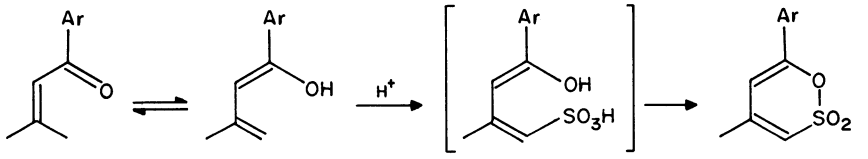
Esterification of sulphonic acids with alcohols usually produces an equilibrium mixture. For example, reaction of trifluoromethanesulphonic acid with ethanol gives an equilibrium mixture of diethyl ether, the ester and the reactants[383,384]. Such an equilibrium may be driven to give the desired sulphonate ester by azeotropic removal of water[385].

Reaction of a hydroxyl group with a sulphonic acid functionality, within the same molecule, in the presence of acid, yields sultones with ring sizes of 5 or 6[386–388], as shown in equation 86. This reaction has also been observed on sulphonation of an α,β-unsaturated aryl ketone with sulphuric acid[389]. In this case the initially formed sulphonic acid spontaneously reacts with the enol form of the carbonyl group to produce the sultone as shown in equation 87.



(86)

Alkylation of sulphonic acids with a wide variety of reagents produces sulphonate esters. Diazomethane[378,390] and other diazoalkanes[358,391] produce the sulphonate ester in good yield, presumably via the carbene, as shown in equation 88. In a similar manner, β-



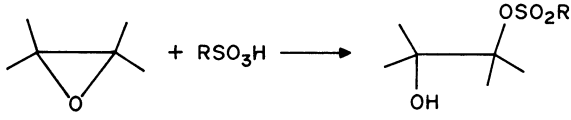
(87)

ketosulphonate esters are produced if the diazo compound contains a carbonyl functionality. These types of sulphonate esters are also produced on reaction of sulphonic acids with ketenes[392].

$$RSO_3H + R'CHN_2 \xrightarrow[-N_2]{} RSO_3CH_2R' \tag{88}$$

Anodic oxidation of iodoperfluoroalkanes in the presence of perfluorosulphonic acids leads to the production of perfluoroalkyl perfluoroalkanesulphonate esters in good yields[393].

Dimethyl sulphate is also a good reagent for the production of methyl esters of sulphonic acids[394]. In addition, reaction of sulphonic acids with ethers[395], some phosphorus-containing alkylating reagents[396,397] and trialkylboranes[398] also leads to the ester. If the ether is present as an epoxide ring, then *trans* stereospecific ring opening occurs[399,400], as shown in equation 89.



(89)

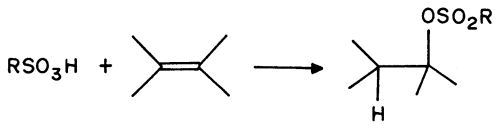
The salts of sulphonic acids may also be alkylated with a variety of reagents to produce the ester. The silver salt of methanesulphonic acid reacts with aryl chloromethyl ethers to give the ester[401] as shown in equation 90. Likewise, the mercury salt reacts with perhalomethanes[402], as shown in equation 91. Alkali metal or silver sulphonates may also be alkylated, with dimethyl sulphate[403–405] or alkyl halides[384,406], to give the ester. When the reaction of silver salts is being used for this preparation, then the best yields are obtained if acetonitrile is used as the reaction medium[407], since in this solvent silver sulphonates are very soluble.

$$ArOCH_2Cl + CH_3SO_3{}^-Ag^+ \longrightarrow ArOCH_2OSO_2CH_3 \tag{90}$$

$$(CF_3SO_2)_2Hg + CXCl_3 \longrightarrow CF_3SO_3CCl_3 \tag{91}$$

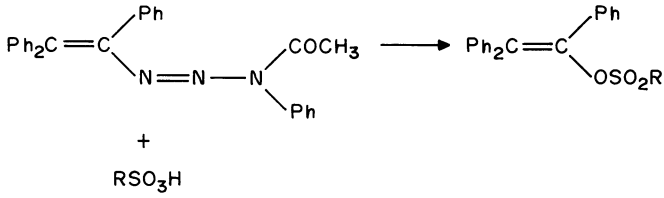
$$X = Cl, Br, I$$

Sulphonic acid esters may be prepared in greater than 90% yield by the reaction of alkenes with the corresponding sulphonic acid[356,383,384,408,409], as shown in equation 92. The reaction proceeds by overall addition of the sulphonic acid to the double bond. If a good leaving group is directly attached to the double bond in the alkene, then reaction leads to direct substitution of the leaving group by the sulphonate moiety, to produce a vinylic sulphonate ester[409,410], as shown in equation 93. Sulphonic acids also react with



(92)

alkynes[410–412] and allenes[411], in a similar fashion to the reaction with alkenes, to produce sulphonate esters, as shown in equations 94 and 95, respectively. In these reactions, one double bond is retained in the product molecule.



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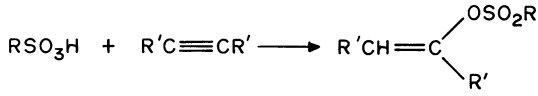

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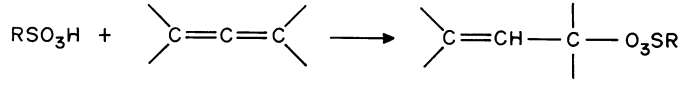


(95)

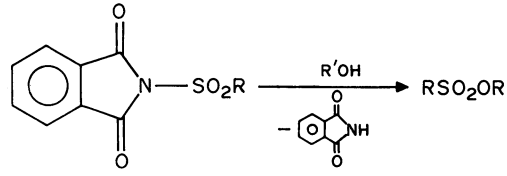
Sulphonic acid anhydrides have been used as precursors for the synthesis of sulphonate esters, by reaction with an alcohol[413–415]. A similar reaction has also been performed using mixed sulphonic–carboxylic anhydrides[413,416,417]. Sulphonyl peroxides also react with alcohols to give sulphonate esters[418]. Reactions of these peroxides, with aldehydes and ketones, has also led to the production of sulphonate esters[419]. Thermal reaction of perfluorosulphonyl peroxides with the corresponding perfluorosulphonic acid yields the ester, with the evolution of sulphur dioxide[420]. The same ester could also be prepared by heating the acid with P_2O_5.

The synthetic utility of these methods is rather restricted since sulphonic anhydrides and peroxides are usually prepared from the sulphonic acid, the latter of which may be directly converted, readily, into the sulphonate ester, as discussed above.

Some aromatic compounds have been shown to be substituted in the ring by sulphonyl peroxides[421,422] to give 50–70% yields of the sulphonate ester, as shown in equation 96. The experimental evidence from this reaction is apparently consistent with an electrophilic aromatic substitution reaction.

$$(ArSO_2)_2O + Ar'H \longrightarrow ArSO_2OAr' + ArSO_3H \tag{96}$$

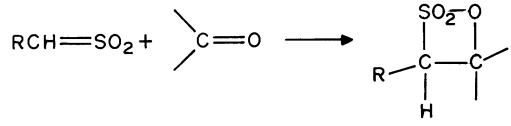
Sulphonamides have also been used for the preparation of sulphonate esters, by reaction with alcohols[423], as exemplified in equation 97.



(97)

Earlier, it was shown that sulphenes, formed by reaction of sulphonyl halides with a base, reacted with alcohols to give sulphonate esters. These same reactive intermediates have also been used for the formation of sultones, by reaction with carbonyl-containing compounds[424–428], as shown in equation 98. If the carbonyl compound contains an α-

hydrogen atom, then a vinyl sulphonate is often the product formed[429] (equation 99).



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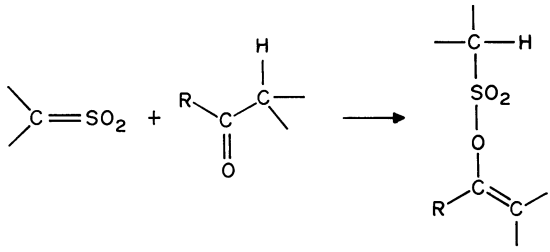
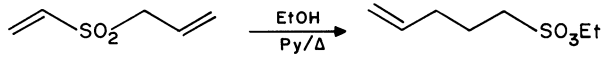


(99)

Finally, in a rather obscure but noteworthy reaction, allyl vinyl sulphone has been converted into ethyl 5-pentenesulphonate upon reaction with ethanol and pyridine[430], as shown in equation 100.



(100)

IV. PREPARATION OF SULPHONAMIDES

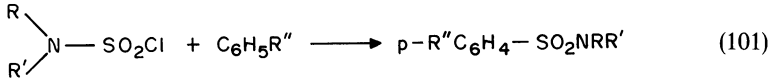
Many sulphonamides are important compounds in the pharmaceutical and other branches of the chemical industry. In fact, sulphonamides were among the first synthetic antibacterial agents that were found to be effective in humans. An excellent account of the uses, manufacture and properties of sulphonamides has been published[431].

Thus much effort has been expended in the search for highly efficient syntheses of these compounds. In most cases, aryl sulphonamides are isolated as stable, colourless solids whilst oils often result when the preparation of alkyl sulphonamides is undertaken. There have been several reviews concerning the synthesis of sulphonamides (see, for example, Reference 4).

A. By C—S(VI) Bond Formation

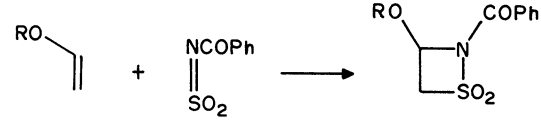
Preparation of sulphonamides by carbon–sulphur(VI) bond formation has been used rather rarely compared with the preparation of sulphonic acids and sulphonyl halides (as discussed in Sections II.A and V.A of this chapter). There have, however, been a few interesting reports of this type of synthetic procedure and these are discussed below.

Reaction of an alkyl-substituted aromatic compound with a sulphamoyl chloride in the presence of a Lewis acid leads to the formation of an arene sulphonamide (equation 101)[432].



(101)

Sulphonamides have also been prepared from sulphamoyl chlorides by a different procedure. In this method, sulphamoyl chlorides are reacted with a tertiary amine to produce an azasulphene, which is then used *in situ* for the formation of sulphonamides. A wide structural variety of sulphonamides may be obtained by reaction of azasulphenes with different substrates. Reaction with some substituted alkenes proceeds via either a [2 + 2] cycloaddition reaction as exemplified in equation 102[433] or a [2 + 4] cycloaddition reaction as shown in equation 103[434,435]. Azasulphenes also react with aromatic compounds that are highly activated towards electrophilic substitution as shown in equation 104[436]. If carboxyethyl azasulphene is used in this reaction, then the unsubstituted aromatic sulphonamide may be obtained in high yield, simply by hydrolysis[436] (equation 105).



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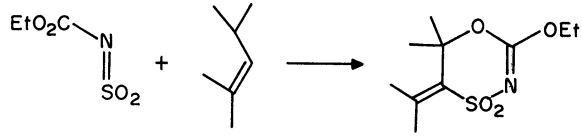

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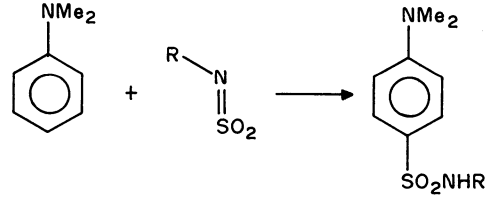

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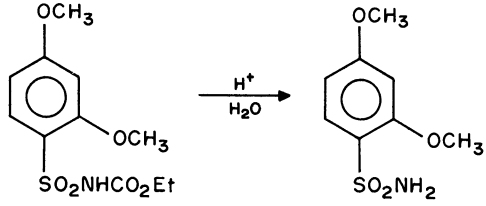
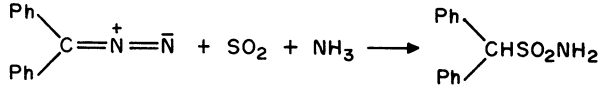


(105)

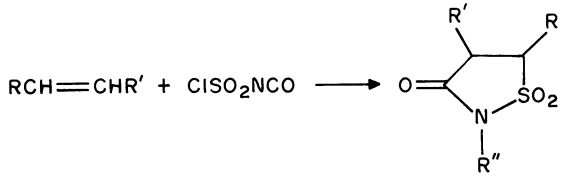
A novel reaction involving carbon–sulphur(VI) bond formation during the preparation of sulphonamides has been described by Kloosterziel and collaborators[437]. In this procedure, diphenyl diazomethane was reacted with sulphur dioxide and ammonia as shown in equation 106. The sulphonamide was realized in good yield.



(106)

Finally, chlorosulphonyl isocyanate has been shown to react with some alkenes to produce a novel series of five-membered cyclic sulphonamides as shown in

equation 107[438], where R″ is derived from the olefin, with a chloro substituent.



(107)

B. By Oxidation

The preparation of sulphonamides by oxidation of organic sulphur-containing compounds has not been the method of choice for many workers. This is probably because of the ease with which other sulphonic acid derivatives may be converted into sulphonamides, in high yields. Notwithstanding this, there have been a few published oxidative methods and these will be discussed in this section.

Direct oxidation of sulphenamides or sulphinamides to the sulphonamide have been performed with a variety of oxidants[439–443]. For example, potassium permanganate oxidation of 2,4-dimethoxy-6-pyrimidine sulphenamide gave the sulphonamide in 64% yield, as shown in equation 108[444]. In another example, *meta*-chloroperbenzoic acid was used to oxidize sulfenamides to the sulphonamide[442]. However, Chiang and collaborators have reported that they were unable to isolate any sulphonamide product after one such attempted oxidation[445].

$$RSNH_2 \xrightarrow{KMnO_4} RSO_2NH_2 \tag{108}$$

Other oxidative methods for the preparation of sulphonamides, from sulphur(II)- or sulphur(IV)-containing compounds, have also been reported and these will now be discussed.

Oxidative amidation of sulphinic acids occurs under rather forcing conditions (18% oleum) to give a sulphonamide as product (equation 109)[446]. The severity of the reaction conditions means that this approach is not one that is generally applicable for the conversion. A far preferable method involves the rather mild oxidation of the ammonium salts of arenesulphinic acids with either hypochlorite ions or chlorine, in aqueous solution (equation 110)[447].

$$RSO_2H + NH_3 + O_2 \longrightarrow RSO_2NH_2 \tag{109}$$

$$ArSO_2^-NH_4^+ \xrightarrow{OCl^-} ArSO_2NH_2 \tag{110}$$

Sulphonamides may also be prepared by the oxidation of sulphinyl chlorides by gaseous chlorine, in the presence of ammonia and a base[447,448]. The same result may also be obtained in a rather surprising manner. Reaction of a sulphinyl chloride with hydroxylamine produces a sulphonamide via a rather complex radical mediated rearrangement reaction[449–451]. In fact, this reaction sequence is one of the few ways in which tertiary alkyl sulphonamides may be formed. The reaction of sulphonic acid derivatives with amines does not usually proceed to the sulphonamide in such a case[450]. Hydroxylamine-*O*-sulphonic acid also reacts with salts of sulphinic acids to give good yields of the corresponding sulphonamide[452].

Reaction of benzenesulphinyl azide with water proceeds via a nitrene to give overall oxidation of the sulphur moiety, to give the sulphonamide[453], as shown in equation 111.

This method has also proved useful for the preparation of trichloromethanesulphonamide, which is not easily made by other means[454].

$$\mathrm{RSON_3 \longrightarrow [RSON:] \xrightarrow{H_2O} RSO_2NH_2} \qquad (111)$$

C. From Other S(VI)-containing Compounds

The normal method of choice for the preparation of sulphonamides is by reaction of sulphonic acid derivatives with ammonia and amines. These reactions are covered in this section, together with other interconversions of sulphur(VI)-containing compounds to sulphonamides.

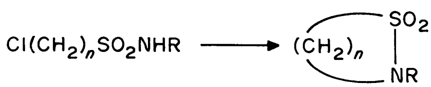
Substituted sulphonamides may be prepared from the corresponding unsubstituted compound by reaction with a base followed by an alkylating reagent[4,455,456]. In particular, this process can be performed using alkyl halides[457–459] and sulphonate esters[460], as shown in equation 112. α,ω-Dihaloalkanes and α,ω-dihaloethers react with unsubstituted sulphonamides, in the presence of lithium hydroxide, to produce cyclic sulphonamides[461]. The reverse of this process is often useful. If *N*-benzyl groups are present, then these may be readily removed by heating with sulphuric acid in toluene, as shown in equation 113[462].

$$\mathrm{RSO_2NHR' + R''SO_3R''' \xrightarrow[-R''SO_3H]{base} RSO_2NR'R'''} \qquad (112)$$

$$\mathrm{RSO_2NHCH_2Ph \xrightarrow[H_2SO_4]{\Delta} RSO_2NH_2} \qquad (113)$$

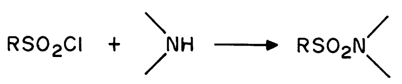
Exchange of substituents in substituted sulphonamides may occur by transamination as shown in equation 114[463]. Helferich and Kleb[464] and others[465,466] have prepared sultams (cyclic sulphonamides) using a similar methodology, as shown in equation 115.

$$\mathrm{RSO_2NR'R'' + R_2'''NH_2{}^+Cl^- \xrightarrow{\Delta} RSO_2NR_2''' + R'R''NH_2^+Cl^-} \qquad (114)$$



(115)

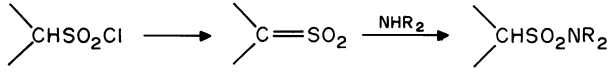
One of the most general, and facile, synthetic routes to both unsubstituted and substituted sulphonamides is by the reaction of ammonia[466–469] or amines[455,465,470–476] with a sulphonyl chloride, as shown in equation 116. Sulphonyl fluorides may also be used as precursors in a similar synthetic procedure[477]. This method is, however, prone to produce disulphonamides as by-products if the stoichiometry of the reaction is not carefully controlled[4], or if the reaction mixture is alkaline[478–481].



(116)

The reaction of a sulphonyl chloride with amines to produce a sulphonamide also occurs in the presence of a base[305,307,482,483]. In this case, it is well established that the reaction proceeds via a sulphene intermediate, as shown in equation 117. Using this method for the preparation, some novel sulphonamides may be obtained. Thus, the reaction of sulphene with phthalimide give *N*-methylsulphonylphthalimide[484,485], as shown in equation 118. Reaction of sulphene with pyridine leads to a novel cyclic

sulphonamide as indicated in equation 119[486] and imines undergo a [2 + 2] cycloaddition with sulphenes to give four-membered, cyclic sulphonamides[487,488].



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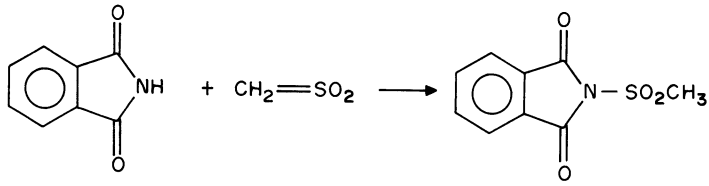

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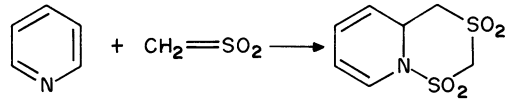


(119)

It was noted above that disulphonamides are often produced as unwanted by-products. There are a few useful synthetic routes to di- and trisulphonamides and these will now be discussed.

If a disulphonamide is the desired product, then an excellent route is by reaction of a sulphonyl chloride with a sulphonamide anion[489]. The same result is obtained if an arenesulphonyl chloride is reacted with ammonium chloride in acetone in the presence of sodium hydroxide[490] (equation 120).

$$ArSO_2Cl + NH_4Cl \longrightarrow (ArSO_2)_2NH \tag{120}$$

If a trisulphonamide is the desired product, then reaction of the silver salt of a disulphonamide with a sulphonyl chloride is probably the best route to follow[491,492].

Sulphonic acids react with primary amines in the presence of either a base[299] or $POCl_3$[493,494] to give a sulphonamide (equation 121). The latter of these two reactions probably proceeds via the sulphonyl chloride.

$$RSO_3H + NH_2R' \xrightarrow{POCl_3} RSO_2NHR' \tag{121}$$

Other sulphonic acid derivatives react with amines to give sulphonamides. Sulphonate esters react with primary amines to give a sulphonamide and an alcohol as shown in equation 122[495]. Anhydrides undergo a similar reaction[496,497] and in this case the second product is an ammonium sulphonate salt (equation 123).

$$RSO_3R' + R''NH_2 \longrightarrow RSO_2NHR'' + R'OH \tag{122}$$

$$(RSO_2)_2O + 2R'NH_2 \longrightarrow RSO_2NHR' + R'\overset{+}{N}H_3\ RSO_3^- \tag{123}$$

Reaction of some of the less common derivatives of sulphonic acids also may lead to sulphonamides. For example, hydrolysis of sulphonyl isocyanates[4,418] and the reduction of sulphonyl azides with zinc in acetic acid[498] lead to sulphonamides, as depicted in equations 124 and 125, respectively, in good yields.

$$RSO_2NCO + H_2O \longrightarrow RSO_2NH_2 + CO_2\uparrow \tag{124}$$

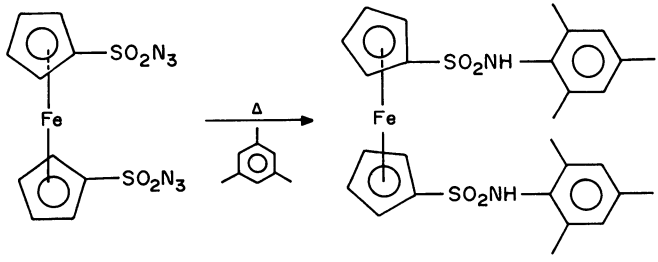
$$RSO_2N_3 \xrightarrow[HOAc]{Zn} RSO_2NH_2 \tag{125}$$

A relatively large number of papers have been published concerning the preparation of sulphonamides from sulphonyl azides. Most of these publications have indicated that the reaction occurs via a nitrene intermediate, although at least one group has indicated that a radical mechanism may also take place[499]. Thus, reduction of sulphonyl azides with zinc[498,500] or their thermolysis[501,502] or photolysis[503] in alcohols gives a synthetically useful yield of sulphonamide as shown in equation 126. Thermolysis of sulphonyl azides in alkaline solvents leads to the production of sulphonamides by the insertion of the intermediate nitrene into a C—H bond[504,505] (equation 127). A novel ferrocene derivative containing two sulphonamide functionalities has been prepared in a similar manner to that described above, as shown in equation 128[506]. Other aryl sulphonamides have also been produced in this manner[507,508].

$$RSO_2N_3 \longrightarrow [RSO_2N:] \xrightarrow{\text{H-donor}} RSO_2NH_2 \tag{126}$$

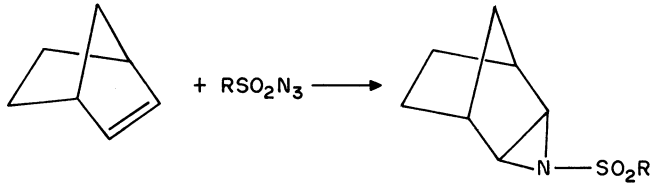
$$CH_3SO_2N_3 \xrightarrow[\text{2,4-dimethylpentane}]{150\ ^\circ C} CH_3SO_2NHR \tag{127}$$

(R signifies different radicals derived from the 2,4-dimethylpentane)



(128)

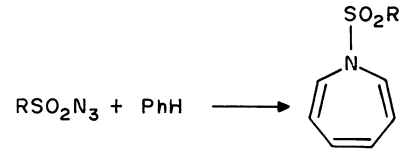
Azacyclopropanes that contain the sulphonamide functionality can be prepared by reaction of a sulphonyl azide with alkenes. For example, norbornene reacts to give the unusual product shown in equation 129[504].



(129)

This insertion process has been used to produce several novel heterocyclic compounds by insertion into other bonds. By this method azepines and sultams may be produced[509], as shown in equations 130 and 131, and the 1,2-thiazepinone (equation 132) has also been prepared in a similar manner[510]. It has unfortunately been shown that the latter reaction is not generally applicable to all ring sizes[511].

Reduction of a range of arenesulphonyl hydrazines, with activated Raney nickel in methanol under reflux, may also be used to prepare unsubstituted sulphonamides[512].



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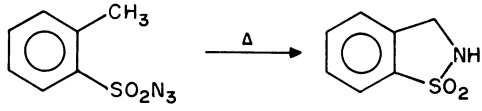

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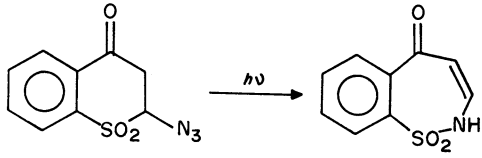


(132)

Both α-disulphones[513] and trisulphones[514] react with amines at elevated temperatures to produce sulphonamides, as shown in equations 133 and 134.

$$RSO_2SO_2R + R'_2NH \longrightarrow RSO_2NR'_2 + RSO_2H \quad (133)$$

$$(RSO_2)_3CPh + R'_2NH \longrightarrow RSO_2NR'_2 + (RSO_2)_2CHPh \quad (134)$$

V. PREPARATION OF SULPHONYL HALIDES

A. By C—S(VI) Bond Formation

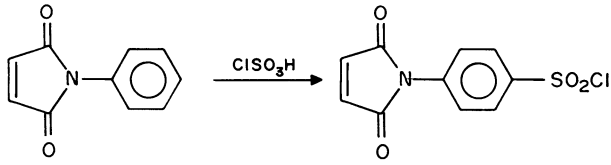
Sulphonyl halides, mainly the chlorides, may be prepared using halosulphonic acids, sulphur dioxide and sulphuryl halides as the most important sources of sulphur. These preparative methods are discussed below.

1. Using halosulphonic acids

Aromatic compounds that are activated towards electrophilic aromatic substitution react with excess halosulphonic acids (at least two equivalents) in chlorinated solvents, at room temperature[5,515–523]. Under these conditions, good yields of aromatic sulphonyl halides are produced, as depicted in equation 135. The solvent is required since, in its absence, unwanted side-reactions usually occur. Less activated aromatic compounds often require heating for reasonable yields to be realized. This halosulphonation reaction may be carried out successfully in the presence of many functional groups attached to the aromatic ring and with aliphatic groups that contain carbonyl, amino and alkene functionalities. One recent report[476] that is worthy of note is the reaction of excess chlorosulphonic acid with *N*-phenylmaleimide, which produced 83% of the sulphonyl chloride shown in equation 136.

$$ArH + XSO_3H \longrightarrow ArSO_2X \quad (135)$$

$$X = F, Cl$$



(136)

It should be noted that in all cases the reaction temperatures should be carefully controlled and kept to a minimum since unwanted di- and tri-sulphonation occurs easily in some instances.

It should also be noted that chlorosulphonylation of aromatic compounds is the first of a two-step process by which sulphonamide derivatives are made[517,524,525]. These derivatives have proved useful in the identification of unknown aromatic compounds.

Aliphatic compounds also react with chlorosulphonic acid, but the yields of sulphonyl chlorides are usually very low[5]. However, it has been found that the reaction of aliphatic carboxylic acids with chlorosulphonic acid, in the presence of $POCl_3$[526], gives excellent yields of disulphonyl chlorides (with concomitant loss of carbon dioxide), as shown in equation 137.

$$RCH_2CO_2H \xrightarrow[POCl_3]{ClSO_3H} RCH(SO_2Cl)_2 + CO_2 \qquad (137)$$

2. *Using sulphur dioxide*

Sulphonyl halides may be prepared by reaction of some organic compounds with sulphur dioxide in the presence of a halogen or halide ion. Compounds which undergo such reactions include aromatic diazonium salts and some aliphatic species.

Aromatic diazonium salts react with sulphur dioxide, either in the liquid state or mixed with an organic solvent, such as acetic acid, in the presence of copper(II) chloride to give 50–90% yields of sulphonyl halides[205,527–529] (equation 138). Nitrogen is evolved during the reaction and higher yields are usually obtained in the presence of a solvent.

$$ArN_2{}^+X^- \xrightarrow[CuCl_2]{SO_2} ArSO_2Cl + N_2 \qquad (138)$$

Sulphonyl chlorides may be obtained by the reaction of some aliphatic compounds with a mixture of sulphur dioxide and chlorine, under conditions which permit the formation of radicals (equation 139)[299,530–533]. Usually a mixture of products is formed with amounts of each product being determined by the stabilities of the intermediate alkyl radicals. Thermodynamic or kinetic control of products may be exercized by control of the reaction temperature.

$$RH \xrightarrow[Cl_2]{SO_2} RSO_2Cl \qquad (139)$$

3. *Using sulphuryl halides*

Sulphuryl halides may be used as reagents in the formation of sulphonyl halides from aromatics, alkenes or alkyl halides. The reaction usually proceeds via a radical mechanism, in the presence of a base (which removes HCl generated in the reaction). If DMF is used as a solvent, yields are often improved[534,535].

Although rarely of synthetic value, aromatic sulphonyl chlorides may be prepared by

the reaction of aromatic compounds with sulphuryl chloride, in the presence of $AlCl_3$[536–538]. It should be noted that in many cases ring chlorination also occurs. Alkenes may also be converted into sulphonyl halides using sulphuryl fluoride[539] or sulphuryl chloride[534,535,540,541].

Sulphochlorination of alkyl halides has also been studied[542]. It has been found that no geminal chloro alkylsulphonyl chlorides were produced and that sulphochlorination on the atom adjacent to the halide was much less likely than reaction at a remote position. Much improved yields of sulphonyl chlorides may be obtained from alkyl halides if they are first converted into the alkyllithium or Grignard reagent. Using this method, very good yields have been obtained from benzyl[543] (equation 140) and other alkyl halides[358,544,545].

$$ArCH_2Cl \xrightarrow{Mg} ArCH_2MgCl \xrightarrow{SO_2Cl_2} ArCH_2SO_2Cl \qquad (140)$$

4. Others

There are several other reports of the formation of sulphonyl halides by direct carbon–sulphur bond formation. Three such reports are mentioned below.

First, upon irradiation, alkyl cobaloximes react with trichloromethanesulphonyl chloride, at 10 °C. A new carbon–sulphur bond is formed and the alkanesulphonyl chloride is produced in excellent yield[546] (equation 141).

$$X\text{—alkyl} \xrightarrow{Cl_3CSO_2Cl} \text{alkyl } SO_2Cl \qquad (141)$$

$$X = \text{cobaloxime}$$

Secondly, alkanes react with chlorine and sulphur trioxide to produce a mixture of sulphonyl chlorides[547,548]. The reaction is similar to that discussed above with sulphur dioxide and aliphatic compounds.

Thirdly, a rather surprising outcome was observed when azulene was treated with thionyl chloride. Azulenesulphonyl chloride was produced in fair yield[549]. This reaction presumably involves the disproportionation of a sulphur(IV)-containing species.

B. By Oxidation

Sulphonyl halides may be prepared from various other sulphur-containing species, by oxidation. By far the most important of these procedures is the oxidation of thiols and disulphides with chlorine. This and other synthetic methods will now be discussed.

1. From sulphenyl halides

Sulphonyl halides are readily prepared by the nitric acid oxidation of sulphenyl halides, which are in turn easily formed by reaction of disulphides with sources of halogens. Thus, alkanesulphenyl chlorides are oxidized to the corresponding sulphonyl chlorides, in high yields[301,550–552], as depicted in equation 142.

$$RSCl \xrightarrow{ox} RSO_2Cl \qquad (142)$$

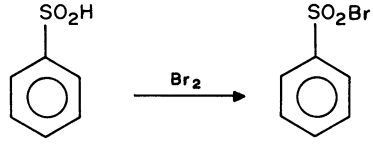
Good yields of sulphonyl chlorides may also be obtained by the use of nitrogen dioxide in the presence of oxygen[5], aqueous chlorine[297,553] and hot hydrogen peroxide[297,554].

2. From sulphinic acid derivatives

Arenesulphinic acids and their alkali metal salts have long been used as precursors for the preparation of sulphonyl chlorides. This oxidation has most often been performed in either water or aqueous acetic acid solution, with chlorine or copper halides, as shown in equation 143[263,553,555–564]. In some cases side-reactions occur, causing ring chlorination[565].

$$ArSO_2H \text{ or } ArSO_2^- \xrightarrow{ox} RSO_2Cl \tag{143}$$

As early as 1893, Limpricht[566] showed that sulphinic acids may be oxidized to the corresponding sulphonyl bromides using bromine. More recently, workers have also indicated the synthetic utility of this reaction[466,555,559,560,564,567], which is shown in equation 144. The product from this reaction is usually a sulphonyl bromide, although a sulphonic acid may be formed depending upon the reaction conditions. Methyl methanesulphinate has also been oxidized with bromine. In this reaction, at 0 °C, the products are methanesulphonyl bromide and bromomethane[568].

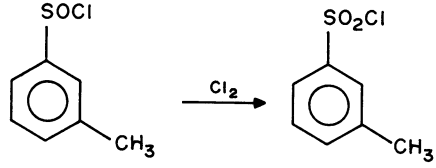


(144)

Iodine has also been used to oxidize sulphinic acids and their salts to sulphonyl iodides (equation 145)[343,559,569–572]. Indeed, this was the first method by which alkanesulphonyl iodides were prepared and isolated[571].

$$RSO_2H \text{ or } RSO_2^- \xrightarrow{I_2} RSO_2I \tag{145}$$

Aryl sulphonyl chlorides may also be synthesized from the sulphinyl chloride, by oxidation with chlorine, in 80% yield[573] (equation 146) or dimethyl sulphoxide[574]. Sulphinate esters may also be utilized as the precursor to sulphonyl halide via oxidative halogenation. For example, methyl methanesulphinate is converted to methanesulphonyl chloride in excellent yield at 0 °C[568].



(146)

Just about the only method for the preparation of tertiary alkanesulphonyl chlorides is by the oxidation of the sulphinate formed on reaction of a tertiary alkyl bromide with sulphur dioxide as shown in equation 147. The method provides a rapid, clean and simple

$$R_3CBr \xrightarrow{Mg} R_3CMgBr \xrightarrow{SO_2} R_3CSO_2^-MgBr^+ \xrightarrow{ox} R_3CSO_2X \tag{147}$$

$$X = Cl, Br$$

route for the preparation of sulphonyl chlorides in good yields and high purity. The method has also been used for the preparation of arenesulphonyl chlorides and the sulphinate salt may be isolated prior to oxidation, or used *in situ*[575-579]. A similar method has been patented using trialkyl organo-aluminium compounds in place of the alkyl halide (equation 148)[580].

$$R_3Al \longrightarrow (RSO_2)_3Al \xrightarrow{ox} RSO_2Cl \tag{148}$$

Alkylmagnesium bromides and alkyllithiums have been used to prepare alkanesulphinate salts, which have then been oxidized to the sulphonyl bromides in high yields[578,579,581]. This is an excellent synthetic route to sulphonyl halides that are not easily obtained by other routes.

Sulphinate salts, obtained by reaction of sulphur dioxide with either alkyllithiums or Grignard reagents, are converted into sulphonyl chlorides upon reaction with sulphuryl chloride[582], as shown in equation 149. The same reaction occurs if thionyl chloride dissolved in DMF is used[583].

$$RSO_2^-Li^+ \xrightarrow{SO_2Cl_2} RSO_2Cl \tag{149}$$

Methane sulphinyl chloride and *para*-nitrobenzenesulphinyl chlorides have been used to reduce sulphoxides to sulphides[584]. During this process, the sulphinyl chloride is oxidized to the corresponding sulphonyl chloride, by direct oxygen transfer. However, it is hard to see how this reaction could be synthetically useful for the preparation of sulphonyl chlorides.

3. *From thiols, disulphides and related compounds*

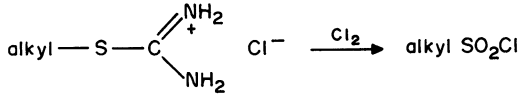
One of the classical methods of preparing sulphonyl halides is by the oxidation of thiols or disulphides with halogens[297,553,565,573,585-592] in the presence of water, acetic acid or nitric acid, as solvent (equation 150). Apparently yields may be improved either in the presence of concentrated hydrochloric acid[588,593] or potassium carbonate[594]. Sulphonyl fluorides have been prepared from purine thiols by oxidation with chlorine in the presence of fluoride ions[591]. The same products have been realized by oxidation of thiols with nitrogen dioxide in the presence of HF[595]. Sulphonyl bromides were formed by the oxidation of disulphides with bromate and bromide ions[596].

$$RSH \text{ or } RSSR \xrightarrow{Cl_2} RSO_2Cl \tag{150}$$

Aromatic sulphonyl chlorides may be prepared, in excellent yields, by the oxidation of a thiocarbamic ester (a masked thiol), after initial Newman–Kwart rearrangement[597], as shown in equation 151. The latter is readily prepared from phenols.

$$ArO-\overset{\overset{S}{\|}}{C}-NR_2 \longrightarrow ArS-\overset{\overset{O}{\|}}{C}-NR_2 \xrightarrow{ox} ArSO_2Cl \tag{151}$$

Finally, sulphonyl chlorides may also be formed by reaction of S-alkyl isothiouronium salts (masked thiols) with aqueous chlorine[598-601], as shown in equation 152. It should be noted, however, that there is some risk of explosion with this procedure[602].



(152)

4. From sulphides, sulphoxides and sulphones

Oxidation of sulphides, sulphoxides and sulphones sometimes gives a useful synthetic route to sulphonyl halides. However, it should be noted that such usefulness is relatively rare due to the forcing conditions that are required to break a C—S bond in most instances. Some of the useful reactions are outlined below.

Halogenated sulphides react with chlorine via the so-called 'sulphohaloform' reaction (this is detailed below) to give alkanesulphonyl chlorides in excellent yields[553,563,603,604]. This reaction also occurs with alkyl benzyl sulphides, where the alkanesulphonyl chloride is formed[605] as shown in equation 153. Methylene dithioethers [$(RS)_2CH_2$] react in a similar fashion to give excellent yields of the sulphonyl chloride[553].

$$RSCH_2Ph \xrightarrow{Cl_2} RSO_2Cl \tag{153}$$

Aqueous chlorination of sulphoxides with excess reagents also leads to the formation of sulphonyl chlorides, via the sulphohaloform reaction, in good yields (equation 154)[563,606,607]. In order for this reaction to be synthetically useful, the sulphoxide used should be symmetrical. The product is presumably formed in a step-wise manner via the sulphinyl chloride [RS(O)Cl] and the sulphinic acid [RS(O)OH]. In the case of chloromethyl dichloromethyl sulphoxide, the only sulphonyl chloride formed is chloromethanesulphonyl chloride, which may be readily separated from the other products by distillation[563,607]. Similarly, oxidation of dichloromethyl methyl sulphoxide and methyl trichloromethyl sulphoxide with chlorine in aqueous acetic acid leads to the formation of methanesulphonyl chloride in 75% and 86% yields, respectively. Other species are also produced but these are much more volatile and thus easily removed. In the absence of acetic acid the yields are somewhat reduced.

$$\underset{RSR}{\overset{O}{\overset{\|}{}}} \xrightarrow{Cl_2} RSO_2Cl \tag{154}$$

Sulphones are blessed with high thermal and chemical stability so that oxidation of these species requires extreme, forcing conditions in most cases. However, polyhalogenated sulphones can be oxidized relatively easily to sulphonyl halides and these reactions will be discussed here.

The direct fluorination of sulphones has been studied[260] and this leads to oxidation. At room temperature dimethyl sulphone produced bis(trifluoromethyl)sulphone and trifluoromethanesulphonyl fluoride in 34% and 15% yields, repectively (equation 155).

$$\underset{\underset{O}{\overset{\|}{}}}{\overset{O}{\overset{\|}{}}}CH_3SCH_3 \xrightarrow{F_2} CF_3SO_2F + \underset{\underset{O}{\overset{\|}{}}}{\overset{O}{\overset{\|}{}}}CF_3SCF_3 \tag{155}$$

A much improved synthesis of perfluoroalkanesulphonyl fluorides from sulphones has been published. This involves the electrolysis of cyclic unsaturated sulphones in anhydrous HF at 8–10 °C using a potential of 5–7 volts. Thus, butadiene sulphone was oxidized to perfluorobutanesulphonyl fluoride in quantitative yield[608].

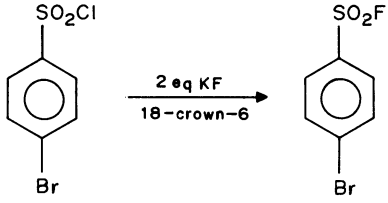
C. From Other S(VI)-containing Compounds

Sulphonyl halides may be prepared from other sulphonic acid derivatives by a variety of means. Amongst these methods, noteworthy are another classical method for the

preparation of sulphonyl chlorides involving the reaction of sulphonic acids with phosphorus pentachloride and the halogen interchange reaction whereby sulphonyl fluorides are made from the corresponding chloride. These and other similar processes are covered below.

The preparation of sulphonyl fluorides, using methods described in the earlier parts of this section, is not usually very successful. Thus there has been much effort expended on the study of the interchange of halogens to form sulphonyl fluorides.

The reaction of alkali metal[301,313,609–612] or zinc[613,614] fluorides with a wide range of both aliphatic and aromatic sulphonyl chlorides gives good yields of the corresponding sulphonyl fluoride. Yields may apparently be improved significantly either by the use of DMF as a solvent or by the use of phase-transfer conditions[615], an example of the latter being shown in equation 156.



(156)

Probably the best method for the conversion of sulphonyl chlorides into sulphonyl fluorides is by use of an ion-exchange resin (equation 157)[616–618]. In one example[616], the use of AGI-X10, a basic quarternary ammonium anion exchange resin, produced the requisite fluorides in more than 90% yield.

$$RSO_2Cl \xrightarrow[\text{resin}]{\text{ion exchange}} RSO_2F \qquad (157)$$

Sulphonyl fluorides may also be obtained from the chloride by heating the latter with SbF_3[619], XeF_2[620] or potassium fluorosulphinate[621]. In addition, perfluoroalkyl sulphonyl fluorides may be prepared in high yield by electrofluorination of unfluorinated sulphonyl precursors[298,496].

Sulphonyl halides, other than fluorides, have also been produced by halide exchange. Thus, sulphonyl chlorides may be made from the fluoride by refluxing with aluminium trichloride[622,623]. Sulphonyl bromides may be prepared from the sulphonyl chloride by reaction with sodium sulphite and base, followed by bromine (equation 158)[624].

$$RSO_2Cl \xrightarrow[2.\ Br_2]{1.\ Na_2SO_3/OH^-} RSO_2Br \qquad (158)$$

There are several reagents that have been used for the preparation of sulphonyl halides from sulphonic acids and their salts; these will now be considered.

Phosphorus pentachloride[381,625–628] and phosphorus pentabromide[629,630] are the most common reagents of choice. This method is a classical one in which a wide range of sulphonic acids may be used (equation 159). However, compounds with hydroxy, alkoxy or amino functionalities may not be used since side-reactions occur. Complexation of the PCl_5 with zinc chloride apparently improves the yields of sulphonyl chlorides[627].

$$RSO_3H \text{ or } RSO_3^- \xrightarrow[X = Cl,\ Br]{PX_5} RSO_2X \qquad (159)$$

Phosphorus oxychloride has also been used for the preparation of sulphonyl chlorides from the acid[625,631,632]. This reagent is milder than phosphorus pentachloride and hence

fewer side-reactions occur. Other reagents that have been used include thionyl chloride[628,633–636], dichloromethyl methyl ether with zinc chloride[637] and both fluoro-[519] and chlorosulphonic[519,638] acids.

Aromatic sulphonyl chlorides have been synthesized from unsubstituted sulphonamides by reaction with PCl_5[639]. On the other hand, *N*-alkyl substituted sulphonamides undergo a rather surprising reaction with the same reagent, as shown in equation 160[640]. Sulphonyl fluorides may be prepared from unsubstituted sulphonamides by reaction of the latter with HF and sodium nitrite[641].

$$RSO_2NHR' \xrightarrow{PCl_5} R-\overset{\overset{O}{\|}}{\underset{\underset{NR'}{\|}}{S}}-Cl \qquad (160)$$

Sulphonyl bromides and iodides are hard to prepare by most routes described in the present section. However, they may be prepared from sulphonyl hydrazides, which are readily available by reaction of hydrazine with a sulphonyl chloride. Thus, reaction of the hydrazide with bromine in chloroform[97,642] or iodine in methanol or in aqueous solution with sodium acetate[643–646] (equation 161) produces good to excellent yields of sulphonyl bromides and iodides, respectively.

$$RSO_2Cl \xrightarrow{H_2NNH_2} RSO_2NHNH_2 \xrightarrow[X = Br, I]{X_2} RSO_2X \qquad (161)$$

Other reactions forming sulphonyl halides from sulphonic acid derivatives include sulphonyl chlorides from esters with PCl_3[647], sulphonyl fluorides from anhydrides with fluoride salts[627] and sulphonyl chlorides from trimethylsilyl derivatives of sulphonic acids by reaction with dichloromethyl methyl ether[648].

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CHAPTER **11**

Sulfonic acids, esters, amides and halides as synthons

KAZUHIKO TANAKA

Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606, Japan

The chemistry of sulphonic acids, esters and their derivatives
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I. INTRODUCTION

In 1967, Corey defined 'synthons' as structural units within a molecule which are related to possible synthetic operations[1]. In organic synthesis, synthetic operations denote structural transformations of the molecule. This chapter deals with a number of very important synthetic operations, namely carbon–carbon bond formation and functional group transformations utilizing sulfonic acids, esters and their derivatives as synthons[2].

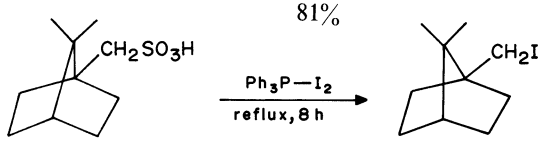
II. SULFONIC ACIDS AS SYNTHONS

A. Iodination of Sulfonic Acids

Aliphatic sulfonic acids are reduced by triphenylphosphine and iodine in benzene solution to give the corresponding iodides in good yields[3] (equations 1 and 2). Sulfonic acids are reduced at first to disulfides or thiols, which are then converted to the iodide upon treatment with triphenylphosphine and iodine.

$$C_5H_{11}SO_3H + 4\,Ph_3P + I_2 \xrightarrow{RT} C_5H_{11}I + 3\,Ph_3PO + Ph_3PS + HI \quad (1)$$

81%



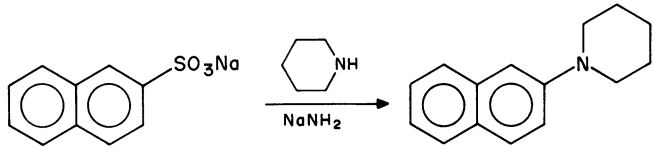
(2)

67%

B. Amination of Sulfonic Acids

Sodium 2-naphthalenesulfonate reacts with piperidine in the presence of sodium amide to give *N*-(2-naphthyl)piperidine in 71% isolated yield[4] (equation 3). By the

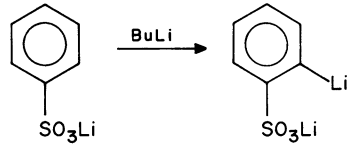
same procedure, *N*-phenylpiperidine and *N*-(1-naphthyl)piperidine are obtained in 94% and 23% yields, respectively, from sodium benzenesulfonate and sodium 1-naphthalenesulfonate.



(3)

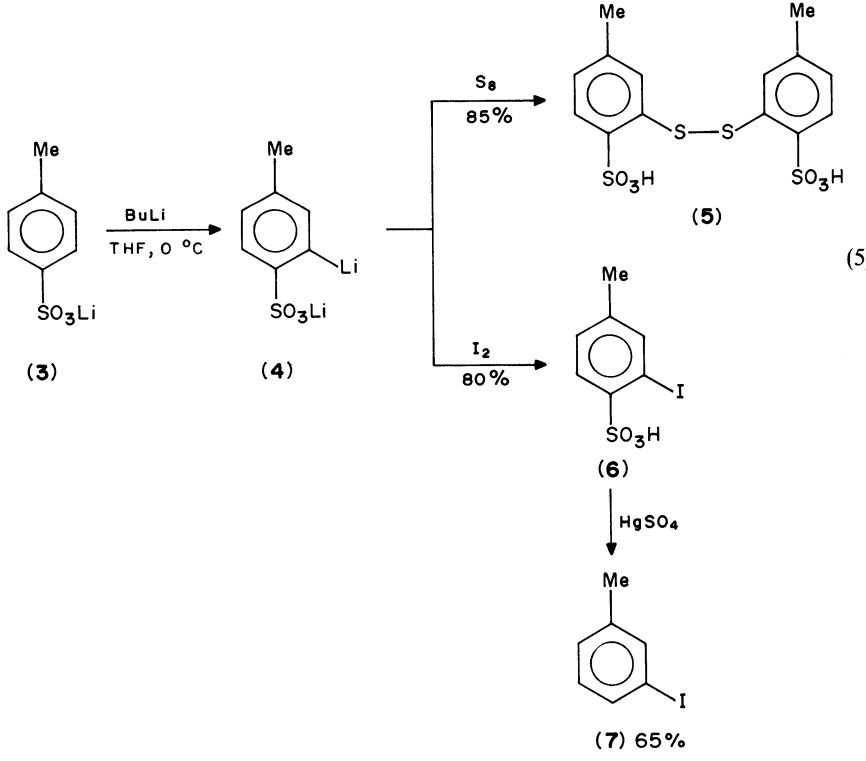
C. *Ortho*-lithiation of Sulfonic Acids

Ortho-directing groups such as $C(OLi)NR_2$[5], NMe_2[6], CH_2NMe_2[7], $CH_2CH_2NMe_2$[8], OMe[9], $CONR_2$[10], SO_2NR_2[11], CF_3[12], F[13], SO_2Ar[14], $C(Ph)_2OMe$[15], 2-oxazoline[16], OLi[17], SLi[18], SCH_2Li[19] and $NHCO_2R$[20] have been utilized in organic synthesis.



(1) (2)

(4)



(5)

Martin and Figuly have found that the lithium salt of aromatic sulfonic acids facilitates the *ortho*-metallation[21]. When the lithium salt (**1**) is treated with 1.1 equivalent of BuLi in THF at 0 °C, the *ortho*-lithiation is complete in 10 min (equation 4). The dilithiated reagent **2** can be stored at −20 °C for several weeks without appreciable decomposition, and its reactions with electrophiles give a variety of *ortho*-substituted arenesulfonic acids. Desulfurization of **6** with $HgSO_4$ in sulfuric acid provides the *meta*-substituted aromatic derivative (**7**) that might be otherwise very difficult to obtain (equation 5).

III. SULFONATES AS SYNTHONS

A. Iodination of Sulfonates

Alkyl alkanesulfonates and alkanethiolsulfonates react with triphenylphosphine and iodine in benzene to give alkyl iodides in high yields[3] (equations 6 and 7).

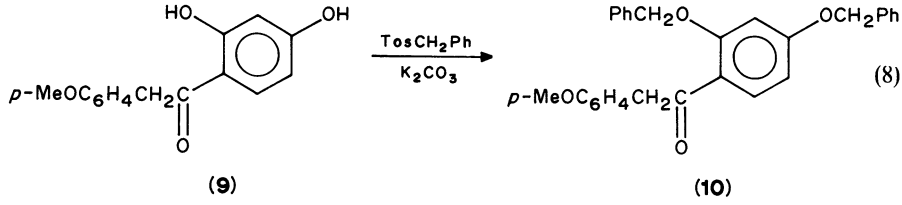
$$C_8H_{17}SO_2OC_5H_{11} + 4Ph_3P + I_2 \xrightarrow{RT} \underset{95\%}{C_8H_{17}I} + \underset{95\%}{C_5H_{11}I} + 3Ph_3PO + Ph_3PS \quad (6)$$

$$C_5H_{11}SO_2SPh + 4Ph_3P + I_2 \xrightarrow[10\,min]{RT} \underset{92\%}{C_5H_{11}I} + 3Ph_3PO + Ph_3PS \quad (7)$$

B. Alkylation of Alcohols and Phenols by Sulfonates

Benzyl *p*-toluenesulfonate (**8**) is a highly O-selective benzylating agent[22]. Reaction of **9** with **8** gives the dibenzyl ether **10** in high yield (equation 8), whereas the yield of the ether is only 18% when benzyl chloride is used as a benzylating agent. Thus, the sulfonate **8** serves as an efficient benzyl synthon.

$$\underset{\text{benzyl synthon}}{PhCH_2} \equiv \underset{(8)}{p\text{-}MeC_6H_4SO_3CH_2Ph}$$

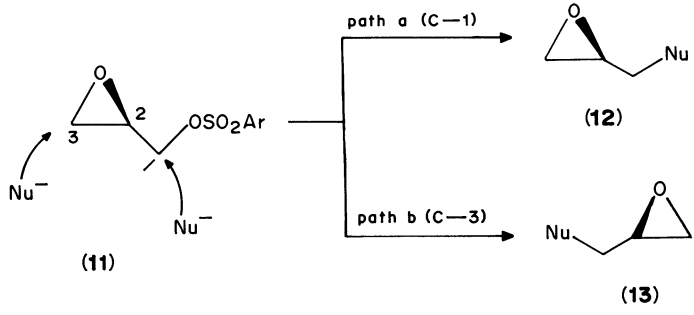


(8)

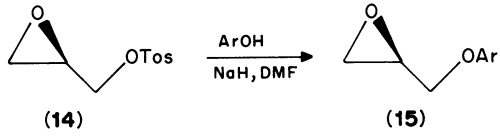
(**9**) (**10**)

Optically active glycidyl arenesulfonates (**11**), which are readily prepared by the Sharpless asymmetric epoxidation[23], are useful building blocks for asymmetric synthesis. The glycidyl arenesulfonates possess two reaction sites toward nucleophiles. Path a (C-1 attack) represents a direct displacement (equation 9). When racemic glycidyl sulfonates are used, initial opening by path b (C-3 attack) followed by displacement of the leaving-group arenesulfonate gives a product indistinguishable from that resulting from path a. When an optically active arenesulfonate is used, the product **12** resulting from path a has the opposite configuration from that of **13** derived from path b. The reaction of (2*S*)-glycidyl tosylate (**14**) of 85% enantiomeric excess (ee) and phenol gives **15a** in 84% yield with 80% ee

(equation 10). The result indicates 94% optical yield, hence the selectivity is 97:3 in favor of direct displacement (path a). As indicated in Table 1, the chiral glycidyl moiety can be transformed to oxygen nucleophiles without loss of optical purity[23].

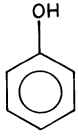
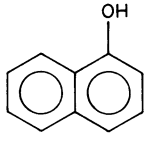
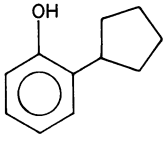
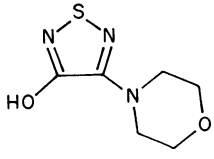


(9)



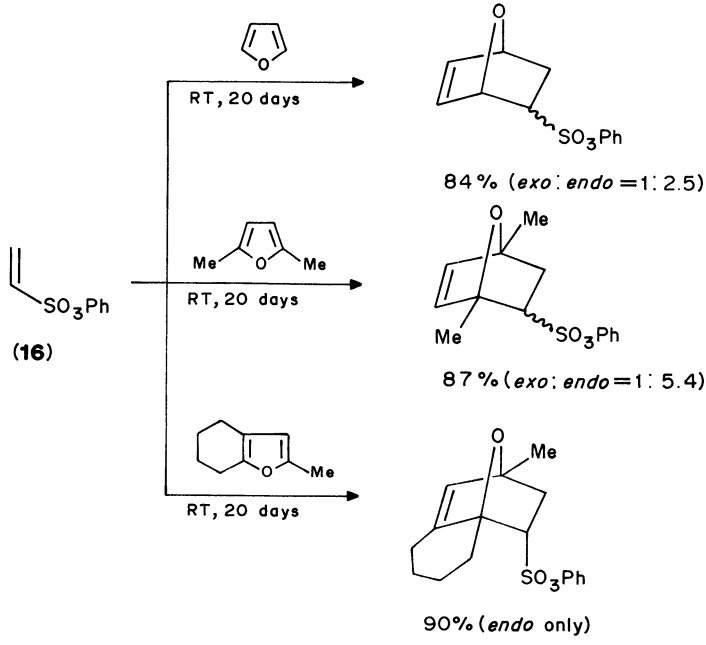
(10)

TABLE 1. Regioselectivity in the reaction of (*S*)-glycidyl tosylate (**14**) with hydroxyaryl nucleophiles

ArOH	Product	Enantiomeric excess of starting material (%)	Yield (%)	Enantiomeric excess of product (%)	Selectivity C—1:C—3
	**15a**	85	84	80	97:3
	**15b**	88	89	85	98:2
	**15c**	88	84	86	99:1
	**15d**	88	72	82	97:3

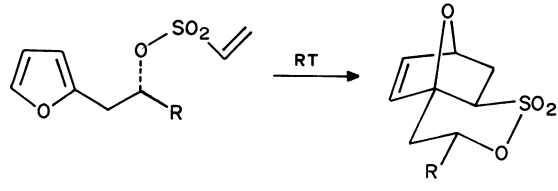
C. Vinylsulfonates as Dienophiles

Phenyl vinylsulfonate (**16**) is an effective dienophile and reacts with furan derivatives, which are known as inert dienes in the Diels–Alder reaction. The sulfonate **16** can be prepared in 85% yield by reaction of β-chlorosulfonyl chloride with phenol in the presence of sodium hydroxide and stored indefinitely at 0 °C[24]. The cycloaddition reaction proceeds at room temperature to give predominantly *endo* adducts as illustrated in equation 11[25]. When the reaction was carried out at higher temperature, the yield of the *endo* adduct and the stereoselectivity decreased due to the retro-Diels–Alder reaction.



(11)

The intramolecular Diels–Alder reaction of vinylsulfonate **17** at room temperature for 3 hours gave a high yield of **18** as a single diastereomer (equation 12). By contrast, the corresponding acrylate does not cyclize even after heating in toluene at reflux for three days[26]. The cycloadduct **18** might be prepared in a one-pot procedure without isolation of **17** by treatment of the corresponding alcohols and vinylsulfonyl chloride.



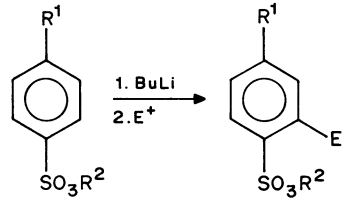
(12)

(**17**) (**18**)

R = Me 90%
R = Et 92%
R = *i*-Pr 87%

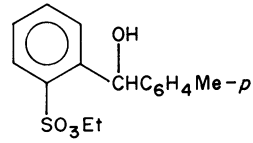
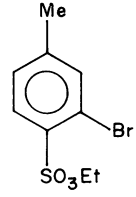
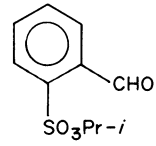
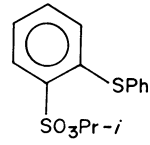
D. *Ortho*-lithiation of Sulfonates

The alkoxysulfonyl group has recently been demonstrated to be an efficient *ortho*-directing substituent. The metallation of **19** can be accomplished in good yields with 1.1 equivalents of BuLi at −78 °C in THF for 5 hours (equation 13). The choice of the appropriate esters is important in this reaction, since with the methyl ester the yield of the product is low due to the competing facile displacement of the methyl group[27]. The results of the *ortho* derivatizations are shown in Table 2. These products can be readily isolated, unlike the acidic products obtained by *ortho*-lithiation of arenesulfonic acids[21].



(19) (20) (13)

TABLE 2. *Ortho*-lithiation of alkyl arenesulfonates

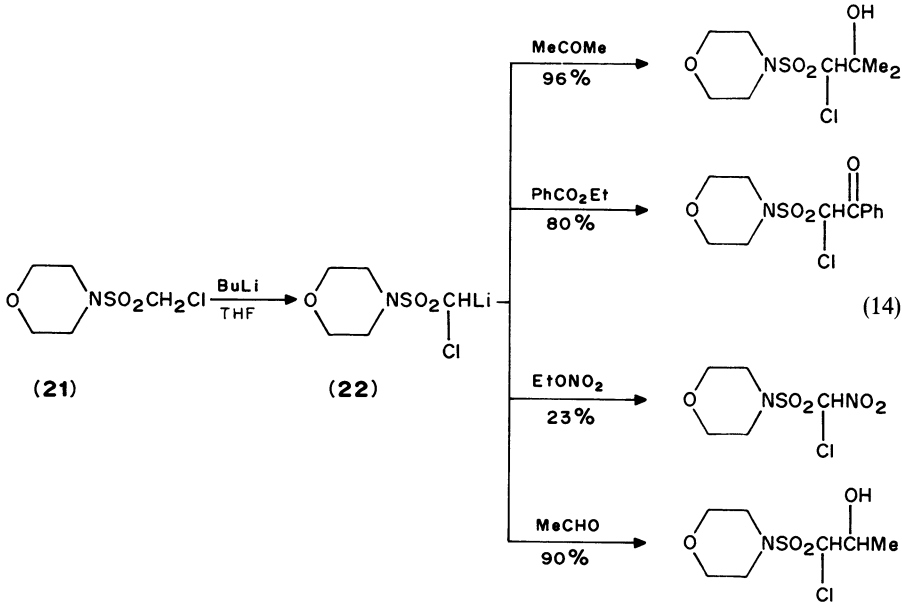
R^1	R^2	Electrophile	Product	Yield (%)
H	Et	*p*-MeC_6H_4CHO		63
Me	Et	$BrCH_2CH_2Br$		85
H	*i*-Pr	DMF		75
H	*i*-Pr	PhSSPh		65

IV. SULFONAMIDES AS SYNTHONS

A. Alkylation of Sulfonamides

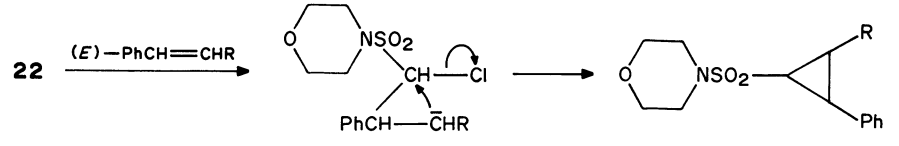
Taking advantage of the sulfamoyl moiety as a strong electron-withdrawing group, several new synthons have been developed.

1-Metalated 1-halosulfonic acid derivatives are extremely reactive species which give a variety of novel 1- and 1,2-functionalized sulfonamides as shown in equation 14[28]. Thus, the α-metalated chloromethanesulfonamide **22** can serve as a useful synthon.



(14)

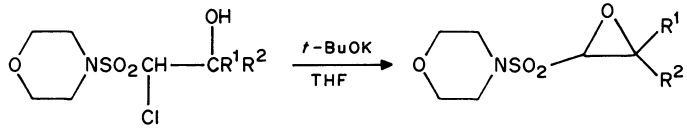
The reaction of **22** with aldehydes at low temperature gives β-hydroxy-α-chlorosulfonamides as a mixture of the *erythro* and *threo* isomers (equation 14). No epoxides are produced under the reaction conditions. In contrast, the reaction of **22** with Michael acceptors gives ring-closed cyclopropanes as *trans*- and *cis*-mixtures in fair to good yields (equation 15)[29].



(15)

R=PhSO2	73%
R=CN	70%
R=NO2	21%

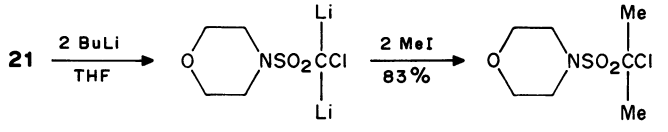
When potassium is substituted as cation by interaction of **25** with *t*-BuOK, an intramolecular displacement occurs readily to give epoxides **26** in good yields as shown in equation 16[30].



(25) (26) (16)

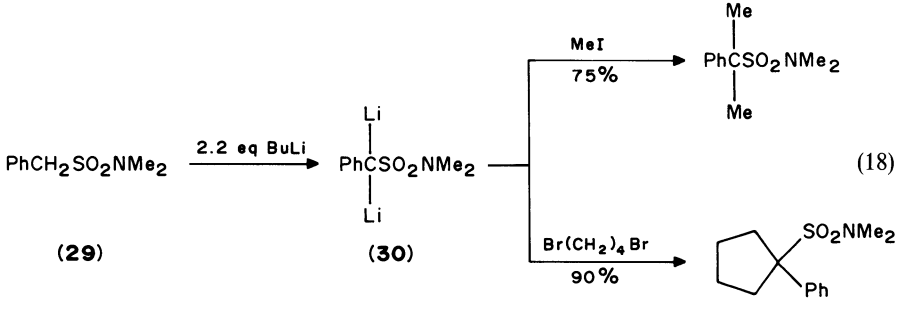
R^1	R^2	Yield (%)
Me	Me	75
Ph	Ph	57
—$(CH_2)_5$—		66

The dianion **27**, derived from 4-(chloromethylsulfonyl)morpholine (**21**) and two equivalents of BuLi, functions as synthon **29**, since the reaction of **27** with methyl iodide in THF at −78 °C gives dialkylated product **28** in 83% yield (equation 17)[31].



(27) (28) (17)

Treatment of *N*,*N*-dimethylphenylmethanesulfonamide with 2 equivalents of BuLi in THF at room temperature for 45 min produces *gem*-dilithio derivatives **30**, which can be trapped by alkylating agents to give α,α-dialkylated products in high yields (equation 18)[32]. The dianion **30** is used as a benzylidenesulfonamide synthon.

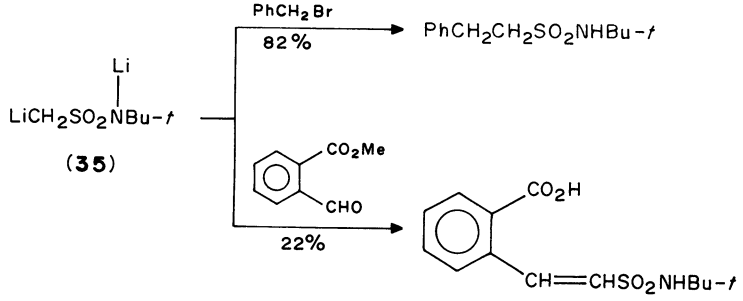


(29) (30) (18)

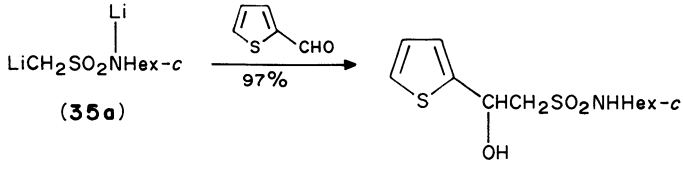
C-Alkylation of methanesulfonamide (**31**) is difficult due to the facile *N*-alkylation reaction (equation 19). The yield of C-methylated sulfonamide **33** is very low. However, when *N*-*t*-butylmethanesulfonamide (**34**) was used, the yield of C-alkylation significantly increased and no *N*-alkylation was observed. Thus, dianion **35** can be readily generated from **34** on treatment with 2 equivalents of BuLi or LDA. The addition of MeI affords *N*-*t*-butylethanesulfonamide (**36**) in 73% yield (equation 20). Removal of the *tert*-butyl substituent can be achieved with trifluoroacetic acid in refluxing xylene giving ethanesulfonamide (**37**) in 90% yield[33]. This method provides a wide variety of substituted sulfonamides that might otherwise prove difficult to prepare. The examples of selective C-alkylation of *N*,*C*-dilithio species (**35** and **35a**) with electrophiles are shown in equations 21 and 22. Thus, these dilithiated species function as methylenesulfonamide synthons.

$$\underset{\textbf{(31)}}{CH_3SO_2NH_2} \xrightarrow[MeI]{2\,eq\ BuLi} \underset{\textbf{(32)}}{CH_3SO_2NMe_2} + \underset{\textbf{(33)}}{CH_3CH_2SO_2NH_2} \tag{19}$$

$$\underset{\textbf{(34)}}{CH_3SO_2NHBu\text{-}t} \xrightarrow{2\,eq\ BuLi} \underset{\textbf{(35)}}{LiCH_2SO_2N(Li)Bu\text{-}t} \xrightarrow{MeI} \underset{\textbf{(36)}}{CH_3CH_2SO_2NHBu\text{-}t} \xrightarrow{CF_3CO_2H} \underset{\textbf{(37)}}{CH_3CH_2SO_2NH_2} \tag{20}$$



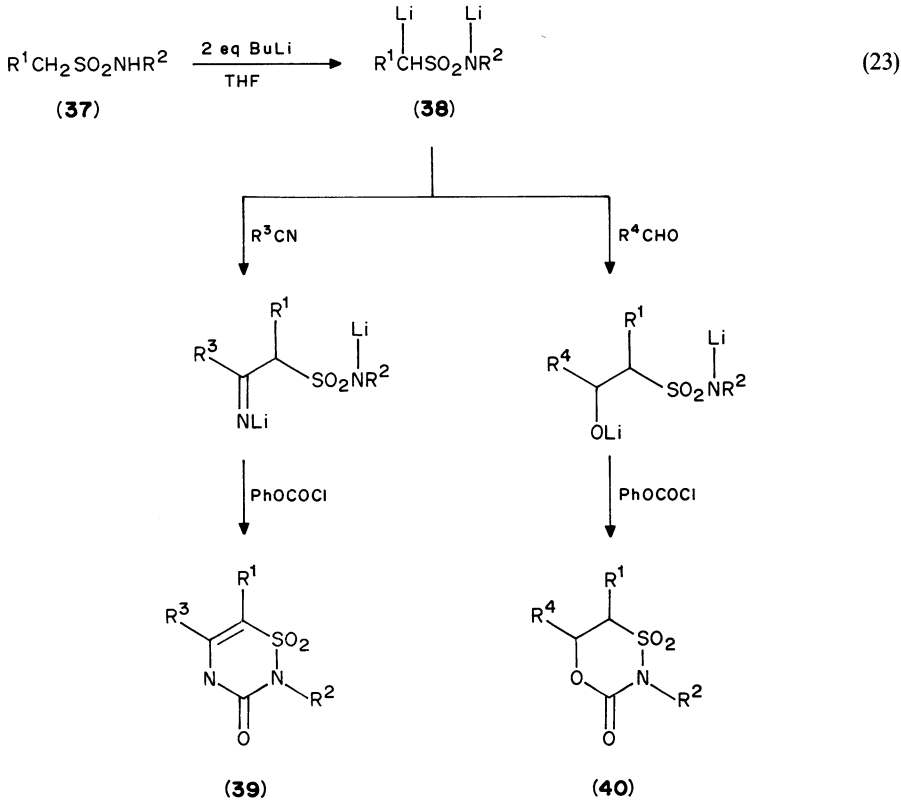
(21)



(22)

Treatment of dianion **38** derived from *N*-monosubstituted alkanesulfonamides **37** with cyanides gives a new imine dianion which, upon treatment with phenyl chloroformate, affords the pharmacologically interesting 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide ring system (**39**) as shown in equation 23[34]. The reported method for these heterocycles required a multistep procedure and was restricted to compounds possessing a phenyl

substituent at the 4-position. New 5,6-dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-dioxides (**40**) are also available from the reaction of the dianion **38** and aldehydes followed by reaction with phenyl chloroformate (equation 23)[34].

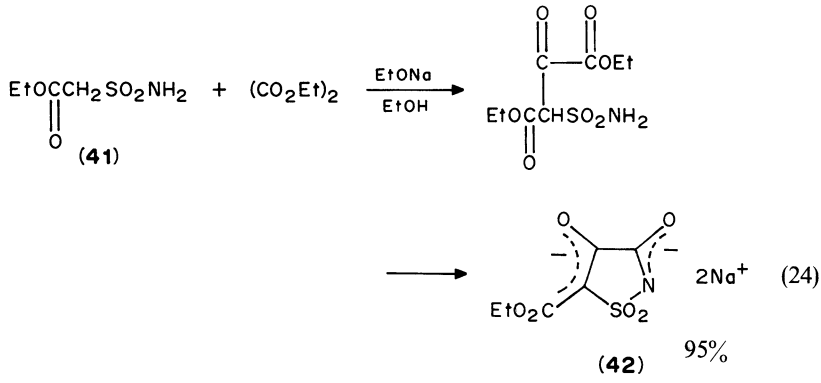


(23)

R^1	R^2	R^3	Yield (%)
H	*t*-Bu	Ph	38
H	*t*-Bu	*i*-Pr	40

R^1	R^2	R^4	Yield (%)
H	*t*-Bu	Ph	40
H	*c*-C_6H_{11}	2-ClC_6H_4	27

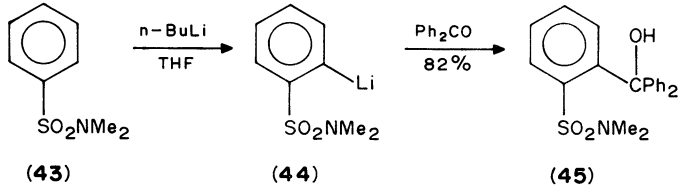
A direct synthesis of trisubstituted isothiazole 1,1-dioxides, which are difficult to prepare by other methods, has been achieved by treatment of a substituted methanesulfonamide with diethyl oxalate in ethanol. Thus, the disodium salt of 3,4-dihydroxy-5-(ethoxycarbonyl)isothiazole 1,1-dioxide (**42**) is obtained in high yield when **41** is treated with diethyl oxalate in the presence of sodium ethoxide at room temperature (equation 24)[35]. Regioselective nucleophilic substitution of 3,4-dichloro- and 4-chloro-3-ethoxy-5-(ethoxycarbonyl)isothiazole 1,1-dioxide, prepared from **42**, oxalyl chloride and ethanol occurs at the C-3 and C-4 positions with alcohol, amines and *N*-(trimethylsilyl)amines.



(24)

B. *Ortho*-lithiation of Sulfonamides

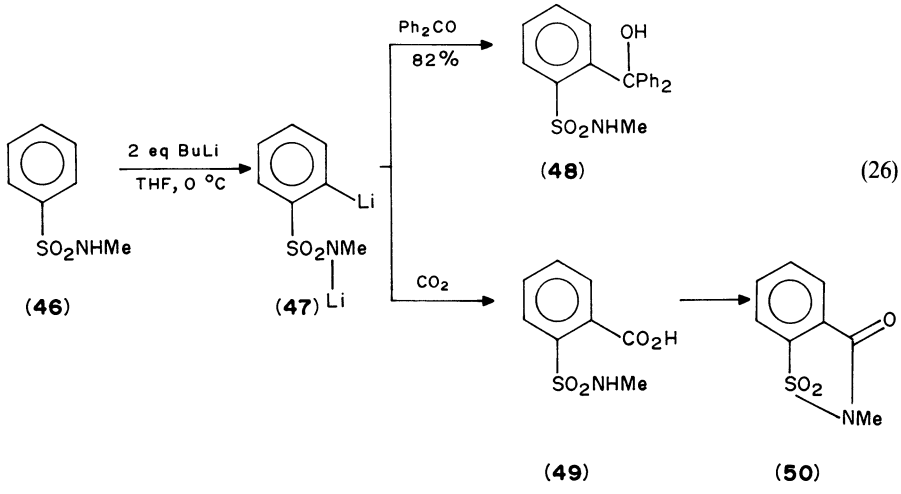
Among various functional groups, sulfamoyl moieties belong to the stronger *ortho*-directing substituents. For example, while *N*,*N*-dimethylbenzamide is attacked by BuLi leading to formation of 1-phenyl-1-pentanone. In contrast, *N*,*N*-dimethylbenzenesulfonamide (**43**) is converted by BuLi to the *ortho*-lithiosulfonamide **44** as shown in equation 25. Subsequent addition of benzophenone, benzonitrile, phenylisocyanate and carbon dioxide gives the corresponding alcohol, imine, amide and acid, respectively. The example of the *ortho*-derivatization reaction of **44** with benzophenone is illustrated in equation 25[36].



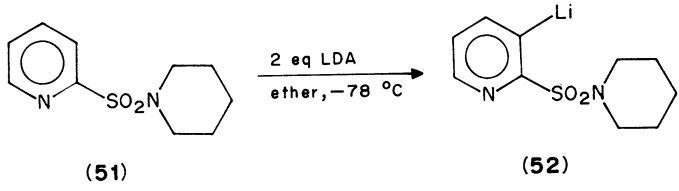
(25)

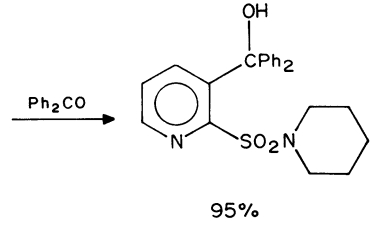
Ortho-metallations were also observed with *N*-methyl- and *N*-phenylbenzenesulfonamides. Thus, the treatment of *N*-methylbenzenesulfonamide (**46**) with 2 equivalents of BuLi in THF at 0 °C gave an orange suspension of the dilithiosulfonamide **47**, which reacted in turn with electrophiles to give *ortho*-derivatives (**48** and **49**) as shown in equation 26[37]. The 2-sulfamoylbenzoic acid **49** cyclizes in sulfuric acid to give **50** in 49% overall yield from **46**.

Electrophilic substitution is difficult with electron-deficient heteroatomic compounds such as pyridine and quinoline. However, an electrophile can be readily introduced when the heterocycles have an effective *ortho*-directing group such as a sulfamoyl moiety. Lithiation of the 2-pyridinesulfonamide (**51**) was performed at low temperature by using 2 equivalents of LDA in ether at −78 °C for 1.5 h (equation 27). Addition of benzophenone to the solution of **52** gave the adduct in high yield[38]. Metallation of the 4-pyridinesulfonamide **53** with 3 equivalents of LDA, followed by reaction with benzaldehyde, afforded the 3,5-disubstituted pyridine **54** (equation 28).

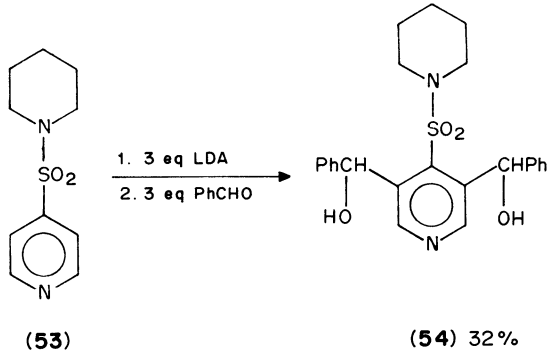

Ph2CO
82%
OH
CPh2
SO2NHMe
(48)
2 eq BuLi
THF, 0 °C
Li
SO2NMe
Li
(46)
(47)
CO2
CO2H
SO2NHMe
O
SO2
NMe
(49)
(50)

(26)


2 eq LDA
ether, −78 °C
Li
N
SO2N
(51)
(52)


Ph2CO
OH
CPh2
N
SO2N
95%

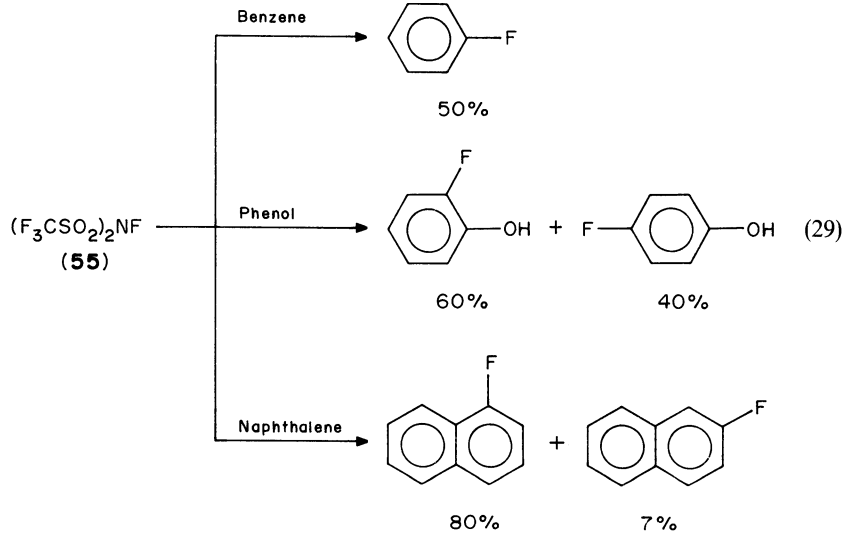
(27)


N
SO2
N
1. 3 eq LDA
2. 3 eq PhCHO
N
SO2
PhCH
HO
CHPh
OH
N
(53)
(54) 32%

(28)

C. Fluorination by *N*-Fluorosulfonamides

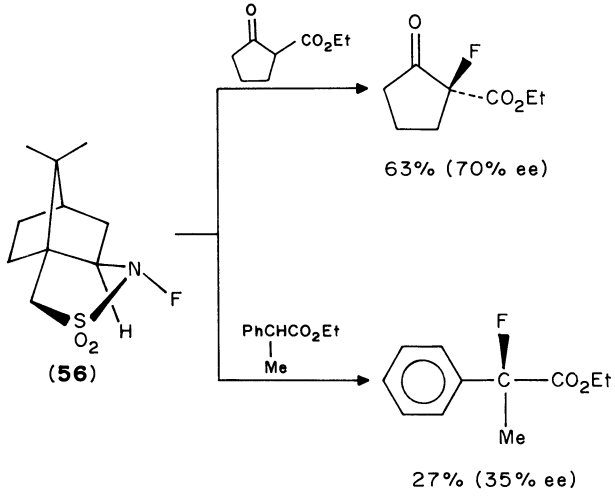
Aromatic fluorinated compounds are of considerable interest for the preparation of biologically active substances. Several fluorination reagents such as CF_3OF or F_2 require special equipment and experience to handle safely. $(CF_3SO_2)_2NF$ (**55**) is stable for long periods at room temperature and found to be an efficient reagent for nuclear fluorination of aromatic compounds. Typical examples are shown in equation 29[39]. In addition to the utility in the direct aromatic fluorinations, **55** is also useful in the fluorination of carbon



(29)

anions. Reaction of **55** with sodium diethyl 1-methylmalonate in $CDCl_3$ at $-10\,^{\circ}C$ gave diethyl 1-fluoro-1-methylmalonate in 96% yield.

The *N*-fluorosultam **56** is the first enantioselective fluorinating reagent which reacts

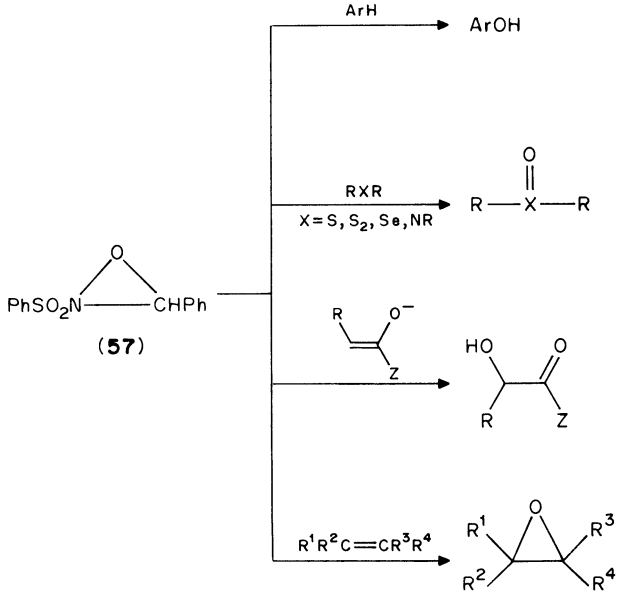


(30)

with various metal enolates to give α-fluoro carbonyl compounds with enantiomeric excess of about 10–70%. The best result (70% ee) is observed in the case of ethyl cyclopentane-2-carboxylate as shown in equation 30[40].

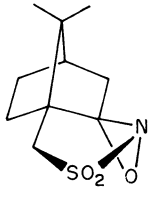
D. Oxidation by Sulfonyloxaziridines

The 2-sulfonyloxaziridine (**57**) is a more selective oxidant than peracids. The reagent has been employed in the oxidation of sulfides to sulfoxides, disulfides to thiolsulfinates, selenides to selenoxides, thiols to sulfenic acids, organometallic reagents to alcohols and phenols, ketone and ester enolates to α-hydroxycarbonyl compounds (equation 31)[41]. The oxidation of chiral amide enolates gives optically active α-hydroxy carboxylic acids with 93–99% enantiomeric excess[42].

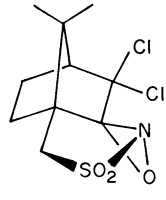


(31)

Davis and coworkers have recently found that asymmetric oxidation of sulfides with (+)-(camphorsulfonyl)oxaziridine (**58**) affords sulfoxides with 8–73% enantiomeric excess. In contrast, (−)-α,α-(dichlorocamphorsulfonyl)oxaziridine (**59**) in $CHCl_3$ affords uniformly high stereoselectivity (66–95% ee of (*S*)-configuration of sulfoxides). The solvent



(**58**)



(**59**)

used in the reaction strongly influences the stereoselectivities in the asymmetric oxidations, possibly due to the fact that **59** has polar Cl groups but not **58**. The results indicate that the electronic or polar effects influence the stereoselectivity[43].

E. Amination by Sulfonamides

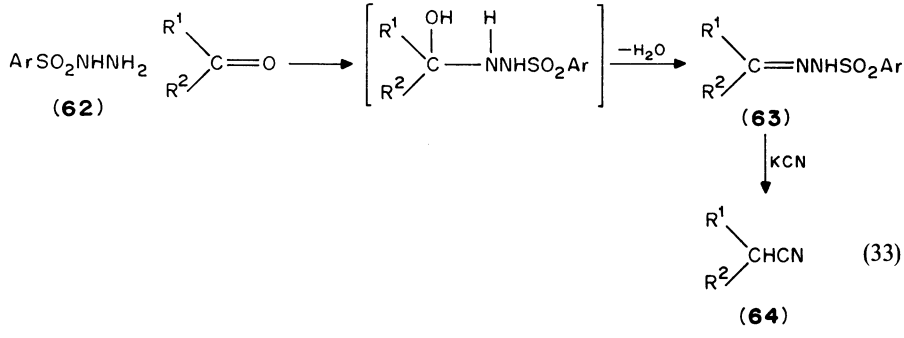
Taking advantage of the good leaving ability of the trifluoromethanesulfonyl moiety, a new useful Gabriel-type synthesis of primary amines **61** has been devised by Hendrickson and coworkers. The reaction outlined in equation 32 was carried out for R = $PhCH_2$ and C_7H_{15} in 70–80% overall yields[44] by using *N*-(trifluoromethanesulfonyl)benzylamine as the aminating reagent.

$$\mathrm{RBr} + \mathrm{PhCH_2NHSO_2CF_3} \xrightarrow{K_2CO_3} \underset{\displaystyle \mathrm{CH_2Ph}}{\mathrm{RNSO_2CF_3}} \quad \textbf{(60)}$$

$$\xrightarrow[2.\ H_3O^+]{1.\ \mathrm{NaH}} \underset{\textbf{(61)}}{\mathrm{RNH_3}^+} + \mathrm{PhCHO} + \mathrm{CF_3SO_2}^- \qquad (32)$$

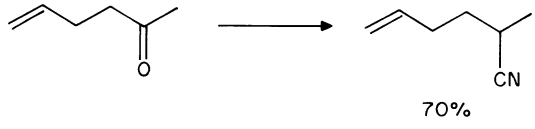
F. Cyanation by Sulfonamides

The transformation of aldehydes or ketones to nitriles is carried out in two steps: (1) conversion of the carbonyl compound to the 2,4,6-triisopropylbenzenesulfonylhydrazone[63], and treatment of the latter with excess of KCN in refluxing methanol (equation 33). Typical examples are shown in equations 34 and 35[45].



(33)

(34)



(35)

G. Iodination of Sulfonamides

Aliphatic sulfonamides react with triphenylphosphine and iodine in benzene to give the corresponding iodides in good yields[3] (equation 36).

$$C_5H_{11}SO_3NHBu + 4\,Ph_3P + I_2 \longrightarrow \underset{85\%}{C_5H_{11}I} + 3\,Ph_3PO + Ph_3PS \qquad (36)$$

V. SULFONYL HALIDES AS SYNTHONS

A. Iodination of Sulfonyl Chlorides

Octanesulfonyl chloride reacts with triphenylphosphine and iodine in benzene solution to give octyl iodide in 75% yield[3] (equation 37).

$$C_8H_{17}SO_2Cl + 4\,Ph_3P + I_2 \xrightarrow[10\,min]{RT} \underset{75\%}{C_8H_{17}I} + 3\,Ph_3PO + Ph_3PS \qquad (37)$$

B. Addition of Sulfonyl Chlorides

Addition of alkane and arenesulfonyl chlorides to olefins and acetylenes occurs in the presence of a metal halide via a free radical process. For example, arenesulfonyl chlorides (**66**) add to styrene (**65**, $R^1 = Ph$) in the presence of $CuCl_2$ to give 1-chloro-1-aryl-2-(arenesulfonyl)ethanes (**67**) by a free radical process. The adducts can be converted to vinylic sulfones in high yields on treatment with triethylamine in benzene (equation 38)[46].

The allylsilane **68** reacts with benzenesulfonyl chloride in the presence of CuCl to give the allysulfone **70** in 50% yield via chlorodesilylation of the adduct **69** (equation 39)[47].

$$\underset{(65)}{R^1CH{=}CH_2} + \underset{(66)}{R^2SO_2Cl} \xrightarrow[Et_3N\cdot HCl,\,MeCN]{CuCl_2} \underset{\underset{Cl}{|}}{R^1CHCH_2SO_2R^2}\ (67) \xrightarrow[benzene]{Et_3N} \underset{78-94\%}{\begin{array}{c}R^1\quad\quad H\\ \diagdown\ /\\ C{=}C\\ /\ \diagdown\\ H\quad\quad SO_2R^2\end{array}} \qquad (38)$$

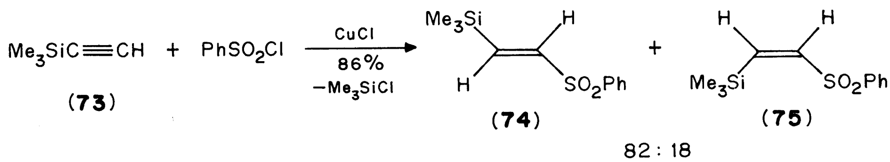
R^1	R^2	Yield(%)
Ph	Ph	75
Ph	Me	66
Ph	$BrCH_2$	80

$$\underset{(68)}{Me_3SiCH_2CH{=}CH_2} + PhSO_2Cl \xrightarrow{CuCl} \underset{\underset{Cl}{|}}{Me_3SiCH_2CHCH_2SO_2Ph}\ (69)$$

$$\xrightarrow{-Me_3SiCl} \underset{(70)\quad 50\%}{CH_2{=}CHCH_2SO_2Ph} \qquad (39)$$

Methanesulfonyl chloride adds to the vinylsilane **71** at 130–140 °C to give **72** under similar conditions (equation 40). The ethynylsilane **73** reacts with benzenesulfonyl chloride to give a mixture of trimethylsilylvinylsulfones (**74** and **75**) as shown in equation 41[47].

$$\underset{(\mathbf{71})}{Me_3SiCH=CH_2} + MeSO_2Cl \xrightarrow{CuCl} \underset{\substack{| \\ Cl \\ (\mathbf{72})\quad 70\%}}{Me_3SiCHCH_2SO_2Me} \qquad (40)$$



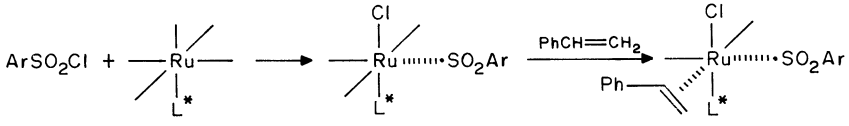
(41)

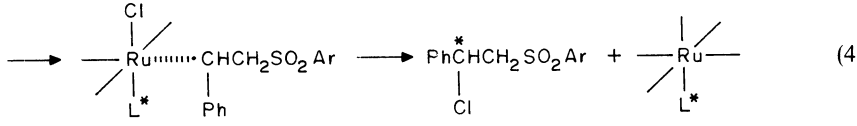
The addition of arenesulfonyl chlorides to styrene in the presence of a catalytic amount of $Ru_2Cl_4[(-)\text{-DIOP}]_3$ (2,3-(isopropylidenedioxy)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) gives optically active 1:1 adducts, 2-chloro-2-phenylethyl aryl sulfones **76**, with 20–40% enantiomeric excess (equation 42)[48]. The reaction can be explained by a radical redox transfer chain which proceeds in the coordination sphere of the ruthenium(II) complex (equation 43). The ruthenium(II) catalyst abstracts a chlorine atom from the arenesulfonyl chloride to give an arenesulfonyl radical and a ruthenium(II) species in which the sulfonyl moiety is complexed with the ruthenium(III) atom, **77**. The π-complex **78** formed between **77** and styrene rearranges to the 2-(arenesulfonyl)-1-phenylethyl radical **79**. The carbon radical in **79** abstracts the chlorine atom from the ruthenium(III) species bearing the chiral ligand to give the adduct **80** and regenerates the ruthenium(II) catalyst[48]. The asymmetric induction, summarized in Table 3, indicates that the sulfonyl and carbon radicals are complexed to the ruthenium species and have different features from those of the unusual sulfonyl and carbon radicals as shown in equations 38–41.

$$R^1SO_2Cl + PhCH{=}CH_2 \xrightarrow{Ru^{III}L^*} \underset{\substack{| \\ Cl \\ (\mathbf{76})}}{PhCHCH_2SO_2R^1} \qquad (42)$$

TABLE 3. Reaction of sulfonyl chlorides with styrene derivatives using ruthenium(II)–DIOP complexes

Catalyst	R^1	Optical yield (%)	Absolute configuration
$Ru_2Cl_4[(-)\text{-DIOP}]_3$	*p*-Tol	29	*R*
$Ru_2Cl_4[(+)\text{-DIOP}]_3$	*p*-Tol	24	*S*
$Ru_2Cl_4[(-)\text{-DIOP}]_3$	*p*-ClC_6H_4	25	*R*
$Ru_2Cl_4[(+)\text{-DIOP}]_3$	*p*-ClC_6H_4	24	*S*
$Ru_2Cl_4[(-)\text{-DIOP}]_3$	*p*-$MeOC_6H_4$	40	*R*
$Ru_2Cl_4[(+)\text{-DIOP}]_3$	*p*-$MeOC_6H_4$	31	*S*





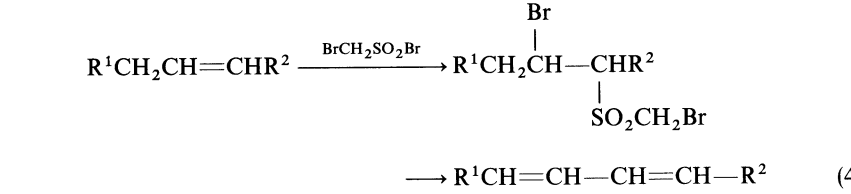
(43)

(L = Ligand)

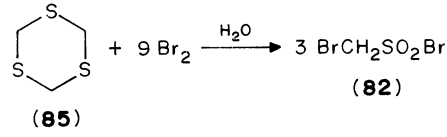
C. Olefin Formation by Sulfonyl Bromides

α-Haloalkanesulfonyl bromides such as chloromethanesulfonyl bromide (**81**), bromomethanesulfonyl bromide (**82**), α-bromoethanesulfonyl bromide (**83**) and iodomethanesulfonyl bromide (**84**) undergo free radical addition to olefins to give adducts which, upon treatment with base, afford dienes in good yields[49]. The general scheme is shown in equation 44. Bromomethanesulfonyl bromide (**82**) can be prepared in 42–48% yield as a slightly yellow oil (bp 68 °C/0.01 mmHg) by addition of 9.5 mol of bromine per mole of 1,3,5-trithiane (**85**) as shown in equation 45. The addition of **82** to double bonds is regiospecific, producing a single isomer in the case of mono-, 1,1-di- and 1,1,2-trisubstituted olefins. When the mixture of **82** and 1-methylcyclohexene was irradiated by a 450-W mercury lamp at −15 °C, a single 1:1 adduct **86** was obtained (equation 46).

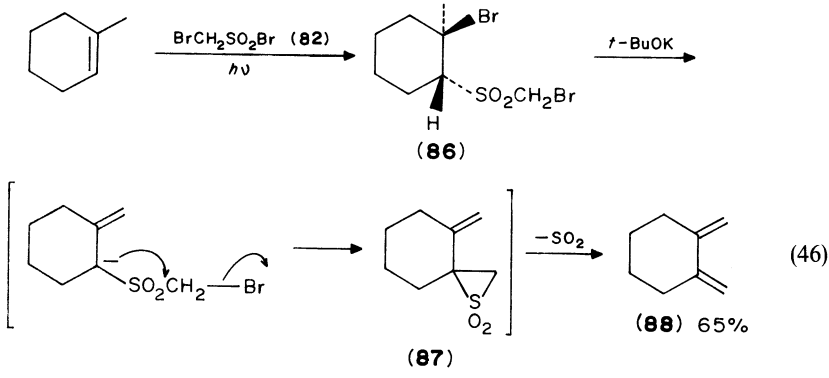
$ClCH_2SO_2Br$ (**81**) $BrCH_2SO_2Br$ (**82**) $CH_3CHBrSO_2Br$ (**83**) ICH_2SO_2Br (**84**)



(44)



(45)



(46)

The reaction involves a free radical chain reaction starting with scission of the light-sensitive S—Br bond as shown in equation 47; analogous free radical additions of other sulfonyl halides are shown in equations 38–40.

$$BrCH_2SO_2Br \xrightarrow{h\nu} BrCH_2SO_2\cdot + Br\cdot$$

(82)

$$BrCH_2SO_2\cdot + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2SO_2CH_2Br$$

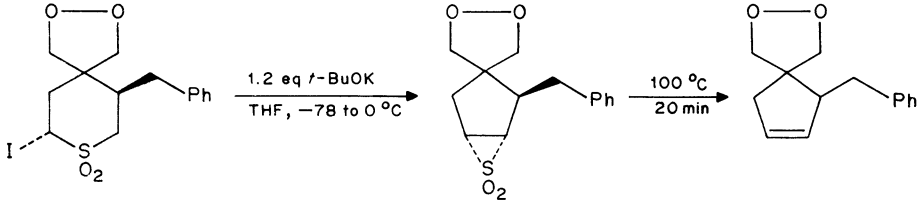
$$R\dot{C}HCH_2SO_2CH_2Br + BrCH_2SO_2Br \longrightarrow \underset{\displaystyle Br}{\underset{|}{RCH}}CH_2SO_2CH_2Br + BrCH_2SO_2\cdot$$

$$BrCH_2SO_2\cdot \longrightarrow BrCH_2\cdot + SO_2$$

$$BrCH_2\cdot + BrCH_2SO_2Br \longrightarrow CH_2Br_2 + BrCH_2SO_2\cdot \qquad (47)$$

Treatment of **86** with 2.5 equivalents of potassium *t*-butoxide in a mixture of *t*-BuOH and THF gave the diene **88** in 65% overall yield based on 1-methylcyclohexene (equation 46). The formation of **88** can be explained rationally by assuming the intermediacy of episulfone **87** and subsequent extrusion of SO_2.

To date, there is no report on the isolation of an episulfone intermediate in the Ramberg–Bäcklund reaction. Taylor and Sutherland have recently succeeded in the isolation of an episulfone[50]. Thus, when iodo-sulfone **89** was treated with potassium *t*-butoxide, episulfone **90** was obtained as a white crystalline solid in 69% yield as illustrated in equation 48. Treatment of **90** with excess potassium *t*-butoxide at −20 °C to room



(48)

temperature gave cyclopentene **91** in 81% yield, or thermolysis of **90** at 100 °C for 20 min gave **91** in 88% yield. The episulfone **90** can be stored at −18 °C without noticeable decomposition over a 2-month period.

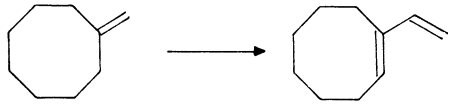
Other examples of the preparation of dienes from olefins using bromomethanesulfonyl bromide (**82**) are shown in equations 49–52[49].

$$\mathrm{BuCH{=}CH_2} \longrightarrow \mathrm{PrCH{=}CHCH{=}CH_2} \quad (49)$$

38% ($E{:}Z = 2{:}1$)

$$(E)\text{-}\mathrm{BuCH{=}CHBu} \longrightarrow (E)\text{-}\mathrm{PrCH{=}CHC(Bu){=}CH_2} \quad (50)$$

68%



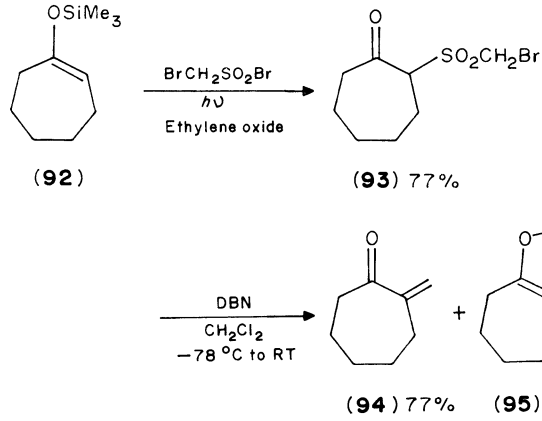
(51)

75%

$$\mathrm{HO(CH_2)_9CH{=}CH_2} \longrightarrow \mathrm{HO(CH_2)_8CH{=}CHCH{=}CH_2} \quad (52)$$

86% ($E{:}Z = 5{:}1$)

The reaction of **82** with olefins substituted with oxygen such as enol acetates, enol ethers or enol silyl ethers is of interest, since the initial adducts with the sulfonyl bromide might give α-halosulfonyl ketones or aldehydes upon hydrolysis. Thus, irradiation of a solution of 1-(trimethylsilyl)oxy-1-cycloheptene (**92**) with **82** in ethylene oxide at −15 °C gave 2-[(bromomethyl)sulfonyl]cycloheptanone (**93**) in 77% yield[49]. Treatment of **93** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in ethanol at room temperature gave 2-methylenecycloheptanone (**94**) along with **95** (equation 53). These sequences provide a new route to α-alkylidene ketones from trimethylsilyl enol ethers[49].



(**92**) (**93**) 77%

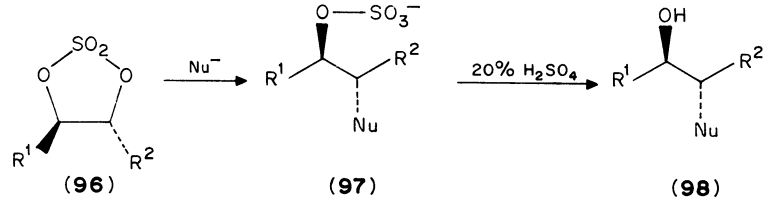
(53)

(**94**) 77% (**95**) 21%

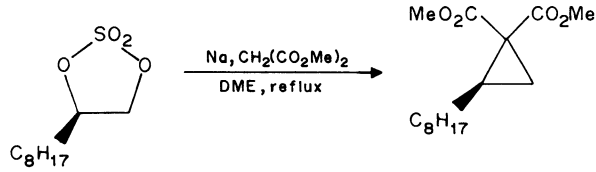
VI. CYCLIC SULFATES AS SYNTHONS

Cyclic sulfates are of great importance as electrophiles in organic synthesis, since they can be converted to a variety of β-functionalized alcohols.

Sharpless and Kim reported a one-pot synthesis of cyclic sulfates **96** from 1,2-diols via catalytic oxidation with ruthenium chloride[51]. The cyclic sulfates **96** thus formed on treatment with nucleophiles give β-sulfates **97**, which in turn are hydrolyzed to the β-hydroxy compounds **98** (equation 54). Hence the cyclic sulfates **96** are synthetically equivalent to epoxides. The results of ring opening of cyclic sulfates **96** are shown in Table 4. When the reaction of **99** with malonate anion is carried out in DME, the β-sulfate moiety serves as a leaving group to give cyclopropane **100** (equation 55)[51].



(96) (97) (98) (54)

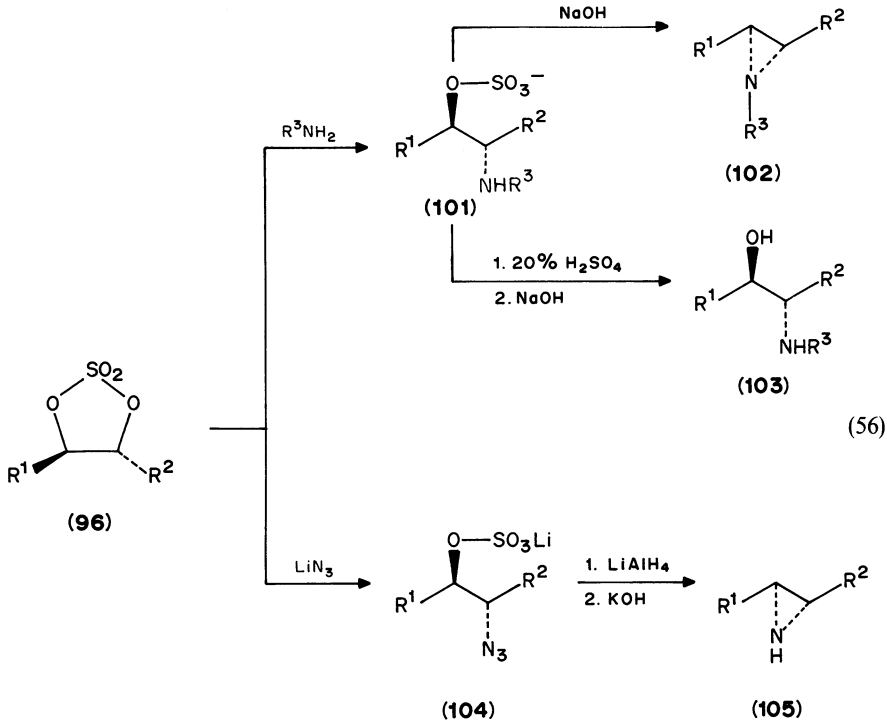


(99) (100) 72% (55)

Functionalized aziridines, especially optically active ones, are important intermediates in organic synthesis. The reaction of cyclic sulfates prepared from homochiral diols with amines or azide ion provides an efficient route to homochiral aziridines (equation 56). Formation of aziridines from cyclic sufates occurs with inversion at the stereogenic center. The reaction of the cyclic sulfates with an excess of a primary amine gives β-

TABLE 4. Reactions of cyclic sulfates (**96**) with nucleophiles

R^1	R^2	Nucleophile	Yield (%) of **98**
CO_2Pr-*i*	CO_2Pr-*i*	H^-	55
CO_2Pr-*i*	CO_2Pr-*i*	N_3^-	81
CO_2Pr-*i*	CO_2Pr-*i*	$PhCO_2^-$	95
CO_2Pr-*i*	CO_2Pr-*i*	$PhCH_2^-$	73
CO_2Et	CO_2Et	H^-	90
$C_{15}H_{31}$	CO_2Me	SCN^-	90
$C_{15}H_{31}$	CO_2Me	F^-	63



(56)

aminosulfonates **101** which, upon treatment with BuLi, cyclize to the aziridines **102** in good to excellent yields. Hydrolysis of the β-aminosulfates **101** with 20% aqueous H_2SO_4 followed by treatment with 20% NaOH gives aminoalcohols **103** in good yield.

Nucleophilic substitution of the cyclic sulfates with LiN_3 gives azidosulfates **104** which, upon reduction with $LiAlH_4$ followed by treatment with 20% KOH, afford *N*-unsubstituted homochiral aziridines **105** in good yields and in high optical yields (equation 56). The results of the ring opening of chiral cyclic sulfates **96** are listed in Table 5[52].

TABLE 5. Preparation of *N*-substituted aziridines from cyclic sulfates

R^1	R^2	RNH_2	**105**, Yield (%)	Enantiomeric excess (%) or diastereomeric excess (%)
(*R*)-*c*-Hex	H	$PhCH_2NH_2$	78	> 96
(*R*)-*c*-Hex	H	(*S*)-*s*-$BuNH_2$	79	> 96
(*R*)-Ph	(*R*)-Ph	$PhCH_2NH_2$	73	> 96
(*R*)-Ph	(*R*)-Ph	(*S*)-*s*-$BuNH_2$	82	> 96

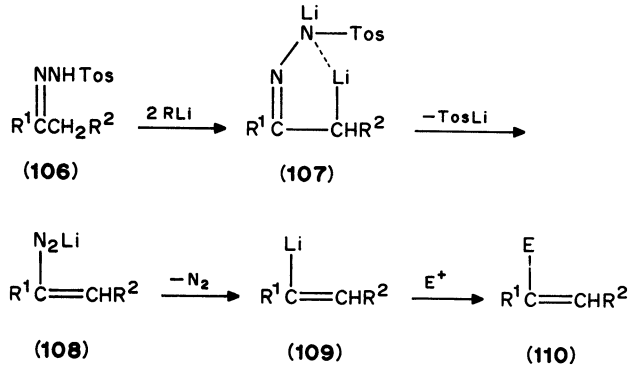
VII. ARENESULFONYLHYDRAZONES AS SYNTHONS

A. Ketone Arenesulfonylhydrazones

1. Preparation of homoallylic alcohols

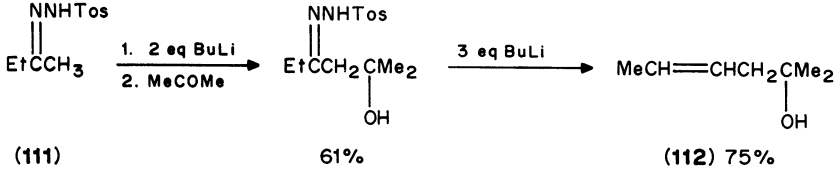
Arenesulfonylhydrazones serve as a convenient source of vinyllithium reagents. The generation of the vinyllithium reagents is known as the Shapiro reaction[53].

Treatment of the tosylhydrazones **106** derived from ketones with 2 equivalents of strong base produces the tosylhydrazone dianion **107**, which decomposes to the vinyllithium **109** via the vinyldiazinyl anion **108** (equation 57)[53]. The vinyl reagents so formed can be trapped with a variety of electrophiles to give **110**[54].

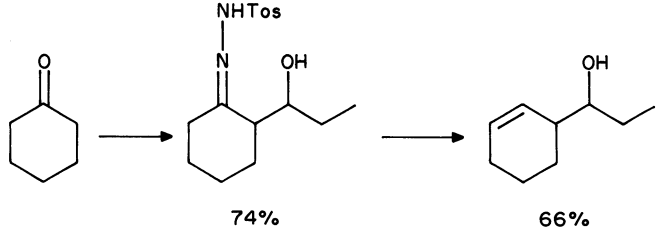


(57)

Regioselective formation of the tosylhydrazone dianion was observed in tosylhydrazones of the type **111** derived from unsymmetrical ketones such as 2-butanone. Abstraction of protons from the less hindered side of **111** and subsequent reaction with acetone gave a β-hydroxytosylhydrazone, which on treatment with alkyllithium gave the homoallylic alcohol **112** in good yield as shown in equation 58[53]. Another example is shown in equation 59.



(58)



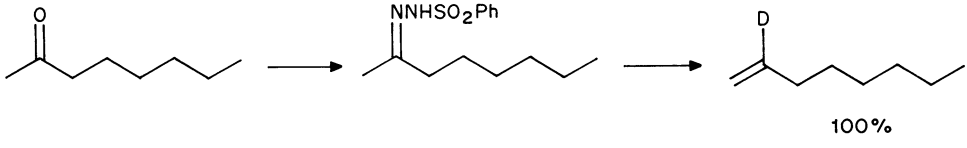
(59)

2. Preparation of olefins and olefinic deuterium compounds

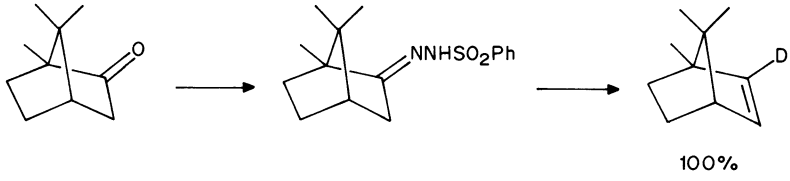
Quenching the vinyllithium compound derived from ketone tosylhydrazones with water constitutes a facile procedure for the preparation of olefins from ketones as shown in equations 60 and 61[55].

$$\underset{\underset{\text{PhCCHMe}_2}{\|}}{\text{NNHTos}} \xrightarrow[\text{TMEDA}]{\text{LDA}} \underset{57\%}{\text{PhCH}=\text{CMe}_2} \tag{60}$$

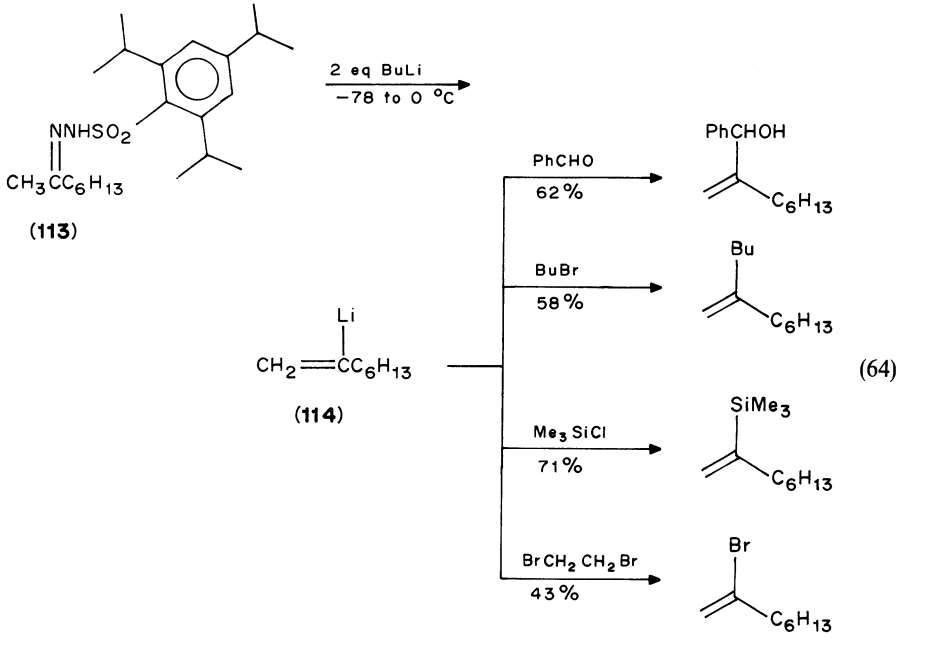
$$\underset{\underset{\text{PrCCH}_2\text{CH}_2\text{Me}}{\|}}{\text{NNHTos}} \xrightarrow[\text{TMEDA}]{\text{LDA}} \underset{55\%\ (E/Z = 8/92)}{\text{PrCH}=\text{CHCH}_2\text{CH}_3} \tag{61}$$



(62)



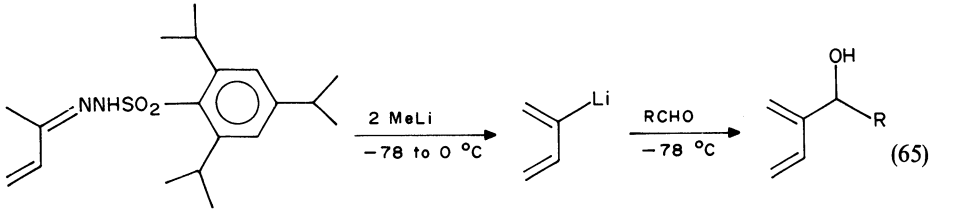
(63)



(64)

When D_2O was added to the vinyllithium reagents derived from ketone tosylhydrazones, deuteriated olefins could be obtained. However, deuterium incorporation is low due to proton abstraction by the vinyllithium reagent from ether solvents and from the tosylhydrazone itself. Stemke and Bond found that TMEDA is an excellent solvent for the deuterium reaction and nearly quantitative yields of olefins can be obtained as illustrated in equations 62 and 63[56]. The reactions were run on benzenesulfonylhydrazones rather than on tosylhydrazones to eliminate the possibility of abstraction of benzylic hydrogen by the vinyllithium reagent. The same authors also found that 2,4,6-triisopropylbenzenesulfonylhydrazones have added advantages, because (i) there is no evidence for benzylic metallation even with excess base, (ii) the dianion can be rapidly generated from **113** and (iii) only 1.0–1.2 equivalents of electrophile are required. The vinyllithium reagent **114** so generated can be trapped with a variety of electrophiles as shown in equation 64[56].

2-Lithio-1,3-butadiene (**116**) can be generated by using the 2,4,6-triisopropylbenzenesulfonylhydrazone **115** derived from vinyl ketone and trapped with a variety of aldehydes to give dienylalcohols **117** as shown in equation 65[57].

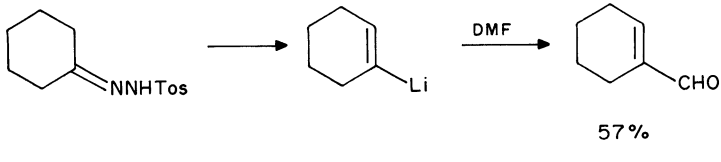


(65)

(**115**) (**116**) (**117**) 32—55%

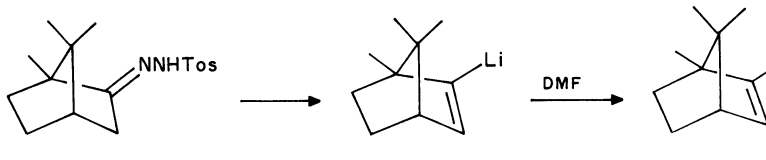
3. *Preparation of α,β-unsaturated aldehydes*

Trapping reactions of vinyllithium derivatives generated from tosylhydrazones with DMF in TMEDA produce α,β-unsaturated aldehydes in 10–65% yields as illustrated in equations 66 and 67[54,58].



57%

(66)

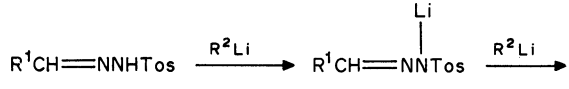


10%

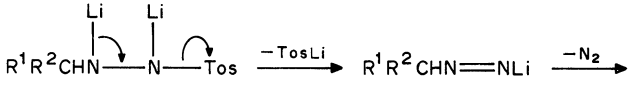
(67)

B. Aldehyde Arenesulfonylhydrazones

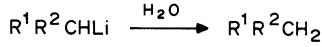
Although it is not possible to generate dianions from aldehyde tosylhydrazones (**118**), alkyllithium reagents add readily to the tosylhydrazone C=N linkage to give **119**. The adduct **119** fragments to the organolithium species **120** and aqueous workup affords the reductive alkylation product **121** as shown in equation 68. Other examples for the conversion of aldehydes RCHO into reductive alkylation products RCH_2R^1 via the tosylhydrazones are illustrated in equations 69–71[59].



(118)



(119)



(120) **(121)** (68)

$$PhCH_2CH_2CH{=}NNHTos \xrightarrow[THF,\ -78\,^{\circ}C]{n\text{-BuLi}} Ph(CH_2)_3Bu\text{-}n \quad (69)$$

49%

$$PhCH_2CH{=}NNHTos \xrightarrow[TMEDA,\ 0\,^{\circ}C]{t\text{-BuLi}} PhCH_2CH_2Bu\text{-}t \quad (70)$$

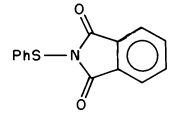
20%

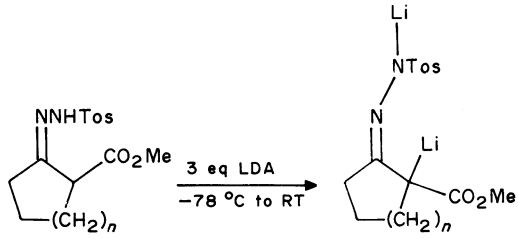
$$PhCH{=}CHCH{=}NNHTos \xrightarrow[THF,\ -22\,^{\circ}C]{t\text{-BuLi}} \begin{matrix} PhCHCH{=}CH_2 \\ | \\ t\text{-Bu} \end{matrix} \quad (71)$$

C. β-Keto Ester Arenesulfonylhydrazones

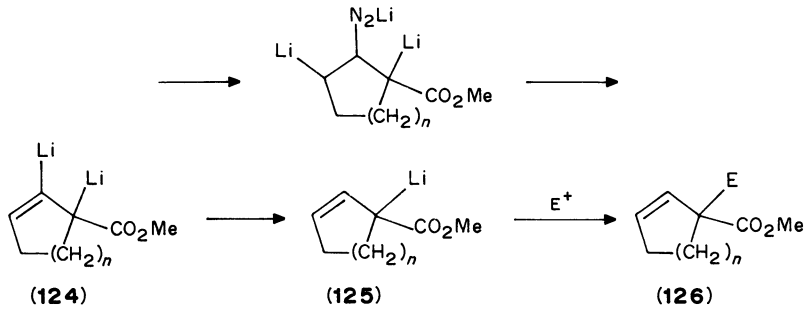
β-Keto ester tosylhydrazones serve as a convenient source of α-functionalized β,γ-unsaturated esters. Thus, the reaction of a variety of β-keto ester tosylhydrazones (containing five-, six- or seven-membered rings, i.e., $n = 1$–3) **122** with 3.1 equivalents of LDA in THF at −78 °C, followed by warming to room temperature, yields α-lithio-β,γ-unsaturated esters **125** (equation 72). When the reaction mixture of **125** was quenched with various electrophiles, α-functionalized β,γ-unsaturated esters **126** were available as shown in Table 6[60].

TABLE 6. Preparation of α-functionalized β,γ-unsaturated esters according to equation 72

	Electrophile (EX)	Yield (%)
$n=1$	MeI	64
$n=1$	$PhCH_2Br$	49
$n=1$		53
$n=2$	MeI	79
$n=3$	MeI	80



(122) (123)

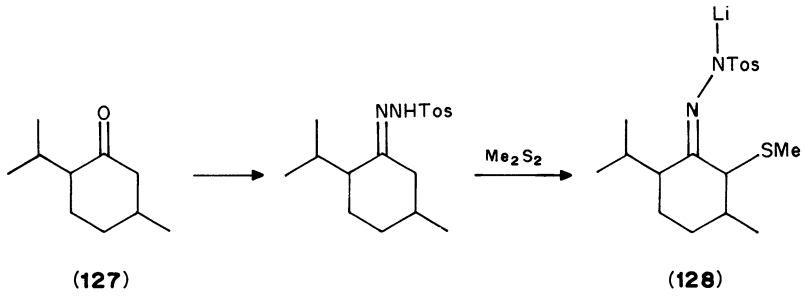


(124) (125) (126)

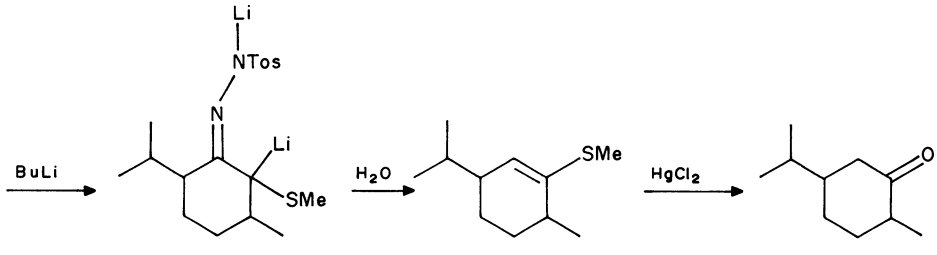
(72)

D. 1,2-Carbonyl Transposition

A new procedure for regioselective 1,2-carbonyl transposition using arenesulfonylhydrazones is reported. Thus, when the dianion derived from the tosylhydrazone of **127** is treated with dimethyl disulfide, the sulfide **128** is obtained regioselectively. The latter, upon treatment with BuLi, produces a deep-red solution of the dianion, which on aqueous workup gives the vinyl sulfide **129**. From this, ketone **130** is obtained by treatment with mercuric chloride in hot aqueous acetonitrile (equation 73)[61]. A similar example is shown in equation 74.

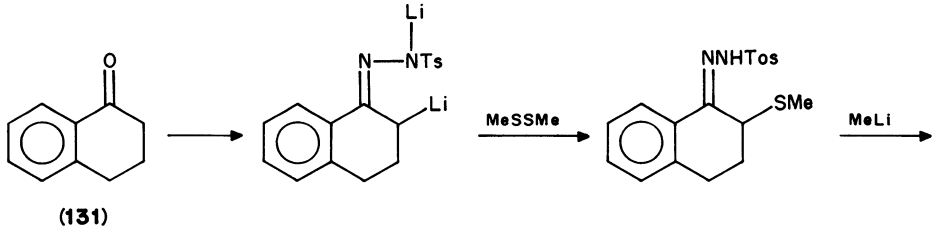


(127) (128)

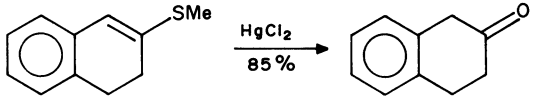


(129) 48% (130) 98%

(73)



(131)

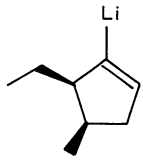


(74)

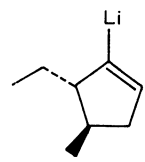
(132)

E. Applications to Natural Products

Cis- and *trans*-4-methyl-5-ethylcyclopentenyllithium reagents (**133** and **134**) serve as building blocks for the preparation of complex natural products such as ikarugamycin. The lithium reagents can be generated from their tosylhydrazones and alkyllithium. In contrast, the corresponding triisopropylbenzenesulfonylhydrazones are not suitable for

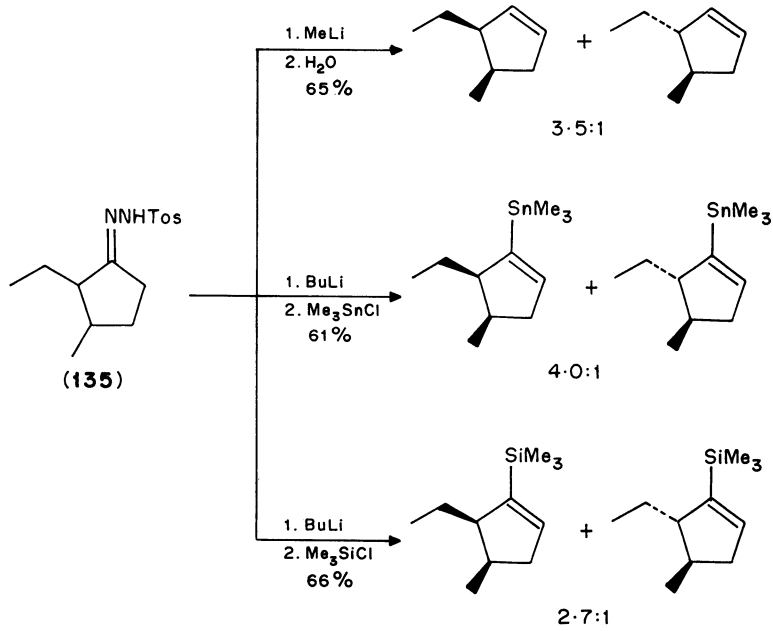


(133)



(134)

the generation of **133** and **134** due to their thermal instability. Trapping with electrophiles gives a mixture of *cis* and *trans* isomers which are separable. Conversion to the iodides and subsequent halogen–lithium exchange can also lead to the formation of the desired lithium reagent[62]. The reactions of **135** with electrophiles are shown in equation 75.

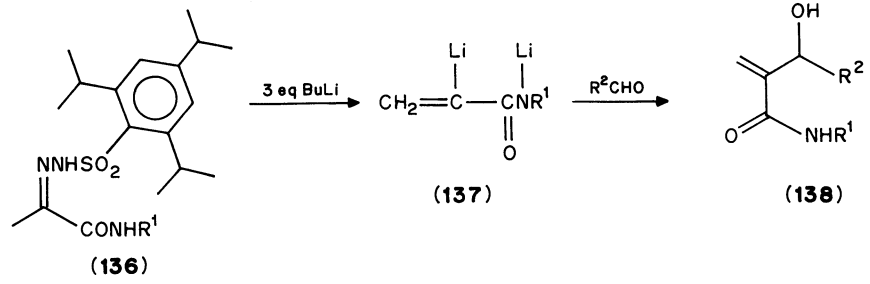


(75)

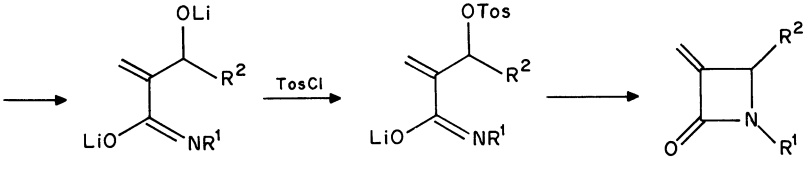
A new method for the preparation of 3-methylene-azetidine-2-one using 2,4,6-triisopropylbenzenesulfonylhydrazone has recently been reported by Barrett and coworkers[63]. The α-lithioacrylate **137** is generated on treatment of the 2,4,6-triisopropylbenzenesulfonylhydrazone of an α-keto amide (**136**) with excess of buLi in DME. The reactions of **137** with aldehydes give 3-hydroxy-2-(methylene)alkanamides **138**, which on treatment with tosyl chloride in THF give the 3-methylene-β-lactams **139** in good yields (equation 76)[63].

α-Methylene-γ-butyrolactones are prepared by a similar procedure. The reaction involves lithiation of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone (**140**) and carbonylation of vinyllithium reagent **142** as shown in equation 77[64].

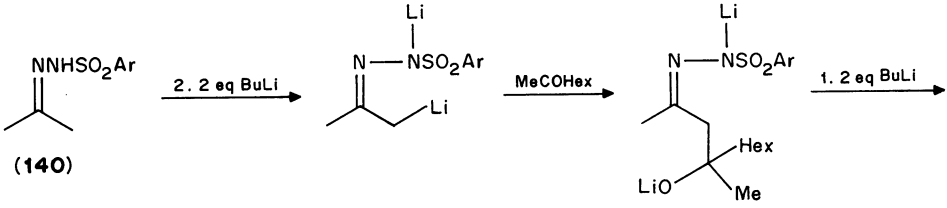
3-Methylene-, 3,6-dimethylene-tetrahydropyran-2-one and 3,5-dimethylenetetrahydrofuran-2-one derivatives are prepared by similar sequences as shown in equation 78[65,66].



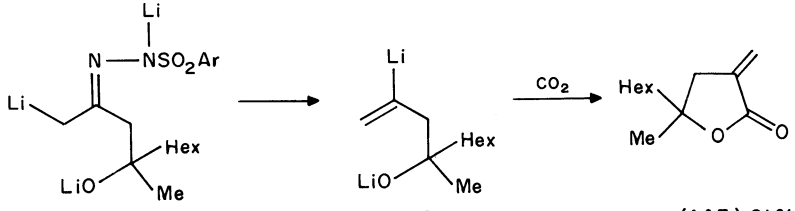
(136) (137) (138)



(139) (76)

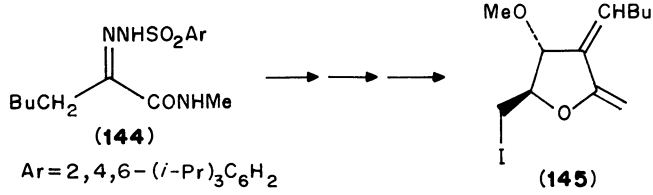


(140) (141)



(142) (143) 61% (77)

Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$



(144) (145) (78)

Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

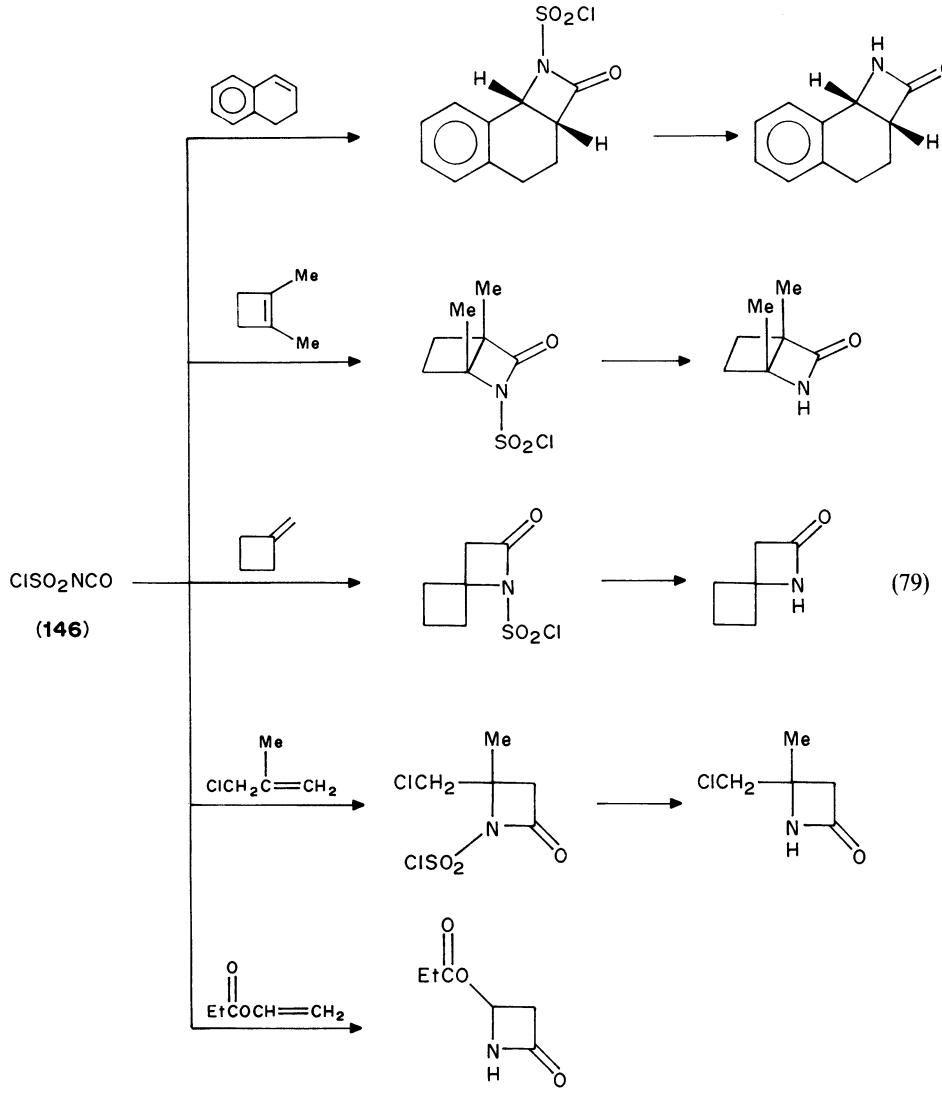
VIII. SULFONYL ISOCYANATES AS SYNTHONS

A. Reaction with Olefins

Chlorosulfonyl isocyanate (**146**, abbreviated as CSI) is a highly reactive isocyanate. It is a colorless, rather stable oil of bp 107–108 °C/760 mm Hg, first prepared by Graf in 1956 from sulfur trioxide and cyanogen chloride[67].

CSI (**146**) undergoes [2 + 2]cycloaddition to a variety of olefins and hydrolysis of the adducts gives β-lactams[68].

The addition of CSI to 1,2-dihydronaphthalene in ether gives in 76% yield a white

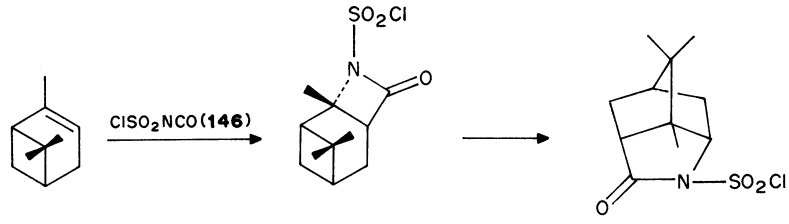


(79)

crystalline adduct[69]. Removal of the chlorosulfonyl group was accomplished with benzenethiol in pyridine to give β-lactams in 46% yield (equation 79)[70,71].

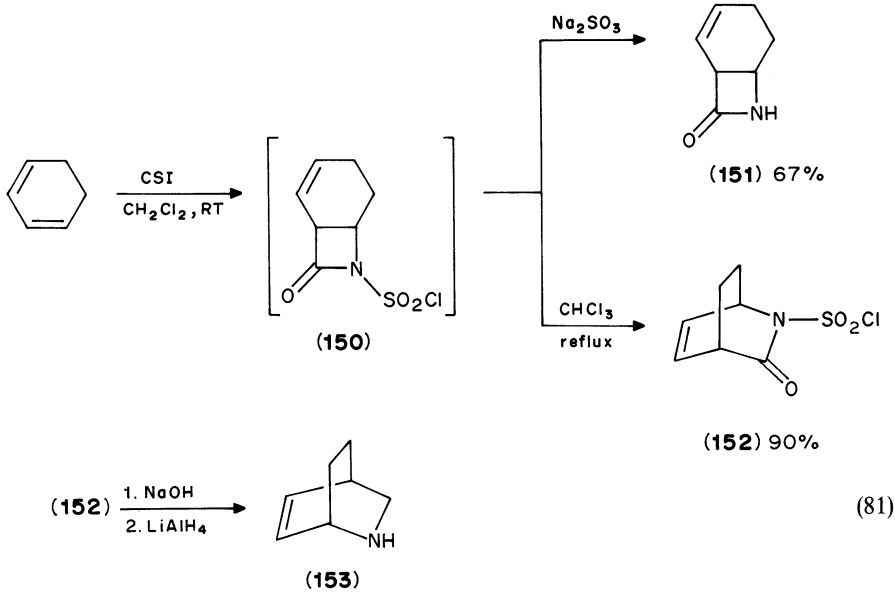
4-(Acyloxy)azetidin-2-ones are prepared by reaction of vinyl esters with CSI (equation 79). The nucleophilic displacement of the acyloxy group occurs readily yielding 4-thio-, 4-alkyloxy-, 4-azido-, 4-diethylphosphinoyl- and 4-arylsulfonyl-β-lactams[72].

Concerted addition of CSI to α-pinene at −70 °C gives 3-chlorosulfonyl-2,8,8-trimethyl-3-azatricyclo[5.1.1.$0^{2,5}$]nonan-4-one **148** in 75% yield which rearranges on standing overnight at room temperature to give **149** in 60% yield (equation 80)[73–75].



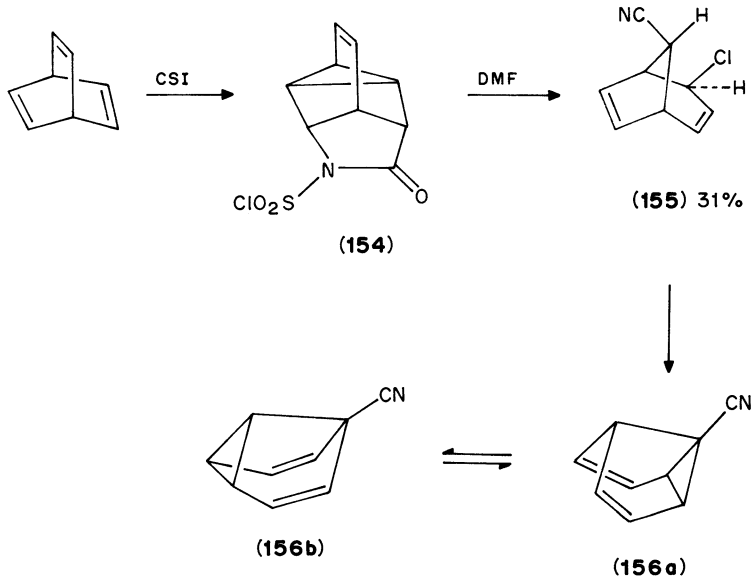
(147) (148) 75% (149) 60% (80)

Unsaturated *N*-chlorosulfonyl-β-lactams are generally unstable and readily rearrange to the product of formal 1,4-addition. Thus, the reaction of 1,3-cyclohexadiene with CSI at room temperature affords a quantitative yield of adduct **150**. Hydrolysis of **150** with benzenethiol in the presence of pyridine gives **151** in 67% yield. When the reaction mixture of CSI and 1,3-cyclohexadiene was refluxed in chloroform, **152** was formed in 90% yield as a viscous oil. Hydrolysis of **152** with aqueous NaOH gave *N*-unsubstituted lactams in 35% yield. 2-Azabicyclo[2.2.2]octene (**153**) can be conveniently prepared by reduction of **152** with $LiAlH_4$ after hydrolysis (equation 81)[76].



(81)

Mixing of equimolecular quantities of barrelene and CSI in dichloromethane solution at − 78 °C followed by gradual warming to room temperature leads to the formation of *N*-(chlorosulfonyl)-*β*-lactam **154** in 74% yield. Heating the latter in DMF at 75–95 °C for 40 h gave the chloronitrile **155** in 31% yield, which on treatment with *t*-BuOK in DMSO–THF gave the semibullavalene **156** in 56% yield as indefinitely stable colorless needles (equation 82)[77].



(82)

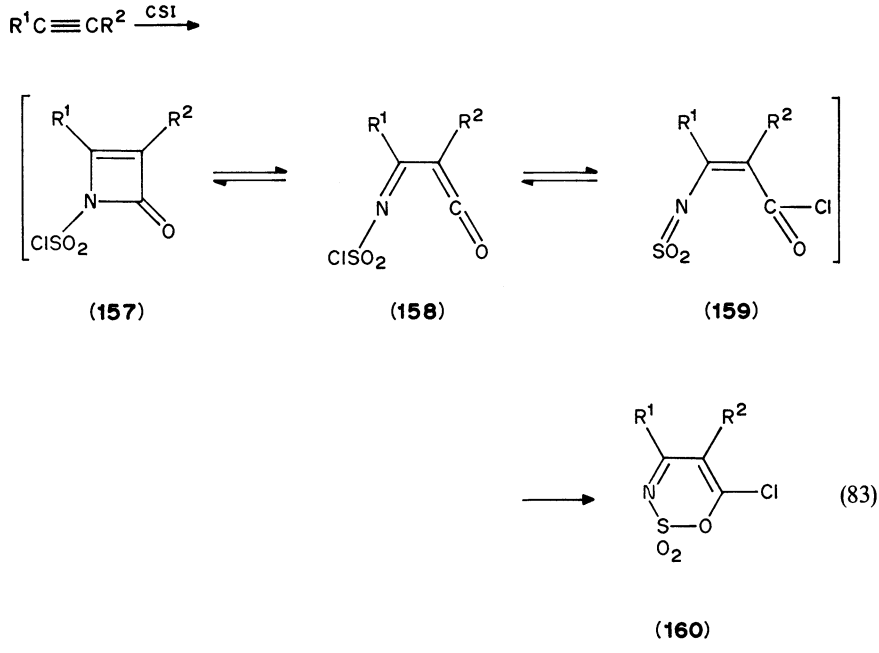
B. Reaction with Acetylenes

Addition of CSI to acetylenes occurs at room temperature to give 1,2,3-oxathiazine 2,2-dioxides **160** (equation 83). The formation of **160** was rationalized by a sequence of cycloaddition to yield **157**, electrophilic ring opening to the ketene-imine-*N*-sulfonyl chloride **158**, 1,5-sigmatropic halogen shift to give **159** and electrophilic ring closure[78]. The yields of **160** are shown in equation 83.

The difference in reactivity of halosulfonyl isocyanates is shown in equation 84. The reaction of **146** with 2-butyne gave the [2 + 2]adduct in moderate yield, which was hydrolyzed to **163** by treatment with methanol. In contrast, 2 equivalents of fluorosulfonyl isocyanate reacted with 2-butyne to give a six-membered heterocycle, which on hydrolysis rearranged to **162**[79].

C. Reaction with Strained Hydrocarbons

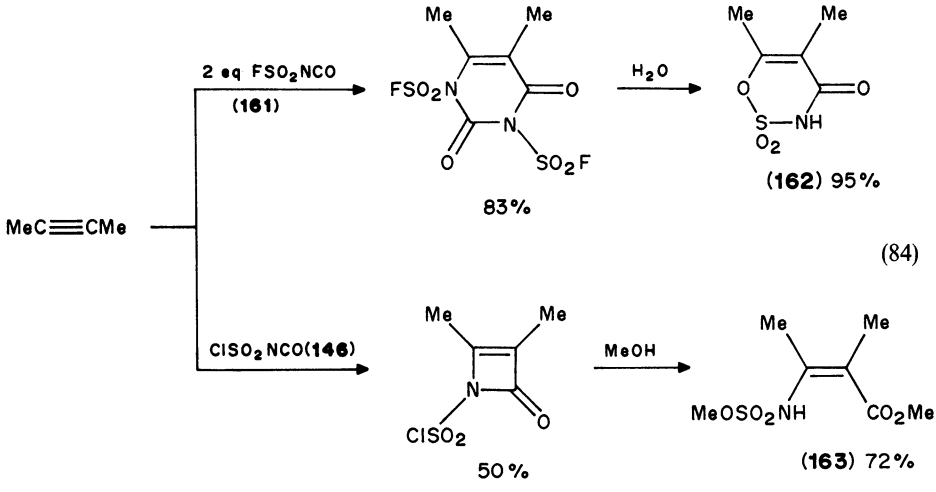
Paquette and coworkers have reported the reaction of CSI with some compounds bearing sigma bonds rich in *p* character[80]. The more highly strained 1,3 bond of **164** is first ruptured by backside attack at C_3 to produce to the more stable carbonium ion **165**, which rapidly rearranges to **166**, leading to the formation of a five-membered lactam **167** as illustrated in equation 85.



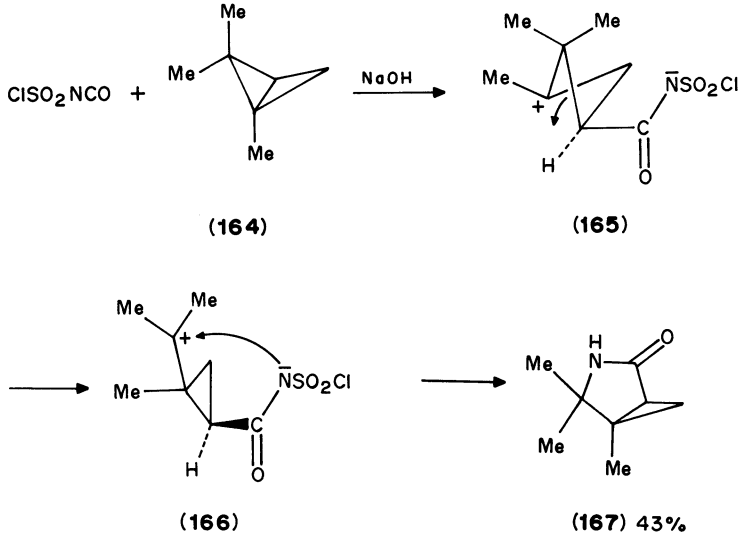
(157) (158) (159) (160)

(83)

R^1	R^2	Yield (%)
Me	Me	42
Et	Et	95
Pr	Pr	86
Ph	Ph	86
Ph	H	48



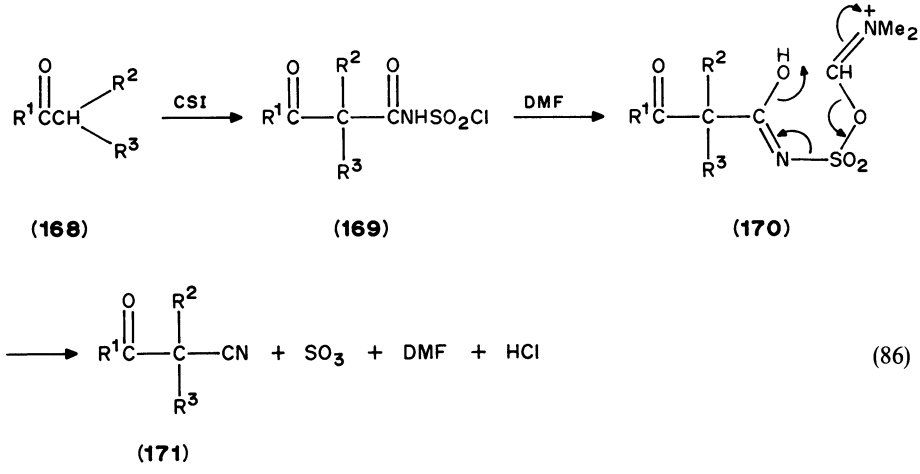
(84)



(85)

D. Preparation of Nitriles

The reaction of CSI with ketones produces *N*-chlorosulfonyl-β-ketocarboxamides **169**, which upon treatment with DMF give β-ketonitriles **171**, important intermediates for the synthesis of many heterocyclic compounds (equation 86)[81]. The examples are shown in Table 7.



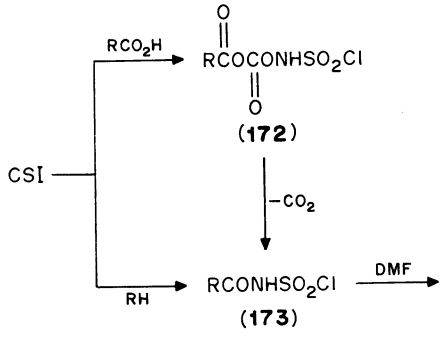
(86)

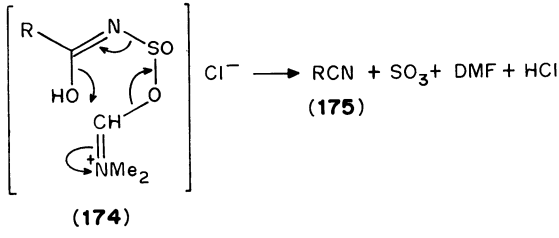
A procedure for the preparation of nitriles from carboxylic acids or heterocycles via *N*-chlorosulfonylcarboxamides (**173**) is illustrated in equation 87. The reaction of carboxylic acids with CSI gives adduct **172**, which loses CO_2 to give *N*-chlorosulfonylcarboxamide

TABLE 7. Preparation of α-cyanoketones

R^1	R^2	R^3	Yield (%)
Ph	Me	H	90
Et	Me	H	71
Me	Me	H	63
Me	MeCO	H	70
	$-(CH_2)_3-$	H	54
	$-(CH_2)_4-$	Me	69

173. Treatment of **173** with DMF affords the corresponding nitriles in good yields (equations 88 and 89)[82].

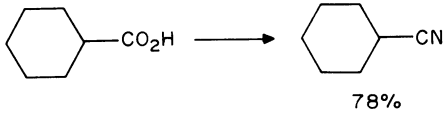




(87)

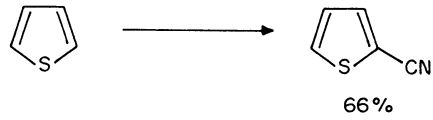
$$MeCH{=}CHCH{=}CHCO_2H \longrightarrow MeCH{=}CHCH{=}CHCN \quad (88)$$

76%

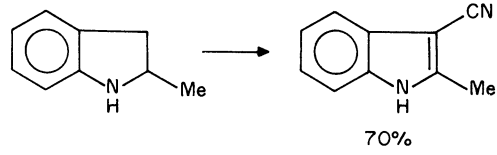


(89)

Electrophilic reaction of heterocycles, such as thiophene or indole, with equimolar amounts of chlorosulfonyl isocyanate in dry ether or acetonitrile at 0–5 °C produces *N*-chlorosulfonyl-substituted heterocycles (**173**), which on treatment with DMF gave nitriles in good yields (equations 90 and 91)[83].



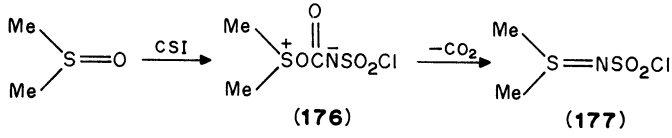
(90)



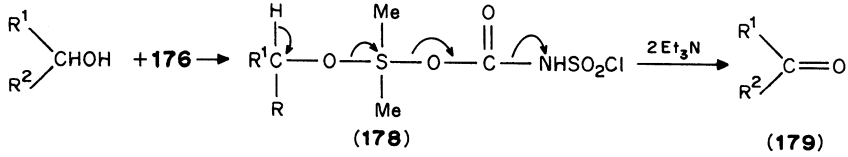
(91)

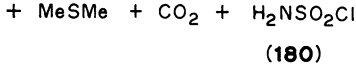
E. Oxidation of Alcohols

The reaction of CSI with DMSO at $-78\,^{\circ}C$ in dichloromethane gave a zwitterionic complex **176** containing an electrophilic sulfur atom. At higher temperature the complex



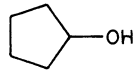
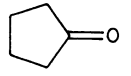
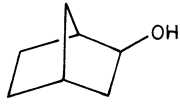
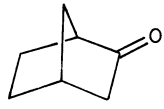
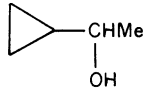
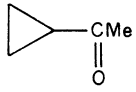
(92)





(93)

TABLE 8. Oxidation of alcohols by chlorosulfonyl isocyanate (**146**)

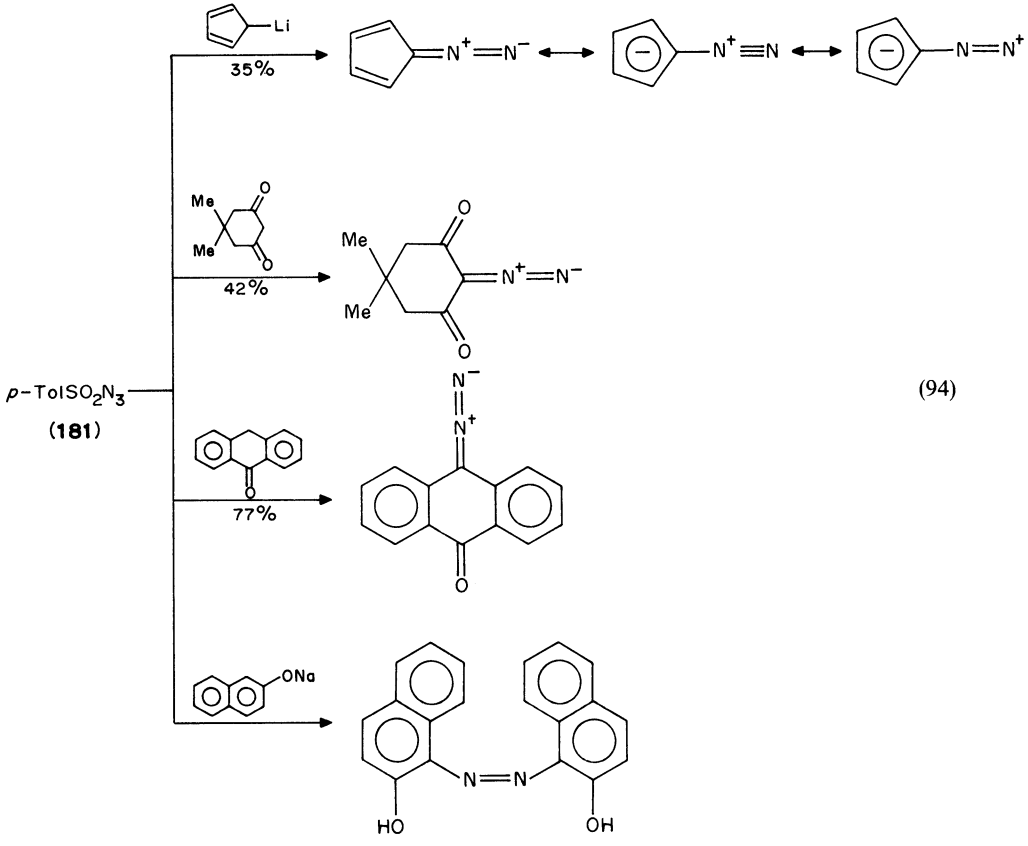
Alcohol	Product	Yield (%)
		81
		86
$PhCH{=}CHCH_2OH$	$PhCH{=}CHCHO$	69
		70

176 decomposed to *N*-(chlorosulfonyl)dimethylsulfonimide **177** with loss of CO_2 (equation 92)[84]. Treatment of **176** with alcohols at − 78 °C in the presence of triethylamine gave the corresponding carbonyl compounds (**179**) in good to high yields (equation 93). Preparation of aldehydes or ketones from some alcohols is shown in Table 8.

IX. SULFONYL AZIDES AS SYNTHONS

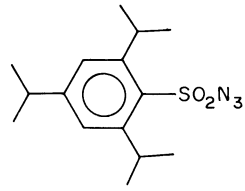
A. Diazo Transfer Reaction

p-Toluenesulfonyl azide (**181**) is an efficient diazo transfer reagent which is prepared from tosyl chloride and sodium azide in 83% yield, mp 22 °C[85]. Diazo transfer reaction from tosyl azide to methylene groups flanked by two electron-withdrawing substituents, such as malonic esters, β-diketones or benzyl ketones, proceeds smoothly, giving high yields of diazo derivatives. Some examples of the diazo transfer reaction are illustrated in equation 94[86].

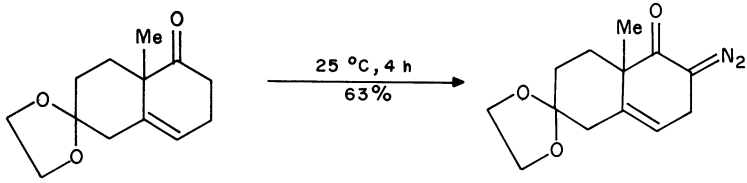


(94)

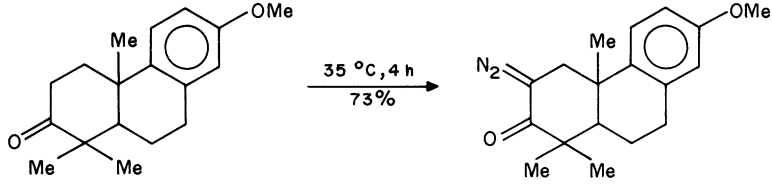
By contrast, less acidic substrates such as simple ketones cannot be converted directly to α-diazoketones by tosyl azide. However, when 2,4,6-triisopropylbenzenesulfonyl azide (**182**) was substituted for tosyl azide, the phase-transfer method gave good results with a



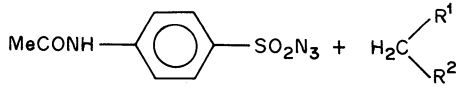
(182)



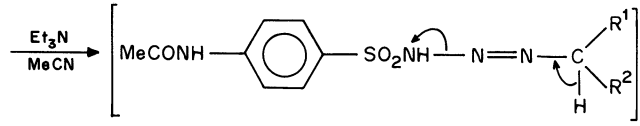
(95)

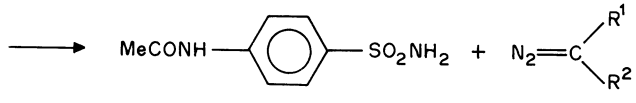


(96)



(183) (184)





(185)

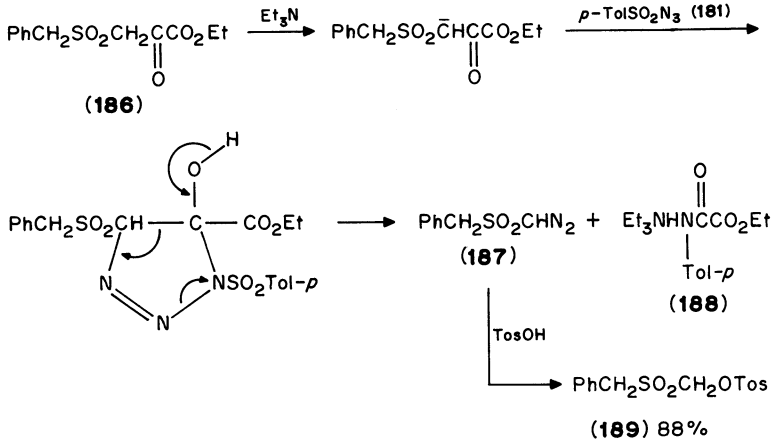
(97)

R^1	R^2	Yield (%)
CO_2Me	CO_2Me	95
COMe	CO_2Et	84
CO_2Et	$CH{=}CHCO_2Et$	84

variety of cyclic ketones[87]. The use of other arylsulfonyl azides, such as mesityl, 4-chlorophenyl, 4-nitrophenyl and 2,4-dinitrophenyl, was found to be unsatisfactory. Tetrabutylammonium bromide and 18-crown-6 catalysts are used in combination and the results are shown in equations 95 and 96.

p-Acetamidobenzenesulfonyl azide (**183**, *p*-ABSA) is a relatively safe reagent and offers advantages over the other alternatives such as tosyl azide[88]. *p*-ABSA can be prepared as a solid of mp 106–108 °C in 73% from *p*-acetamidobenzenesulfonyl chloride and sodium azide in acetone or in methylene chloride–water under phase-transfer conditions. The reaction with active methylene compounds is shown in equation 97.

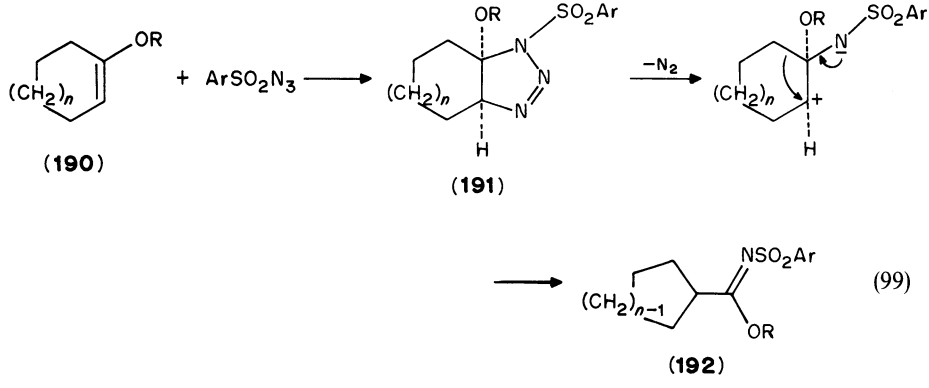
When tosyl azide is treated with ethyl (benzylsulfonyl)pyruvate **186** in the presence of triethylamine[89], benzyl diazomethyl sulfone (**187**) is obtained in 64% yield via the intermediate (equation 98). The latter serves as a useful reagent for the preparation of benzyl tosyloxymethyl sulfone (**189**) from *p*-toluenesulfonic acid.



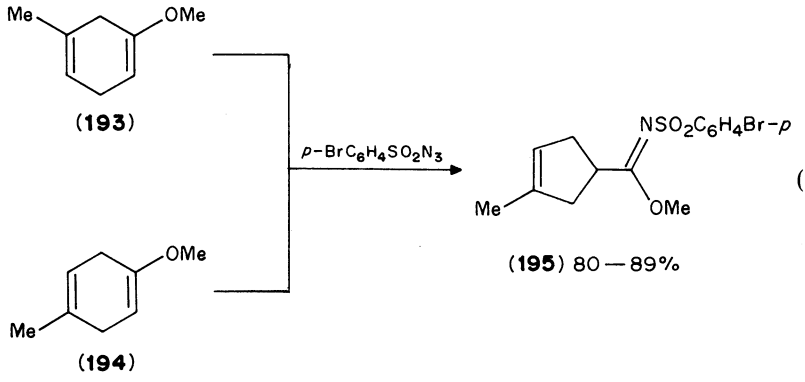
(98)

B. Ring Contraction of Cyclic Enol Ethers

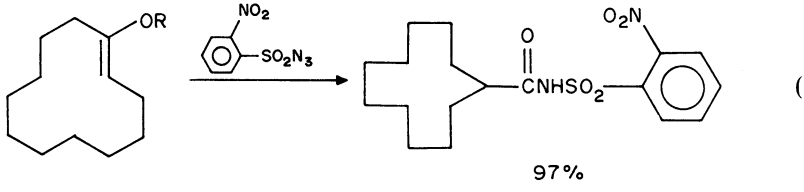
Arenesulfonyl azides react at ambient pressure with enol ethers of simple cyclic ketones to give ring contracted arenesulfonylimidate esters in good yields (equation 99)[90]. The addition–rearrangement is highly stereoselective as shown in equations 100–102.



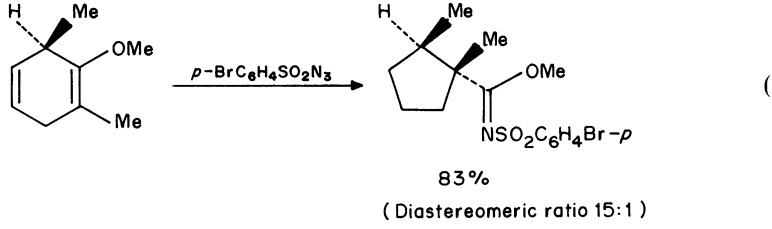
(99)



(100)



(101)



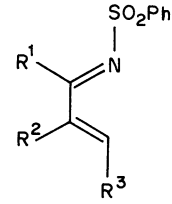
(102)

X. SULFONYL IMINES AS SYNTHONS

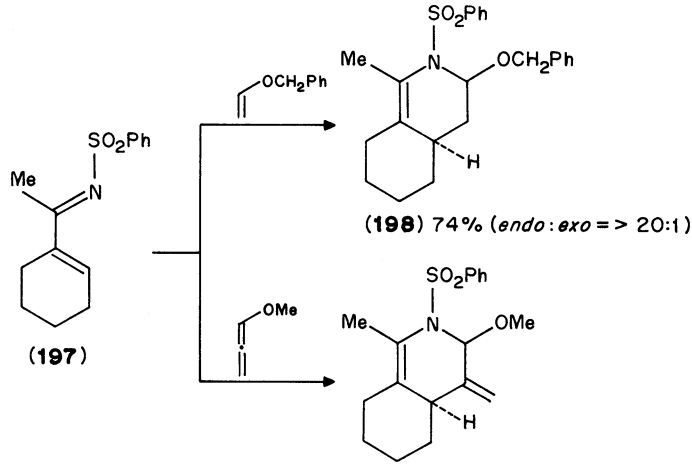
A. [2 + 2]Cycloaddition Reaction

α,β-Unsaturated *N*-benzenesulfonylimines (**196**) are highly reactive enophiles in [4 + 2]cycloaddition reactions and serve as 1-aza-1,3-butadiene synthons as illustrated in equation 103[91]. In contrast, oximes or *O*-methyloximes do not react even under high pressure. The *N*-benzenesulfonylimines are readily accessible through the rearrangements of the *in situ* generated *o*-phenylsulfinyl compounds or through the direct condensation of benzenesulfonamide with α,β-unsaturated aldehydes.

N-Benzenesulfonyl aldimines (R^1 = H in **196**) are more reactive than *N*-benzenesulfonyl ketimines (R^1 = Me or Ph in **196**) and electron-withdrawing substituents at C-3 ($R^2 = CO_2R$) accelerate the cycloaddition[91]. Thus **200**, possessing an additional C-3 electron-withdrawing substituent, reacts with 1,1-dimethyloxyethylene within 5 minutes at 25 °C to give the adduct **201** in 79% yield (equation 104).



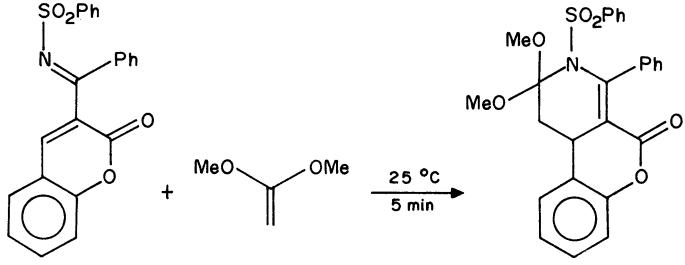
(196)



(198) 74% (*endo*:*exo* = > 20:1)

(199) 23% (*endo*:*exo* = > 20:1)

(103)

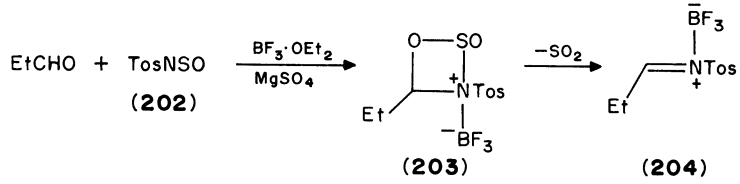


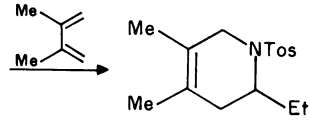
(200) (201) 79%

(104)

B. [4 + 2]Cycloaddition Reaction

N-Tosylimine is a powerful dienophile in the imine Diels–Alder reaction which provides an efficient route to tetrahydropyridines[92,93]. Thus, the treatment of propionaldehyde with *N*-sulfinyl-*p*-toluenesulfonamide (**202**) and BF_3 etherate gives [2 + 2]adduct **203**, which loses sulfur dioxide to afford a Lewis acid complexed iminium salt **204**. The iminium

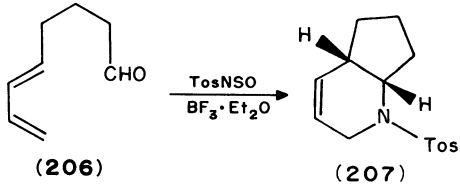




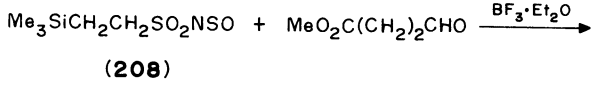
(105)

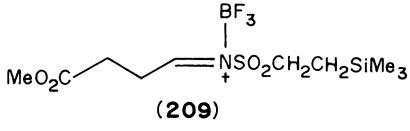
salt is trapped with 2,3-dimethylbutadiene to give the tetrahydropyridine **205** in 79% yield as shown in equation 105.

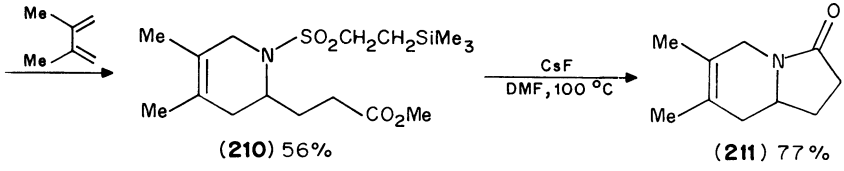
Intramolecular cycloaddition leads to the formation of 2-azabicyclo[4.3.0]nonane **207** (equation 106). When *N*-sulfinyl-2-(trimethylsilyl)ethanesulfonamide (**208**) is used in the imine Diels–Alder reaction, the 2-(trimethylsilyl)ethanesulfonyl group of **210** can be readily removed by cesium fluoride in DMF (equation 107).



(106)



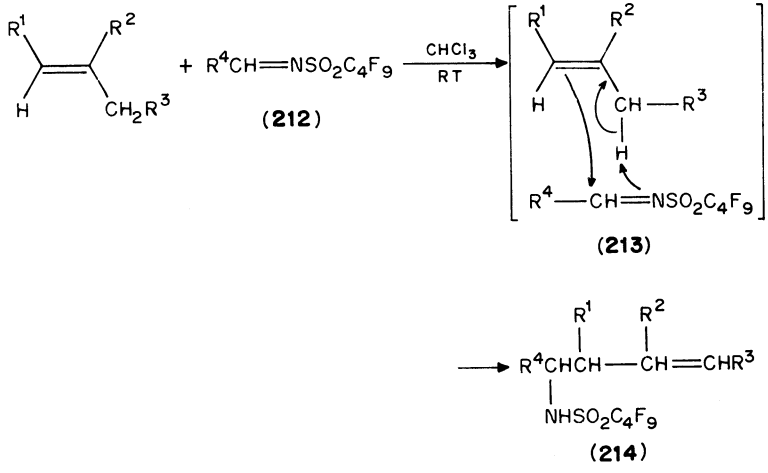




(107)

C. Ene Reaction

N-Perfluoroalkanesulfonyl imines are reactive enophiles compared to *N*-tosyl imines. The imines **212** can be prepared by treatment of butyl glyoxalate or anhydrous chloral with *N*-sulfinyl-*N*-nonafluorobutanesulfonamide[94]. In chloroform solution, the imine **212** reacts smoothly with alkenes at room temperature to give allylglycine derivatives **214** in fair to good yields as shown in equation 108. The results of the ene reactions are summarized in Table 9.



(108)

TABLE 9. Preparation of **214** by ene reaction

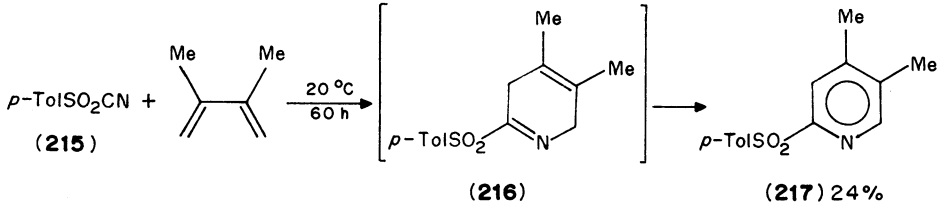
R^1	R^2	R^3	R^4	Yield (%)
H	H	Ph	BuO_2C	90
H	H	Ph	Cl_3C	77
H	Cl	H	Cl_3C	90
Me	Me	H	BuO_2C	78
Me	Me	H	Cl_3C	67

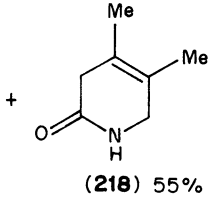
XI. MISCELLANEOUS SYNTHONS

A. Sulfonyl Cyanides as Synthons

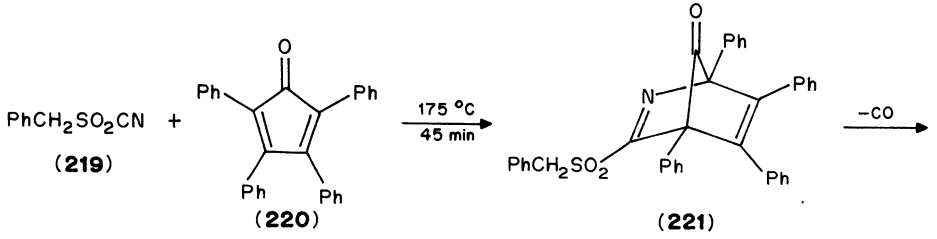
While organic cyanides normally display rather low reactivity as dienophiles in [4 + 2]cycloaddition reaction, sulfonyl cyanides are the most reactive cyanodienophiles towards simple acyclic dienes. The sulfonyl cyanides are prepared from the corresponding sodium sulfinates and cyanogen chloride[95]. The reaction of **215** with 2,3-dimethyl-1,3-butadiene occurs even at room temperature to give 2-tosylpyridine **217** and dihydropyridone **218** the latter via the hydrolysis of intermediate **216** (equation 109)[96].

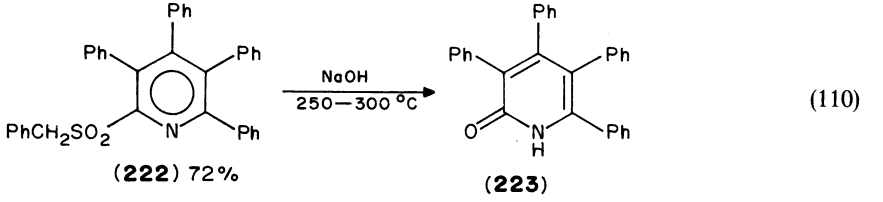
In contrast, the reaction with isoprene, 1,3-butadiene or tetracyclone requires a higher reaction temperature. For example, the reaction with tetracyclone occurs at 175 °C





(109)





(110)

(equation 110). The loss of carbon monooxide from the initial adduct **221** gave **222** whose structure was confirmed by conversion into the known 3,4,5,6-tetraphenyl-2-pyridone **223**.

B. Sulfonyl Thiocyanates as Synthons

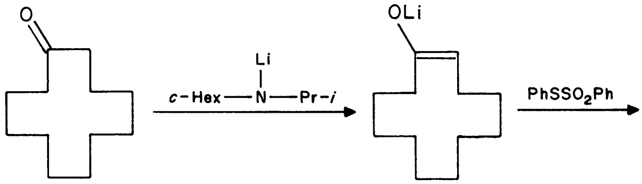
Sulfonyl thiocyanates undergo free radical addition to olefins or acetylenes to give β-thiocyanate sulfones in fair to good yields (equation 111)[97]. *p*-Toluenesulfonyl thiocyanate (**224**) is prepared from sodium *p*-toluenesulfinate and thiocyanogen in benzene

solution as a moderately stable whilte solid, mp 37–39 °C, and undergoes only slow decompsotion when stored in a refrigerator. The β-thiocyanate sulfones **225** can be converted to α,β-unsaturated sulfones in high yields on treatment with sodium borohydride.

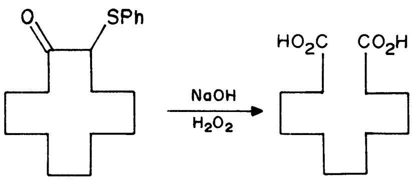
$$\underset{}{PhCH{=}CH_2} + \underset{\textbf{(224)}}{p\text{-}TolSO_2SCN} \longrightarrow \underset{\textbf{(225)}\quad 43\%}{PhCH(SCN)CH_2SO_2Tol\text{-}p} \qquad (111)$$

C. Thiolsulfonates as Synthons

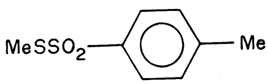
β-Keto sulfides such as **227** are versatile intermediates in organic synthesis, which give 1,2-diketones or *p*-acetoxy-α,β-ketones on acetoxylation by lead tetraacetate. The diacid **228** is obtained in good yields when the β-keto sulfides are treated with basic hydrogen peroxide (equation 112)[98]. Phenyl benzenethiolsulfonate is the reagent of choice for preparation of the β-ketosulfide **227** from enols since, with methyl *p*-toluenethiolsulfonate (**229**) and methyl methanethiolsulfonate (**230**), the abstraction of hydrogen from the methyl group is a serious problem[99,100].



(**226**)



(**227**) (**228**) (112)

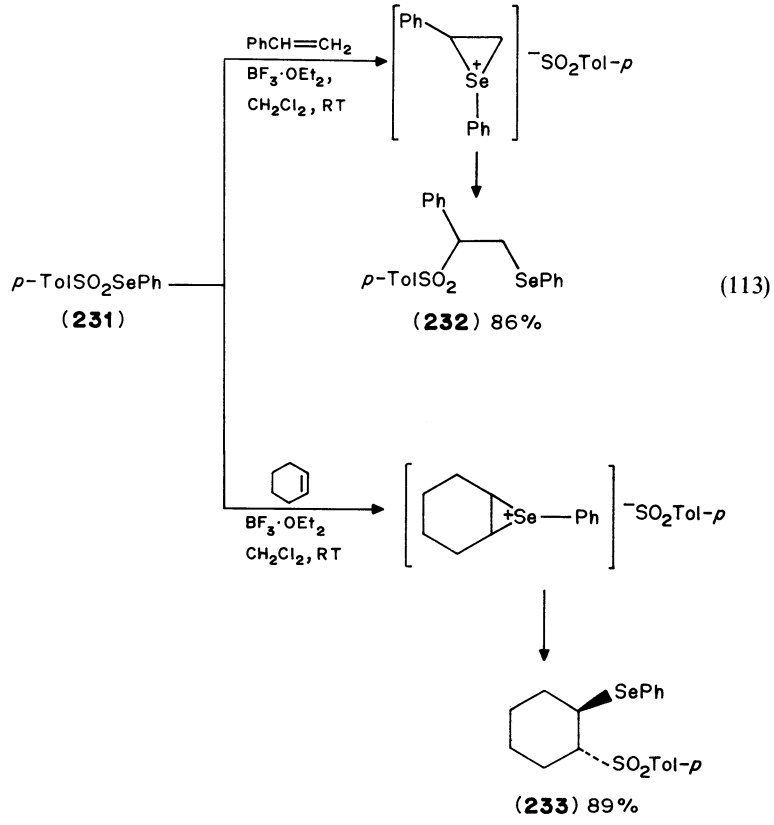


$MeSSO_2Me$

(**229**) (**230**)

D. Selenolsulfonates as Synthons

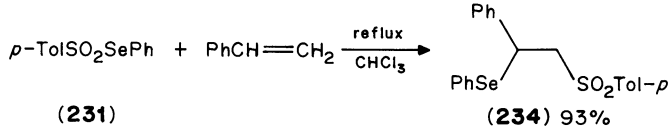
Back and Collins found that selenolsulfonates **231** reacted with a variety of unhindered olefins to afford novel β-phenylselenosulfones (**232** and **233**) in a highly regio- and stereoselective fashion as shown in equation 113[101]. The selenolsulfonates can be



(113)

prepared by the addition of a dichloromethane solution of a sulfonylhydrazide to a suspension of benzeneseleninic acid in dichloromethane; *p*-TolSO$_2$SePh (92%, mp 56–58 °C), Mesityl SO$_2$SePH (92%, 80 °C), *p*-MeOC$_6$H$_4$SO$_2$SePh (83%, 79–80 °C), *m*-NO$_2$C$_6$H$_4$SO$_2$SePh (82%, 125–127 °C), 2,4-(NO$_2$)$_2$C$_6$H$_3$SO$_2$SePh (68%, 147–150 °C) and MeSO$_2$SePh (65%, 88–90 °C) were these obtained[102].

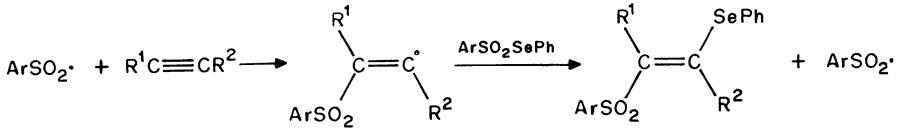
The reaction of **231** with styrene was catalyzed by boron trifluoride to give the Markovnikoff adduct **232** (equation 113), while the addition of **231** to cyclohexene gave solely the *trans* adduct **233**. The uncatalyzed reaction with styrene afforded the anti-Markovnikoff adduct **234** (equation 114). The reaction of selenolsulfonates with acetylenes proceeds in refluxing benzene or chloroform without boron trifluoride etherate[103,104], and produces only a single adduct **237** in a stereo- and regioselective fashion (equation 115). The addition of selenolsulfonates to acetylenes is shown in Table 10. When



(114)

$$ArSO_2SePh \xrightarrow{heat} ArSO_2\cdot + PhSe\cdot$$

(235)



(236) (237) (115)

5 mol% of the radical initiator such as AIBN is added, the reaction is very rapid. This result is consistent with the free radical mechanism indicated in equation 115. β-Selenovinylsulfones **237** serve as useful intermediates for the preparation of γ-sulfonyl substituted α,β-unsaturated dicarbonyls, dinitriles, enzynes, ketene dithioacetals and β-cyanovinyl sulfones, on treatment with *m*-chloroperbenzoic acid followed by reaction with anions like diethyl malonate, ethyl acetoacetate, malononitrile, 1-(trimethylsilyl)propyne, 1,3-dithiane and KCN[105,106].

Table 10. Addition of selenolsulfonates to acetylenes

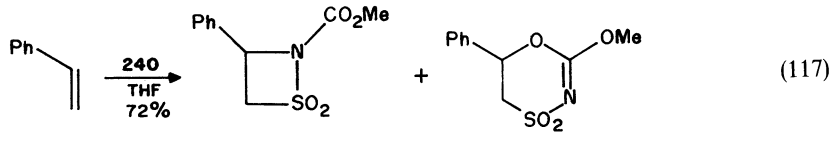
R^1	R^2	Ar	Yield(%)
Ph	H	*p*-Tol	86
$Me(CH_2)_4$	H	*p*-Tol	52
Et	Et	*p*-Tol	75

E. *N*-Sulfonylurethans as Synthons

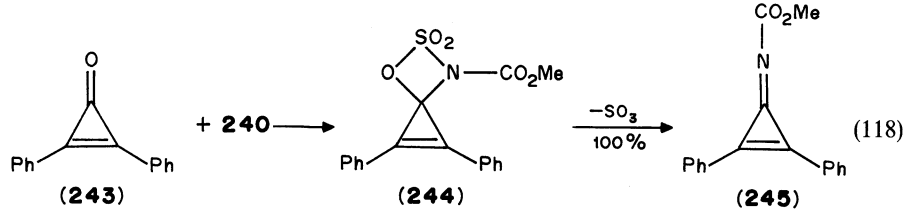
Methyl *N*-sulfonylurethan (**240**) demonstrates a high degree of electrophilic reactivity in cycloadditions with substituted alkenes to give the corresponding 2-methoxycarbonyl-1,2-thiazetidines ([2 + 2]cycloadducts) and 2,3-dihydro-6-methoxy-1,4,5-oxathiazines ([2 + 4]cycloadducts)[107]. Methyl *N*-sulfonylurethan (**240**) can be generated by treatment of methoxycarbonylsulfamoyl chloride (**238**) with sodium hydride at − 78 to 30 °C in THF (equation 116). The reactions of **240** with styrene gives a mixture of **241** and **242** in a ratio

$$MeO_2CNHSO_2Cl \xrightarrow[THF,\,-78\,^\circ C]{NaH} [MeO_2C\bar{N}SO_2Cl]Na^+ \longrightarrow MeO_2CN{=}SO_2$$

(238) (239) (240) (116)



(241) 1:3.1 (242) (117)



of 1:3.1 in 72% overall yield (equation 117) and the reaction of **240** with diphenylcyclopropenone (**243**) leads to the formation of **245** via a [2 + 2]cycloadduct (equation 118).

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CHAPTER 12

Rearrangements

JIM ILEY

Physical Organic Chemistry Research Group, Department of Chemistry, The Open University, Milton Keynes, MK7 6AA, UK

I. INTRODUCTION

Rearrangements of sulphonic acids and their derivatives are many and varied. Surprisingly, though a few reviews exist for sulphonic acids and sulphonamides, this general class of compounds has not been reviewed extensively, particularly as a coherent set. This

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review sets out to remedy that deficiency. The main thrust of the review is to highlight for each functional group the known types of rearrangement and, while there has been an attempt to be comprehensive, certain reactions no doubt have been omitted.

One question that immediately arises in a review of this type is: 'What constitutes a rearrangement?' We have taken the general, though not hard and fast, view that a rearrangement is a reaction in which all of the atoms in the starting material are present in the product. Thus, reactions which involve migration of a group with the extrusion of a small molecule, e.g. SO_2, N_2, do not fall within such a definition. However, there are one or two important reactions of this class involving sulphonic acid derivatives, so for completeness they are discussed briefly. Reactions that are not discussed at all are those in which the sulphonyl group is formed by a rearrangement reaction, and those in which the sulphonyl group, though present in the molecule, has no involvement in the rearrangement process.

There are many ways in which to present the extant information. Two of the most obvious are by rearrangement type or by compound class. The former is potentially more succinct and satisfying from a chemical point of view, while the latter provides easier access to the literature for the reader. This review is organized along the latter lines starting with sulphonic and sulphamic acids, followed by a discussion of their esters, proceeding to thiosulphonates then sulphonamides and sulphamides and finishing with sulphonyl azides. As is clear from this description, we have chosen to include sulphamic acid derivatives though they are not strictly sulphonic acids. This decision can be justified by the common rearrangements and common mechanisms often followed by sulphonic and sulphamic acids and their derivatives. Indeed, in some instances (see Section II), both types of compound are involved in the same rearrangement process.

II. SULPHONIC AND SULPHAMIC ACIDS

Substituted arenesulphonic acids undergo rearrangement upon heating in sulphuric acid, the reaction mixture tending toward an equilibrium distribution of isomers[1]. Thus, the toluenesulphonic acids in 74% sulphuric acid at 141 °C yield a mixture of 2-, 3- and 4-toluenesulphonic acid in which the thermodynamically most stable 3- isomer predominates (Table 1). Table 1 lists the isomer distributions for other arenesulphonic acids, and it is clear that the rearrangement is not confined to substituted benzenesulphonic acids. For some of the entries the equilibrium content of isomers is not specified. This is simply a result of the lack of such information in the original article. In such cases, the isomers are listed such that those listed first undergo rearrangement to those lower on the list. In general the rate of isomerization depends upon the sulphuric acid concentration, for example, increasing from 69 to 74% sulphuric acid for the toluenesulphonic acids but decreasing from 90 to 100% sulphuric acid for benzenedisulphonic acids. These

TABLE 1. Isomer distribution for the rearrangement of some arenesulphonic acids

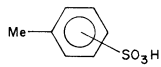
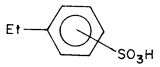
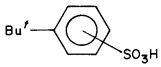
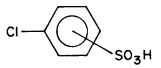
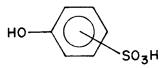
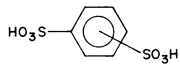
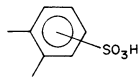
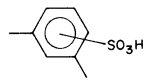
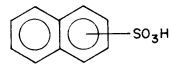
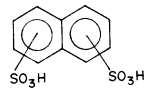
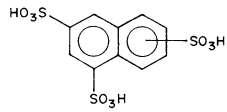
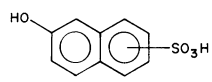
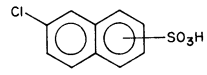
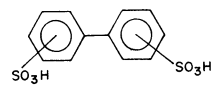
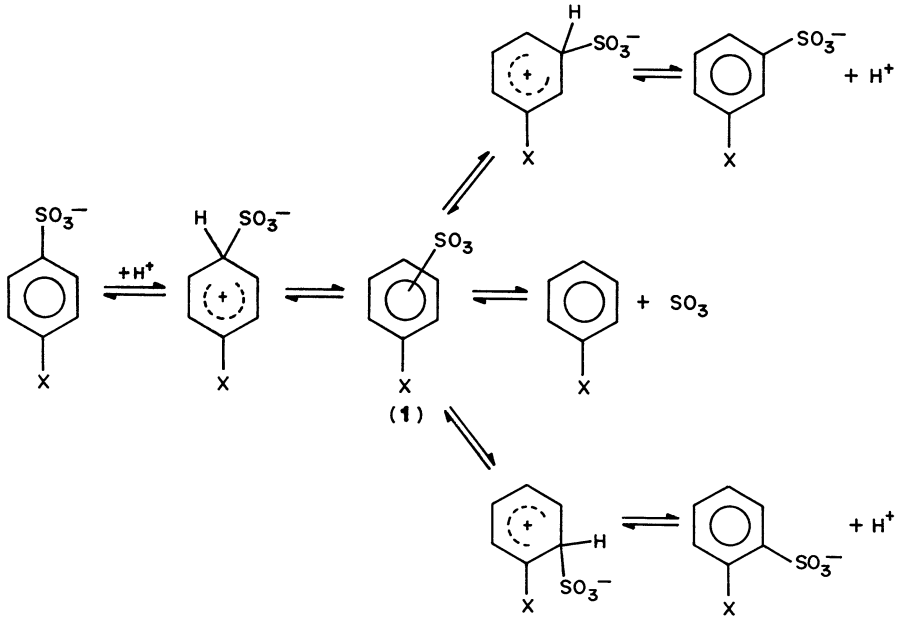
Sulphonic acid	Conditions	Isomers present (%)	Ref.
	74% H_2SO_4 141 °C	2- (3.2) 3- (59.6) 4- (37.2)	1
		2- (1.2) 3- (57.9) 4- (40.9)	2

TABLE 1. (*continued*)

Sulphonic acid	Conditions	Isomers present (%)	Ref.
	74% H_2SO_4 141 °C	3- (66) 4- (34)	1
	79% H_2SO_4 222 °C	3- (55) 4- (45)	1
	55% H_2SO_4 160 °C	2- (2-3) 3- (48) 4- (50)	3
	87% H_2SO_4 235 °C	3- (66.3) 4- (33.7)	1
	74% H_2SO_4 141 °C	3- (2.0) 4- (98.0)	4
	74% H_2SO_4 141 °C	2- (0) 4- (18.1) 5- (81.9)	4,5
	85% H_2SO_4 160 °C	1- (15) 2- (85)	1
	58% H_2SO_4 130 °C	1,5-[a] 1,6- 1,7- 2,7- 2,6-	6
	96% H_2SO_4 161 °C	1,3,5- (63)[a] 1,3,6- 1,3,7-	7
	100% H_2SO_4 $HgSO_4$, 234 °C	1,3,5-[a] 1,3,6- (54) 1,3,7-	8
		1-[a] 6- 7-	9, 10
		6-[a] 7-	11
	75% H_2SO_4 180 °C	2,3′-[a] 2,2′- 2,4′- 4,4′- 3,3′- 3,4′-	12

[a]See text.

observations are readily understood in terms of a mechanism, illustrated by Scheme 1 for substituted benzenesulphonic acids, that involves desulphonation of the sulphonic acid to form the parent arene, followed by intermolecular resulphonation of the arene by the sulphuric acid medium. Consistent with such an interpretation is the observation that the arene-2-sulphonic acid isomerizes most rapidly, generating first the arene-4-sulphonic acid, which in turn isomerizes to the arene-3-sulphonic acid at a slower rate. The rate of isomerization of the arene-3-sulphonic acid is the slowest of all (Table 2)[13]. Rapid desulphonation of the arene-2-sulphonic acid is most probably the result of a release of steric interactions between the substituents.



SCHEME 1. Mechanism for the isomerization of substituted arenesulphonic acids

The involvement of some sort of π-complex such as **1** arises from the results obtained from isotopic labelling studies using naphthalenesulphonic acids. labelling of C-1 in naphthalene-1-sulphonic acid revealed that rearrangement to naphthalene-2-sulphonic acid involved migration of the —SO_3H group to the 1-, 4-, 5- and 8-positions with equal

TABLE 2. Rate constants for the isomerization of toluenesulphonic acids in 74% H_2SO_4 at 141 °C

Isomerization	10^6k (s^{-1})
2- ⟶ 4-	388
2- ⟶ 3-	32
4- ⟶ 2-	35.6
4- ⟶ 3-	12.9
3- ⟶ 2-	2
3- ⟶ 4-	8

probability[14]. Using ^{35}S-labelled substrate, it was found that in *ca* 95% H_2SO_4 at 160 °C intermolecular exchange of label with the medium occurs. This result is confirmed using unlabelled substrate by the incorporation in the product of ^{35}S from labelled H_2SO_4. Nonetheless, a considerable part of the reaction proceeds without sulphur exchange. In *ca* 75% H_2SO_4, almost complete intermolecular exchange is observed[15,16]. Similar results have been obtained for 2- and 4-toluenesulphonic acids[17], and the lack of complete intermolecular exchange can be understood to imply a higher probability of the departing sulphonic acid group attacking the same arene molecule from which it is leaving. That is, some sort of π-complex intermediate is involved. Diffusion of the SO_3 moiety out of the π-complex must therefore be solvent-dependent. Complete exchange with the medium is thus only possible when dissociation of the π-complex to arene and SO_3 is extensive.

An alternative argument, that rearrangement occurs via sulphonation followed by desulphonation, is unlikely on both kinetic and product grounds[1,12]. For example, the rates of isomerization of 2- and 4-toluenesulphonic acids are faster than that for the desulphonation of 2,4-toluenedisulphonic acid[1]. Moreover, because of the *meta* directing effect of the $-SO_3H$ group 3,3′-biphenyldisulphonic acid would yield 3,3′,5-biphenyltrisulphonic acid which on desulphonation would form 3,3′-biphenyldisulphonic acid. The observed product is 3,4′-biphenylsulphonic acid[12].

Arenesulphonate salts undergo rearrangement on heating, but there has been no subsequent work reported since this area was last reviewed[1].

Polyalkylbenzenesulphonic acids rearrange by a process (or processes) that involve alkyl group migration. The reaction, known as the Jacobsen reaction, is restricted to the tetra- and penta-alkyl derivatives[1]. Pentamethylbenzenesulphonic acid disproportionates in 98.4% H_2SO_4 to give a mixture of hexamethylbenzene, and 2,3,4,5- and 2,3,4,6-tetramethylbenzenesulphonic acids[18]. The disproportionation can be understood by the sequence of reactions in Scheme 2. Pentamethylbenzenesulphonic acid is desulphonated by the sulphuric acid medium to form pentamethylbenzene, which can be protonated at the C1 or C2 carbon atoms. Either of these two species then undergoes intermolecular alkylation by pentamethylbenzene to yield hexamethylbenzene, forming in the process 1,2,3,4- and 1,2,3,5-tetramethylbenzenes. In turn, the latter are sulphonated by the medium to yield the isomeric tetramethylbenzenesulphonic acids. Gradually the 2,3,4,6-isomer rearranges to the 2,3,4,5-derivative under the conditions of the reaction.

$$Me_5C_6SO_3H + H_2SO_4 \rightleftharpoons Me_5C_6H + H_2S_2O_7$$

$$Me_5C_6H + H^+ \rightleftharpoons 1\text{-}HMe_5C_6H^+$$

$$Me_5C_6H + H^+ \rightleftharpoons 2\text{-}HMe_5C_6H^+$$

$$1\text{-}HMe_5C_6H^+ + Me_5C_6H \longrightarrow Me_6C_6 + 1,2,3,4\text{-}Me_4C_6H_2 + H^+$$

$$2\text{-}HMe_5C_6H^+ + Me_5C_6H \longrightarrow Me_6C_6 + 1,2,3,5\text{-}Me_4C_6H_2 + H^+$$

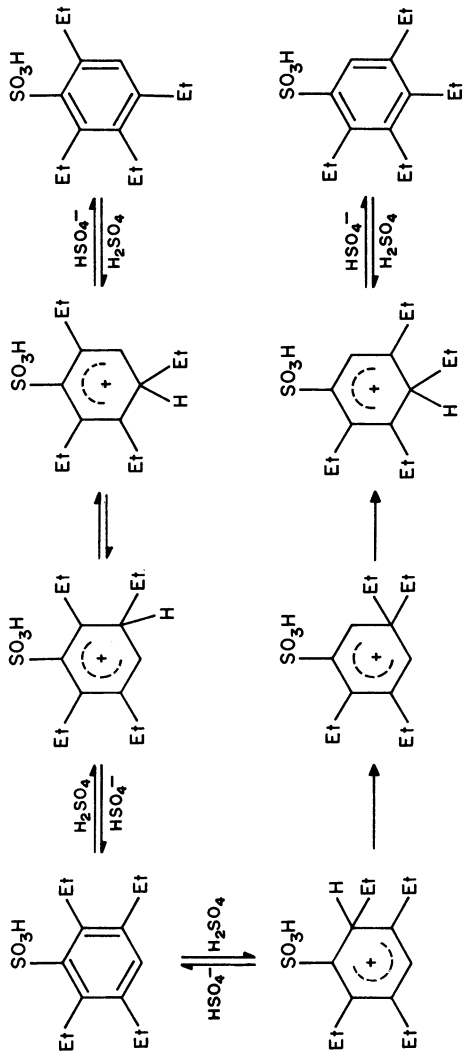
$$1,2,3,4\text{-}Me_4C_6H_2 + H_2S_2O_7 \rightleftharpoons 2,3,4,5\text{-}Me_4C_6HSO_3H + H_2SO_4$$

$$1,2,3,5\text{-}Me_4C_6H_2 + H_2S_2O_7 \rightleftharpoons 2,3,4,6\text{-}Me_4C_6HSO_3H + H_2SO_4$$

$$Me_6C_6 + H^+ \rightleftharpoons Me_6C_6H^+$$

SCHEME 2. Disproportionation of pentamethylbenzenesulphonic acid in H_2SO_4

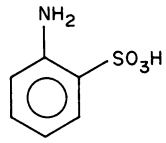
The individual 2,3,4,6- and 2,3,5,6-tetramethylbenzenesulphonic acids themselves isomerize in 98.4% H_2SO_4 to the 2,3,4,5-isomer via series of reactions similar to those outlined in Scheme 2[18]. In contrast, tetraethylbenzenesulphonic acids undergo a Jacobsen rearrangement in 98.4% H_2SO_4 that involves [1,2]-shifts of the ethyl group[19]. Thus, both



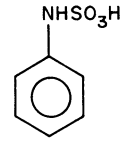
SCHEME 3. Isomerization of tetraethylbenzenesulphonic acids in 98.4% H_2SO_4

2,3,4,6- and 2,3,5,6-tetraethylbenzenesulphonic acids rearrange to the 2,3,4,5-isomer (Scheme 3).

A discussion of the rearrangement of aminoarenesulphonic acids, e.g. **2**, is best combined with one for *N*-arylsulphamic acids, e.g. **3**, since both appear to involve common intermediates.

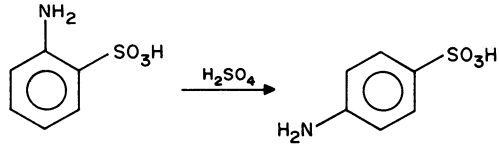


(**2**)



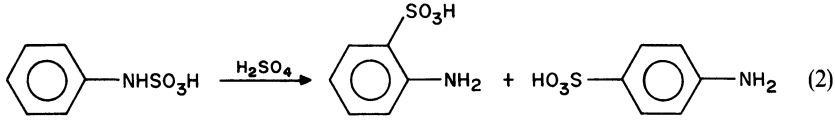
(**3**)

2-Aminobenzenesulphonic acid (orthanilic acid) rearranges at 156 °C in concentrated H_2SO_4 solutions to the corresponding 4-aminobenzenesulphonic acid (sulphanilic acid) (equation 1)[20]. Below 100 °C, no rearrangement is observed. Using $H_2{}^{35}SO_4$ complete incorporation of ^{35}S from the medium has been observed, verifying that the rearrangement involves an intermolecular process[21,22]. No 4-aminobenzene-1,3-disulphonic acid, the product of direct sulphonation of orthanilic acid, was detected in these reactions, and aniline itself formed only sulphanilic acid under the conditions of rearrangement. Thus, a potential mechanism for the rearrangement, based on the general mechanism for substituted arenesulphonic acids, is protiodesulphonation of orthanilic acid to form aniline, followed by resulphonation at the 4-position. Further studies on the sulphonation of aniline in H_2SO_4 solutions have shown, however, that at 100 °C in 96.8% H_2SO_4 the isomer content of the aminobenzenesulphonic acids is 2- (20%), 3- (5%) and 4- (75%)[23]. The proportion of the 3-isomer increases with (i) increasing H_2SO_4 concentration, (ii) decreasing temperature and (iii) decreasing substrate concentration, and this isomer undoubtedly comes from sulphonation of the anilinium ion. The presence of the 3-isomer suggests that the rearrangement of orthanilic to sulphanilic acid does not involve the free anilinium ion.



(1)

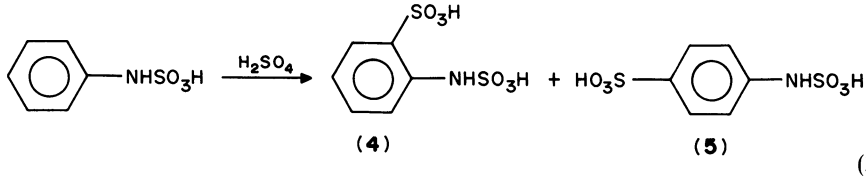
Vrba and Allan investigated the sulphonation of aniline and also the rearrangement of phenylsulphamic acid. In H_2SO_4 phenylsulphamic acid rearranges to 2- and 4-aminobenzenesulphonic acids (equation 2), and gives an identical distribution of the 2-



(2)

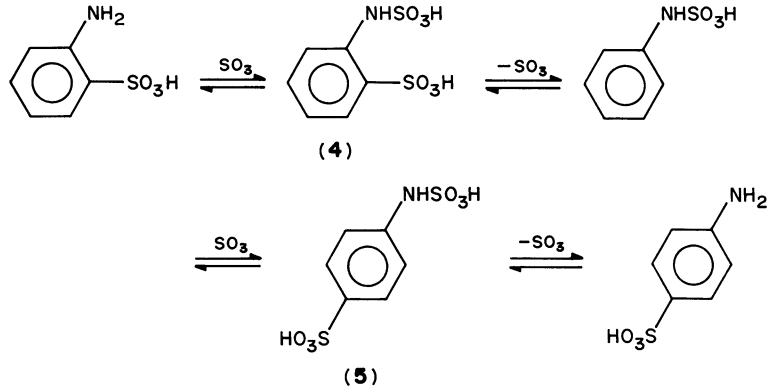
and 4-isomers, 15% and 85% respectively, as was found for the sulphonation of aniline[24,25]. Thus, it was concluded that *N*-phenylsulphamic acid was an intermediate in the sulphonation of aniline. Potentially, therefore, phenylsulphamic acid is also an intermediate in the rearrangement of orthanilic to sulphanilic acid. Under conditions of thermodynamic control (excess 97% H_2SO_4, 180 °C), these deductions appear to have some credence. Thus, the sulphonation of aniline or the rearrangement of orthanilic,

sulphanilic or *N*-phenylsulphamic acids all yield identical reaction mixtures containing the 2-, 3- and 4-aminobenzenesulphonic acids as well as 4-aminobenzene-1,3-disulphonic acid in the proportions 1:50:2:10[26]. Moreover, *N*,*N*-dimethylaniline, which cannot form a sulphamic acid, is not sulphonated[27]. A more detailed examination of the rearrangement of *N*-phenylsulphamic acid in H_2SO_4 reveals the rapid formation, from the neutral form of the substrate, of intermediate species having structures **4** and **5** (equation 3)[28]. Though such species were too unstable to be isolated in this study, analogous intermediates have been identified and independently synthesized in a study involving *N*-(4-tolyl)sulphamic acid[29]. These two species undergo loss of the *N*-SO_3H group to form the 2- and 4-aminobenzenesulphonic acids (equation 2). The isomer distribution varies with acidity; in 96% H_2SO_4 the product mixture contains 28.3% 2- and 71.7% 4-, whereas in 99.7% the corresponding amounts are 21.5% and 78.5%. Above 99.7% H_2SO_4 significant amounts of disulphonation are observed, due to further sulphonation of the intermediates **4** and **5**. The rearrangement of *N*-phenylsulphamic acid to orthanilic and sulphanilic acids is thus an intermolecular process.



(3)

Despite the above discussions, the mechanism of rearrangement of orthanilic acid to sulphanilic acid is not at all clear. One possibility, that does not contradict the known facts, is the *N*-sulphonation of orthanilic acid, followed by *C*-2 desulphonation, resulphonation at *C*-4 and finally *N*-desulphonation (Scheme 4). This mechanism avoids the intermediacy of free anilinium ion formed by protiodesulphonation, which appears to be in some doubt. It also involves the principle of microscopic reversibility, in that the intermediates **4** and **5** are involved in the formation of orthanilic and sulphanilic acids from *N*-phenylsulphamic acid and are therefore potential intermediates in the reverse reactions.

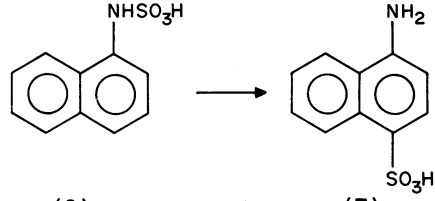


SCHEME 4. Possible mechanism for the rearrangement of orthanilic acid to sulphanilic acid

Aminonaphthalenesulphonic acids and *N*-naphthylsulphamic acids appear to be involved in similar types of processes as the aminobenzenesulphonic acids and *N*-

phenylsulphamic acids, but they are less well studied. Thus, the sodium salt of 1-aminonaphthalene-4-sulphonic acid rearranges in high yield (88%) to the isomeric salt of 1-aminonaphthalene-2-sulphonic acid on heating[30], a process that has been patented[31]. 2-Aminonaphthalene-1-sulphonic acid rearranges in 96% H_2SO_4 to 2-aminonaphthalene-5- and 2-aminonaphthalene-8-sulphonic acids[1]*. 1-Aminonaphthalene-8-sulphonic acid is known to isomerize to 1-aminonaphthalene-4-sulphonic acid[1].

Spillane and colleagues studied the reactions of *N*-(1- and 2-naphthyl)sulphamic acids in dioxan–sulphuric acid, and found that the 1-naphthyl compound rearranged cleanly to 1-aminonaphthalene-4-sulphonic acid at 100 °C (equation 4) whereas the 2-naphthyl analogue did not undergo rearrangement[32,33]. Neither **6** nor **7** rearrange to 1-aminonaphthalene-2-sulphonic acid (**8**) under the conditions of the rearrangement of **6** to **7**, though the rearrangement of **7** to **8** at higher temperatures may involve the intermediacy of **6**[30]. The rearrangement of **6** to **7** appears to be more complex than the equivalent reaction of the benzene analogue **2**. Radiolabelling experiments imply the operation of two mechanisms: one involving intermolecular sulphonation, the other involving rearrangement without participation of the medium. The 'intramolecular' process remains obscure, since a mechanism involving a π-complex (as discussed above for alkylbenzenesulphonic acids) would be expected to yield detectable amounts of the 1-aminonaphthalene-2-sulphonic acid whereas none is observed. The intermolecular process is probably similar to that for *N*-phenylsulphamic acid, i.e. the *N*-naphthylsulphamic acid (**6**) is first sulphonated and then followed by *N*-desulphonation. This would explain the observed rapid loss of substrate, and relatively slow formation of product.



(4)

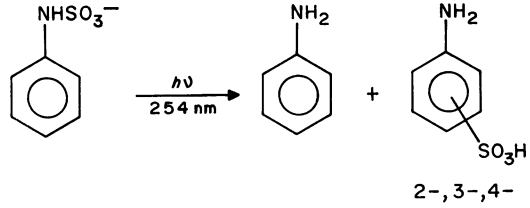
(**6**) (**7**)

Rearrangement of an *N*-alkylsulphamic acid is known. *N*-(2-hydroxyprop-1-yl)sulphamic acid (**9**) rearranges, on heating to reflux in dry mesitylene, to the corresponding aminoalkyl hydrogen sulphate ester (**10**) (equation 5)[34].

$$MeCH(OH)CH_2NHSO_3H \longrightarrow MeCH(OSO_3H)CH_2NH_2 \quad (5)$$

(**9**) (**10**)

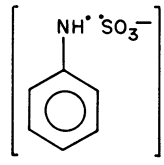
The rearrangements described above are thermal processes, usually in sulphuric acid medium. The sodium salt of *N*-phenylsulphamic acid also rearranges under photolysis in alcohol solvents (equation 6)[35]. The product distribution of the 2-, 3- and 4-aminobenzenesulphonic acids is 33%, 7.7% and 59.3%, respectively. The formation of the rearranged



(6)

*The nomenclature used here is chosen such that the migration of the sulphonic acid group is apparent.

products involves an excited triplet state that undergoes homolysis of the S—N bond to form a triplet radical pair **11**. This triplet radical pair then forms a singlet radical pair by intersystem crossing, and the singlet radical pair undergoes coupling reactions to form the product[35].

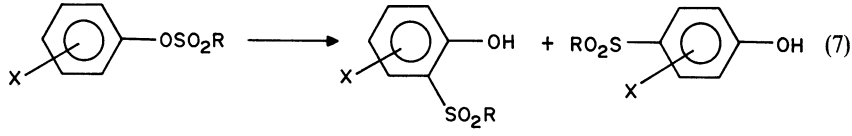


(11)

III. SULPHONATE AND SULPHAMATE ESTERS

A. The Fries Rearrangement of Arylsulphonates

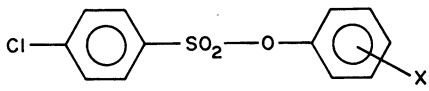
The rearrangement of an *O*-aryl ester to an *ortho*-hydroxyphenyl ketone is known as the Fries rearrangement. *O*-Aryl sulphonate esters undergo similar rearrangement to form hydroxyaryl sulphones (equation 7). Such reactions require an inert solvent (e.g. nitrobenzene), high temperatures (130–150 °C) and a Lewis acid catalyst, commonly anhydrous $AlCl_3$. The reaction has been examined for aryl esters of various arenesulphonic acids, but not for those of alkanesulphonic acids. Yields vary considerably but are generally in the 40–60% range. The reaction is compatible with a variety of arene groups; compounds in which R = Ph, 4-Tol, 4-ClC_6H_4, 4-IC_6H_4, 4-BrC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl and 2-naphthyl have all been subjected to rearrangement[36–45]. The literature is somewhat confused as to which isomer, the 2-hydroxy or the 4-hydroxy, predominates. In general, it appears that the 4-hydroxy isomer predominates (when that position is unsubstituted), but in some cases the situation is less clear cut. Thus, phenyl 4-chlorobenzenesulphonate forms 2- and 4-hydroxyphenyl 4-chlorophenyl sulphones in a $\frac{1}{2}o$: *p* ratio of 0.15[38]. However, while both 1-naphthalene and 2-naphthalene sulphonate esters of 2-hydroxybenzoic acid have been reported to rearrange to the 4-hydroxy isomer[37], elsewhere the 1-naphthalene sulphonate of phenol yields the 2-hydroxyphenyl sulphone whereas 2-naphthalenesulphonate of phenol yields the 4-hydroxyphenyl sulphone[39]. Similar observations can be made for 4-chlorobenzenesulphonate esters[38]. This may be a problem of steric crowding, but the lack of material balance in these reactions precludes definitive conclusions at this stage.



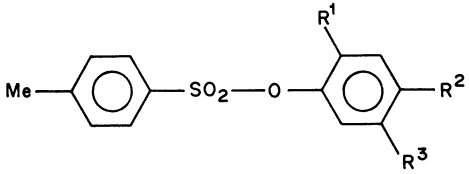
(7)

Likewise, it is not clear what role the substituent in the aryl ring plays in these reactions. Thus, the rearrangement of compounds (**12a-c**) yield predominantly the *para* isomer, whereas compounds (**12d, e**) give the *ortho* isomer as the major product[38]. However, a similar report for compounds of structure **13** reveals that the *para* isomer predominates for $R^2 = H$, and that the *ortho* isomer arises when $R^2 \neq H$[40]. Clearly, this reaction requires further mechanistic study.

As with acyl esters of phenols, the photochemical Fries rearrangement of aryl sulphonates is known. Thus, compounds **14a,b** were photolysed at 300 nm for 12–24 h to



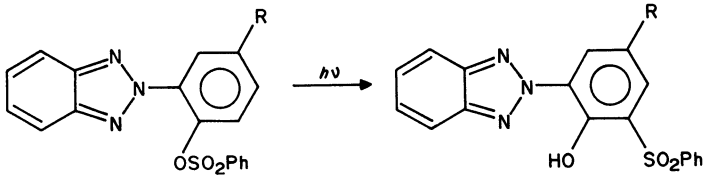
(12)(a) X=H
(b) X=3-Me
(c) X=2-NO_2
(d) X=2-Me
(e) X=2-Cl



R^1=H, Cl, Me, NO_2, CO_2Me
R^2=H, Cl, CO_2Me, NO_2
R^3=H, Me

(13)

yield the corresponding 2-hydroxyphenyl sulphones **15a,b** (equation 8)[46]. This reaction is reported to be very specific for benzenesulphonate esters; methanesulphonate esters do not rearrange, and 1-naphthalenesulphonate esters only undergo 25%, and 1-phenylmethanesulphonate esters less than 10%, rearrangement after prolonged irradiation. The products **15** are useful UV absorbers that may protect plastics from photochemical degradation.

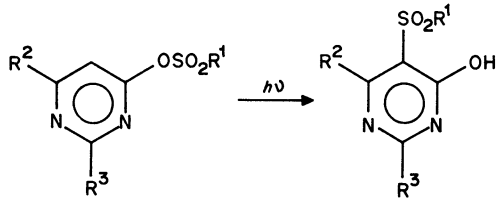


(8)

(14)(a) R=Me
(b) R=octyl

(15)

In contrast to these observations, Snell studied the photo-Fries rearrangement of sulphonate esters of 6-substituted 4-hydroxypyrimidines (equation 9) and found efficient conversion for a variety of alkane- and arenesulphonates [e.g. R^1 = Me, Et, Bu, $(CH_2)_3Cl$, Ph, 4-Tol, 4-ClC_6H_4, 4-BrC_6H_4, 4-An, 2,5-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$][47]. Yields vary between 20–60%, and the reaction does not proceed for $R^3 = NH_2$ or NHAc. The reaction has synthetic utility, since the product sulphones are inaccesible via the Friedel–Crafts procedure.



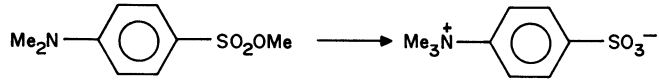
(9)

R^2= Me, H; R^3=Me_2N, morpholino, piperidino, pyrrolidino

B. *O*- to *N*-Rearrangement of Alkyl Aminoarenesulphonates and of Sulphamates

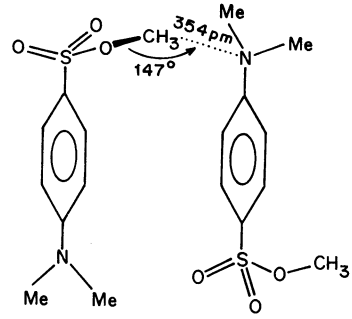
1. Alkyl aminoarenesulphonates

Methyl 4-dimethylaminobenzenesulphonate (**16**) is stable in organic solvents for long periods of time (months or more). At ambient temperatures, however, the same compound rearranges in the crystalline state to give 4-trimethylammoniobenzenesulphonate (**17**) in *ca* 20 days (equation 10)[48].



(16) (17) (10)

Isotopic labelling of the methyl groups with deuterium and performing a scrambling experiment with the unlabelled material has demonstrated that the reaction is predominantly (and most probably, completely) intermolecular[48]. The role of the crystalline state is central to this reaction; at 81 °C in the crystal the reaction is 90% complete with 2 h, whereas in the melt at 95 °C after 2 h the reaction has progressed to only 15% completion. The effect of the crystal is thus most probably one of orienting correctly the alkyl sulphonate and amino groups rather than simply acting as a concentrated reaction medium. Significantly, an X-ray diffraction study of compound **16** reveals that the molecules stack with alternating sulphonate and dimethylamino groups, as in **18** such that the interatomic distance between the amino *N* atom and the methyl sulphonate *C* atom is only 354 pm and the *N*—Ĉ—O angle is 147°[48].

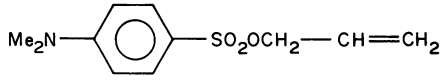


(18)

Interestingly, the reaction is specific for the methyl ester: the allyl, 1-butyl and 2-butyl esters do not undergo similar rearrangement. This may well be a result of different molecular orientations in these crystals. From a Raman phonon spectroscopic study of the rearrangement, it has been deduced that reaction 10 proceeds by a heterogeneous transfer mechanism; that is, the reaction is initiated at random throughout the crystal and terminates where there are random molecular dislocations[49].

Though rearrangement of **16** to **17** does not occur in 'normal' solvents, it has been observed in a highly ordered smectic B solvent[50]. The reaction proceeds more slowly than in the crystal. In contrast to the situation in the crystal, the reaction is second order, with an Arrhenius activation energy of 85 kJ mol^{-1}. Thus, the dilute smectic solution favours rearrangement via a bimolecular process rather than the chain mechanism followed in the crystal. This has important ramifications for this type of rearrangement in general. Thus,

the allyl ester **19**, which does not rearrange in the crystalline state, undergoes rearrangement at 38 °C in a smectic B solvent[50]. Indeed, compound **19** is *ca* 3–5 times more reactive towards rearrangement than compound **16**, as might be predicted form the intervention of an S_N2'-like process in the smectic phase. The role of molecular orientation within the crystal is therefore crucial to rearrangement taking place.



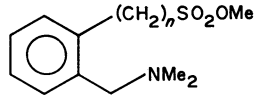
(19)

In contrast to these 'solid state' reactions, alkyl dialkylaminoalkanesulphonates (**20**) rearrange readily in solution, e.g. in $CHCl_3$ at 37 °C to the corresponding betaine (equation 11)[51]. Crossover experiments involving equimolar amounts of **20** and its perdeuteriomethyl isotopomer reveal the reaction to be completely intermolecular, and the reaction is bimolecular in [**20**][51]. Though several possibilities present themselves, the most probable mechanism for the reaction is one that involves the betylate* intermediate **21** (equation 12). An intramolecular rearrangement has been identified for compound (**22**, $n = 2$), but not for (**22**, $n = 1$); even for (**22**, $n = 2$) the major pathway is intermolecular (> 84%)[52]. The ability of dialkylaminoalkanesulphonate, but not dialkylaminoarene-sulphonate, esters to rearrange presumably stems from the differing nucleophilicities of the amino nitrogen atoms in these systems.

$$\underset{\textbf{(20)}}{Me_2N(CH_2)_4SO_2OMe} \longrightarrow Me_3\overset{+}{N}(CH_2)_4SO_3^- \qquad (11)$$

$$2Me_2N(CH_2)_4SO_2OMe \rightleftharpoons \underset{\textbf{(21)}}{Me_3\overset{+}{N}(CH_2)_4SO_2OMe\ Me_2N(CH_2)_4SO_3^-}$$

$$\longrightarrow 2Me_3\overset{+}{N}(CH_2)_4SO_3^- \qquad (12)$$



(22)

2. Alkyl sulphamates

The rearrangement of alkyl sulphamate esters **23** to the corresponding betaine **24** (equation 13) was first reported in 1884[53]. Since then, the reaction has been investigated several times[22] and the following conclusions drawn. First, crossover experiments identify the reaction as proceeding via an intermolecular pathway. Thus, rearrangement of a mixture of Me_2NSO_2OEt and $MeEtNSO_2OMe$, which individually rearrange at similar rates, gives rise to $Me_3\overset{+}{N}SO_3^-$[54]. Furthermore, rearrangement of an equimolar mixture of **23** and its predeuteriated isotopomer gives rise to a 1:1:1:1 mixture of $Me_3\overset{+}{N}SO_3^-$, $Me_2CD_3\overset{+}{N}SO_3^-$, $Me(CD_3)_2\overset{+}{N}SO_3^-$ and $(CD_3)_3\overset{+}{N}SO_3^-$[55]. Second, the rate of reaction is solvent-dependent. Thus, in xylene at 138 °C, **23** did not rearrange, but at the same

*This term has been proposed for structures like **21** and **25** by J. F. King and T. M.-L. Lee, *Can. J. Chem.*, **59**, 356 (1981), since simple nucleophilic substitution generates a betaine.

temperature in trichlorobenzene it did so with a first-order rate constant of 10^{-5} s^{-1}[54]. Third, the substituents on nitrogen have a greater influence on the rearrangement than does the *O*-alkyl group. Thus, for *N,N*-dimethylsulphamates methyl, ethyl, propyl, *tert*-butyl, 1-phenylethyl and diphenylmethyl groups can migrate from the oxygen to the nitrogen atom[54,56,57] whereas for *N*-ethyl-*N*-methylsulphamates and *N,N*-diethylsulphamates rearrangement of even methyl or ethyl groups is precluded[54]. Since pyrrolidino- and piperidinosulphamates undergo rearrangement, the effect of the nitrogen substituents is presumably steric. Fourth, the reaction is catalysed by added electrophiles, e.g. $MeOSO_2F$, $MeOSO_2CF_3$[58]. The catalysed reaction proceeds by way of a betylate intermediate **25** (equation 14) which, when R^1 = Ph, can be isolated[59].

$$\underset{\textbf{(23)}}{Me_2NSO_2OMe} \xrightarrow{\text{heat}} \underset{\textbf{(24)}}{Me_3\overset{+}{N}SO_3^-} \tag{13}$$

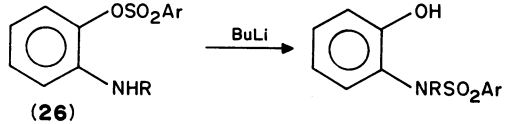
$$\begin{aligned} Me_2NSO_2OR^1 + R^2OSO_2F &\longrightarrow [\underset{\textbf{(25)}}{Me_2R^2\overset{+}{N}SO_2OR^1}\ \ FSO_3^-] \\ &\longrightarrow Me_2R^2\overset{+}{N}SO_3^- + R^1OSO_2F \end{aligned} \tag{14}$$

By analogy, the uncatalysed reaction probably involves a similar process (equation 15), but the uncertainty surrounding the kinetic order of the reaction in the investigations so far undertaken[54,58] must be resolved before this can be considered correct. Interestingly, the rearrangement bears many similarities to the sulphonimidate–sulphonamide rearrangement (Section V.E) which is known to proceed by a mechanism strictly analogous to that in equation 15. Indeed, both reactions appear to be thermodynamically driven, and are essentially irreversible.

$$\begin{aligned} 2\,Me_2NSO_2OMe &\rightleftharpoons [Me_3\overset{+}{N}SO_2OMe\ Me_2NSO_3^-] \\ &\longrightarrow 2\,Me_3\overset{+}{N}SO_3^- \end{aligned} \tag{15}$$

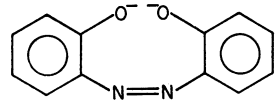
C. *O*- to *N*-Rearrangement of Aminoaryl Sulphonate Esters

Aryl sulphonate esters, e.g. **26**, that contain a primary or secondary amino group in the aryl ring upon treatment by an alkyl lithium undergo migration of the sulphonyl group from the oxygen to the nitrogen atom (e.g. equation 16)[60]. The reaction is compatible with R = H, Me and Ar = 4-Tol, 4-An, 4-$Bu^tC_6H_4$ and 2,4,6-$Me_3C_6H_2$, though the yields drop dramatically as the steric hindrance, provided by the R and Ar groups, increases. Thus, for **26**, Ar = 4-Tol, R = H a yield of 95% was obtained, whereas for **26**, Ar = 4-Tol, R = Me and **26**, Ar = 2,4,6-$Me_3C_6H_2$, R = H the yields were 43% and 10%, respectively. Crossover experiments suggest that the reaction is intramolecular[60,61]. Unfortunately, the mechanism of the reaction is unclear. Though the rearrangement would appear to be a straightforward nucleophilic attack of the nitrogen anion at the sulphur atom, a mechanism involving a quinoneimine (equation 17) has not been eliminated conclusively. Indeed, the formation of a small amount of azobenzene (**27**) in some of these reactions is consistent with a quinoneimine intermediate. However, the fact that compound **28** also undergoes rearrangement, yet cannot form a quinoneimine, probably indicates that for this



(26) (16)

compound the reaction does involve nucleophilic attack at sulphur. Further insight into this reaction has been obtained from the analogous rearrangement of the corresponding sulphonimidates **29**[61]. As well as producing the sulphonimidamide **30** in 45% yield, an almost equimolar amount of the sulphinamide **31** is formed. The sulphinamide arises from an elimination process analogous to that shown in equation 17.



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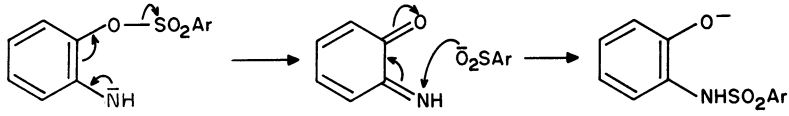
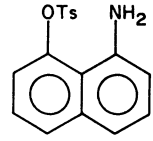


(17)



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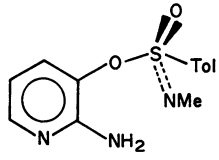

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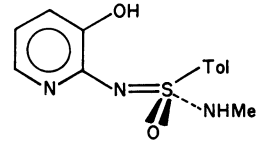

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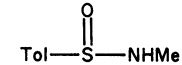
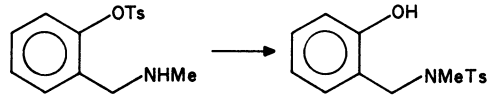


(31)

Reaction of compound **32** with LDA involves an inter- rather than an intra-molecular process to give the expected product **33**[61].



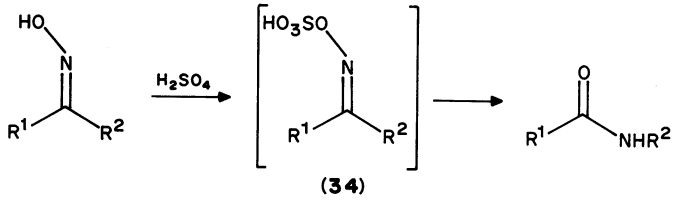
(32) **(33)**

D. Beckmann and Similar Rearrangements of Oxime Sulphonates

The Beckmann and similar rearrangements are technically outside the scope of this review, since they involve rearrangement with loss of the sulphonate group. Moreover, for obvious reasons such rearrangements are not limited to sulphonate esters. Nonetheless, mention must be made here of these reactions since the formation of sulphonate esters from oximes is a common method of activation in order to carry out the Beckmann rearrangement.

1. Beckmann-type rearrangements

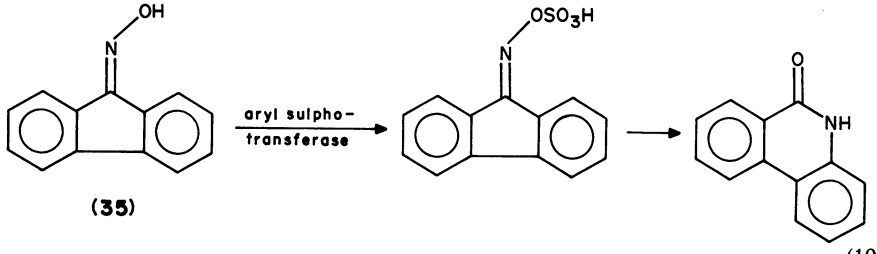
The Beckmann-type rearrangements of oximes (equation 18) in concentrated sulphuric acid involves, amongst other species, the *O*-sulphate ester **34**. This is directly detectable by ^{1}H NMR spectroscopy[62]. Such oxime sulphate esters (**34**) can be synthesized independently from the parent ketone and hydroxylamine *O*-sulphonic acid[63,64], and they undergo spontaneous[63] or acid-catalysed[64] rearrangement to the product amide. The non-catalysed process is compatible with cyclic, acyclic, dialkyl and aryl alkyl ketones and aqueous solutions, and requires between 20–80 h to give yields of *ca* 70%[63]. The acid (formic) catalysed process requires less than 7 h for acceptably high yields (*ca* 90%), and is compatible with diaryl ketones as well as large ring alicyclic ketones[64].



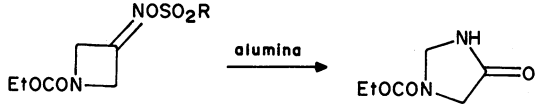
(34) (18)

A biological analogue of the above reaction is known. Aryl sulphotransferase isozyme I readily sulphates 9-fluorenone oxime (**35**) at pH 7–9 to form the sulphate ester, which then rearranges non-enzymically to phenanthridone (equation 19)[65]. This Beckmann rearrangement accounts for only a part of the transformation of the oxime **35**.

Not surprisingly, sulphonate esters of oximes are also able to undergo the Beckmann reaction. One of the most useful catalysts is alumina, in both its neutral and basic forms[66,67], and both arene- and alkanesulphonate esters undergo rearrangement. Indeed, the procedure has proved a valuable route to 4-imidazolidinone via ring enlargement of an axetidin-3-one (equation 20)[67]. Moreover, Beckmann rearrangement of arenesulphonate esters of cyclic oximes has provided a route to halogen-free lactams, the corresponding procedure using the parent oxime and $SOCl_2$ as catalyst giving rise to lactams containing > 100 ppm Cl[68]. Halogen-free lactams are required in the polymer industry.



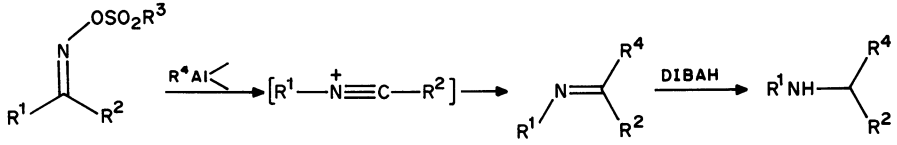
(35) (19)



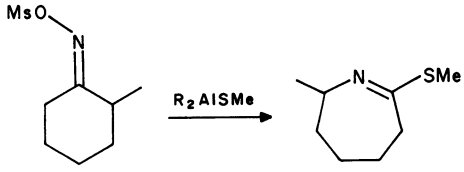
R=Me, 4-Tol (20)

In a series of papers, Yamamoto and colleagues have explored the Beckmann rearrangement of oxime sulphonates catalysed by organoaluminium and Grignard

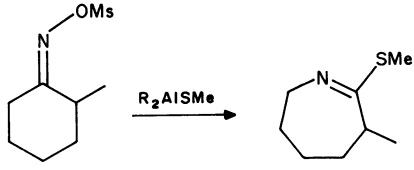
reagents[69–73]. These reactions, exemplified in equation 21, involve treating oxime methane- or 4-toluenesulphonate esters with a 2–3-fold excess of an organoaluminium reagent, e.g. Me_3Al, Pr^n_3Al or Bu^i_2AlH, and reducing the so-formed imine *in situ* with DIBAH. Thus, the organoaluminium reagent traps the intermediate nitrilium ion of the Beckmann rearrangement. Other aluminium reagents, e.g. $R^1_2AlSR^2$,$R^1_2AlSeR^2$ and R_2AlCl/Me_3SiCN, are able to trap the nitrilium ion with a variety of other nucleophiles[69]. In common with the majority of such rearrangements, the group *anti* to the sulphonate group migrates[69] (equation 22 and 23). Oxime methanesulphonates have proven to be particularly useful functional groups for chemoselective activation in the presence of olefins[70]. Thus, compound **36** upon treatment with Et_2AlCl, followed by DIBAH, yields the tetrahydropyridine **37** via intramolecular trapping of the nitrilium ion by the terminal olefin (equation 24).



(21)



(22)



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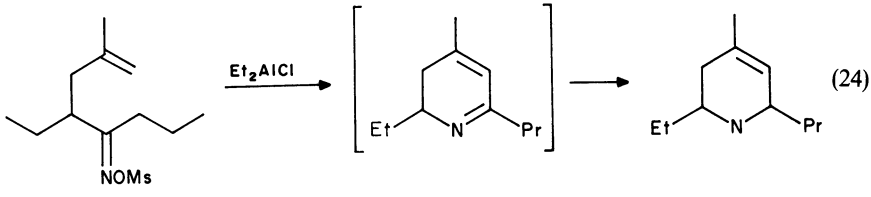
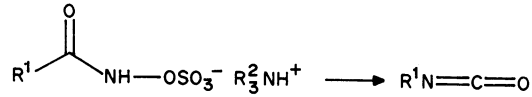


(24)

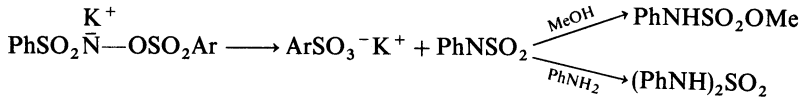
(36) **(37)**

The Lossen reaction involves the rearrangement of a hydroxamic acid to an isocyanate and is catalysed by a dehydrating agent. In the same way that oxime sulphates undergo the Beckmann rearrangement, *O*-sulphates of hydroxamic acids undergo the Lossen rearrangement (equation 25) upon catalysis by base[74].



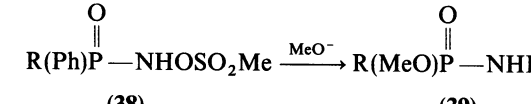
(25)

Lossen-type rearrangement of an *O*-sulphonate ester of *N*-hydroxybenzenesulphonamide (equation 26) is also known[75]. The intermediate sulphonylamine can be trapped by solvent methanol or by added aniline.



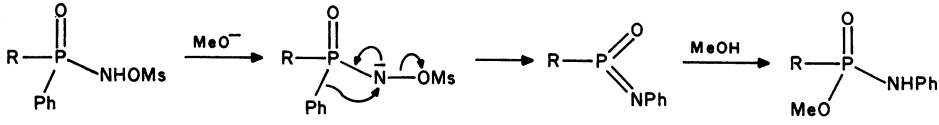
(26)

In a reaction reminiscent of the Lossen rearrangement, the *O*-methanesulphonate ester of *N*-(diphenylphosphinoyl)hydroxylamine (**38**, R = Ph) undergoes base-catalysed rearrangement to the methyl phosphonamidate **39** (equation 27)[76]. Analogous reaction of **38**, R = Me, Et or Pr^i reveals that only the phenyl group migrates, and also that compounds **38**, R = Me and **38**, R = Pr^i react at almost equal rates[77]. The most probable mechanism for this rearrangement is that shown in Scheme 5, rather than one involving nucleophilic attack of MeO^- at the phosphorus atom.



(27)

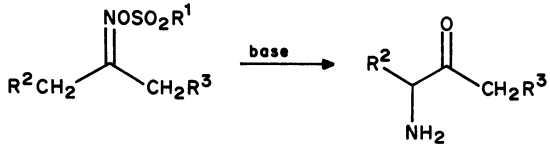
(**38**) (**39**)



SCHEME 5. Rearrangement of *O*-methanesulphonates of *N*-(alkylphenylphosphinoyl)-hydroxylamines

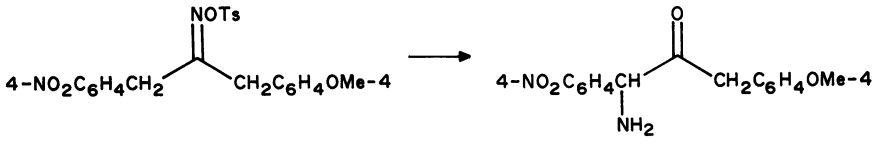
2. *Neber rearrangement*

The Neber rearrangement of oxime sulphonate esters (equation 28) is a useful method for the synthesis of α-aminoketones[78]. The reaction is base catalysed and involves abstraction of the most acidic proton α to the oxime functional group, as exemplified by the exclusive formation of compound **40** in this rearrangement (equation 29).



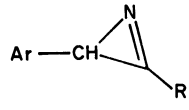
(28)

Pyridine is a sufficiently strong base to promote reaction, but alkoxide ions are more commonly employed. The reaction proceeds by way of an azirine intermediate **41**, which has been isolated in some instances[79]. Usually, however, this undergoes direct transformation to the α-aminoketone. The rearrangement has been little studied since the last review

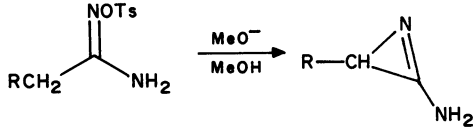


(40) (29)

was published[78], but it appears that it provides a useful access to 2-aminoazirines (**42**) from amidoxime tosylates (equation 30)[80]. This latter reaction requires R groups which are strongly electron withdrawing, e.g. COR or SO_2R, since it is not observed for R = Ph.



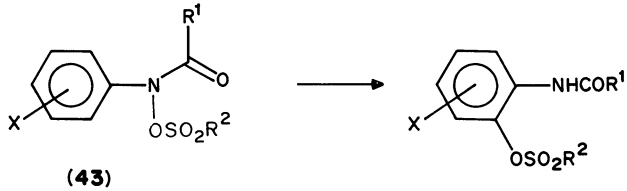
(**41**) Ar = 2,4-$(NO_2)_2C_6H_3$
R = Me, Ph



(**42**) (30)

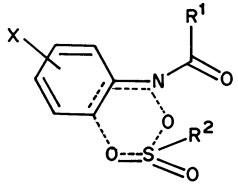
E. Rearrangement of Sulphonate Esters of *N*-Arylhydroxamic Acids

O-Sulphate and *O*-sulphonate esters of *N*-arylhydroxamic acids, e.g. **43**, undergo rearrangement of the sulphonyloxy group from the nitrogen atom to the *ortho* position of the *N*-aryl ring (equation 31)[81–90]. Only small amounts of the *para* isomer are observed, *o*:*p* ratios being > 6[85,87,88].

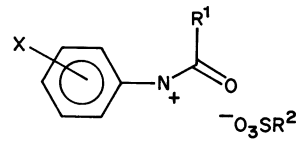


(**43**) (31)

Interest in compounds such as **43** stems from the carcinogenicity of arylamines, which is thought to be due to the formation of an electrophilic nitrenium ion by hydroxylation, acylation and sulphation processes. On the basis of ^{18}O labelling studies it was originally suggested that the rearrangement proceeded via a six-membered transition state, such as **44**[83,84]. Subsequently, these studies were reinvestigated and the results questioned[85]. An intimate ion pair consisting of arylnitrenium and sulphonate ions (**45**) was proposed as an intermediate. Firm evidence for a nitrenium ion intermediate was found from a Hammett study, which showed correlation with σ^+ and gave a ρ value of -9.24[81]. Heterolysis of the N—O bond is thus clearly involved.



(44)



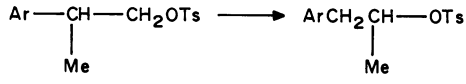
(45)

The rearrangement can be observed in protic solvents, e.g. H_2O and MeOH, as well as in aprotic organic solvents[86–90]. However, in such media the intimate ion pair is able to generate a solvent separated ion pair. The intimate ion pair gives rise to the rearranged product; the solvent separated ion pair undergoes solvolytic capture of the nitrenium ion. Added nucleophiles, e.g. Cl^-, can also interact with the nitrenium ion.

F. Rearrangements of Alkyl Sulphonates

The rearrangement of alkyl sulphonate esters during their solvolysis has long been known and is well documented. The reactions have been investigated mechanistically in detail, and have been extensively reviewed elsewhere[91,92]. Therefore, we shall not discuss them in depth, but some examples of such reactions are given in equations 32–34. It is apparent that they involve Wagner–Meerwein type rearrangement within the alkyl groups; the reaction illustrated by equation 32 involves scrambling of a labelled CH_2 group, that in equation 34 involves racemization of the substrate. However, not only is rearrangement of alkyl group possible; scrambling of the oxygen atoms, as in equation 35, can occur also[93–100]. Such scrambling is observed in simple secondary alkyl systems, e.g. R^1 = 2-propyl, 2-octyl, cyclopentyl, 2-norbornyl, as well as the more elaborate *endo*-bicyclo[3.2.1]octan-2-yl and *threo*-3-(4′-anisyl)but-2-yl tosylates.

(32)



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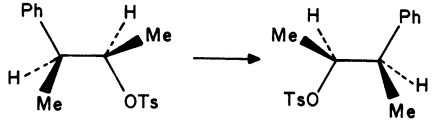
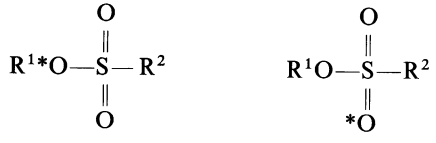


(34)



(46A) (46B)

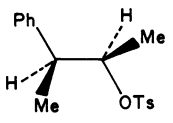
(35)

Mechanistic studies have identified several intermediate steps in the solvolysis of secondary alkyl tosylates[91]. These involve formation of an intimate ion pair (**47**), a solvent separated ion pair (**48**) and finally dissociated carbonium ion (Scheme 6). In principle, any

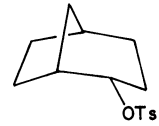
of these cationoid species are able to be trapped or rearrange[91], and much of the recent effort has been directed towards understanding the extent of both alkyl group rearrangement and sulphonate oxygen scrambling at the various stages outlined in Scheme 6. Investigation of sulphonate oxygen scrambling originally involved tedious degradation procedures to release CO_2[97], later involved GC/MS of more simple cleavage products[97] and most recently has been studied directly, on a small scale, using either ^{17}O NMR[98] or ^{18}O isotope shifts on the ^{13}C NMR spectra[100]. It has been generally observed that, under the conditions of the scrambling experiments, intermolecular exchange with dissociated arenesulphonate ion contributes less than 10% to the rate of oxygen equilibration (Table 3). Thus, oxygen equilibration (and, for 4-AnCH(Me)CH(Me)OTs, substrate racemization) is largely intramolecular, involving intimate and solvent separated ion pairs. Goering and Jones have shown that oxygen scrambling in 4-AnCH(Me)CH(Me)OTs involves both intimate and solvent separated ion pairs[96]. The contribution of each can be separated out by studying the reaction in the absence and presence of $LiClO_4$. The ratio of the rate constants for oxygen equilibration to substrate racemization for the solvent separated ion pair, k_{eq}/k_{rac}, is approximately 1. That is, reformation of substrate by external ion-pair return results in complete randomization of the sulphonate oxygen atoms. In contrast, the k_{eq}/k_{rac} ratio for intimate ion-pair return is *ca* 0.5, a value that has been obtained for other substrates, viz. **49** and **50**[94]. The conclusion reached from these observations is that the sulphonate oxygen atoms are not equivalent in the intimate ion-pair intermediate (which, for all three substrates, is symmetrical) that returns to form racemic substrate. In fact, it has been deduced that formation of substrate from the intimate ion pair in such circumstances involves trapping of the cationoid species with 50% of the sulphonate having undergone complete equilibration and 50% having undergone no equilibration, i.e. species **51A** and **51B**[95]. It is still unclear why such a situation is manifest.

$$\underset{}{R{-}OSO_2R'} \rightleftharpoons \underset{\textbf{(47)}}{R^+O_3SR'} \rightleftharpoons \underset{\textbf{(48)}}{R^+ \| {}^-O_3SR'} \rightleftharpoons R^+ + R'SO_3^-$$

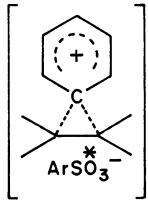
SCHEME 6. Intermediates in the solvolysis and rearrangement of alkyl tosylates



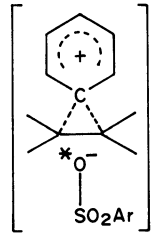
(49)



(50)



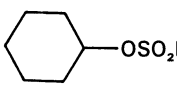
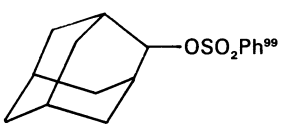
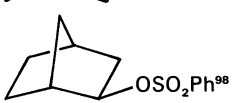
(51A)



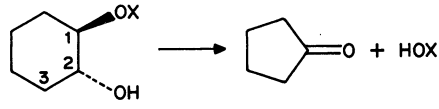
(51B)

trans-Cyclohexane-1,2-diol monosulphonate esters (**52**) undergo the pinacol rearrangement (equation 36). The reaction involves a [1,2]-shift involving breaking the C2—C3

TABLE 3. Extent of intermolecular exchange in the scrambling of sulphonate oxygen atoms during the solvolysis of sulphonate esters

Substrate	Medium	Added $ArSO_3H$	% O equilibration	% $ArSO_3$ exchange	% Racemization of substrate
HexCH(Me)—OBs[93]	AcOH	TsOH	—	*ca* 3	—
	$AcOH/AcO^-$	TsOH	—	*ca* 20	—
	$CF_3CO_2H/CF_3CO_2^-$	TsOH	—	*ca* 6	—
4-AnCHMe—OTs[96]	AcOH	TsOH	57	8.5	62
	$AcOH/LiClO_4$	TsOH	11	2.2	19
	CF_3CO_2H	TsOH		0	
	CF_3CO_2H	TsOH		0	
	EtOH	$4\text{-}BrC_6H_4SO_3H$		0	

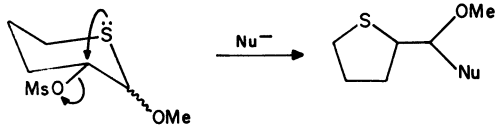
bond and formation of a new bond between C1 and C3. An interesting study has recently compared crystal structures of compounds **52** with varying leaving-group ability of OX^- in an attempt to observe ground-state geometry changes, e.g. lengthening of the C1—O and shortening of the C3—C1 interatomic distances, corresponding to the rearrangement process[101]. Indeed, Table 4 shows that there is an apparent decrease in C3—C1 as C1—O lengthens. However, the presence of the sulphonate group has little effect over and above that of 2,4-dinitrobenzoyl even though they have significantly different pK_a values, and the trend in Table 4 has been ascribed to difference in puckering of the cyclohexane ring rather than a reflection of varying geometries along the reaction pathway of the pinacol rearrangement.



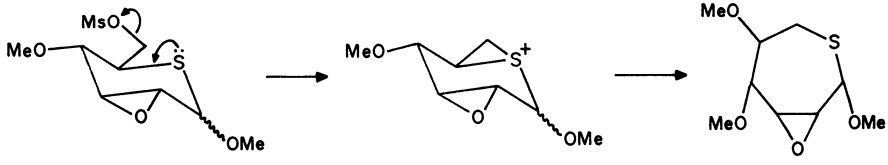
(36)

(**52**) X=RSO_2

In reactions that resemble the pinacol rearrangement, thiopyranoside sulphonate esters undergo ring contraction and expansion reactions via the intermediacy of sulphonium ions, e.g. equations 37 and 38[102]. Similarly, cyclic sulphonates are able to trap oxime anions at the carbon atom (equation 39)[103]. Such carbon alkylation of oxime ions is rare, and by suitable choice of substrate both ring-contraction and ring-expansion reactions are possible[103].



(37)

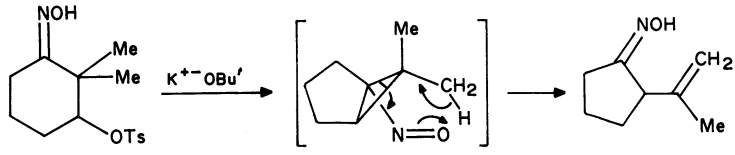


(38)

TABLE 4. Comparison of geometries of various derivatives of *trans*-cyclohexane-1,2-diol (**52**)

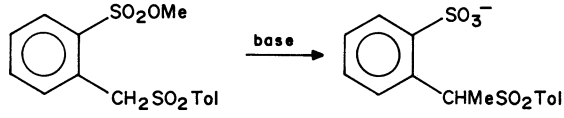
X	pK_a OX^-	C1—O (Å)	C1—C3 (Å)	θ (deg)[a]
H	15.74	1.429	2.504	178.7
Ph	9.95	1.437	2.487	179.1
4-$NO_2C_6H_4CO$	3.44	1.466	2.466	179.5
2,4-$(NO_2)_2C_6H_3CO$	1.5	1.473	2.478	176.0
$PhSO_2$	−6.65	1.476	2.469	175.7
4-$TolSO_2$		1.476	2.478	174.8
2-$NaphSO_2$		1.480	2.473	174.4

[a]Torsion angle C3—C2—C1—O.



(39)

Intramolecular alkylation of an α-sulphonyl anion in the methyl sulphonate ester **53** is potentially possible. Though the rearrangement (equation 40) is observed, deuterium labelling experiments reveal that the reaction involves intermolecular methyl transfer[104]. This is attributed to the preference of S_N2 reactions for backside attack at the tetrahedral carbon atom.

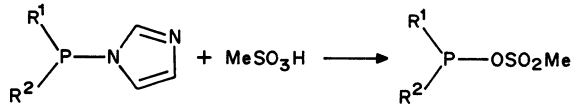


(40)

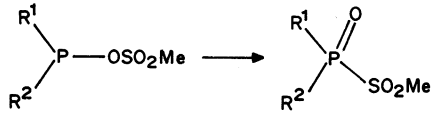
(53)

G. Miscellaneous

Reaction of 1-phosphinylimidazoles with methanesulphonic acid at −60 °C gives the phosphinyl sulphonate esters **54**. These compounds are unstable at ambient temperatures and undergo a [1,2] − *O* to *S* rearrangement of the phosphinyl moiety to yield phosphinoyl sulphones **55**[105]. Little is known about this reaction except that, if both R^1 and R^2 are alkoxy groups, the rearrangement is not observed.



(54)

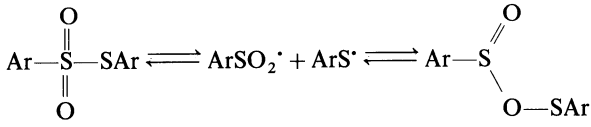


(55)

IV. THIOSULPHONATES

Photolysis (1 kW Hg–Xe arc) at 210 K or thermolysis at 400 K of 10^{-4} M solutions of *S*-aryl arenethiosulphonates (**56**) gives rise to the formation of arenesulphinyl radicals, ArSO•. Spin trapping, using Bu^{t}NO, provides evidence for the generation of both arenesulphonyl, $ArSO_2$•, and arenethiyl, ArS•, radicals as intermediates in this reaction (equation 41)[106]. The reaction is thus conceived of as involving a [1,2] *S* to *O* shift of the arylthio moiety to form *O*,*S*-sulphenyl sulphinate (**57**). Indeed, this is largely the scheme proposed for the formation of *S*-arylthiosulphonates (**59**) from the reaction of sulphinyl chlorides with lithium tributyltin (equation 42), except that in the latter case the formation of a *vic*-disulphoxide (**58**) is implicated[107]. It seems likely that such an intermediate lies between the *O*,*S*-sulphenyl sulphinate (**57**) and the arenesulphinyl radical in equation 41.

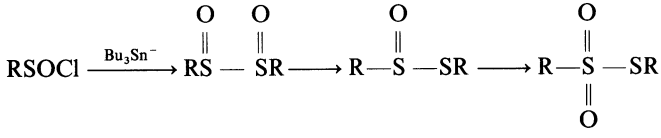
Ab initio MO calculations at the 6-31G* level verify these conclusions and reveal that (i) disproportionation of arenesulphinyl radicals to arenesulphonyl and arenethiyl radicals is exothermic by $-13.6\,kcal\,mol^{-1}$ and (ii) that the sulphenyl sulphinate structure **57** is $28\,kcal\,mol^{-1}$ more stable than the *vic*-disulphoxide **58**[108].



(41)

(56) **(57)**

Ar = Ph, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-Tol, 3,5-Bu^t_2-4-HO-C_6H_2



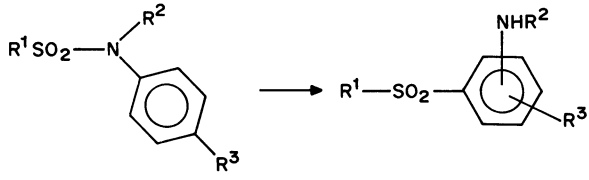
(42)

(58) **(59)**

V. SULPHONAMIDES AND SULPHAMIDES

A. [1,3]-*N*- to *C*-rearrangements in Sulphonamides and Sulphamides

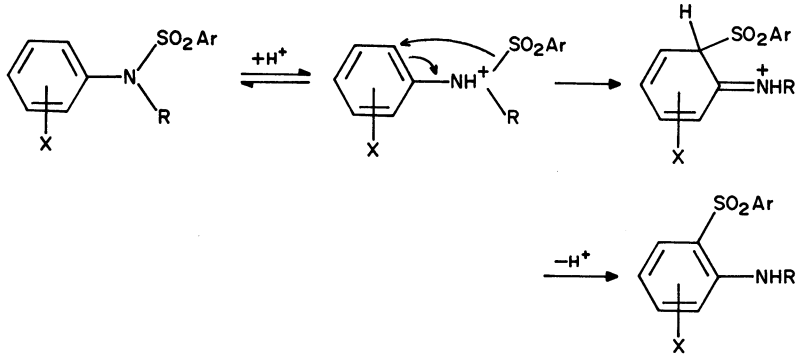
The rearrangement of an *N*-arylsulphonamide, or an *N*-arylsulphamide, to the isomeric aminoaryl sulphonyl compound (equation 43) is now a well-known reaction. The reaction is the nitrogen analogue of the Fries rearrangement (Section III.A.). For sulphonamides, acid-catalysed, base-catalysed, thermally promoted and photochemically promoted rearrangements have been observed; for sulphamides, only the thermal and base-catalysed processes have been reported.



(43)

The proton-catalysed sulphonamide to aminosulphone rearrangement has been reviewed elsewhere[109]. The reaction proceeds via two pathways. The major, and most common, is the migration of the sulphonyl group to the *ortho* position (equation 44). Crossover experiments reveal this reaction to be intramolecular. The rate of rearrangement follows a Hammett relationship, giving rise to a ρ value of -1.7, which is consistent with a reduction in electron density at the nitrogen atom in the formation of the transition state. (Of course, this ρ value incorporates the ρ for protonation as well as that for the true rearrangement, which is therefore probably smaller than that quoted here). However, under certain circumstances the products of intermolecular reaction are seen. Thus, the arenesulphonyl group has been observed to migrate to the *para* position[109,110]. The presence of a 2-nitro group in the arenesulphonyl moiety both enhances the rate of rearrangement and increases the amount of the *para* isomer formed. This has been tentatively ascribed to stabilization of the arenesulphonyl cation **60** by the adjacent nitro

group. Little mechanistic work has been undertaken on this reaction, and it has been used infrequently for synthetic purposes[110–112].



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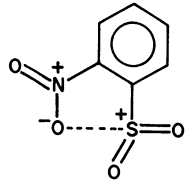
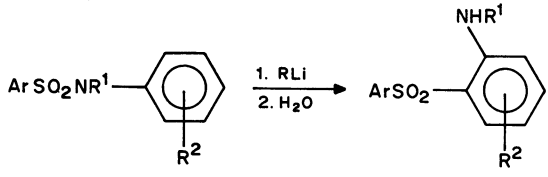


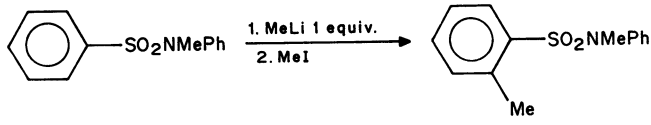
(60)

In contrast, the synthetic utility of the base-catalysed sulphonamide–aminosulphone rearrangement has been clearly demonstrated, independently, by the groups of Hellwinkel[113] and Closson[114]. In general, the reaction involves treatment of tertiary *N*-arylsulphonamides with an organolithium compound in an organic solvent (THF). The product is the *ortho*-aminophenyl sulphone (equation 45). Several features of the reaction are worth highlighting[114]. First, the rearrangement only occurs for tertiary sulphonamides; secondary sulphonamides deprotonate at nitrogen and are recovered unchanged. Second, it appears that more than one equivalent of the organolithium base is required (though see later). One equivalent, or less, of base generates a yellow anion that, on quenching with water, yields starting material. Quenching the anion with iodomethane yields a methylated derivative at the *ortho* position of the arene ring of the arenesulphonyl group (equation 46). The use of more than one equivalent of base initially forms the yellow anion which gradually produces a red-brown solution. Quenching of the red-brown solution with water yields the aminosulphone. Third, various bases are able to bring about the rearrangement, e.g. MeLi, PhLi, Bu^{t}Li, Bu^{n}Li, Pr^i_2NLi. Methyllithium has been reported the most efficient[114], though this is not always so[113]. Bases which do not effect rearrangement are NaH, LiH, $NaNH_2$, Li, MeMgI. Fourth, methyl substituents in



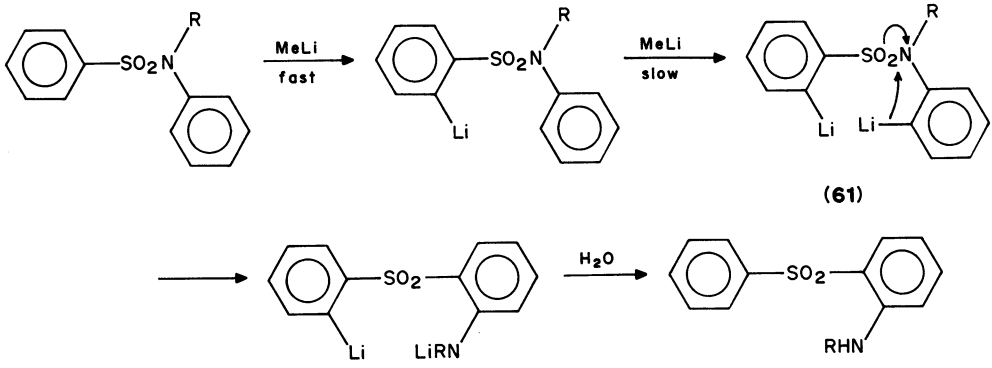
(45)

the arenesulphonyl ring interfere with the course of the reaction, by undergoing metalation of the benzylic position.



(46)

Closson has interpreted these observations by the sequence of reactions shown in Scheme 7[114]. Initial deprotonation occurs, as anticipated, at the *ortho* position of the arenesulphonyl ring. Subsequent deprotonation, to form the red-brown dianion **61** then takes place more slowly, and it is this dianionic species which rearranges to the isomeric dianion of the aminosulphone. Quenching by protonation releases the aminosulphone. Crossover experiments using 4-$MeOC_6H_4SO_2NMeC_6H_4OMe$-4 and 4-TolSONMePh, though not conclusive, point to the rearrangement of the dianion **61** being intramolecular, no crossover products could be detected[114].

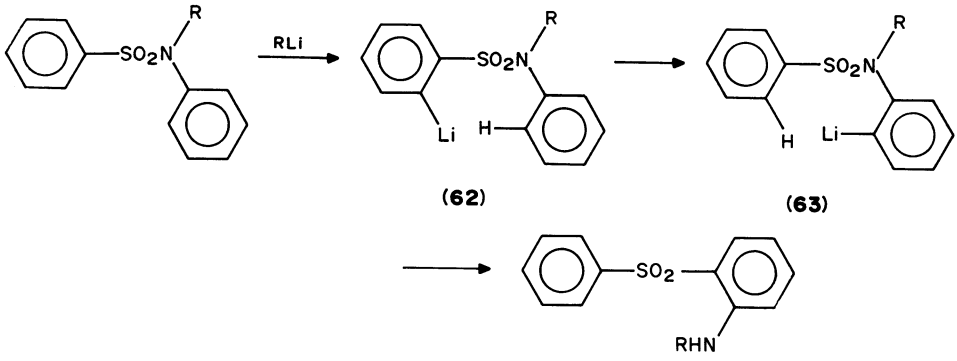


SCHEME 7. Mechanism of the sulphonamide—aminosulphone rearrangement (after Closson[114])

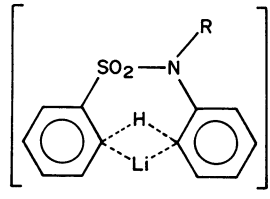
The above observations differ slightly from those of Hellwinkel and colleagues[113,115–118], who showed that only one equivalent of base was necessary to promote rearrangement of acyclic *N*-phenylsulphonamides. Initial deprotonation occurs at the *ortho* position of the arenesulphonyl ring, and this is followed by intramolecular transmetalation of the *N*-phenyl ring (Scheme 8). This species then undergoes rearrangement as previously described. The transmetalation of **62** to **63** is rate-limiting, and can occur at *ca* $-30\,^{\circ}C$ for R = Ph, but requires temperatures $>0\,^{\circ}C$ for R = Me. It is envisaged as proceeding via a transition state such as **64**. Indeed, compound **65**, in which the *N*-phenyl group is unable to approach the *ortho* positions of the arenesulphonyl group (as required by transition state **64**), is stable for extended periods of time when only one equivalent of base is employed. On addition of a second equivalent of base, appropriate deprotonation can occur and rearrangement to form **66** is observed (equation 47)[115,117].

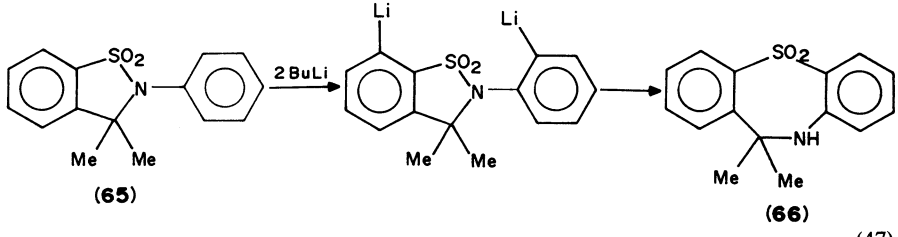
It has been noted that all these rearrangements, including acyclic sulphonamides, proceed more efficiently in the presence of two equivalents of base, i.e. under conditions favouring the second metalation[117].

Independent evidence for the mechanism in Scheme 8 comes from the use of halogen metal exchange reactions[115,116]. Thus, both compounds **67** and **68** undergo reaction with BuLi to yield the corresponding aminosulphone (Scheme 9). However, they do so at vastly



SCHEME 8. Mechanism of the base-catalysed sulphonamide-aminosulphone rearrangement (after Hellwinkel)





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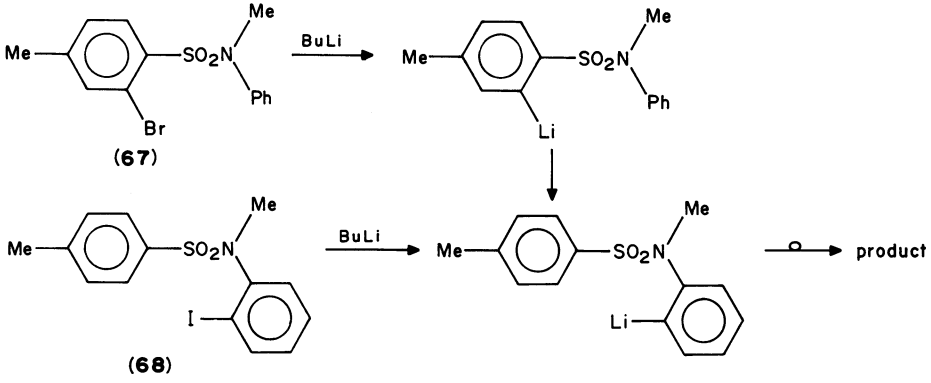
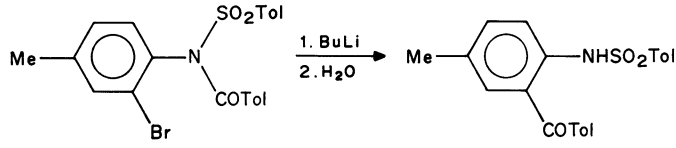


SCHEME 9. Sulphonamide–aminosulphone rearrangement via halogen–metal exchange

differing rates; compound **67** at 0 °C produces only 0.5% of rearranged product after 4 h, whereas under the same conditions compound **68** yields 95% of the aminosulphone[116].

The migratory ability of the sulphonyl group in these reactions is influenced by the presence of a carbonyl group. Thus, compound **69** undergoes rearrangement of the acyl group exclusively (equation 48)[117]. However, the cyclic analogue **70** rearranges with migration of the sulphonyl group (equation 49)[117]. This difference between **69** and **70** is thought to be a consequence of intramolecular nucleophilic attack in general occurring preferentially at the carbonyl centre, but that for **70** the intermediate (or transition state) **71** is precluded for steric reasons whereas the intermediate (or transition state) **72** for attack at the sulphonyl group involves an acceptable trigonal bipyramidal *S* centre.



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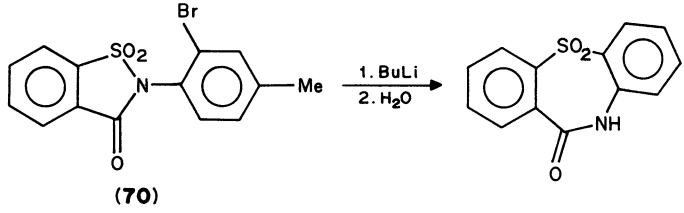
(69)



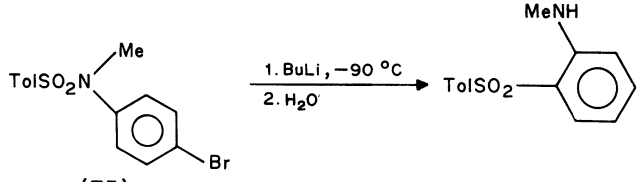
(49)

(70)

(71) (72)

Attempts to extend this [1,3]-base catalysed process to [1,5] systems, e.g. **73** and **74**, result in a series of transmetalations to form the product of a [1,3]-sulphonyl shift (equations 50 and 51)[118].

The purely thermal rearrangement process has been reported only infrequently[116,119–122] and mixture of *ortho*- and *para*-aminophenyl sulphones result (equation 43). The *para*-isomer appears to predominate[119,121,122]. Thus, *N*-phenylbenzenesulphonamide at 300 °C gives a 3.4% yield of the corresponding amino-



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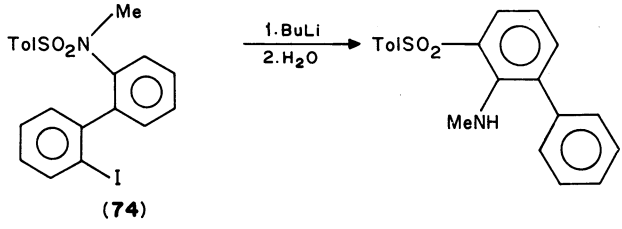
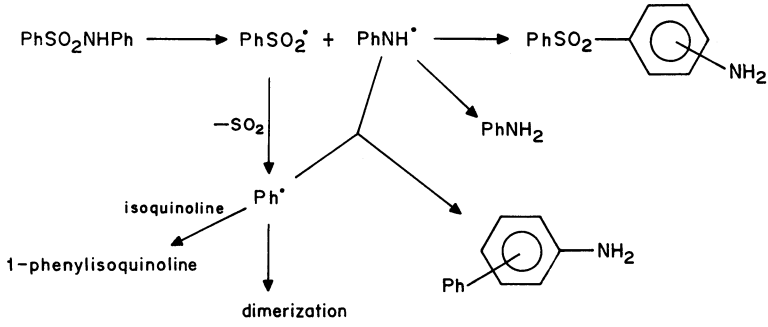


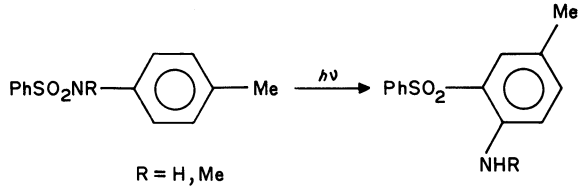
(74) (51)

phenyl sulphones in an *ortho* to *para* ratio of 1:3. The presence of the radical scavenger isoquinoline inhibits the rearrangement and the scavenger is itself phenylated. This points to an intermolecular mechanism for the thermal rearrangement involving homolysis of the S—N bond (Scheme 10). The yields of the thermal rearrangement are extremely variable, ranging from only a few percent up to *ca* 95%. High temperatures (> 200 °C) are required to observe rearrangement in the neat compounds, though in DMF solution temperatures of 130–150 °C are effective[120,121].



SCHEME 10. Pathways involved in the thermolysis of *N*-phenylsulphonamides

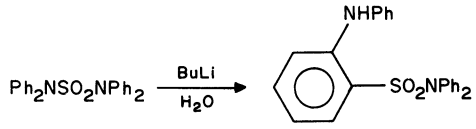
The photochemical rearrangement, using a high-pressure mercury lamp, of *N*-(4-tolyl) and *N*-methyl-(*N*-4-tolyl)benzenesulphonamides to the corresponding 2-aminophenyl sulphones takes place in *ca* 16% yield (equation 52)[118]. Elsewhere it has been stated that such rearrangement is not photolytically promoted[119], but with so few reports pertaining to this reaction a clear understanding of the role of light remains to be developed.



(52)

As mentioned above, sulphamides are also subject to a base-catalysed rearrangement process[22]. Thus, *N*,*N*,*N*′,*N*′-tetraphenylsulphamide on treatment with butyllithium results in an 80% yield of *N*,*N*-diphenyl(2-phenylamino)benzenesulphonamide (equation 53)[116]. In contrast, rearrangement of *N*,*N*′-diphenylsulphamide under neutral conditions (neat aniline) yields 2-amino- and 4-aminobenzenesulphonanilides in roughly equal amounts (equation 54)[123]. Rapid exchange between the aniline of the medium and

both the starting material and 4-aminobenzenesulphonanilide product has been observed, precluding a study of the intra- or intermolecularity of the reaction[123]. However, using dimethylaniline as the medium results in the formation of compound **75**, which suggests that the rearrangement is intermolecular, possibly similar to that of the analogous sulphonamides[109].



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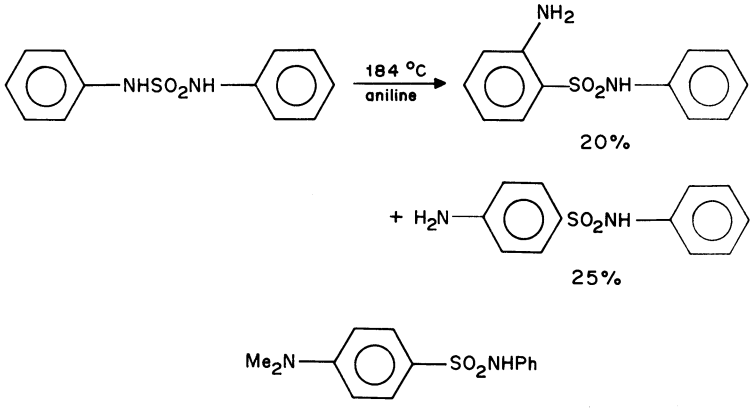

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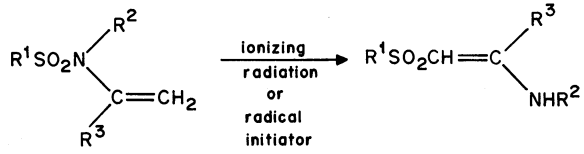
(75)

N-Alkyl-*N*-vinylsulphonamides **76** undergo a similar [1,3]-*N* to *C* rearrangement of the sulphonyl group to form 2-sulphonylvinylamines **77** (equation 55)[124,125]. The reaction is induced photochemically[125], thermally[125], or by ionizing radiation such as X rays or an electron beam[124]. Alternatively, radical initiators, e.g. α,α′-azodiisobutyronitrile, catalyse the rearrangement in solution[124]. Yields of the rearranged product are high (> 70%) for arenesulphonyl derivatives but low (< 10%) for alkanesulphonamides. Table 5 contains representative data for the compounds studied. The reaction clearly depends on the physical state of the starting material. The high *G*-values, the fact that radical initiators promote the reaction, and the observation that oxygen inhibits the photochemical reaction indicate that the rearrangement involves a radical chain mechanism (Scheme 11). The radical chain is initiated by cleavage of the sulphonamide, most probably at the S—N bond, by the ionizing radiation, or from an externally added initiator. This radical, R•, can then add to the vinyl group to form the radical **78** (step A), which can cleave to form the sulphonyl radical, $R^1SO_2{}^{\bullet}$[126] and an imine (step B). The propagation of the radical chain can then take place by the addition of the sulphonyl radical at the *N*-vinyl moiety of the



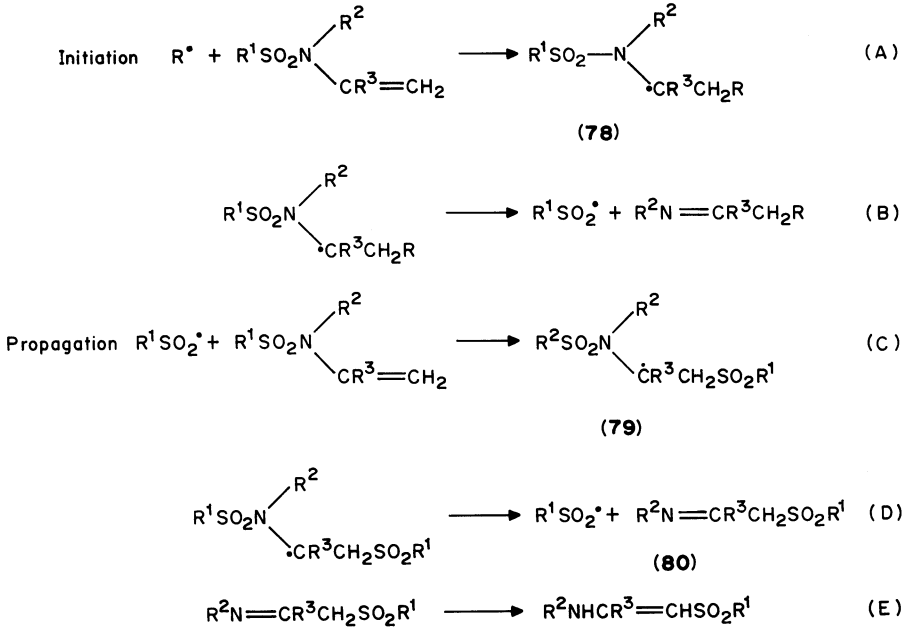
(55)

(76) (77)

TABLE 5. Isomerization of *N*-vinylsulphonamides, $R^1SO_2NR^2(CR^3{=}CH_2)$[124,125]

R^1	R^2	R^3	Yield (%)	Method	*G*-value
Ph	Me	H	72	Electron beam	26[a]
			10	X-ray	4900[b]
			8	X-ray	450[c]
			1	X-ray	60[d]
4-Tol	Me	H	72	Electron beam	63[a]
			13	X-ray	1300[b]
			4	X-ray	450[c]
			5	X-ray	500[d]
			10	*hv*,N_2	
4-Tol	Bu	H	68	Electron beam	32[a]
4-Tol	Me	Ph	94	Electron beam	350[a]
			0	X-ray	0[b]
			48	X-ray	48[c]
			60	*hv*,N_2	
			0	*hv*,air	
2-Naph	Me	H	10	Electron beam	4[a]
Bu	Me	H	7	Electron beam	3[a]
Me	Me	H	5	Electron beam	6[a]

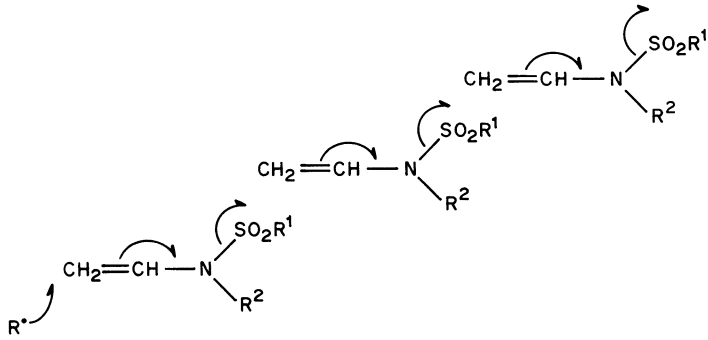
[a]Per 100eV of energy absorbed.
[b]Crystal.
[c]Supercooled liquid.
[d]Liquid.



SCHEME 11. Radical chain mechanism for the [1,3]-sulphonyl group migration in *N*-vinylsulphonamides

starting material to generate the radical **79** (step C). This radical can then fragment to form the imine **80** and regenerate $R^1SO_2^{\bullet}$ (step D). In the final, product-forming step (step E), the imine **80** tautomerises to the 2-sulphonylvinylamine.

The effect of state on the efficiency of the rearrangement (Table 5) probably relates to the relative orientation of the molecules. It has been proposed that if the sulphone group of one molecule is proximate to the terminal alkene carbon of another, then the rearrangement can proceed in a radical chain mechanism with little atomic displacement (Scheme 12).



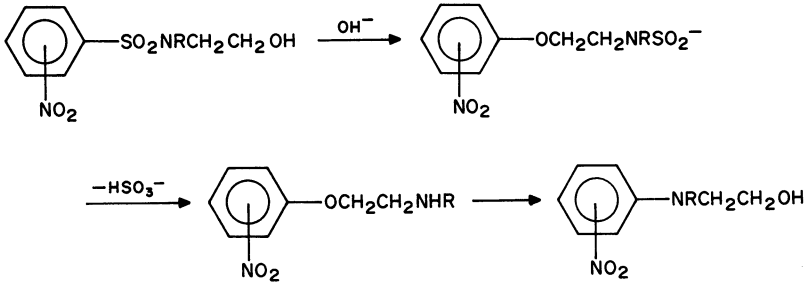
SCHEME 12. Possible mechanism for the rearrangement of *N*-vinylsulphonamides in the crystalline state

The crystal structures of the *N*-vinylsulphonamides are unknown, and it would be informative if such determinations were made, but the effect of molecular orientation in the crystalline state is one that has been invoked in the rearrangement of aminoarenesulphonate esters (Section III.B).

B. Smiles and Similar Types of Rearrangement of Arenesulphonamides

The Smiles and related rearrangements involve the initial formation of sulphinamates which rapidly extrude SO_2. However, because of their potential interest and synthetic utility we include them here.

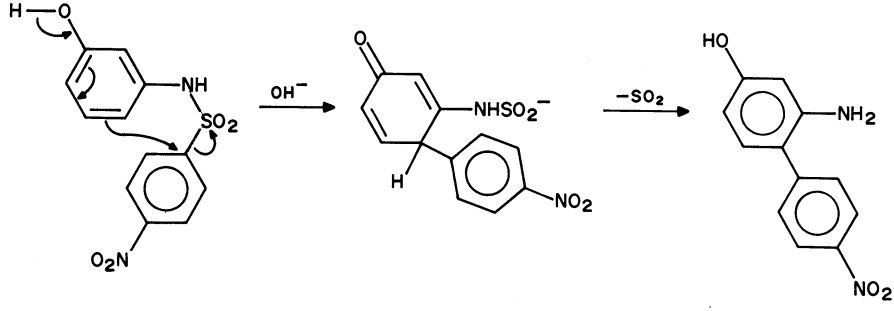
N-(2-Hydroxyalkyl)-*ortho*- and *para*-nitrobenzenesulphonamides undergo rearrangement in base to yield first an aminoalkyl *o*- or *p*-nitrophenyl ether, which subsequently rearranges to the corresponding *N*-(2-hydroxyalkyl)-*o*- or *p*-nitroaniline (equation (56)[127–130].



(56)

The reaction involves the oxyanion of the alcohol which then undergoes an S_NAr attack at the *ipso* sulphonyl carbon atom of the activated aryl ring. The S_NAr process is faster for secondary sulphonamides, than for tertiary ones, i.e., R = H ≫ Et > Me ≈ Ph. This is attributed to formation of the sulphonamide anion and that this anion adopts a preferred conformation conducive to the S_NAr reaction[127]. Alkyl substituents in the hydroxyalkyl group also increase the rate of the rearrangement reaction[127].

A similar type of base-catalysed rearrangement can be observed in activated *N*-(hydroxyphenyl)arenesulphonamides, in which the nucleophilic centre is a carbon atom *ortho* or *para* to the hydroxy group of the *N*-hydroxyphenyl ring (e.g. equations 57 and 58)[131]. The hydroxy group is required for activation, and at least one of the positions *ortho* or *para* to this group must be unsubstituted. The arenesulphonyl ring must be activated towards nucleophilic attack by the inclusion of electron-withdrawing groups, such as NO_2, RSO_2 or RCO, in the *ortho* or *para* positions. The reaction can be extended to vinylogous nitrostyrene sulphonamides (**81**), from which diphenylethenes result (equation 59).



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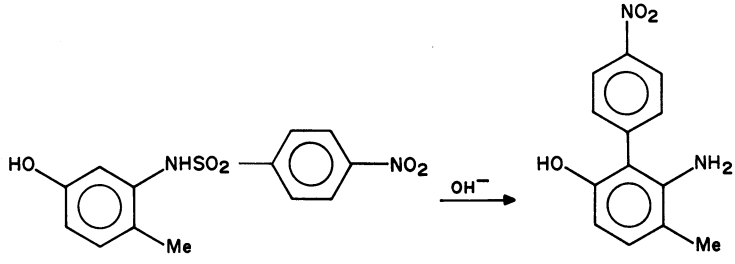

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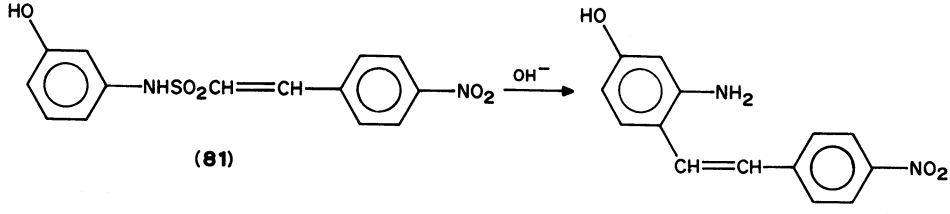
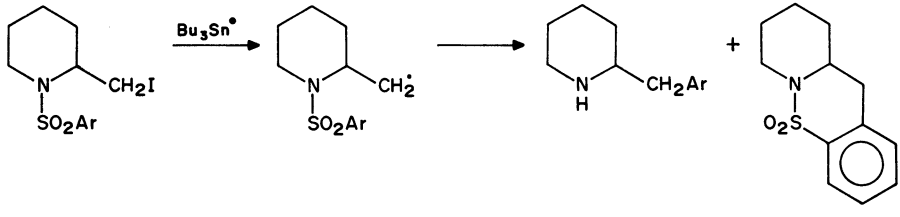


(81)

(59)

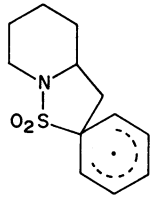
The above reactions involve the nucleophilic attack of a sulphonamide β-carbon at the carbon atom α to the sulphonyl group. A radical analogue of this reaction is known[132,133].

Thus, the *N*-(arenesulphonyl)piperidine **82** reacts with tributyltin radicals to form, at about 90 °C, equal amounts of the rearranged product **83** and the product of arenesulphonyl ring substitution **84** (equation 60). Temperature has a profound effect on the product ratio; at 190 °C, the rearranged product dominates giving a ratio of 7:1. The formation of **83** is thought to involve **85**.



(82) **(83)** **(84)**

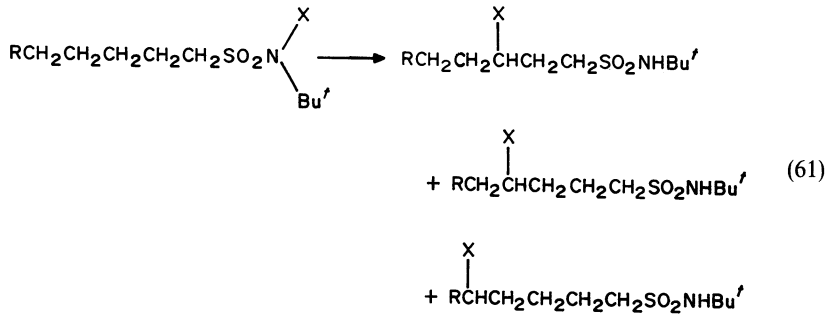
(60)



(85)

C. *N*-Halosulphonamides

The rearrangement of *N*-halosulphonamides has been briefly reviewed previously[134]. *N*-Bromo or *N*-chloro-*N*-*tert*-butyl alkanesulphonamides rearrange upon photolysis to the corresponding *N*-*tert*-butyl-3-, -4- and -5-haloalkanesulphonamides (equation 61). Substitution of the halogen at the 3-position of the alkanesulphonyl group predominates (Table 6). After initial photolytic cleavage of the N—X bond, three processes can be envisaged to contribute to the formation of products: (1) intramolecular hydrogen abstraction by the sulphonamide radical, (2) intermolecular hydrogen abstraction by the sulphonamide radical and (3) hydrogen abstraction by the halogen atom. The formation of the 5-chloro derivative cannot be attributed to an intramolecular hydrogen abstraction process and, moreover, the absolute yield of this isomer drops dramatically on purging the reaction with nitrogen (Table 6). Thus, the 5-chloro derivative is the product of hydrogen abstraction by Cl•[137]. The isomer ratio for the 3- and 4-chloro derivatives increases with nitrogen purging to a value similar to that from the analogous *N*-bromosulphonamides. Clearly, some of the 4-isomer arises from hydrogen abstraction, but the ratio obtained for the *N*-bromo compound is considered to be that for intramolecular hydrogen atom abstraction by the sulphonamide radical. General support for intramolecular hydrogen atom abstraction by the sulphonamide radical comes from the invariance of the product isomer distribution with concentration of starting material (Table 6). For *N*-chlorosulphonamides, intramolecular sulphonamide radical hydrogen atom abstraction can be promoted by the use of aqueous acetic acid as solvent. This is thought to be largely due to the reduction in reactivity of Cl• by solvation[137].



(61)

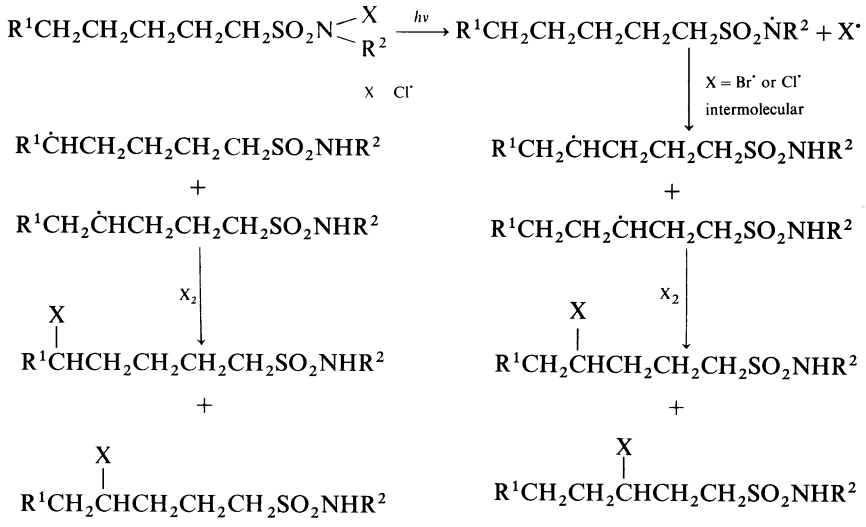
Thus, the photolytic rearrangement of *N*-halosulphonamides proceeds via the mechanism in Scheme 13. The ratio of the 3-halogen to 4-halogen substituted products can be rationalized by either, or both, of two arguments. Thermodynamically, the carbon radical formed at C-3 is more stable than that at C-4 whichever mechanism (intra- or intermolecular hydrogen atom abstraction) is in operation. Moreover, for intramolecular hydrogen atom abstraction, the transition state for [1,5]transfer of a hydrogen atom **86** is likely to be energetically more favourable than that for [1,6] transfer **87**. Both rationales lead to a greater fraction of the products substituted at the 3-position. However, as the length of the alkanesulphonyl group increases, the difference in stability between the C-3 and C-4 radicals is diminished and the ratio of C-3 to C-4 substituted product is reduced.

Interestingly, product compositions similar to those obtained from the photolytic decomposition of *N*-halosulphonamides are obtained from the parent sulphonamides upon reaction with the $Na_2S_2O_8/CuCl_2$ system (equation 62)[139,140]. The logical inference is that these reactions, too, involve the sulphonamide radical as an intermediate. However, in this system it has been observed that for *N*-alkyl chains, such as n-C_5H_{11}, substitution into the C-4 position of the *N*-alkyl group, via a six-membered transition state, is also

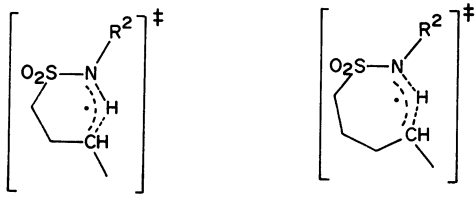
TABLE 6. Product composition from the photolytic rearrangement of *N*-halosulphonamides, $R^1SO_2NXR^2$

Sulphonamide			Yield and position of substitution R^1			
R^1	R^2	X	3-	4-	5-	Ref.
n-C_6H_{13}	Bu^t	Br	55.3	28.2		135
		Cl	30.8	25.7	20.5	137[a]
			50.4	31.4	3.1	137[b]
n-C_5H_{11}	Bu^t	Br	50.0	42.1		135
		Cl	40.3	37.1		136
n-C_4H_9	Bu^t	Br	79.3	—		135, 138
		Cl	61.9	15.1		136[c]
			60.5	15.5		136[d]
			71.1	11.3		137[b]
n-C_4H_9	Me	Cl	20.3	0.5		136
			89.7	1.0		137[e]

[a]No purging with N_2.
[b]Rapid purging with N_2.
[c]Conc. of starting material = 0.52 mol dm^{-3}.
[d]Conc. of starting material = 2.58 mol dm^{-3}.
[e]In AcOH–H_2O (1.75:1).



SCHEME 13. Pathway for the photolytic rearrangement of *N*-halosulphonamides



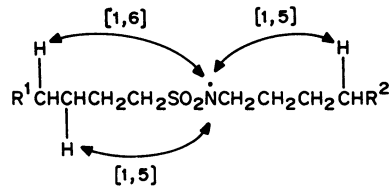
(86) (87)

possible (equation 63)[140]. Substitution into the *N*-alkyl group is somewhat less favourable than into the alkanesulphonyl group, the amount varying from 30 to 80% of that seen for alkanesulphonyl substitution[140]. Unfortunately, photochemical studies employing *N*-alkyl-*N*-halo alkanesulphonamides in which the alkyl and alkane groups are of similar length have yet to be reported, so comparison with the $Na_2S_2O_8/CuCl_2$ is not possible. However, photolytic rearrangement into the 4-carbon of the *N*-alkyl chain has been reported for *N*-chloro arenesulphonamides[141] and *N*-halo ethanesulphonamides[142]. It would be instructive to study systems such as $R^1(CH_2)_4SO_2NBr(CH_2)_4R^2$ photolytically

$$R^1CH_2CH_2CH_2CH_2SO_2NHR^2 \xrightarrow[CuCl_2]{Na_2S_2O_8} R^1CHClCH_2CH_2CH_2SO_2NHR^2 + R^1CH_2CHClCH_2CH_2SO_2NHR^2 \quad (62)$$

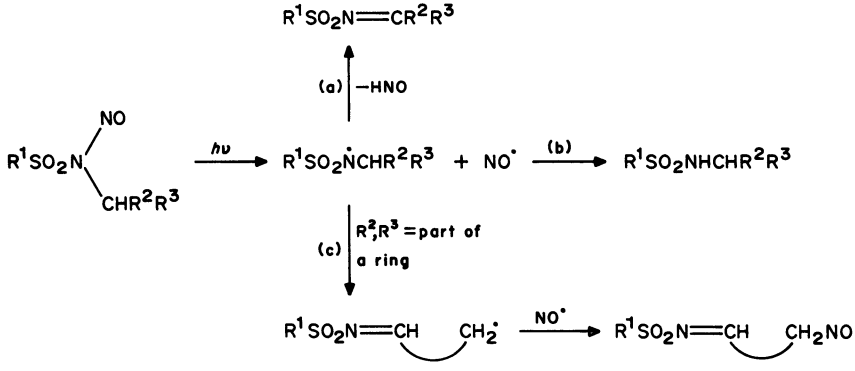
$$Bu^nSO_2NHC_5H_{11} \xrightarrow[CuCl_2]{Na_2S_2O_8} CH_3CHCl(CH_2)_2SO_2NHC_5H_{11} + Cl(CH_2)_4SO_2NHC_5H_{11} + Bu^nSO_2N\langle + MeCHCl(CH_2)_2SO_2N\langle \quad (63)$$

in order to determine more directly the relative propensity of the sulphonamide radical to hydrogen atom abstract from the *N*-alkyl and alkanesulphonyl groups:

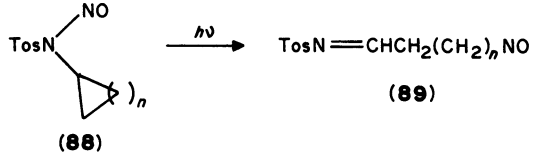


D. *N*-Nitrososulphonamides

The photolysis of *N*-nitrososulphonamides proceeds, as with their *N*-halo counterparts (Section V.C), via the formation of sulphonamide radicals due to the rupture of the N—N bond (Scheme 14)[143,144]. Thereafter, several processes may be observed, viz. hydrogen atom abstraction to form an imine (a), hydrogen atom abstraction from the solvent to form the parent sulphonamide (b), or sulphonamide radical rearrangement followed by recombination with NO• to form a nitrosoalkane isomer of the *N*-nitrososulphonamide (c). Simple *N*-alkyl-*N*-nitroso sulphonamides react via the first two pathways[145], but the sulphonamide radical can be intercepted and diverted into the rearrangement pathway by use of *N*-cycloalkyl substituents[143,144]. Thus, *N*-cyclopropyl-*N*-nitroso 4-toluenesulphonamide (**88**, $n = 1$) undergoes photolytic rearrangement to *N*-(4-toluenesulphonyl) 3-nitrosopropanimine (**89**, $n = 1$) (equation 64). The corresponding *N*-cyclobutyl derivative (**88**, $n = 2$) also undergoes this reaction, but incursion of the hydrogen atom abstraction process (a) (Scheme 14) is more prevalent. For the cyclopentyl derivative (**88**, $n = 3$), no rearrangement process could be detected.

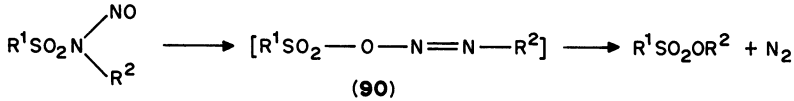


SCHEME 14. Pathways for the photolytic degradation of *N*-nitrososulphonamides

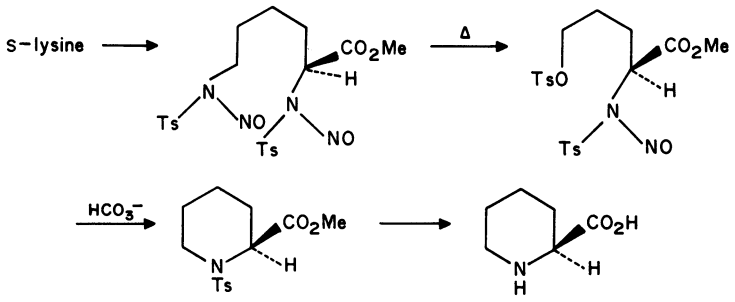


(64)

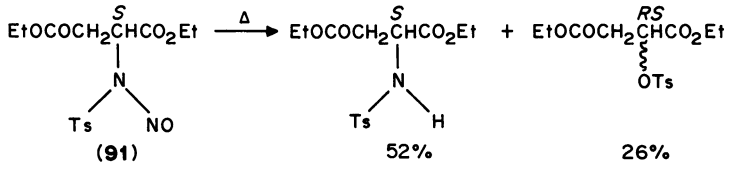
The thermal rearrangement of *N*-nitrososulphonamides yields the corresponding sulphonate ester[146], in a similar manner to the analogous *N*-nitrosoamide-ester rearrangement[147]. The reaction probably involves a diazo ester intermediate **90** (equation 65). However, the N—N bond of *N*-nitrososulphonamides appears more sensitive to rupture on thermolysis and denitrosation often occurs more readily than rearrangement. This is especially so for *N*-alkyl-*N*-nitrososulphonamides containing higher alkyl groups[148], and also for the *N*-cyclopropyl derivative[144]. Nevertheless, clever use has been made of the *N*-nitrososulphonamide–sulphonate ester rearrangement in the synthesis of *S*-pipecolic acid (equation 66)[149]. Similar thermal rearrangement of compound **91**, obtained from *S*-aspartic acid, is mechanistically informative (equation 67). Denitrosation is the major pathway, rearrangement yields optically inactive sulphonate ester and a small amount of alkene is produced via an elimination pathway[149]. Rearrangement thus involves complete racemization, probably via carbocation formation from the appropriate diazoester (**90**).



(65)



(66)

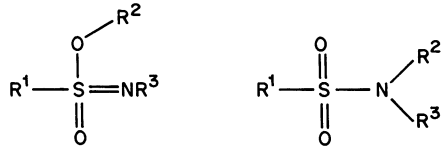


(67)

E. [1,3]-Rearrangement of Sulphonimidates to Sulphonamides

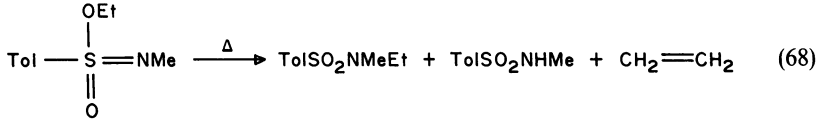
Sulphonimidates **92** are tautomeric with sulphonamides **93**. For $R^2 = H$ no evidence for the existence of the sulphonimidic acid has been adduced, the sulphonamide structure being thermodynamically the more stable. For $R^2 = R_3Si$, the sulphonamide structure is generally the major tautomer[150]. Only when strongly electron-withdrawing groups are attached to the nitrogen atom, e.g. $R^3 = Cl$, NMe_2, can the sulphonimidate tautomer be observed, the equilibrium constant for (**92**, $R^2 = Me_3Si$)⇌(**93**, $R^2 = Me_3Si$) varying between 0.4–0.75 in benzene at 25 °C[150]. The effect of the electronegative groups attached

to nitrogen is to reduce S—N π-bond character in the sulphonamide tautomer. This is discussed elsewhere in this volume[151].

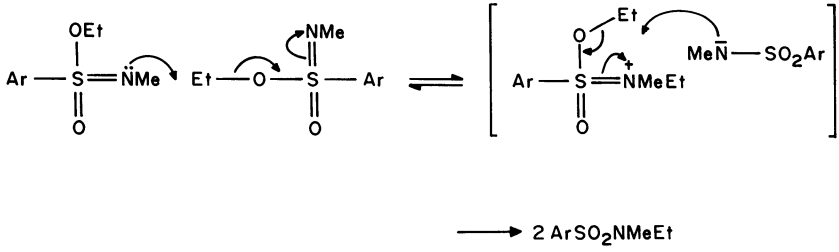


(92) (93)

For R^2 = alkyl or aryl the sulphonimidate isomer is sufficiently stable to be isolated[152–154]. Nonetheless, *O*-alkyl sulphonimidates are thermodynamically unstable with respect to the *N*-alkylsulphonamide, and are observed to rearrange to the sulphonamide on heating (equation 68)[154]. Concurrent elimination is also observed. The mechanism of this purely thermal reaction is bimolecular, and most likely involves the formation of an ion pair by the intermolecular alkylation of the sulphonimidate nitrogen atom by a second sulphonimidate molecule (Scheme 15). *O*-Aryl sulphonimidates do not rearrange to the corresponding *N*-arylsulphonamides. Thus, the Chapman rearrangement appears to be confined to carboximidate–carboxamide systems.

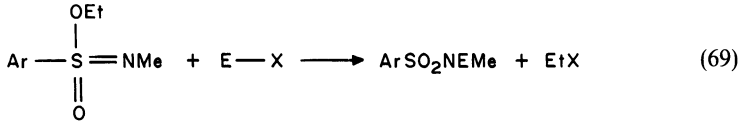


(68)



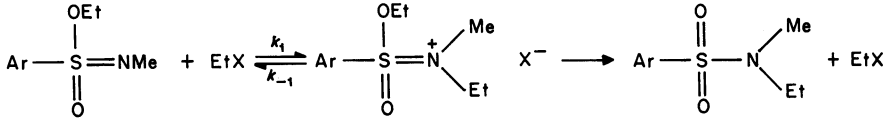
SCHEME 15. Mechanism of the thermal rearrangement of *O*-alkyl sulphonimidates of *N*-alkylsulphonamides

The *O*-alkyl sulphonimidate–*N*-alkylsulphonamide rearrangement is catalysed by electrophiles, e.g. RX (X = I, Br, SO_3F), HX, ZnI_2[154]. Electrophilic catalysis results from the formation of EtX by the reaction of the sulphonimidate with the electrophile (equation 69). The liberated EtX itself can react with the sulphonimidate in a manner (Scheme 16) similar to that for the purely thermal rearrangement. The catalytic role of EtX is apparent. The reaction proceeds most rapidly in polar solvents, consistent with the

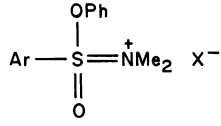


(69)

formation of an ion pair. Indeed for *O*-phenyl sulphonimidates, the ion pair **94** can be isolated, and the equilibrium k_1/k_{-1} established. The rate of rearrangement depends on the nature of X, decreasing in the order $FSO_3 > I > Br > Cl$ consistent with formation of the ion pair being rate-limiting[154].



SCHEME 16. The catalysed rearrangement of *O*-alkyl sulphonimidates to *N*-alkylsulphonamides

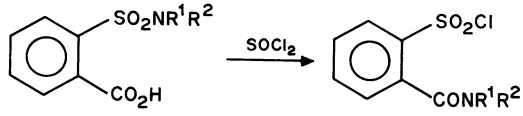


(94)

F. Miscellaneous Rearrangements of Sulphonamides

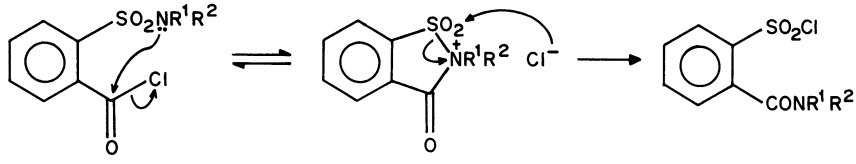
In this section we include a variety of disparate rearrangements that cannot easily be classified elsewhere.

Reaction of *N,N*-dialkyl (*o*-carboxybenzene)sulphonamides (**95**) with thionyl chloride (or bromide) results in the formation of *N,N*-dialkyl (*o*-chlorosulphonyl)benzamides rather than the expected benzoyl chlorides (equation 70)[155]. The reaction involves the formation of the expected benzoyl chloride which rearranges via nucleophilic attack of the sulphonamide nitrogen atom at the acyl halide (Scheme 17). The rate of rearrangement depends on the pK_a of R^1R^2NH, and if this is less than 9 no rearrangement takes place. The rearrangement is intramolecular, reaction of the *para* isomer of **95** with $SOCl_2$ stops at the formation of the benzoyl chloride and no subsequent (intermolecular) rearrangement is seen. For *N*-benzylsulphonamides, collapse of the intermediate ion pair (Scheme 17) follows a different course; debenzylation is observed. Attempts to extend the reaction to a six-membered analogue obtained from **96** met with no success.

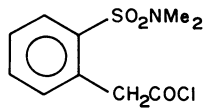


(95)

(70)

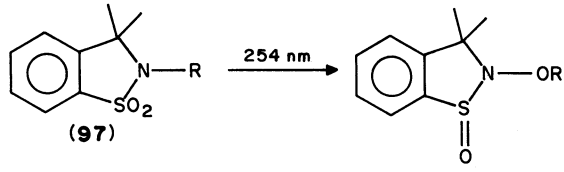


SCHEME 17. Rearrangement of *o*-chloroformylbenzenesulphonamides to *o*-chlorosulphonylbenzamides



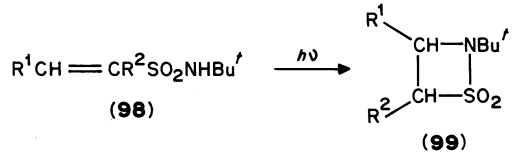
(96)

Photoisomerization of the saccharin derivatives **97** occurs efficiently in methanol solution (equation 71)[156]; the mechanism of this unusual rearrangement remains to be elucidated, but the reaction occurs for R = H and CH_2OMe but not for R = Me.



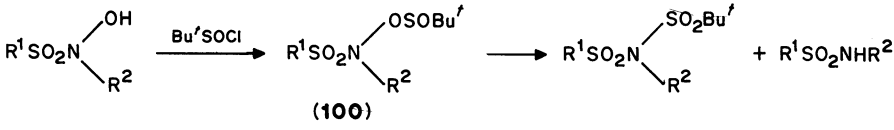
(97) (71)

N-tert-Butyl alkenesulphonamides have been investigated for potential photoisomerization reactions[157] and it has been found that compound **98**, R^1 = Ph, R^2 = Me undergoes photocyclization to the sultam **99** (equation 72). Other substrates (R^1 = Ph, R^2 = H; $R^1 = R^2$ = Ph; R^1 = 4-$NO_2C_6H_4$, R^2 = Ph) do not undergo similar rearrangement.

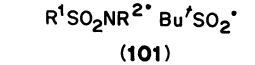


(98) (99) (72)

N-Hydroxysulphonamides react with *tert*-butylsulphinyl chloride to form *N*-sulphinyloxysulphonamides **100**[158]. Such compounds are unstable and spontaneously undergo rearrangement to form sulphonimides, and dissociation to form the sulphonamides, *tert*-butylsulfonic anhydride and *tert*-butyl *tert*-butylthiosulphonate (equation 73). The products are consistent with the intermediacy of the radical pair **101**, formed from N—O bond homolysis of **40**, and CIDNP of the signals in the ^1H and ^{13}C NMR spectra provides compelling evidence that this is so. The rearranged sulphonimide product arises from an in-cage recombination of the radical pair, whereas the sulphonamide arises from escape of the radicals from the cage.



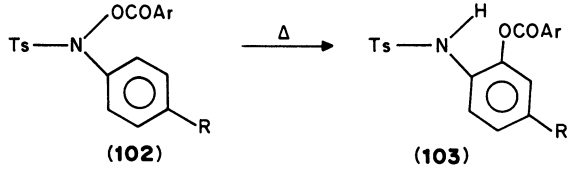
(100) (73)



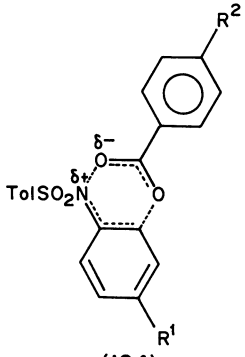
(101)

N-Aryl *N*-benzoyloxysulphonamides (**102**) rearrange on heating to the corresponding *N*-(2-benzoyloxyaryl) sulphonamides (**103**) (equation 74)[159]. Unlike the *N*-sulphinyl-

oxysulphonamides described above, the rearrangement of **102** does not involve a radical process. Rather, it appears to involve a six-membered cyclic transition state, **104**, that has some ionic character. Thus, ^{18}O labelling experiments reveal that (a) no scrambling of the oxygen atoms occurs, and (b) the carbonyl oxygen atom of the starting material ends up as the ester oxygen in the product. This pattern of ^{18}O labelling is unaffected by solvent polarity. Further, the rate is largely independent of solvent polarity, being only 1.3 times as fast in CH_3CN as in $CHCl_3$. However, the effect of the group R^2 in the aryl ring of the acyl group is to increase the rate when R^2 is electron-withdrawing ($\rho = +1.5$), indicating an increase in electron density in the acyl moiety in the transition state. Conversely, electron-donating R^1 groups increase the rate of rearrangement, consistent with the decrease in electron density in the *N*-aryl part of the molecule as formulated in **104**.

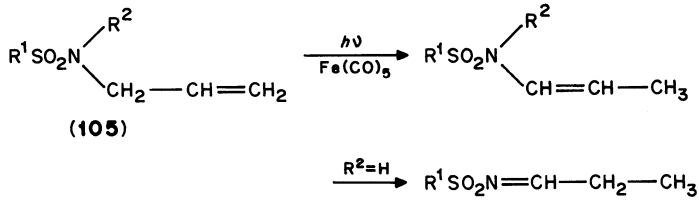


(102) (103) (74)



(104)

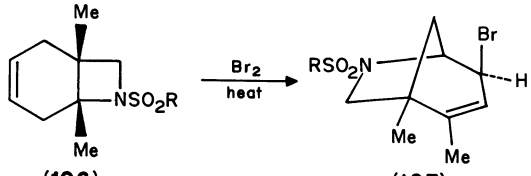
N-Allylsulphonamides (**105**) are readily isomerized by UV light in the presence of iron pentacarbonyl (equation 75)[160]. The first formed product is an *N*-vinyl sulphonamide, most probably formed via an intramolecular [1,3]-hydrogen migration, which for secondary sulphonamides ($R^2 = H$) can undergo a further [1,3]-hydrogen shift to form an *N*-sulphonylimine. Under these conditions, the *N*-vinylsulphonamides do not appear to undergo rearrangement to 2-aminoalkyl sulphones (Section V.A)



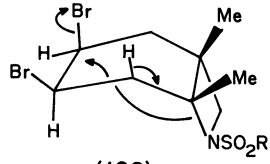
(105) (75)

Sulphonamides are weakly nucleophilic species and react only with the more reactive electrophiles e.g. $MeSO_3F$[154]. However, participation of the sulphonamide nitrogen atom in the rearrangement of bicyclic *N*-sulphonyl amines has been occasionally repor-

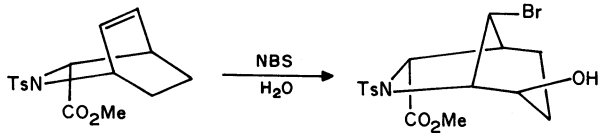
ted[161,162]. Thus, the *N*-sulphonyl derivative of *cis*-1,6-dimethyl-7-azabicyclo[4.2.0]oct-3-ene (**106**) undergoes rearrangement on reaction with Br_2 and heating to the product **107** (equation 76)[161] via the intermediate dibromo compound **108**. Similarly, bromination of the *N*-tosyl 2-azabicyclo[2.2.2]oct-5-ene **109** yields the bicyclo[3.2.1]octane derivative **110** (equation 77)[162].



(106) (107) (76)



(108)



(109) (110) (77)

VI. SULPHONYL AZIDES

Under thermolytic or photolytic conditions azides undergo reaction via extrusion of nitrogen. Sulphonyl azides are no exception. Thermolysis generates a sulphonyl nitrene which is involved in a variety of reactions including hydrogen abstraction, inter- and intramolecular insertion into C—H bonds and insertion into C=C double bonds[163,164]. However, it has been reported that thermolysis of 2,4,6-trimethylbenzenesulphonyl azide gives rise to both 2,4,6-trimethylaniline and a small amount of the corresponding azobenezene (equation 78) as well as the products of abstraction and insertion processes[163]. These results were interpreted as evidence for the formation of a sulphonyl nitrene (**111**) which rearranges to an *N*-sulphonylaniline (**112**) that is capable of forming arylnitrene (equation 79)[163]. The *N*-sulphonylaniline is also a potential intermediate in the photolysis of arenesulphonyl azides. Though a mechanism involving a concerted rearrangement process cannot be excluded, the products obtained from the photolysis of benzenesulphonyl azide in methanol contained *ca* 25% of methyl *N*-phenylsulphamate

$$ArSO_2N_3 \xrightarrow{\Delta} ArNH_2 + ArN{=}NAr \tag{78}$$

$$ArSO_2N_3 \xrightarrow{-N_2} ArSO_2\ddot{N}: \longrightarrow ArN{=}SO_2 \xrightarrow{-SO_2} Ar\ddot{N}: \tag{79}$$

(**111**) (**112**)

113[75]. This can be thought to arise by the trapping of the *N*-sulphonylaniline by solvent methanol (equation 80). Thus, arenesulphonyl azides are able to undergo Curtius-type rearrangements.

$$PhSO_2N_3 \xrightarrow{h\nu} PhN{=}SO_2 \xrightarrow{MeOH} PhNHSO_2OMe \quad (80)$$

(113)

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CHAPTER 13

Photochemistry and radiation chemistry

WILLIAM M. HORSPOOL

Department of Chemistry, University of Dundee, Dundee, DD1 4HN, Scotland, UK

The chemistry of sulphonic acids, esters and their derivatives
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For the purpose of this review the compounds included are those containing hexavalent sulphur bonded to a hetero atom as in C—SO_2—X where X can be Br, Cl, I, O— or N= or another carbon. The photochemical reactions covered involve, in the main, S—X bond fission. This area is a well trodden path with copious examples throughout the literature. The review by Block[1a] is reasonably comprehensive for the literature prior to 1969 and other informative review articles are the appropriate chapters in *Photochemistry*[1b]. Specific reviews are included in the text at the appropriate places.

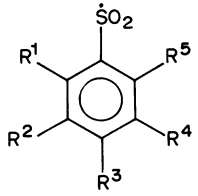
I. SULPHONYL HALIDES

A. Sulphur–Chlorine Bond Fission

The photochemical reactivity of sulphonyl chlorides is dominated by the weak S—Cl bond. Irradiation results in fission into chlorine atoms and sulphonyl radicals. Typical results from such irradiations have been reported by Horowitz[2] in the irradiation of methanesulphonyl chloride in cyclohexane at 150 °C. The principal gaseous products were identified as cyclohexyl chloride, methane and sulphur dioxide with a trace of methyl chloride. All of these products arise by free radical paths. Another study has shown that the irradiation of cyclohexanesulphonyl chloride in the presence of oxygen brings about oxidation of the cyclohexanesulphonyl radical to yield cyclohexanesulphonic acid[3]. A kinetic study of the recombination of sulphonyl radicals in the liquid phase has been reported. These radicals are formed by the pulse photolysis of RSO_2Cl (R = pentyl or cyclohexyl) affording $RSO_2^{\bullet}$ and chlorine atoms[4]. γ-Radiolysis is also effective in reactions with sulphonyl chlorides with the formation of sulphonyl radicals being detected by conventional means[5,6]. Other studies have demonstrated that pulse radiolysis of alkanesulphonyl chlorides (RSO_2Cl, R = Me, Et or Pr) also yields the sulphur-centred radical ($RSO_2^{\bullet}$)[7]. A series of radiolysis experiments by Dzhagatspanyan and coworkers[9] also illustrates the ease with which the S—Cl bond is cleaved in cyclohexanesulphonyl chloride and hexane-1-sulphonyl chloride.

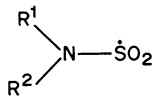
A detailed study by ESR of the arenesulphonyl radicals **1** has been reported following the irradiation of the corresponding chlorides in toluene[9]. The spin distribution in the radicals was determined as was the rotation around the S—C aryl bond. A similar study was performed using the sulphonamidyl chlorides **2**. This clearly showed that the radical was still sulphur-centred and that there was little interaction with the adjacent nitrogen[10]. A review of the reactivity and the formation of sulphur-centred radicals has been published[11].

Apart from product analysis and ESR studies on the free radicals generated by the irradiation, other methods for the detection of the generated free radicals have been used. This area is of some synthetic value since it can be shown that the irradiation using a tungsten lamp of benzenesulphonyl chloride in the presence of either *cis*- or *trans*-but-2-ene affords 1:1 adducts **3**[12,13]. Photoaddition of *p*-toluenesulphonyl chloride to norbor-



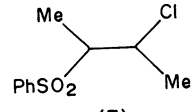
(1)

R^1	R^2	R^3	R^4	R^5
Me	H	Me	H	Me
Me	Me	H or Me	Me	Me
Me	H	Me	Me	Me
Cl	H	Cl	H	H
Br	H	Br	H	H
Br	H	H	Br	H

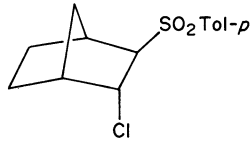


(2)

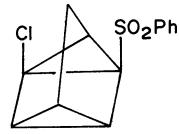
$R^1=R^2=H$ or Me



(3)



(4)



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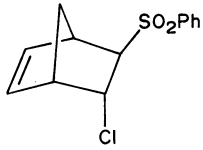

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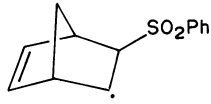

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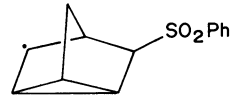


(8)

Cl_3CSO_2Cl $Cl_3C\dot{S}O_2$

(9) **(10)**

nene yields the *trans*-adduct **4** in 64% yield. This process is selective and does not bring about structural rearrangement of the norbornane skeleton nor is the *cis*-adduct formed[14]. Skeletal rearrangement does occur on the photoaddition of benzenesulphonyl chloride to norbornadiene[15]. This reaction affords the rearrangement product **5** and the *trans*-adduct **6**. The reactivity of benzenesulphonyl chloride is poor and better yields of adducts are obtained using the corresponding bromo- and iodo-sulphonyl compounds. The yield of the *trans*-adduct increases with the change from bromine to iodine. The results favour the presence of the two intermediates **7** and **8** rather than a non-classical species. Reviews of the synthetic utility of these reactions have been published[16,17]. Other applications have also been reported. Thus the irradiation of the sulphonyl chloride **9** brings about S—Cl fission and the formation of the sulphur-centred radical **10**. This reaction system has been used to halogenate alkanes where it was found to be more specific than sulphuryl chloride. Sulphur dioxide and chloroform are by-products of the reactions shown in equation[18–20].

$$\mathbf{10} + RH \longrightarrow Cl_3CSO_2H + R\cdot$$

$$R\cdot + Cl_3CSO_2Cl \longrightarrow RCl + \mathbf{10} \quad (1)$$

$$PhSO_2F \xrightarrow{h\nu} Ph\dot{S}O_2 + F\dot{S}O_2 + \dot{P}h \quad (2)$$

B. Miscellaneous Halides

Other sulphonyl halides have also attracted attention. Thus Kandror and collaborators have studied the irradiation of benzenesulphonyl fluoride and have shown that the radicals shown in equation 2 are formed; proof was obtained by ESR studies and spin trapping techniques. A similar treatment was carried out for benzenesulphonyl chloride. Interestingly the irradiation of benzenesulphonyl fluoride results in aryl C—S bond fission in preference to S—F fission[22]. The corresponding sulphonyl bromide undergoes S—Br fission solely, while benzenesulphonyl chloride follows both the C—S and S—Cl paths[22]. Again the justification of these results comes from ESR and spin trapping experiments.

C. Sulphonyl Iodides

Sulphonyl iodides are also photochemically labile and undergo S—I fission. In a flash photochemical study of the photodecomposition of the arenesulphonyl iodides (**11 a–d**) presence of the radicals **12** was observed[23]. The relative reactivity of the sulphonyl radicals **12** was studied following irradiation of the iodides **11c** and **13**. Electron-donating substituents decrease the selectivity of the radical[24]. Sun-lamp irradiation of the sulphonyl iodide **14** also brings about S—I bond fission to afford the sulphonyl radical (**12**, Ar = $PhCH_2$) and an iodine atom. Cage reactions result in the formation of benzyl iodide in 89.4% yield[25].

$ArSO_2I$

(**11**) (**a**) Ar = *p*-tolyl — $ArSO_2^{\cdot}$ (**12**)
(**b**) Ar = Ph
(**c**) Ar = p-ClC_6H_4
(**d**) Ar = 2,4,6-tri-$Pr^iC_6H_2$

(**13**) (**a**) Ar = *p*-$MeOC_6H_4$
(**b**) Ar = *p*-$AcNHC_6H_4$
(**c**) Ar = *m*-$NO_2C_6H_4$

(**14**) Ar = Ph CH_2

The free radicals produced by the irradiation of the sulphonyl iodides can also be trapped by double bonds in a reaction akin to those described for the sulphonyl chlorides (Section I.A). Thus the irradiation of *p*-toluenesulphonyl iodide (**11a**) in the presence of acrylonitrile and butadiene affords the adducts **15** and **16**, respectively. In the absence of an alkene or diene, irradiation affords the anhydride **17** and the disulphone **18**[26]. Truce and coworkers[27] have also utilized this reaction mode in a study of the light-induced addition of sulphonyl iodides to allenes.

p-$MeC_6H_4SO_2CH_2CHICN$ (**15**) — *p*-$MeC_6H_4SO_2CH_2CH=CHCH_2I$ (**16**)

$(p\text{-}MeC_6H_4SO_2)_2O$ (**17**) — $(p\text{-}MeC_6H_4SO_1)_2$ (**18**)

II. SULPHONES AND SULTONES

There are many examples of the photochemical behaviour of these classes of compounds. The photochemistry is dominated by the fission of a C—S bond affording a carbon radical and a sulphonyl radical. The UV absorptions of these compounds are dependent upon the type of substituent attached to the sulphonyl group. Thus a dialkyl sulphone (**19**) shows an

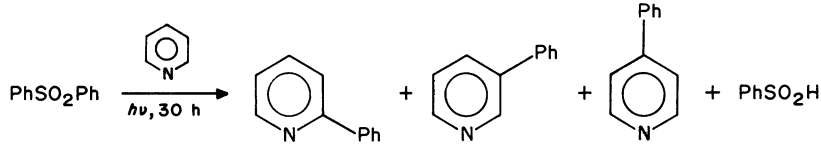
absorption around 180 nm[28]. Diphenyl sulphone (**20**), however, shows absorption at 201 ($\varepsilon = 31700$), 235 (15500), 260 (1740), 266 (2140) and 274 (1390)[29,30]. Sultones also exhibit differences due to changes in substitution as shown by the sultone **21** with a high intensity absorption at 291 nm ($\varepsilon = 33400$)[31] while the naphthalene derivative **22** has absorptions at 225 nm (38000), 274 (4300), 286 (5000) and 316 (410)[32]. These values show that a variety of conditions can be used to effect excitation of such compounds. Photoelectron spectroscopy of a series of sultones related to **23** and **24** has also been studied[33].

Reviews by Mustafa[34] and Coyle[35] have reported on some aspects of the photochemical behaviour of sulphur compounds. Reid[36] has reviewed the photochemical behaviour of sulphur heterocycles in a general survey of the photolysis of heterocyclic compounds.

(**23**) (**24**)

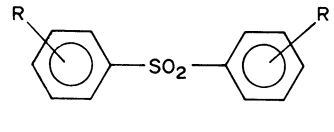
A. Diaryl Sulphones

Studzinskii and collaborators[37] have published a review in Russian dealing with the spectral properties of arenesulphonyl compounds and the results of their irradiation. These arenesulphonyl compounds have been used as a source of phenyl radicals. Thus the irradiation of diphenyl sulphone (**20**) at 254 nm leads to phenyl radicals and SO_2[38]. These phenyl radicals can be used to arylate a variety of substrates and one example of this is the irradiation in pyridine which affords the phenylated pyridines shown in Scheme 1[39]. Di-*p*-tolyl sulphone behaves in a similar manner[40]. The symmetrical aromatic sulphones (**25**) are also photochemically reactive in aromatic solvents with irradiation again bringing about C—S bond fission and the production of aryl radicals. These combine with the solvent to afford the corresponding biphenyls. The sulphone **26** is unreactive under such conditions[41,42]. Other mechanistic details have been sought and the irradiation of diphenyl sulphone (equation 3), labelled as shown with ^{14}C, affords sulphinic acid (**27**) and biphenyl (**28**). No scrambling of the label was detected[43]. Flash photolysis of aromatic sulphones has identified arenesulphonyl radicals as the reactive intermediates[44]. An EPR



28.1 66.1 5.8

SCHEME 1



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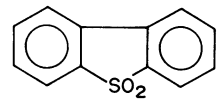
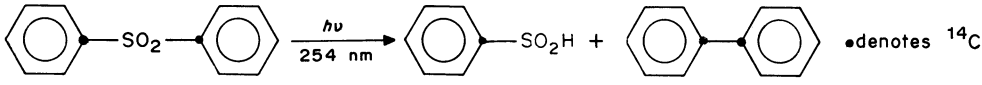


(26)



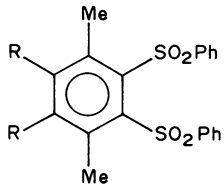
(27) (28) (3)

$R^1—SO_2—R^2$

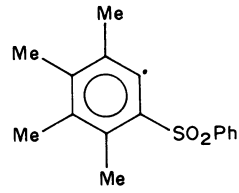
(29) $R^1=R^2=$Me, Et, *n*-Pr, *i*-Pr, *t*-Bu, CH_2Ph
$R^1=$Me, $R^2=$Et, $R^1=$Me, $R^2=$Ph

study of the irradiation of a series of sulphones has also been carried out[45]. γ-Radiolysis brings about fission of C—S bonds in diphenyl sulphone (**20**) with the formation of phenyl radicals. Radiolysis is also effective with dialkyl sulphones and the C—S fission of a series of these (**29**) has been studied[46].

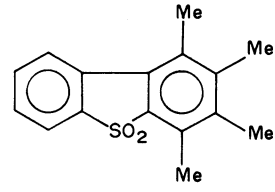
The disulphone **30**, R = Me acts as a single-electron acceptor when irradiated in DMSO/PhSH/PhSNa. This affords the σ-radical **31** by C—S bond fission and yields ultimately the two products **32** and **33**. The ratio **32**:**33** is dependent on the PhSNa/PhSH ratio. When the disulphones **30**, R = H is reacted under similar conditions, the thioether **34** is formed[47].



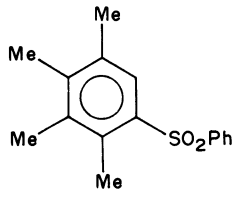
(30)



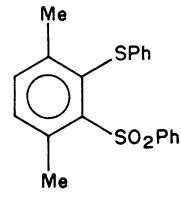
(31)



(32)



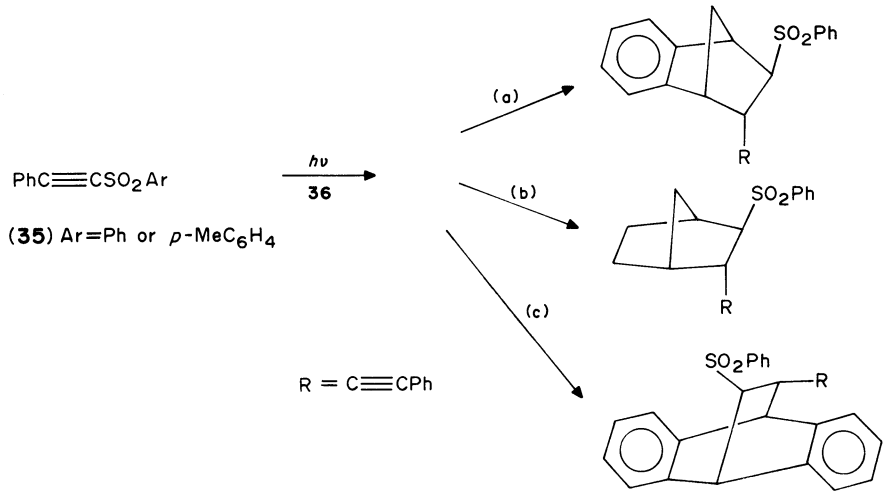
(33)



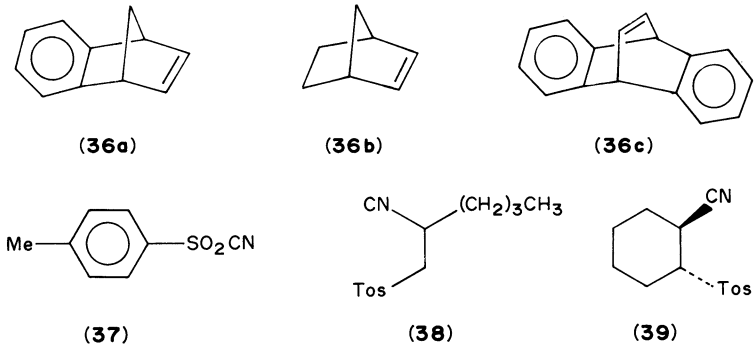
(34)

B. Miscellaneous Aryl Sulphones

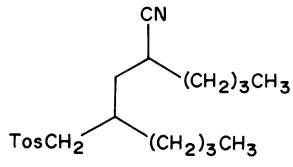
The photochemistry of compounds of this type is also dominated by the fission of the C—S bond and the formation of the corresponding radicals. An example of this is found in



SCHEME 2



the irradiation of the acetylene derivatives **35**. The radicals formed by this reaction path add efficiently to the alkenes **36** to afford the products shown in Scheme 2[49]. In all cases the addition takes place without skeletal rearrangement of the alkene and the adduct has the *trans* arrangement reminiscent of the additions reported in Section I.A. The sulphonyl cyanide **37** also undergoes 1,2-addition to alkenes (hex-1-ene or cyclohexene) to afford 1:1 adducts **38** and **39**, respectively, in high yield[49]. This reaction presumably involves free radicals whereby the tosyl radical adds initially to the alkene. This is exhibited in neat hex-1-ene when the 1:1 addition product **38** is formed in competition with the formation of the 1:2 product **40**. With norbornadiene the rearranged adduct **41** is formed in 22% yield. The sulphone **42** follow a different decomposition path whereby irradiation in benzene solution for 6 h yields the acetylenes, 1-tosylprop-1-yne and 2-tosylphenylacetylene, in 47% and 64% yield, respectively[50].



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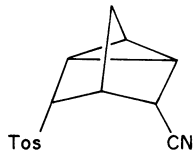
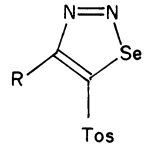


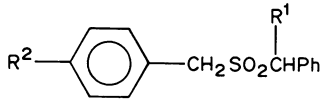
(41)



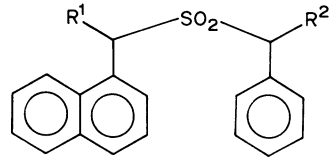
(42)

C. Benzyl Sulphones

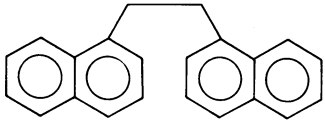
A study of the photochemical decomposition of benzyl sulphones has shown that the extrusion of sulphur dioxide is efficient and typically dibenzyl sulphone photochemically yields bibenzyl[51]. The photoextrusion of SO_2 from dibenzyl sulphone can be sensitized using *N,N,N',N'*-tetramethylbenzidine[52]. The photochemistry of a series of optically active sulphones has been studied to determine the operation of hidden return processes. From this work benzyl and β-naphthyl systems have been shown to react mainly from the singlet state while α-naphthyl reacts from the triplet. No evidence for ionic processes was detected[53]. It is of interest to note that structural factors are also important. Thus extrusion of sulphur dioxide from the 1-naphthyl sulphone ($ArCH_2SO_2CH_2Ph$, Ar = 1-naphthyl) arises from the singlet state while extrusion from the 2-naphthyl isomer is mainly from the triplet. The free radicals produced from the triplet state escape from the solvent cage while the singlet biradicals react within the cage[54,55]. Benzyl 4-chlorobenzyl sulphone decompose on irradiation in benzene into bibenzyl, 4-chlorobibenzyl and 4,4'-dichlorobibenzyl in a ratio of 1.0:1.8:0.9. It is interesting to note in many of these reactions that sulphur deposits are detected and it is not certain in every case that SO_2 is the extruded species[56]. A study of the decomposition of the sulphones **43** and **44** has been carried out. The types of products obtained is typified by the photochemical reactivity of the tolyl derivative **43b** which yields bibenzyl, 1-phenyl-2-tolylethane and ditolylethane. A laser flash study shows that the reaction again involves free radicals. In the naphthyl systems fission of the naphthyl C—S bond is favoured over the benzyl C—S bond. Micellar effects on the photoproduct ratios were also examined[57]. Others have shown that 1,2-dinaphthylethane (**45**) is formed efficiently on irradiation of the sulphone **46**[58].



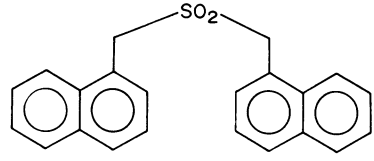
(**43**) (**a**) $R^1=R^2=H$
(**b**) $R^1=H, R^2=Me$
(**c**) $R^1=Me, R^2=H$



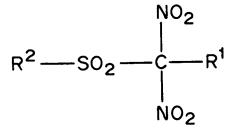
(**44**) (**a**) $R^1=R^2=H$
(**b**) $R^1=H, R^2=Me$
(**c**) $R^1=Me, R^2=H$



(**45**)



(**46**)



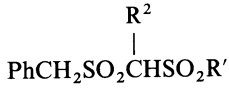
(47) $R^1 = NO_2$, Me or Cl
R^2 = Me, p-$NO_2C_6H_4$, CF_3, 2,4-$(O_2N)_2C_6H_3$

Pulsed radiolysis is also effective in the fission of such systems, as has been demonstrated for the sulphones **47** which results in S—C bond fission to afford the corresponding sulphonyl free radicals[59].

$$PhCH_2SO_2R \xrightarrow{h\nu} PhC\dot{H}_2 + \dot{S}O_2R \longrightarrow HSO_2R + PhCH_2CH_2Ph$$

(48)	(49)	(50)
(a) R = Me		(a) 63%
(b) R = Et		(b) 59%
(c) R = n-Pr		(c) 60%
(d) R = $ClCH_2CH_2$		(d) 40%
(e) R = $PhCH_2CH_2$		(e) 54%

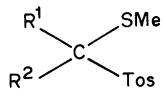
SCHEME 3



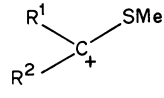
R^1 = Ph or Me
R^2 = H, Me, $PhCH_2$
(51)

Pincock and coworkers[60] have studied the photodecomposition of a series of benzyl sulphones (**48**). This work shows that the benzyl C—S bond is broken, resulting in the formation of the radical pair **49** on irradiation in methanol or isopropanol. However, SO_2 is not extruded and the sulphinic acids **50** are formed in reasonable yields (Scheme 3). This reaction was extended to the bis-sulphones **51**.

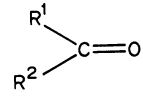
The previous examples all undergo cleavage to afford biradicals. Other workers have demonstrated that in some systems fission results in the formation of ionic species. Thus the irradiation of the sulphones **52** effects C—S heterolysis, the expulsion of the sulphinate and the formation of the ion **53**. In water, this is trapped and undergoes fission to yield the ketones and aldehydes (**54**)[61]. The study has been extended to more complicated systems



(52)



(53)



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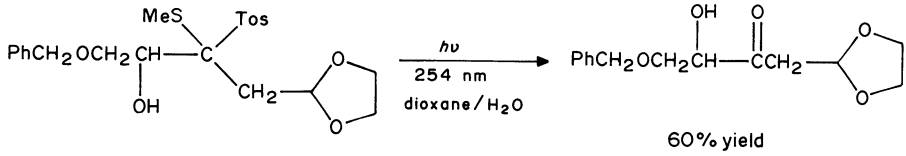
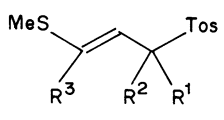
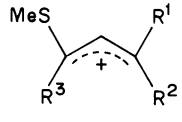


SCHEME 4

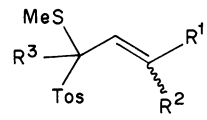
(Scheme 4) where again efficient heterolysis results on irradiation at 254 nm. Subsequent trapping and hydrolysis affords the products shown[62]. An ionic mechanism is also proposed to account for the 1,3-*p*-toluenesulphonyl migration in the allyl compounds **55a**[63]. The photoinduced (at 254 nm in dioxane/water) heterolysis affords the allyl carbocation **56**. Recombination affords the isomeric mixture of **55a** and **55b** in the ratios shown. A 1,3-sulphonyl shift is also reported to occur on irradiation of the sulphones **57**[64]. Interestingly, benzyl 3-phenylallyl sulphone does not rearrange but undergoes loss of SO_2 followed by recombination of the benzyl and the phenylallyl radicals produced, affording a variety of products[65].



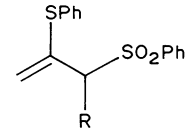
(**55a**)



(**56**)

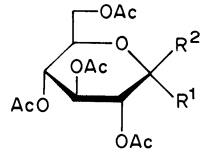


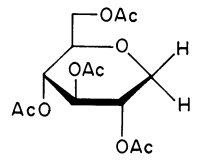
(**56b**) $R^1=R^2=Me, R^3=H$
ratio **a**:**b** 38:62
$R^1= n\text{-}C_{10}H_{21}, R^2=R^3=H$
ratio **a**:**b** 49:51



R=Me, Et, $CH_2CH{=}CH_2$ or CH_2Ph

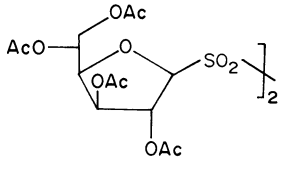
(**57**)



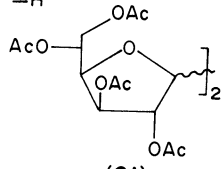


(**58**) $R^1=H, R^2=SO_2Ph$
$R^1=SO_2Ph, R^2=H$

(**59**)

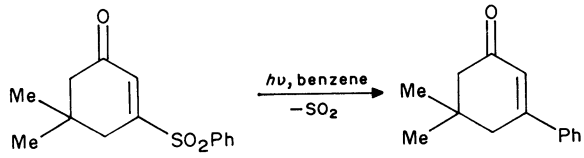


(**60**)

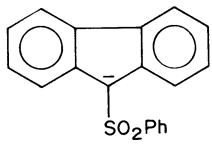


(**61**)

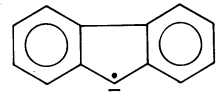
Collins and Whitton[65] report that the sulphone **58**, either as the α- or β-isomer, undergoes S—C bond fission on irradiation (through quartz) in benzene. The products formed arise by a free radical path affording the reduced compound **59** as well as products of benzene incorporation[66]. Radicals are also involved in the conversion of the α- or β-derivatives of the sulphone **60** into the dimer **61**[67]. Binkley[69] has reviewed the photochemical reactivity of carbohydrate sulphone derivatives. The unsaturated ketolsulphone (Scheme 5) also undergoes loss of SO_2 and recombination[69].



SCHEME 5



(62)



(63)

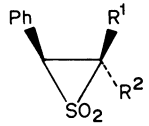
A flash photometric study of electron transfer involvement of the anion **62** has shown that fission of the S—C bond in THF yields the radical anion **63**[70,71].

D. Sultones

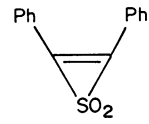
Much of the photochemistry carried out on the cyclic sulphones has had a leaning towards the synthesis of novel and strained compounds. The compounds studied range from three-membered ring species up to large ring compounds and the material will be treated in this sequential manner. The photochemistry of these compounds and others has been reviewed recently[72].

1. *Three-membered rings*

Bordwell and collaborators[73] have demonstrated that UV irradiation of phenylthiirane 1,1-dioxide (**64**) affords styrene and sulphur dioxide. The 2,3-diphenyl dioxide (**65, 66**) (as a mixture of *cis* and *trans* isomers) also decomposes and affords a mixture of *cis* and *trans* stilbene. Loss of SO_2 occurs on irradiation of 2,3-diphenylthiirene-1,1-dioxide (**67**) in methanol giving diphenylacetylene in 93% yield[74]. The photodecomposition of three-ring compounds has been reviewed[75].



(**64**) $R^1=R^2=H$
(**65**) $R^1=Ph, R^2=H$
(**66**) $R^1=H, R^2=Ph$

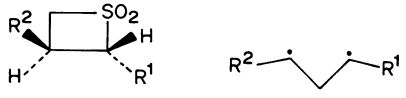


(**67**)

2. *Four-membered rings*

Irradiation of the sulphone **68** at 147.0, 123.6 and 106.7–104.8 nm results in decomposition. The principal step is the extrusion of sulphur dioxide and the formation of the biradical (**69**, $R^1=R^2=H$) from which cyclopropane, propene and ethylene are

formed[76]. Substitution does not appear to have an adverse effect on the extrusion as shown by Durst and coworkers[77,78] in the formation of phenylcyclopropane from the sultone (**70**). The synthesis of a number of cyclopropanes has been carried out by this route[79]. An analogous observation has been made for the formation of **71** from **72**[80]. The ease of SO_2 loss is attributed to the stabilization of the biradical (**69**, R^1 = Ph, R^2 = COPh). In the absence of stabilizing groups, as with the sulphone **73**, no photochemical decomposition was observed[81].

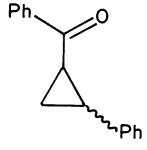


(**68**) $R^1=R^2=H$

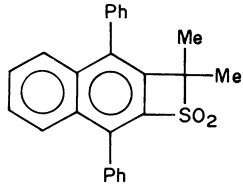
(**70**) $R^1=H, R^2=Ph$

(**72**) $R^1=Ph, R^2=COPh$

(**69**)

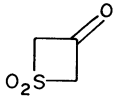


(**71**)

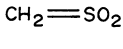


(**73**)

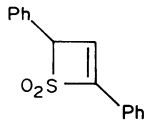
In some instances extrusion of SO_2 does not occur, as with the ketosulphone (**74**) which fragments to yield ketene and the sulphene (**75**). Both the singlet and the triplet excited states are reactive. There is some doubt as to the concertedness of the process and a 1,4-biradical is proposed as an intermediate formed by C—S bond fission[82]. Irradiation of the sulphone (**76**) in acetonitrile or dichloromethane also results in the formation of a sulphene (**77**) which loses SO to afford the ketone (**78**). An alternative reaction path, that of SO_2 extrusion, affords a biradical from which 1,3,4,6-tetraphenylcyclohexa-1,4-diene is formed[83].



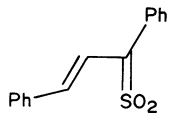
(**74**)



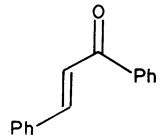
(**75**)



(**76**)



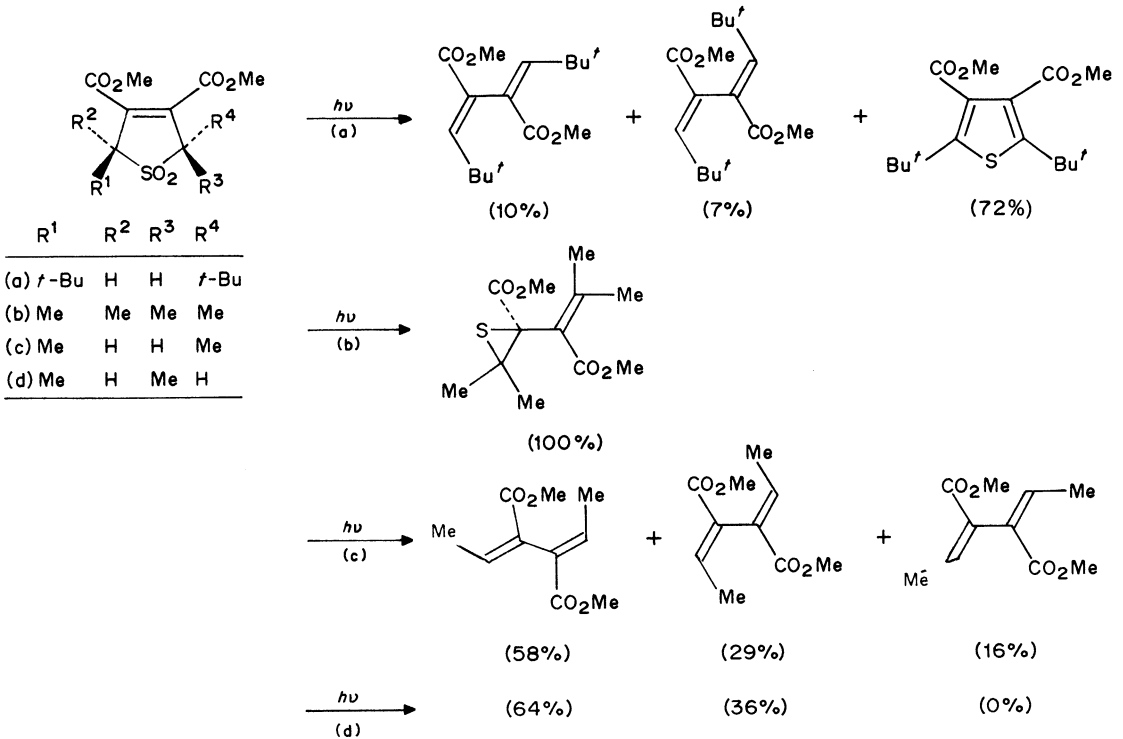
(**77**)



(**78**)

3. *Five-membered rings*

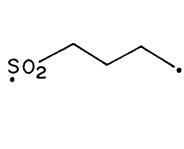
Loss of SO_2 from tetramethylenesultone on irradiation at 147 nm[94] or low-temperature radiolysis[95] has been described. Both of these reactions involve the formation of the biradical **79** formed by fission of a C—S bond. According to one report, rebonding within this biradical, formed by irradiation of neat tetramethylenesultone, affords the sulphinate **80**[96]. The triplet states (populated by benzene sensitization) of the sulpholenes **81** undergo fragmentation and loss of sulphur dioxide to yield dienes. The geometry of diene **82** formed from **81a** is in accord with the prediction of fragmentation via the conrotatory opening of the excited state. The minor product **83** must arise from the fragmentation of a vibrationally excited ground state[87]. Others[88,89] have also studied the formation of dienes from sulpholenes and obtained the results shown in Scheme 6. Interestingly similar extrusion of SO_2 takes place from **84** affording the azines **85**[90]. In the previous examples the biradical formed on loss of sulphur dioxide decayed to dienes. However, a study by Johnson and coworkers[91] has shown that SO_2 loss by irradiation can form ring-closed species such as the β-lactams **86** and **87** formed from the sulphone **88**. The fact that both the *cis* and the *trans* isomers are formed from the *cis* starting material is indicative of a free



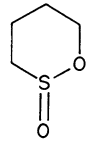
	R^1	R^2	R^3	R^4
(a)	*t*-Bu	H	H	*t*-Bu
(b)	Me	Me	Me	Me
(c)	Me	H	H	Me
(d)	Me	H	Me	H

SCHEME 6

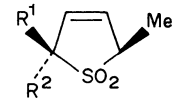
radical process. Such reactions have been reviewed[92]. Ring closure is also observed following irradiation of **89** affording **90**[93] while irradiation of **91** ultimately forms the styrenes **92** by way of the methide **93** which undergoes a 1,5-hydrogen shift to yield the final products[94]. Interestingly 1,3-dihydroisothianaphthene 2,2-dioxide (**94**) affords the benzocyclobutene (**95**) when heated to 200–350 °C and irradiated at the same time. A small yield of dibenzocyclooctadiene (**96**) is also formed[95]. However, Cava and his coworkers[96–99] have observed that **94** is unreactive while **97** undergoes facile loss of SO_2 to yield *trans*-1,2-diphenylbenzo[*c*]cyclobutene. The naphthalene analogue **98** is also reactive.



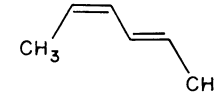
(79)



(80)



(81)(a) R^1=Me, R^2=H
(b) R^1=H, R^2=Me
(c) R^1=R^2=H



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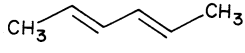

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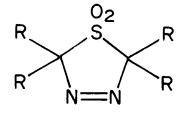
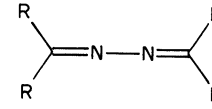
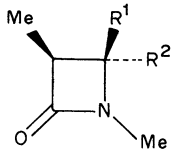


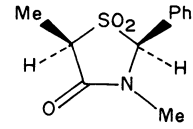
(84)



(85)



(86) R^1=Ph, R^2=H (31%)
(87) R^1=H, R^2=Ph (8%)



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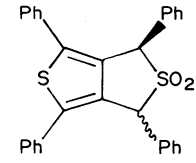
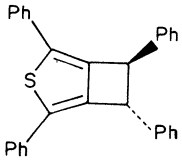
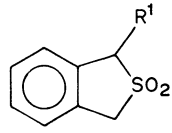


(89)

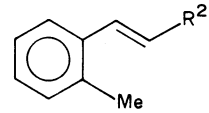


(90)



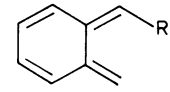
R^1=CH_2Ph or $CH_2CH{=}CH_2$

(91)



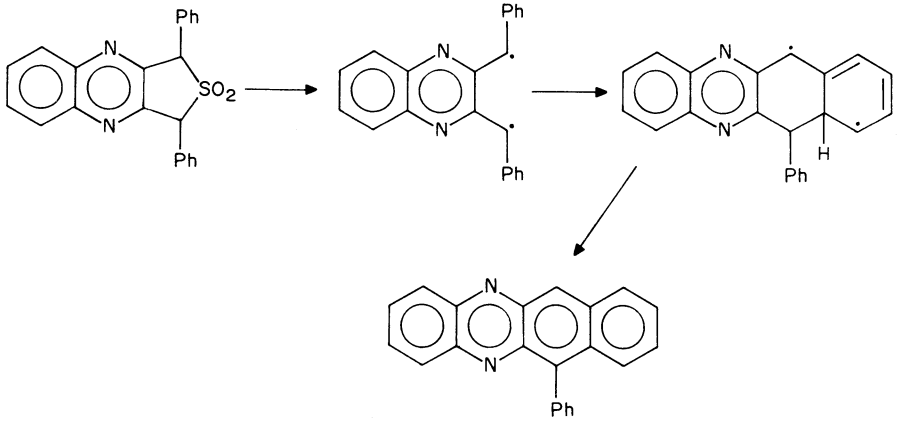
R^2=Ph or $CH{=}CH_2$

(92)

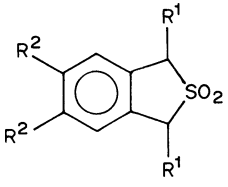


(93)

The phenazine derivative (Scheme 7) also undergoes loss of sulphur dioxide on irradiation. Rather than straightforward ring closure the resultant biradical cyclizes as shown[99]. C—S Bond cleavage and loss of SO_2 from the sulphone **99** affords the ketone **100** as the final product of a biradical path involving incorporation of the solvent benzene[100]. Arenes are formed in high yield on irradiation of the dicyclopropenyl sulphones (**101**) in benzene. The path for the arene formation involves (2 + 2)-cycloaddition to yield **102**



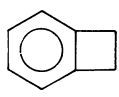
SCHEME 7



(94) R^1=H, R^2=H

(97) R^1=Ph, R^2=H

(98) R^1=Ph, R^2—R^2= —(—CH=CH—)$_2$—



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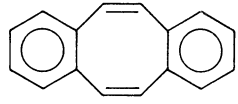

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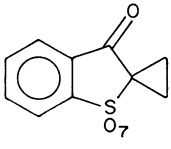
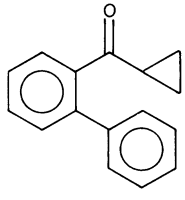


(99)



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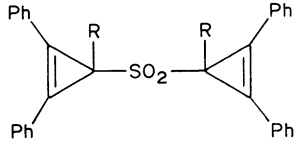

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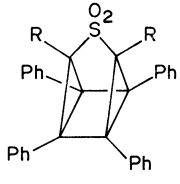

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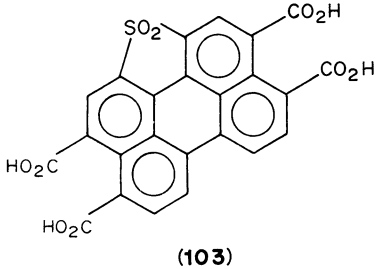
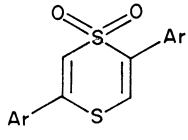


(103)

followed by sulphur dioxide extrusion[101]. Photoextrusion of SO_2 from perylene-3,4,9,10-tetracarboxylic acid 1,12-sultone (**103**) has been described[102].

4. Six-membered rings

A novel extrusion of SO_2 is reported for the dithiine dioxides **104** to afford low yields of the thiophenes **105** and **106**. The exact step at which the SO_2 loss occurs is not known but the proposed intermediates **107** and/or **108** have support from the formation of pyrrole derivatives when the reaction is carried out in the presence of n-butylamine[103]. Sunlight-induced extrusion of sulphur dioxide from the pyranone dioxide **109** is similar to the above and results in the formation of the reactive cyclopentadienone **110** which can be trapped by dienophiles or in their absence forms a trimer[104]. The platinum complex **111** is photochemically labile and decomposes into benzyne on irradiation[105].



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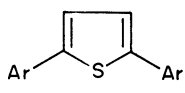

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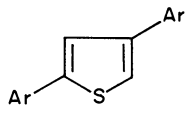

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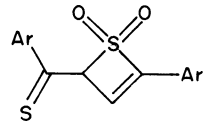

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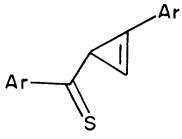

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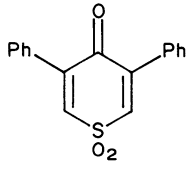

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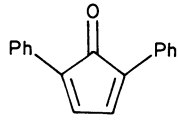

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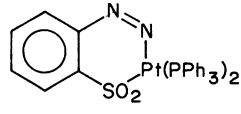
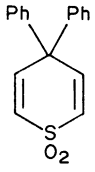


(111)

In some instances loss of sulphur dioxide does not take place on irradiation. This is exhibited by the sulphone **112** which exhibits di-π-methane reactivity involving vinyl–vinyl bridging to afford the product **113**. In competition with this, addition of methanol yields the adduct **114**[106]. Addition of methanol also occurs on the irradiation of the sulphone **115** in methanol affording the ether **116**[107]. Another photoreaction mode of **115** brings about the formation of the sulphene **117** by ring opening. This species is trapped by the addition of methanol to yield the sulphonate **118** in 30% yield. In an earlier report Hall and Smith[108] reported that the sulphone (**119**) ring opened on irradiation in methanol to afford the sulphene **120**, which was not trapped by methanol but underwent cyclization to afford the three products **121a–c**.



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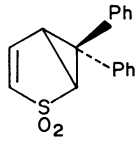

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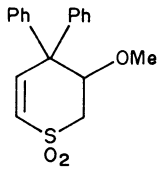

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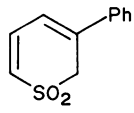

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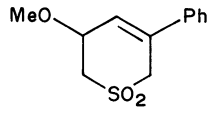

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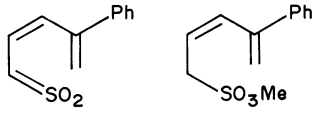
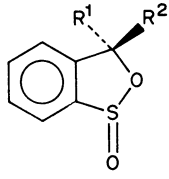
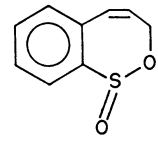


(117) (118) (119) (120)



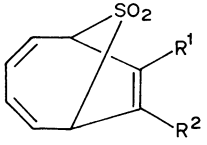
(121)
(a) R^1=H, R^2=vinyl (25%)
(b) R^1=vinyl, R^2=H (30%)



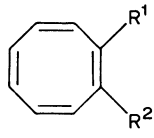
(121c)

5. Bridged sulphones

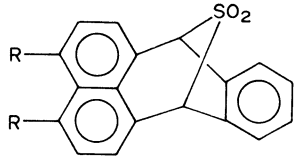
The bridged sulphones **122** all undergo photochemical loss of sulphur dioxide on irradiation in acetone to yield the cyclooctatetraene derivatives **123**[109]. The related benzylic sulphones **124** and **125** are also photochemically reactive and, using 280–320 nm irradiation, affords the dimers **126** and **127** respectively, where extrusion of sulphur dioxide has occurred[96–98]. The related sulphone **128** also extrudes sulphur dioxide to yield **129**[110]. Photoextrusion of sulphur dioxide from the thiaadamantane **130** is accompanied by rearrangement to afford the sulphone **131**, which is stable to further irradiation[111]. Dutta and Butcher have observed that the irradiation of the sulphone **132** at 248 nm results in a zwitterionic singlet state. This excited state effectively cleaves the sulphones to afford cations which are trapped by water[112,113].



(122) (a) R^1=R^2=Me
(b) R^1—R^2=$(CH_2)_4$ or $(CH_2)_5$
(c) R^1—R^2=-(-CH=CH-)$_2$-



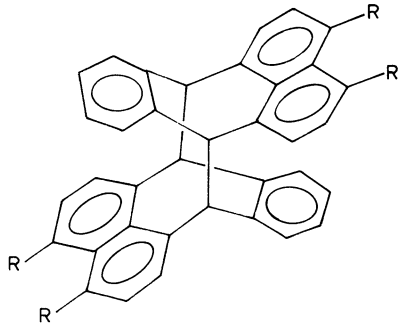
(123) (a) 11%
(b) 91%
(c) 91%



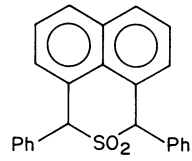
(124) R—R=CH_2 CH_2
(125) R=H

6. Large-ring sulphones

One of the most interesting synthetic uses for the sulphur dioxide extrusion process has been the application to the synthesis of cyclophanes, a subject reviewed by Boekelheide[114] and by Givens[115] in his review of photoextrusion of small molecules. The earliest example of this was reported in 1973 by Rebafka and Staab[116] who demonstrated that the irradiation of **133** affords a good yield of **134**. A similar approach was used by Boekelheide and his coworkers[117] in the conversion of **135** into **136** in 30% yield. Givens and collaborators[119,119] have also demonstrated the use of the reaction in the conversion of **137** and **138** into **139** and **140** respectively.



(126) R—R=CH_2CH_2
(127) R=H



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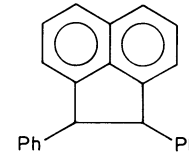

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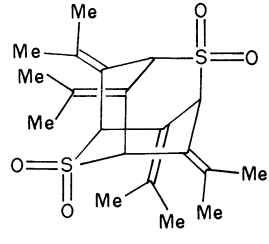

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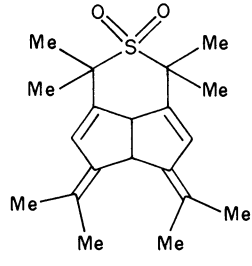

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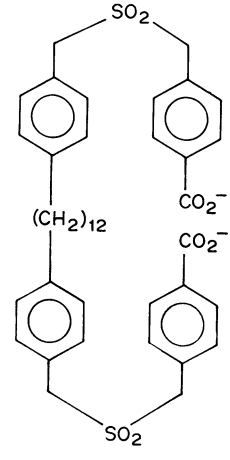

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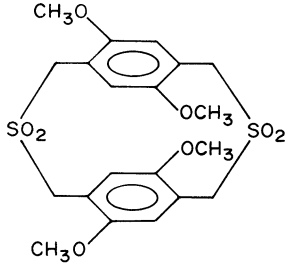

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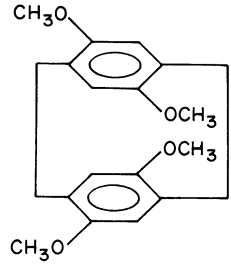

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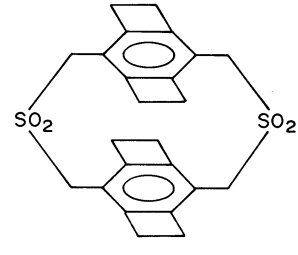

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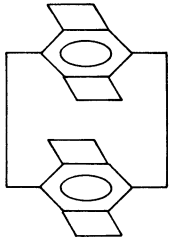

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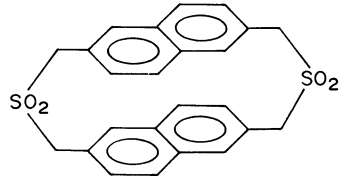

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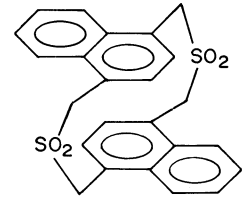

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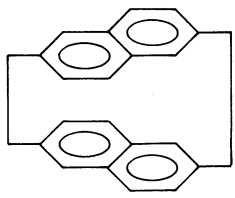

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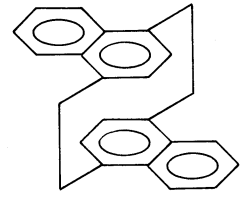
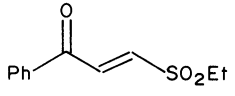


(140)

E. *Cis–trans* Isomerization and Cycloaddition Reactions

1. *Cis–trans isomerization*

Trans–cis isomerization is reported for the *E*-enones **141** which on irradiation in benzene/methanol yield the *Z*-isomers in 70% yield[120]. Several reports have dealt with the *E–Z* isomerization of sulphones of the type represented by **142**[121–124]. The sulphone **143** is converted to a mixture of isomers on irradiation (Scheme 8)[125] and a study of the *E–Z* isomerization of 1-sulphonyl substituted 2-methylbutadienes has been carried out[126]. The photochemical interconversion of the alkenes **144** and **145** has been studied[127]. The acetone-sensitized irradiation of **146** brings about *trans–cis* isomerization.



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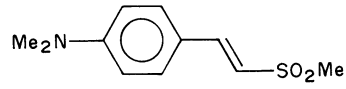

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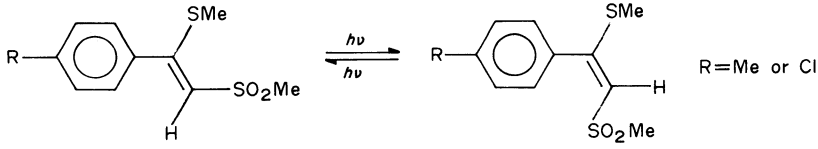

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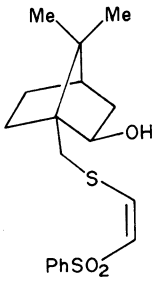
SCHEME 8



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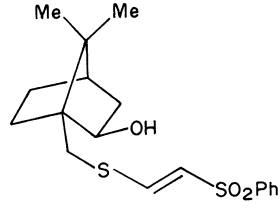

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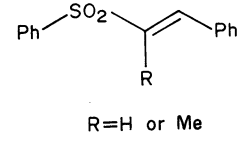
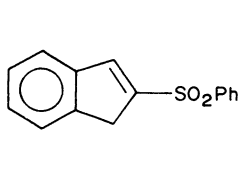


R=H or Me

(146)

The alkene **146** does not undergo (2 + 2)-cycloaddition because of energy wasting by this rapid isomerization process. However, the more rigid sulphone **147** does afford the adduct **148** on irradiation in cyclohexene[128]. Cycloaddition also occurs with 2,3-dimethylbut-2-ene and cyclopentene. The *trans*-dimer **149** (12%) is obtained on irradiation of an ethereal solution of the thiete dioxide **150**. The phenyl-substituted derivative **151** failed to undergo dimerization under similar conditions[31]. (2 + 2)-Photocycloaddition of the enone **152** results in the formation of the two adducts **153** and **154** in the yields shown[129]. Photochemical addition of cyclohexene to the sulphone **155** affords the thiepinone **156** by way of an unstable cyclobutane derivative **157**[139]. Other sulphones have been reported to undergo dimerization. Thus sunlight irradiation of the derivatives **158** leads to (2 + 2)-dimerization affording either **159** or **160**. The thiophene dioxide **161** is also reactive, yielding a high melting crystalline dimer **162** or **163**[131,132]. Hopkinson and coworkers[133] report that the dimers **164** and **165** are formed in a ratio of 9:1 when the monomer **166** is irradiated in solution at 313 nm. The head- to-head dimer **164** is reported to be formed via a monomeric triplet state while the head-to-tail dimer **165** arises from an excimer.



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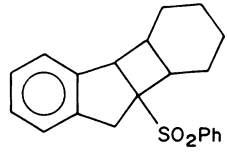
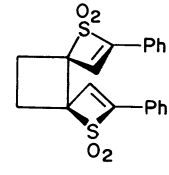


(148)



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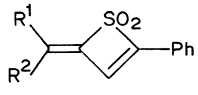
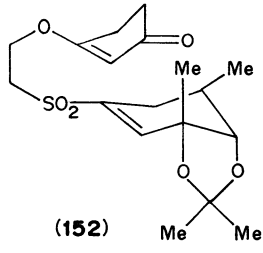
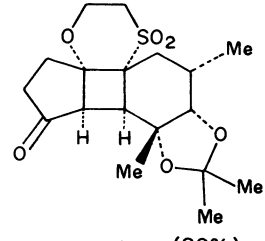


(150) $R^1=R^2=H$

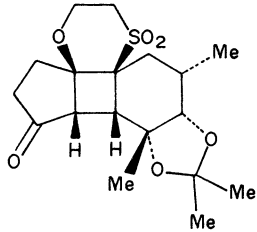
(151) $R^1=Ph, R^2=H$



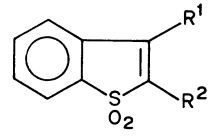
(152)



(153) (20%)



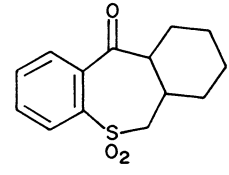
(154) (74%)



(155) R^1=OAc, R^2=H

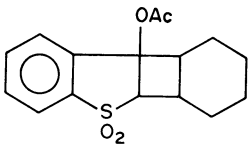
(158) R^1=Br or H, R^2=H

(166) R^1=H, R^2=Me

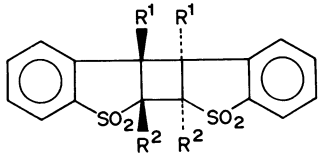


(156)

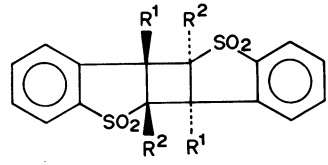
The thiophene dioxide **166** (R = Me) photochemically adds to citraconic anhydride **168** to yield the adduct **169**. This was subsequently used in a total synthesis of 10-hydroxygeraniol[134]. The parent sulpholene **167** (R = H) also undergoes (2 + 2)-photoaddition with dichloromaleimide to afford the adduct **170** (54%)[135].



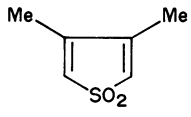
(157)



(159) R^1=Br or H, R^2=H
(164) R^1=H, R^2=Me



(160) R^1=Br or H, R^2=H
(165) R^1=H, R^2=Me



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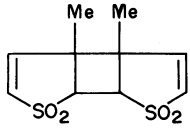

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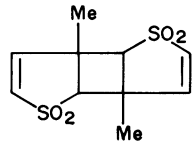
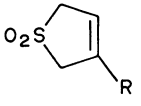


(163)



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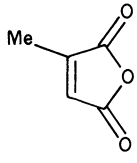

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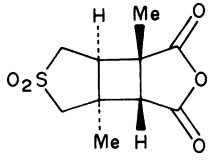

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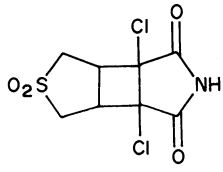
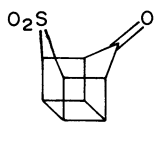
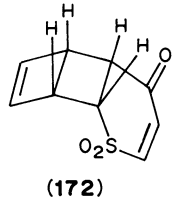


(170)

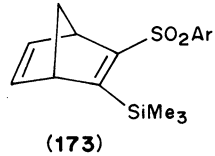
The cage compound **171** is formed on irradiation of the adduct **172**[135]. Sulphone derivatives also undergo norbornadiene/quadricyclane transformations as demonstrated by the photoconversion of **173** into **174**[137]. Others have also examined this problem[138]. Paquette and Kuenzer[139,140] have reported the first example of a quadricyclane–quadricyclane rearrangement in compound **175**. This on irradiation affords **176** only when the double bond is substituted by an electron-withdrawing group. An electron transfer process is thought to be involved.



(171)



(172)



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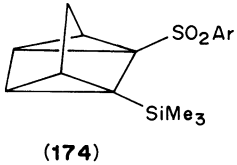

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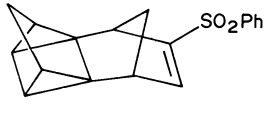
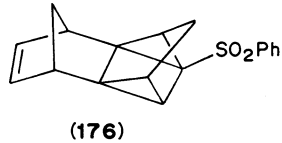


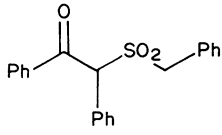
(175)



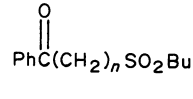
(176)

F. β-Ketosulphones

C—S Bond fission also dominates the photochemistry of the benzyl sulphone **177**. Irradiation affords 1,2-diphenylethane and 1,2,3,4-tetraphenylbutan-1,4-dione by combination of the radicals formed on loss of sulphur dioxide from the starting material[141]. A study of the influence of a sulphone group on the Norrish Type II reactivity of aryl ketones **178** has been reported. In addition the influence of the sulphone group on the triplet lifetime, γ-hydrogen abstraction or charge transfer interactions was assessed[142]. The photochemical reactivity of the ketosulphones **179** has been reported. A variety of reaction paths result in the formation of several products. However, the predominant path involves C—S bond fission to yield the radical pair **180** and **181**[143,144]. Diller and Bergmann[145] have shown that the principal reaction undergone on photolysis of the ketosulphone **182** is C—S fission to yield ultimately the cyanoketone **183**, Norrish Type I fission occurs in competition with the above. Fujii and coworkers[146] have demonstrated that the β-ketosulphones **184a-h** can be desulphonylated in good yield on irradiation of the sulphone in the presence of Hantzsch ester and a ruthenium(II) salt. The reaction involves an electron transfer process from the ester to the sulphone. Typical yields are shown in Scheme 9.



(177)



$n = 1-4$

(178)

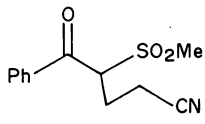
$R^1SO_2CH_2COR^2$

$R^1 = PhCH_2$, $R^2 = Me$
$R^1 = PhCH_2$, $R^2 = Ph$
$R^1 = Bu^t$, $R^2 = Me$

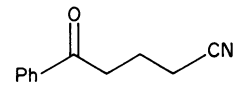
(179)

(180)

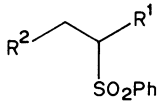
(181)



(182)



(183)



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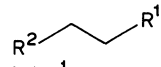


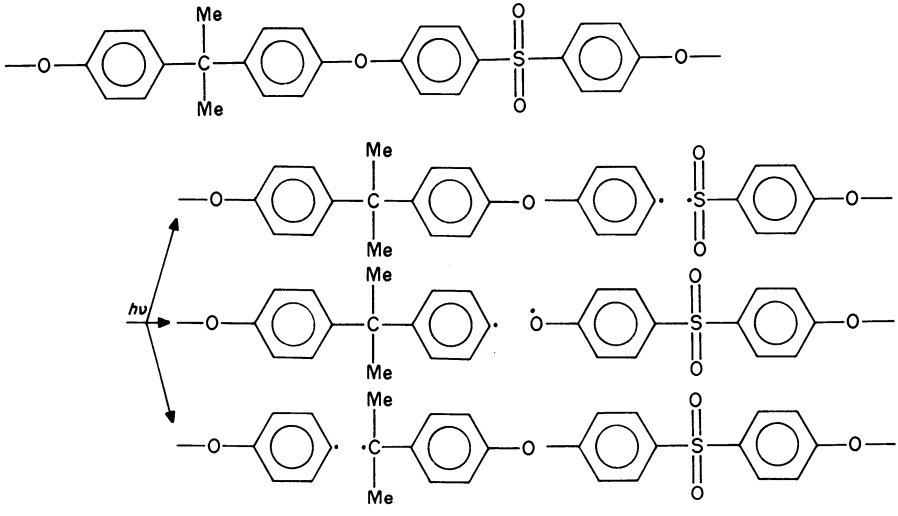
(a) R^1=COMe, R^2=Ph; 97%
(b) R^1=COMe, R^2=C_5H_{11}; 87%
(c) R^1=COMe, R^2=2-styryl; 83%
(d) R^1=Ph, R^2=vinyl; 94%

SCHEME 9

III. POLYMERIC SULPHONES

These materials, the polymeric sulphones, also come into the category of hexavalent sulphur compounds and are derivatives of sulphonic acids. The photochemistry and the radiation chemistry of these substances have been reviewed in a variety of texts. Thus the radiation chemistry was reviewed in considerable detail in 1988[147]. Other texts have reviewed photodegradation and photooxidation of polymers in general with some reference to the polysulphones[149]. It appears that polysulphones have low thermal stability and as a result have failed to undergo commercial utilization[149].

In general polysulphone degrade under UV irradiation in the 320–340 nm region. Typical fission processes encountered are shown in Scheme 10[150–154]. Some studies on the photophysical behaviour have been reported[155].



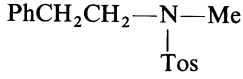
SCHEME 10

IV. SULPHONAMIDES AND RELATED COMPOUNDS

A. Photodeprotection

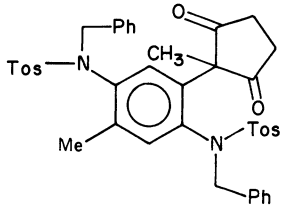
One of the more common photochemical reactions of sulphonamides and their derivatives is fission of the S—N bond and the liberation of the free amine, a process referred to as deprotection of functional groups. The synthetic usefulness of this reaction sequence has been reviewed by Pillai[156]. A typical example of this type is that of the SET (single electron transfer) reactivity of the sulphonamides (**185**). These compounds can be readily detosylated on irradiation in the presence of electron-donating sensitizers (1,2-dimethoxybenzene or 1,4-dimethoxybenzene) and reductants such as ammonia, borane, hydrazine or sodium tetrahydroborate. These conditions afford high yields of the corresponding amines (**186**)[157,158]. SET photochemistry of the toluenesulphonylamide **187** using 1,5-dimethoxynaphthalene as the electron donor brings about double detosylation and cyclization to yield the product **188**[159]. Photodetosylation of the cyclic sulphonamides **189** has been reported to be an efficient process. Thus irradiation in a mixture of ethanol/sodium carbonate and sodium borohydride yields the amines **190** in the yields shown[160–162]. The reductant is important and its absence leads to products of

elimination and oxidation. The presence of the 1,2-dimethoxybenzene moiety suggests that an intramolecular electron transfer sensitization is involved.



(185)

(186)



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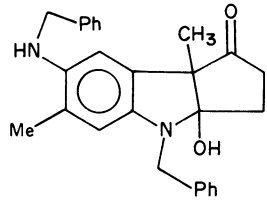
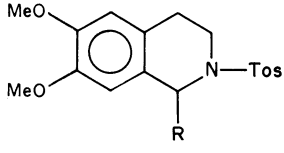
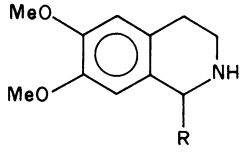


(188)

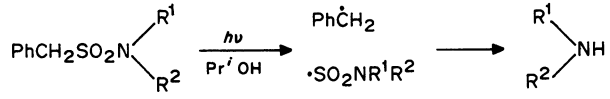


(189) (a) R=H
(b) R=Me
(c) R=Ph
(d) R=$PhCH_2$

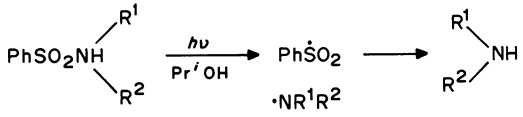


(190) (a) 83%
(b) 77%
(c) 71%
(d) 99%

Deprotection is also effective on direct irradiation as reported by Pincock and Jurgens[163]. A variety of derivatives was studied using the conditions shown in Scheme 11. The yields of amines obtained vary from 10–98%. Two mechanistic paths are proposed. One involves C—S bond fission for sulphonamides **191** with the formation of the radical pair **192**, which then undergoes loss of SO_2. The other path is followed by the sulphonamides **193** where S—N bond fission is operative. Pete and his coworkers[164,165] have also demonstrated the ease of deprotecting amines by the photochemical cleavage of a series of *p*-toluenesulphonamides in ether. Direct irradiation brings about photochemical cleavage of 5-dimethylamino-1-naphthalenesulphonyl (dansyl) protected amines, amino acids and peptides. The photoremovable group in this case is the dansyl group. Irradiation of, for example, dansyl glycine (**194**) in acidic medium affords dansylic acid (**195**), glycine (95%) and ammonia (7%). The reaction is sufficiently mild that peptide links are not damaged[166–168]. Irradiation of the sulphonamides (**196**) at 350 nm in isopropanol under nitrogen results in the formation of the free amines in yields ranging from 32–96% and liberation of the protecting group[169]. This system was developed following earlier discoveries that 2-arylquinoline derivatives could be photochemically cleaved[170,171]. Loss of the *N*-protecting group is also reported from the irradiation of the pyrazoline derivative **197**[172].

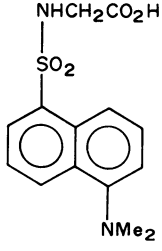


(191)(a) $R^1=R^2=C_4H_9$ (192) (a) 78%
(b) $R^1=H, R^2=(CH_2)_8CH_3$ (b) 81%
(c) $R^1=H, R^2=C_6H_{11}$ (c) 98% (in MeOH)
(d) $R^1=H, R^2=Ph$ (d) 10%



(193) (a) $R^1=R^2=C_4H_9$ (a) 81%
(b) $R^1=H, R^2=C_6H_{11}$ (b) 96%

SCHEME 11



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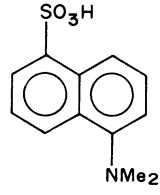

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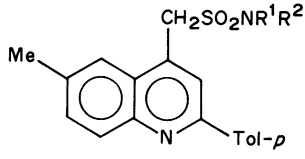

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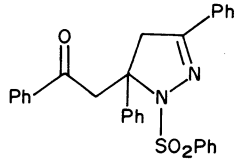
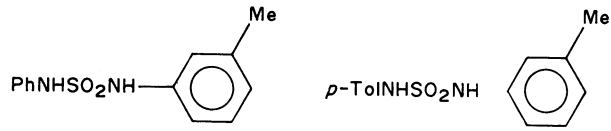


(197)

B. Loss of Sulphur Dioxide

1. *Open-chain sulphonamides*

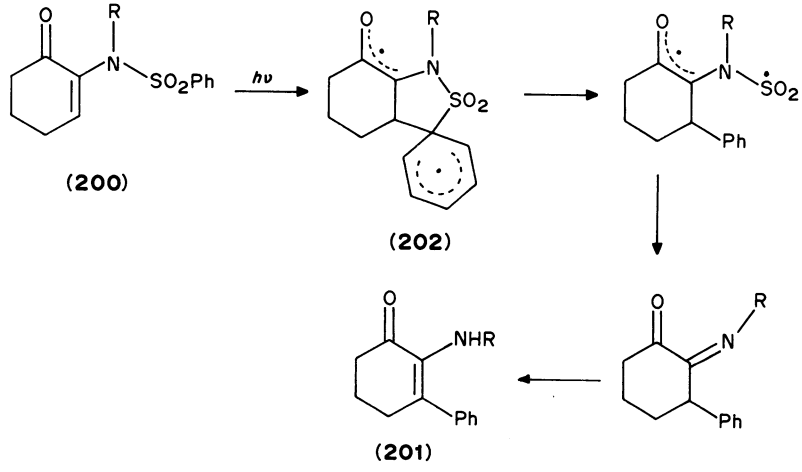
Forster and coworkers[173] report that the sulphonamides **198** undergo loss of sulphur dioxide on excitation, yielding azobenzene and aniline. The former product is thought to arise by an intramolecular path, since the photolysis of the tolyl derivative **199** yields only 3-methylazobenzene and no mixed derivatives. In contrast, *N*-arylbenzenesulphonamides



(198) (199)

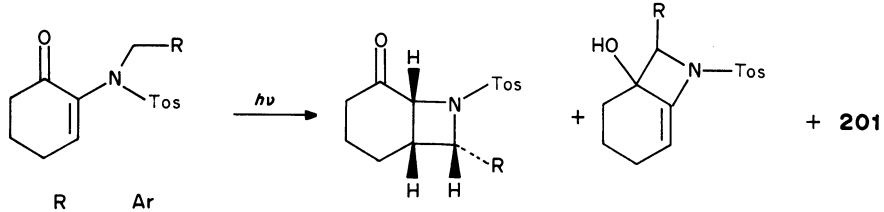
follow a different reaction path and the products formed are those from reaction of benzenesulphonyl and arylaminyl radicals[174].

Pete and his coworkers have demonstrated that the enones **200** can be readily and efficiently converted into the 3-substituted enones **201**. A mechanism involving a biradical **202** (Scheme 12) followed by loss of SO_2 may be responsible for this transformation[175,176].



(200) (202) (201)

SCHEME 12

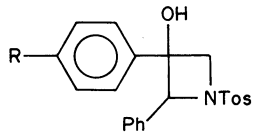


R	Ar
(a) Me	tolyl
(b) Ph	tolyl
(c) tolyl	tolyl

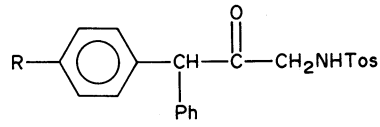
(203)	(204)	
(a) 30%	(a) —	(a) 25%
(b) 50%	(b) —	(b) 10%
(c) 40%	(c) 35%	(c) 15%

SCHEME 13

Further studies have shown that the outcome of the reaction is dependent upon the type of substituent on the sulphonamide side-chain. If hydrogen abstraction is possible, competing reactions occur affording the azetidine derivatives **203** and **204**



(205)

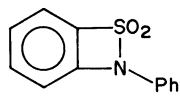


(206)

(Scheme 13)[177,178]. Azetidinols (**205**) also undergo ring fission to afford the sulphonamides (**206**) by a path involving N—C bond fission. The resultant biradical rearranges to the final products **206** by aryl migration, the efficiency of which is determined by the substitution on the aryl group[179].

2. Cyclic sulphonamides

The photochemical decomposition of the thiazete **207** in benzene at 30 °C affords carbazole **208**[190]. The reaction presumably involves the formation of a biradical by S—N bond fission which, on loss of SO_2, undergoes cyclization to yield the final product. Loss of sulphur dioxide also occurs on irradiation of the sultam **209** yielding the quinomethane imine **210**, which ring closes to the azetidine **211**[181]. Irradiation of the sulphobenzimide **212** in benzene yields the amide **213** by a free radical reaction path[182].



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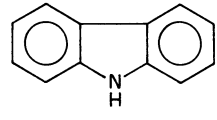

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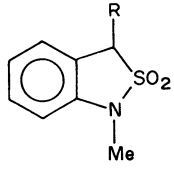
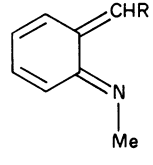


(209) R=H or Me



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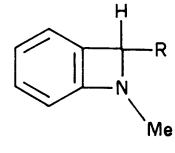

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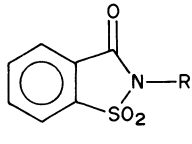
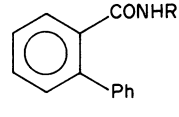


R=H or Me

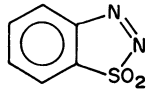
(212)



(213)

Benzyne is formed on irradiation of the thiadiazole **214**[183] by loss of SO_2 and nitrogen. Extended irradiation of the dioxide **215** in benzene yields the thiete dioxide **216** in 25%

yield and the dimeric species **217** in 3% yield[184,185]. Irradiation of the thiete **216** in ethanol affords a 54% yield of the dimer **217**. The photolysis of **218** also leads to extensive fission with the formation of benzonitriles **219**[186,187]. Rupture of the N—S bond is the dominant photoreaction of the sultam **220** affording the intermediate **221**. In the absence of an external nucleophile, ring closure affords the pyrrole **222** but with added n-butylamine intermolecular trapping affords the sulphonamide **223**[188]. S—N Bond fission is thought to account for the initial step in the conversion of the sulphonamide **224** into the sulphoxide **225**[189].



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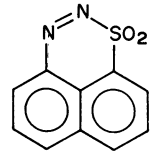

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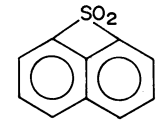

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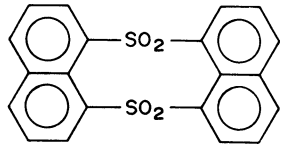

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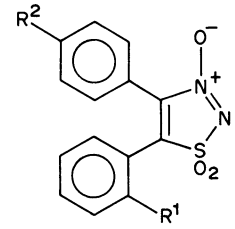
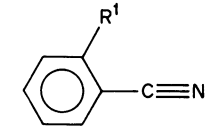


(218) $R^1=R^2=H,OMe$; $R^1=Me,R^2=OMe$



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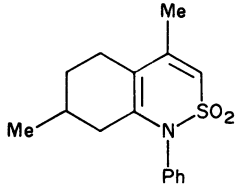

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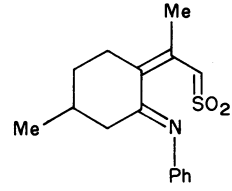

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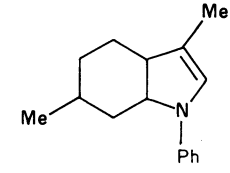

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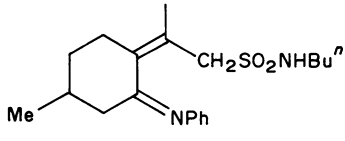

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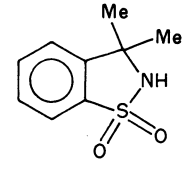

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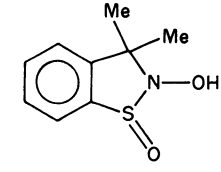
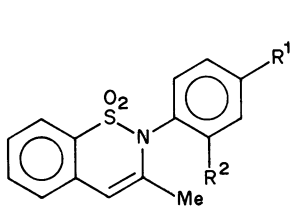


(225)

The sulphonamides **226** are photochemically reactive and on irradiation in benzene or methanol afford the ring-expanded products **227**. The process involves S—N bond fission to the biradical **228**, which ultimately rebonds to yield **229**. A 1,3-hydrogen migration completes the reaction affording the products in 50–70% yields. A laser flash study has identified the presence of long-lived transients[190].



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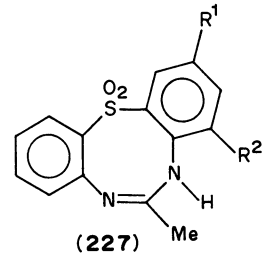
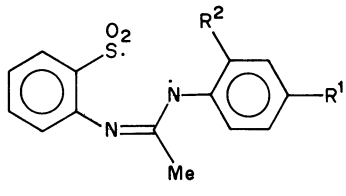


(227)

R^1=H, Me, OMe or *p*-$C_6H_4CO_2Me$

R^2=H or Me



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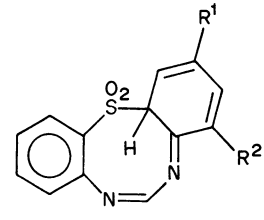
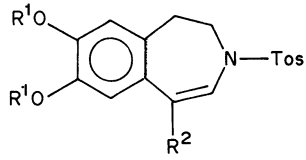


(229)

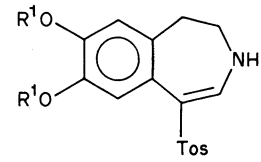
C. Photo-Fries Reactions

A 1,3-tosyl migration occurs on irradiation of the *N*-tosyl derivative **230**. This affords a 40% yield of the enamine **231**[191]. Hayazaki and Shirai have reported the photochemical migration of toluenesulphonyl groups in the irradiation of the phenoxazine derivative **232** which rearranges into the derivative **233**[192]. The mechanism and the intramolecular nature of the process have been investigated [193]. The foregoing are examples related to the photo-Fries process, which has been reviewed by Bellus[194]. A classical of such a process is the rearrangement of the *N*-phenylsulphonamides (**234**) which on irradiation are converted into the *o*- and *p*-amino substituted sulphones (**235**) in the yields shown[195]. Nozaki and coworkers[196] have studied the irradiation of the sulphonamides **236**. The rearrangements of these yield the sulphones and the arylamines as shown in Scheme 14. The rearrangement products arise by cage capture while the amine is a result of escape from the cage. The *N*-substituted indoles (**237**) are photochemically reactive and can be converted into the 3-, 4- and 6-isomers (Scheme 15) in varying yields[197]. It is interesting to note that the migration terminus can be the pyrrole ring as well as the benzene ring. The *N*-sulphonylcarbazole (**238**), on irradiation at 254 nm, affords the sulphones **239** and **240** by a 1,3- or a 1,5-sulphonyl migration. The process is typical of the photo-Fries reaction and also yields carbazole. The reaction shows some solvent dependency but is apparently unaffected by change in wavelength[199]. The *N*-tosyl derivative **241** undergoes a photo-Fries rearrangement affording a low yield of **242** on irradiation under direct or sensitized conditions in benzene solution[199].



R^1=Me, R^2=H,D or Cl

(230)



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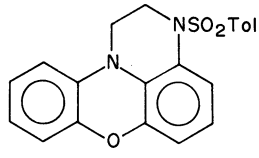

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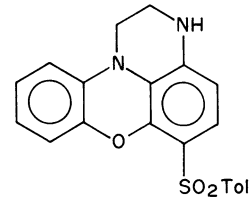
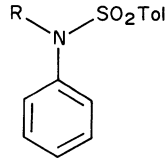
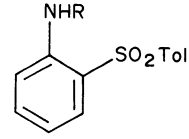


(233)

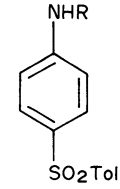


(234)

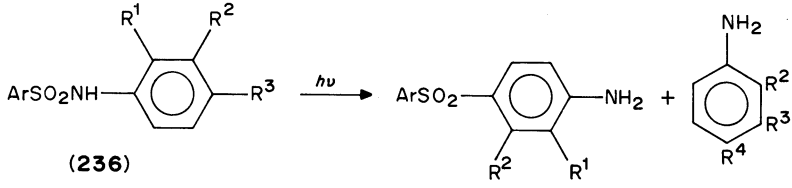


6—35%

(235)



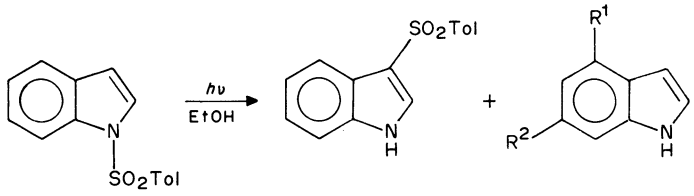
13—35%



(236)

Ar′= *p*-tolyl,	R^1=R^2=R^3=H	25%	68%
Ar′=Ph,	R^1=R^2=R^3=H	12%	30%
Ar′=Ph,	R^1=Me, R^2=R^3=H	14%	25%
Ar′=Ph,	R^2=Me, R^1=R^3=H	6%	43%
Ar′=Ph,	R^3=Me, R^1=R^2=H	—%	41%

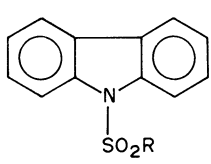
SCHEME 14



(237)

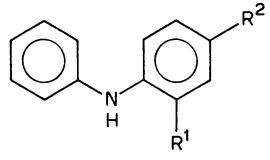
R^1=H, R^2=SO_2Tol
R^1=SO_2Tol, R^2=H

SCHEME 15

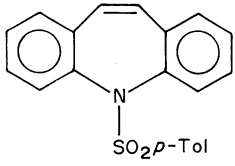


R=Ph, *p*-Tol or Me

(238)



(239) R^1=SO_2R, R^2=H
(240) R^1=H, R^2=SO_2R



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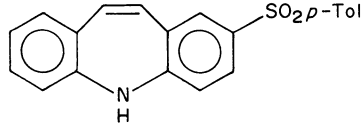
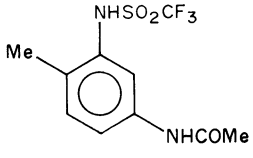


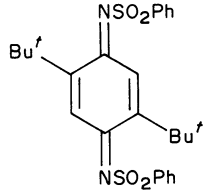
(242)

D. Miscellaneous Reactions

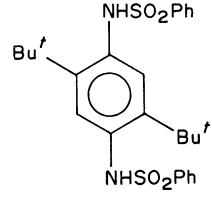
The sulphonamide Sustar (**243**) is reactive on irradiation in water at pH 7.5 under an atmosphere of oxygen. This treatment yields a variety of products among which those of desulphonylation are important[200]. Baxter and Mensah[201] report that irradiation of the bisimine **244** in acetic acid affords the four products shown in Scheme 16 while irradiation in benzene yields only the reduced product **245**. These observations are closely related to the results from the irradiation of the sulphonimide **246** in ethanol which yields the



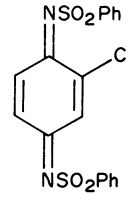
(243)



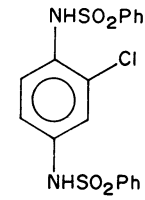
(244)



(245)

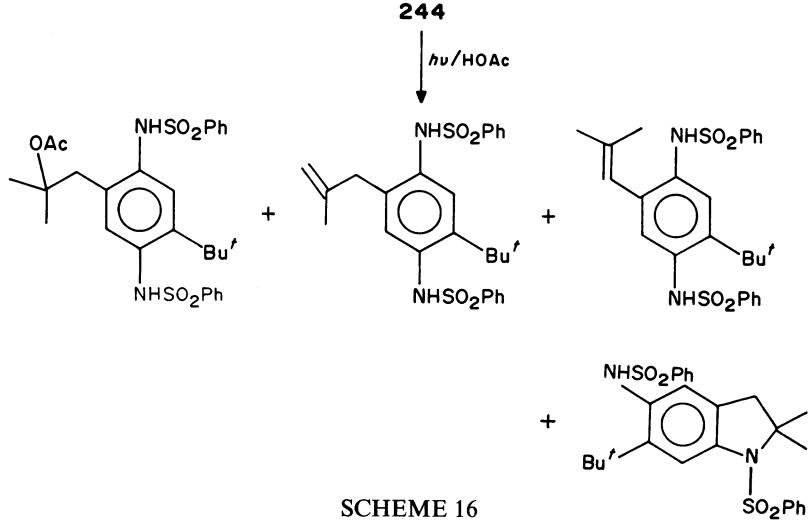


(246)

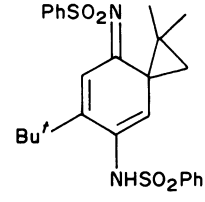


(247)

reduction product **247**[202]. The formation of the products from **244** in acetic acid presumably involves the abstraction of a hydrogen from the *t*-butyl group and the formation of the intermediate **248**, which is subsequently transformed into products. Such reactivity is reminiscent of the photochemical behaviour of *p*-quinones.



SCHEME 16

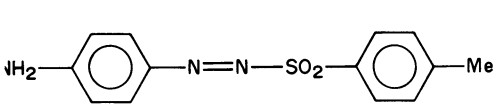


(248)

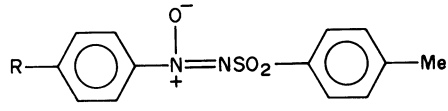
E. Diazosulphones and Related Species

The amethyst violet sensitized photolysis of the diazosulphone **249** has been studied in ethanol/water mixtures and shown to undergo homolytic fission. The fission results in the

formation of aryl and sulphonyl free radicals identified by ESR and spin trapping techniques[203-205]. Aryl free radicals are obtained on the irradiation of the sulphonylazo compound **250**[206]. S—N Bond fission results on irradiation of the sulphonyl sulphoximine **251** in benzene at 254 nm. The reaction is a useful source of aryl radicals[207,208].

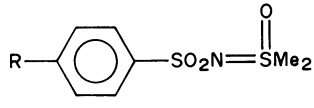


(249)



R=H, Me, MeO, Me_2N

(250)



R=H or Me

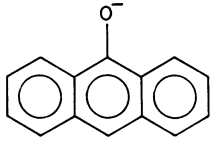
(251)

V. SULPHONIC ACIDS

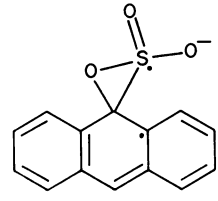
Irradiation of benzenesulphonic acid in water under an atmosphere of nitrogen yields only sulphur dioxide and tarry organic products. The products arise from phenyl radicals which are also formed on irradiation of the sodium salt where small quantities of biphenyl are produced[209]. The sulphonic acid salts **252** are photochemically reactive on irradiation in DMSO at 254 nm. After 50 min irradiation the corresponding arenes **253** are formed in the yields shown[210]. Shapiro and Tomer have reported that the irradiation of *p*-toluenesulphonate in the presence of methyllithium brings about the formation of *p*-xylene in low yield[211].

	$ArSO_3^-$		ArH
(252)	**(a)** Ar = 9-anthryl	**(253)**	**(a)** 60%
	(b) Ar = 1-naphthyl		**(b)** 3%
	(c) Ar = 2-naphthyl		**(c)** 7%
	(d) Ar = *o*-tolyl		**(d)** 3%
	(e) Ar = *p*-tolyl		**(e)** 3%
	(f) Ar = phenyl		**(f)** 7%

The irradiation of sodium 9-anthracenesulphonate in DMSO follows two paths. The first is loss of sulphur dioxide to afford the arene oxide **254** via the intermediate **255**[212,213].

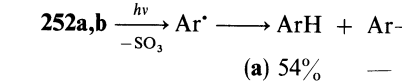


(254)

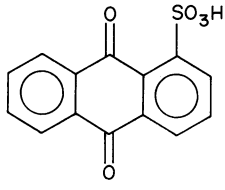


(255)

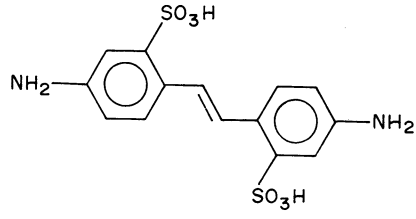
Aerial oxidation of this affords anthraquinone in 37% yield. Both 1-naphthyl and 2,4-dimethylbenzene sulphonates follow the same path but yield only traces of the corresponding quinone. In the last case, 2,4-dimethylbenzenesulphonate, the quinone is accompanied by 0.8% of 2,4-dimethylphenol. The second path involves loss of sulphur trioxide to yield aryl radicals which afford the products, the arene and/or the biaryl, shown in Scheme 17[212,213]. Other studies have shown that anthraquinone-1-sulphonic acid (**256**)[214,215] and anthraquinone-2-sulphonate[216] are also photochemically labile. A study of the photochemical reactivity of azulene sulphonic acids has also been reported[217]. Photochromism has been studied with respect to the stilbene derivative **257**[218].



SCHEME 17

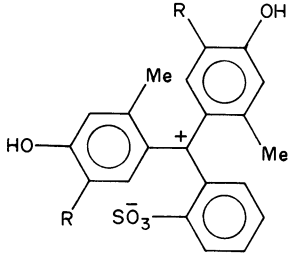


(**256**)



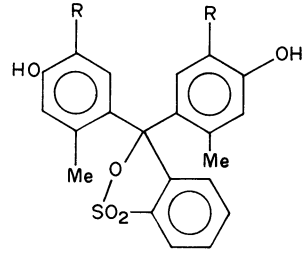
(**257**)

Several reports have been made on the flash photochemical studies of Bromocresol Green and related indicators. Transients such as **258** and the sultone **259** have been detected[219–221]. The radiation chemistry of a series of indicators has been reported[222].



R=Me or Pr^i

(**258**)

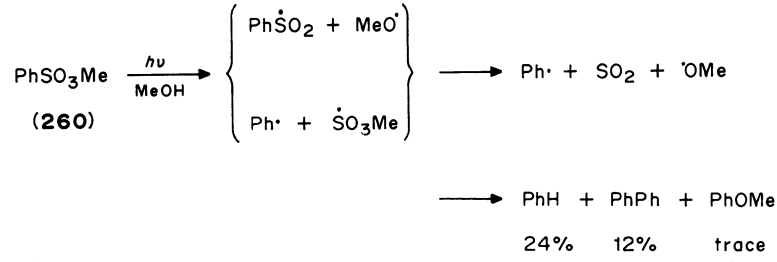


(**259**)

VI. SULPHONATES

A. Open-chain Systems

The reaction of sulphonates has been shown to involve the singlet excited state. The reactions for the conversion of the esters into the free sulphonic acids are reasonably efficient with quantum yields in the 0.02 to 0.07 range. The processes involve homolytic

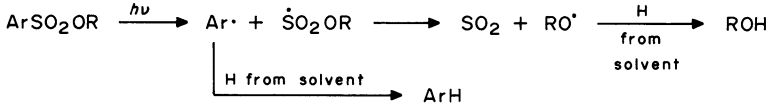


SCHEME 18

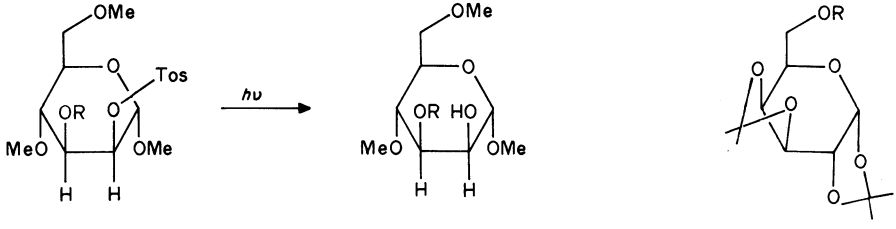
fission. This is substantiated by the work of Izawa and Kuromiya[223], who demonstrated that the irradiation of the sulphonate ester **260** in methanol affords benzene (24%), biphenyl (12%) and a trace of anisole. The formation of products is thought to involve two free radical paths, either S—O or S—C bond fission as shown in Scheme 18[223]. Jaeger[224] has described the photochemical reactivity of 2-(3,5-dimethoxyphenyl)ethyl methanesulphonate. Interestingly, photomethanolysis of *trans*-2-(3,5-dimethoxyphenyl)cyclopentyl methanesulphonate is efficient while the *cis* isomer is unreactive[225].

B. Deprotection

The S—C bond fission path has been exploited as a method for photodeprotection of alcohols. The earliest examples of this were reported by Pete and his group[226–228], who demonstrated that the free alcohol could be obtained in reasonable yields on irradiation of tosyloxy derivatives. Scheme 19 shows the proposed mechanism for the process where irradiation brings about S—C bond fission affording a biradical. Loss of SO_2 affords the alkoxy radical and ultimately the alcohol. Many examples of this deprotection path have been reported over the years. This area of study has been reviewed by Binkley in a number of articles[229–231] with particular reference to deprotection of carbohydrate derivatives. Thus the compounds shown in Scheme 20 are converted into the free alcohols on irradiation in yields up to 87%[232,233]. Even higher yields can be obtained as with the irradiation of **261** which affords 100% detosylation affording **262**[234].

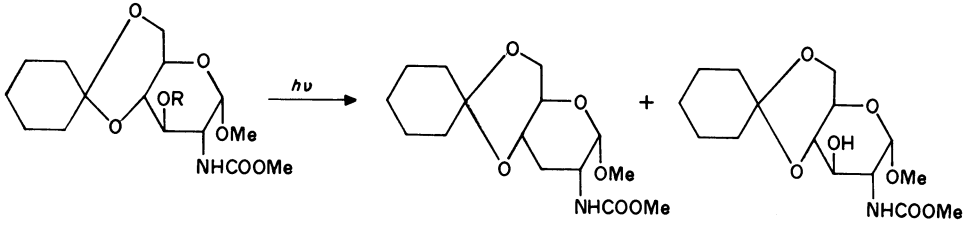


SCHEME 19



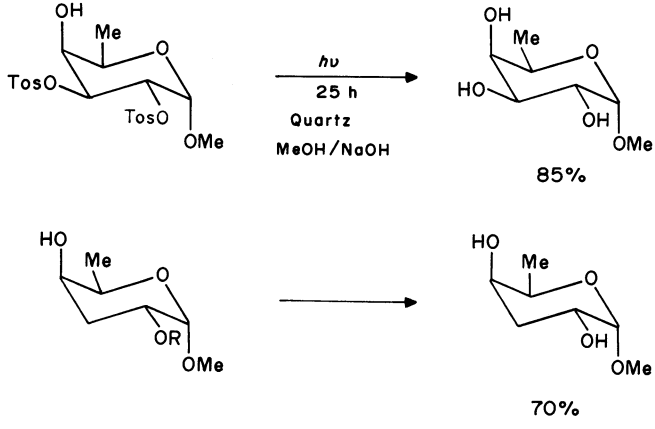
SCHEME 20

Other examples extending the scope of the process have been reported[235-240]. Solvent changes are also important as in the use of hexamethylphosphoric triamide/water. Under these conditions and using light of 254nm the conversions shown in Scheme 21 were effected[241,242]. No reaction was detected on irradiation at 300 nm. Irradiation of steroidal tosylates in the presence of sodium borohydride can also bring about deprotection with the formation of the corresponding alcohols[243]. It is interesting to note that Zen and collaborators[234] carried out the deprotection using methoxide as a key ingredient. Binkley[244] has demonstrated (Scheme 22) that under such conditions an ionic and not a free radical mechanism is involved. Thus the fate of the alkoxy radical is dependent upon the conditions under which the reaction is carried out and in the presence of base such as Et_3N or MeO^- a SET is involved and the alkoxy radical is converted to an alkoxide. The alkoxide path is substantiated by the detosylation of carbohydrate derivatives in base without epimerization of the carbon. Other studies have shown the efficient detosylation of the carbohydrate derivatives (Scheme 23) in the presence of benzyl groups[245,246].

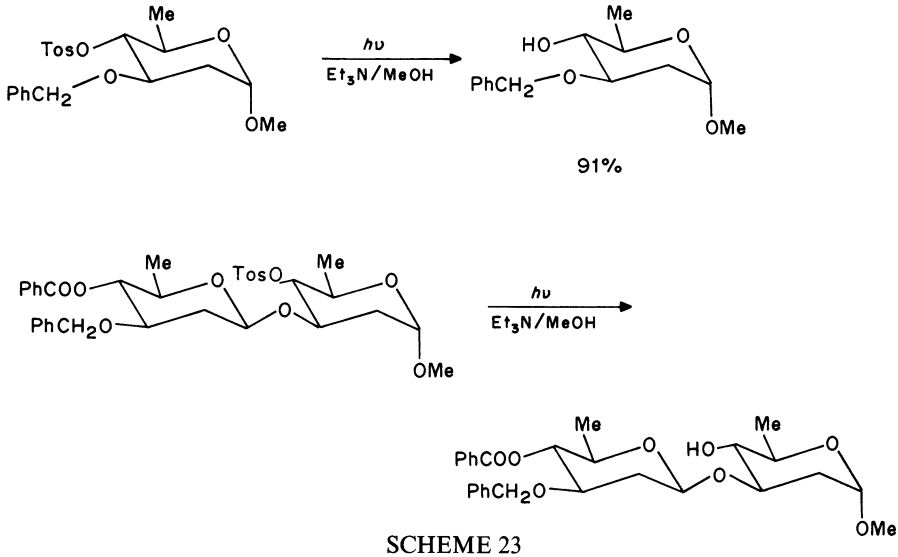


(a) R=Me_2NSO_2	—	—
(b) R=$MeSO_2$	trace	86%
(c) R=p-$MeC_6H_4SO_2$	—	91%

SCHEME 21



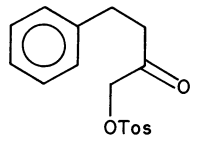
SCHEME 22



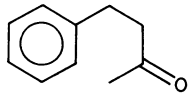
SCHEME 23

C. Sulphur–Carbon Bond Heterolysis

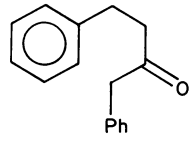
S—C Bond heterolysis dominates the photochemical reactivity of the keto tosylate **263**[247]. Irradiation in benzene gives *p*-toluenesulphonic acid in 74% yield. The other products formed from this reaction are the ketones **264** and **265**. The reaction is presumed to proceed via the intermediate carbocation **266** formed by S—C bond fission. The tosylate **267** is more able to undergo intramolecular addition due to the electron-donating methoxy group and gives **268** and **269** in 24% and 23% yields. An analogous mechanism is involved in the conversion of the sulphonate **270** on irradiation in benzene into the two products **271** and **272** in a ratio of 4:1[249]. The formation of the major product **271** presumably involves the heterolytic fission of an O—C bond to afford a cation which



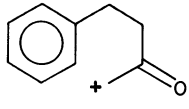
(263)



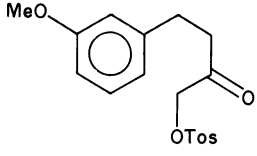
(264)



(265)



(266)



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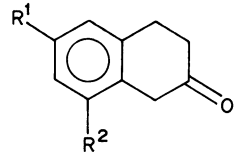
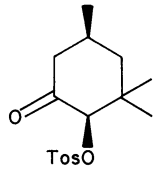


(268) R^1=MeO, R^2=H
(269) R^1=H, R^2=MeO



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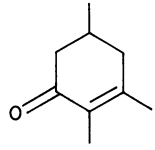

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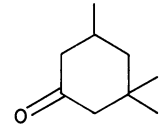

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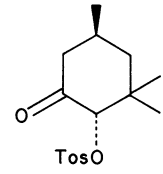
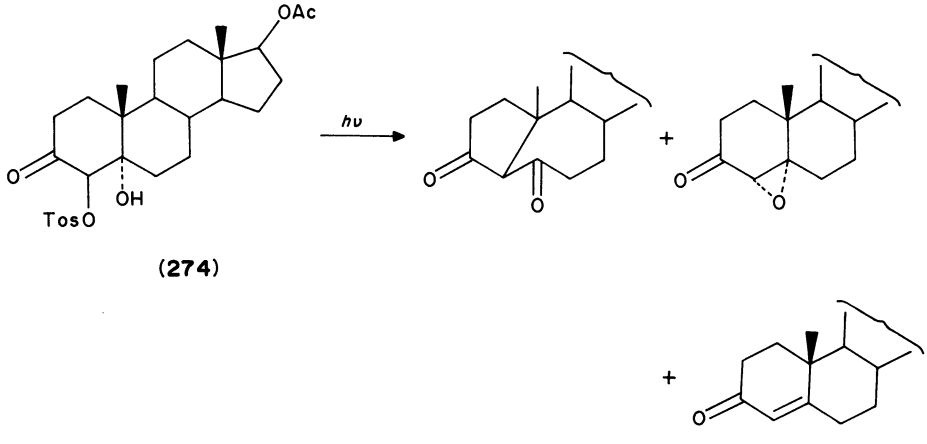


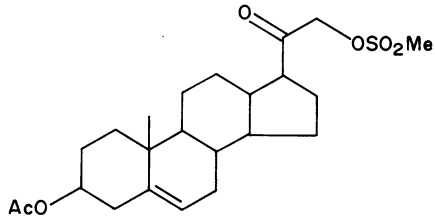
(273)

undergoes a methyl migration. It is interesting to note that the isomeric compound **273** is unreactive. Cationic paths are reported to be involved in the phototransformation of the steroidal sulphonates **274** into the products shown in Scheme 24[249]. Proof of involvement of cationic intermediates in the irradiation at 254 nm of the sulphonates **275** in the presence of naphthalene is obtained by the isolation of the α-naphthyl derivative **276**[250]. These studies have been the subject of a review[251].

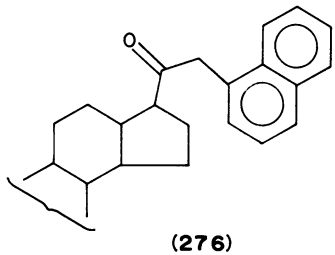


(274)

SCHEME 24



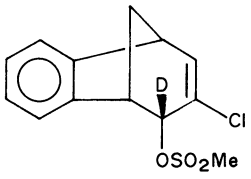
(275)



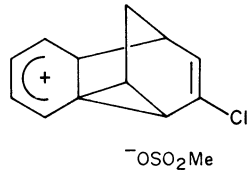
(276)

Cationic intermediates are also involved on irradiation at 254 nm of the sulphonate **277** in acetonitrile. The reaction is thought to involve the formation of the ion pair **278** formed from **279**, the result of intramolecular SET in the starting material[252].

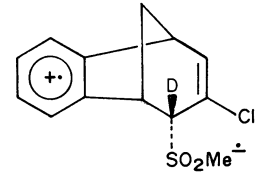
Pete and his coworkers have described the photochemical reactivity of the sulphonates



(277)

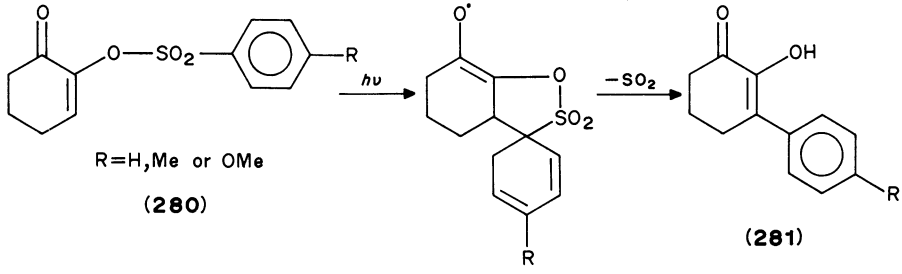


(278)



(279)

280 of cyclohexenone derivatives. The irradiation of these compounds brings about loss of SO_2 and the apparent 1,3 migration of the aryl group. The mechanism proposed for this reaction is shown in Scheme 25 and involves bonding between the β-carbon of the enone and the aryl ring. The resultant biradical extrudes SO_2 to yield, ultimately, the 3-aryl cyclohexenone **281**[253–255]. In an earlier section (IV.B.1) an analogous reaction has been described for the corresponding sulphonamides. Others have demonstrated that the same type of reaction occurs with the cyclopentenone **282** affording **283**[256].

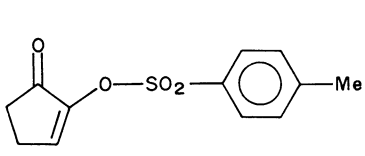


R=H,Me or OMe

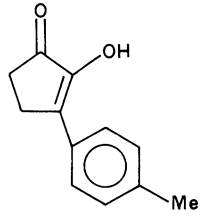
(280)

(281)

SCHEME 25



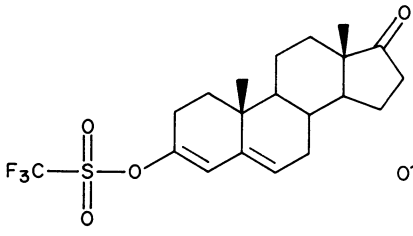
(282)



(283)

D. Miscellaneous Sulphonates

The steroidal dienol triflate **284** in pyridine photo-extrudes SO_2 and forms the 6β-trifluoromethyl derivative **285** presumably via a free radical reaction path[257]. The anhydride **286** undergoes S—O bond fission to afford radicals. When the reaction is carried out in aromatic solvents such as benzonitrile or nitrobenzene, hydrogen abstraction reaction or addition to the aryl groups of the solvent takes place[256]. Cadogan and Rowley[259] report that the irradiation of the tosyloxy compounds **287** results in N—O bond fission to afford phthalimido radicals. These react with solvent (arene) to afford



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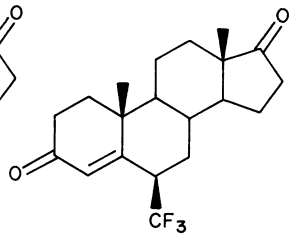

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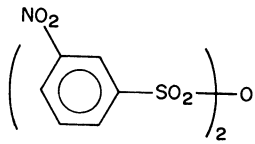

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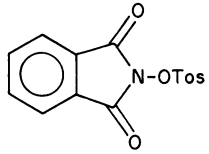

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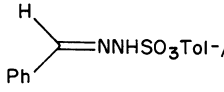
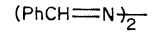
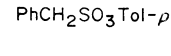


(288)



(289)

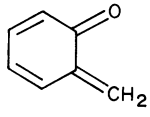


(290)

phthalimide derivatives from which aryl amines can be liberated. Typical of this is the reaction in benzene which yields *N*-phenylphthalimide in 18% yield. When anisole is used as the substrate the three possible phthalimido anisoles (*ortho*, *meta* and *para*) are obtained in 55, 3 and 42% yields, respectively. The irradiation of the hydrazone **288** involves N—N bond fission yielding **289**. Loss of nitrogen also competes affording **290**[260].

E. Cyclic Sulphonates

The *o*-quinomethide **291** is formed on irradiation of the sultone **292** at room temperature[261]. S—O Bond fission is also the result of irradiation through quartz of the cyclic sulphonate **293**. In this case the resultant biradical does not extrude SO_2 but ring closes to afford the sulphonamide **294**[262].



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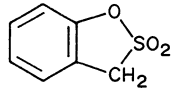

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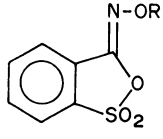
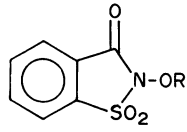


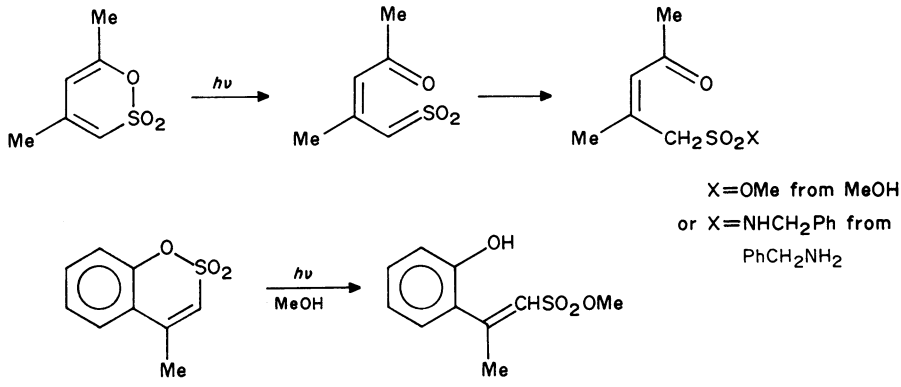
(293)



(294)

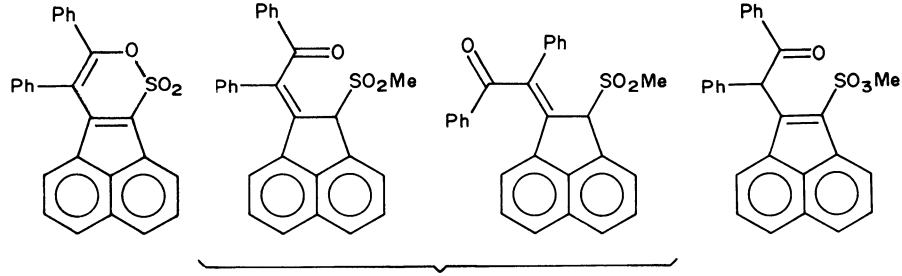
R=Me or $PhCH_2$

De Mayo and his coworkers[262–264] have reported the photochemical isomerization of the sultones shown in Scheme 26. These compounds ring open in a manner analogous to linearly conjugated cyclohexadienones affording a sulphene intermediate. This intermedi-

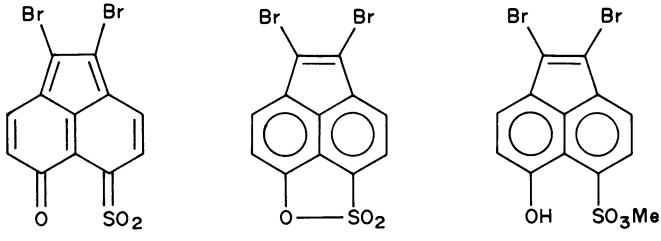


SCHEME 26

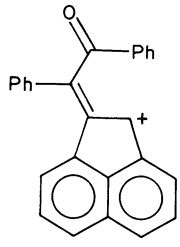
ate can be readily trapped by alcohols or amines affording the products shown. Several examples of this process were reported. A review of sulphenes produced in this fashion or by other methods has been published[265]. Charlton and de Mayo[266] report that the irradiation of **295** in methanol/base affords the products **296** and **297**. A flash photolytic study indicated a route to products where methanol attacked the sulphone directly and that a sulphene is not involved. Direct irradiation of **295** in glyme yields sulphur dioxide. However, a later study implicated a sulphene intermediate on the irradiation of this sultone **295** and this is trapped as the esters **296**[267]. The sulphene **298** is formed by irradiation of the sultone **299** in methanol. This is trapped as the ester **300**[269]. Loss of SO_2 also competes in the irradiation of **295** and affords the carbocation **301** which undergoes intramolecular cyclisation to yield **302**[267]. Sulphur dioxide is also extruded on irradiation



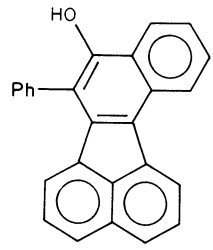
(295) (296) (297)



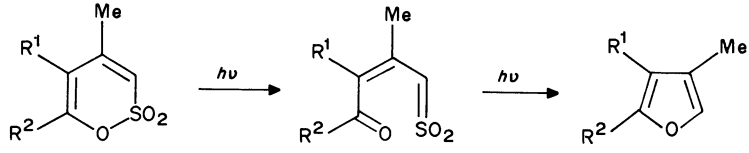
(298) (299) (300)



(301)



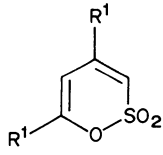
(302)



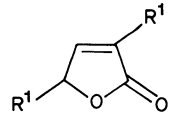
(a) R^1=H, R^2=Me
(b) R^1—R^2=$CH_2CHCHMeCH_2$

(a) 18%
(b) 43%

SCHEME 27



(303)



(304)

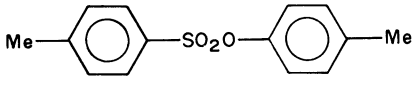
of the sultones shown in Scheme 27. Again the sultones are thought to undergo ring opening and extrusion of SO_2 from the sulphene intermediate. Subsequent cyclization yields the furans shown[269]. This account is different from an earlier report[270]. The sultone **303** on direct irradiation in the absence of nucleophiles undergoes photochemical loss of SO with the formation of the butenolide **304**[271].

F. Photo-Fries Reactions

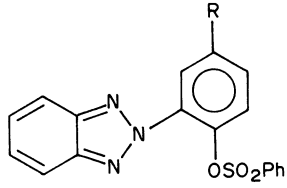
In an earlier section (IV.C) it was mentioned that Bellus[194] had reviewed the photo-Fries reaction. This review includes the work on sulphonic acid esters and sulphonamides. There are earlier reviews[272,273] on this topic but these are prior to the reports of the photo-Fries reactivity of sulphonates.

Typical of this work is the rearrangement of phenyl *p*-toluenesulphonate into 2-hydroxyphenyl and 4-hydroxyphenyl *p*-tolyl sulphones[274]. Ogata and coworkers[275] have shown that phenyl benzenesulphonate also rearranges on irradiation in ethanol and yields both 2-hydroxyphenyl and 4-hydroxyphenyl phenyl sulphones as well as phenol, small amounts of diphenyl ether and polymer. Interestingly, the tolyl derivative **305** does not rearrange and only *o*- and *p*-cresol are isolated. Irradiation (330 nm) of the sulphonates **306** in ethyl acetate affords the hydroxysulphones **307** in 66% yield. The reaction of **306** also

occurs in polymer films exposed to sunlight. The process is quite specific for benzenesulphonates and little or no rearrangement takes place with naphthalene- or alkanesulphonates[276]. Snell[277] has reported that the pyrimidine esters **308** are also photoreactive and afford the isomerized products **309** as well as the desulphonylated compound **310**. Others have also shown the ease of rearrangement of such systems[278].

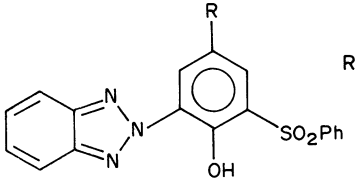


(305)

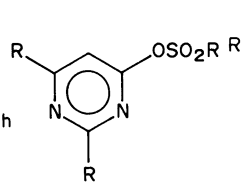


R = Me or C_8H_{17}

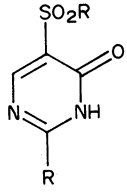
(306)



(307)



(308)



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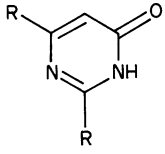
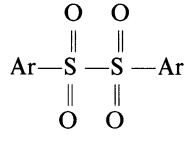


(310)

VII. SULPHUR–SULPHUR AND SULPHUR–SELENIUM BOND FISSION

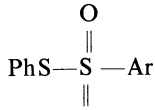
A. Sulphur–Sulphur Bond Fission

The disulphones **311** are photoreactive on irradiation at 254 nm and undergo S—S fission to produce sulphonyl radicals. These undergo a variety of reactions[279]. In contrast, the thiosulphone **312** is not photochemically reactive[290]. Extrusion of sulphur dioxide is the major path for the photodecomposition of the thiosulphonate **313**. The products formed are produced by radical reactions as shown in Scheme 28[281]. Photochemical loss of sulphur dioxide from **314** affords the biradical **315** which is converted into benzalacetophenone[281]. Irradiation of **316** in benzene produces the thiaquinone methide **317** in a reaction analogous to that reported in Section VI.E. This intermediate can be trapped by dienophiles such as *N*-phenylsuccinimide to afford the adduct **318**[283]. Photochemical loss of sulphur dioxide from the dioxide **319** affords the thiet **320**[284,285].

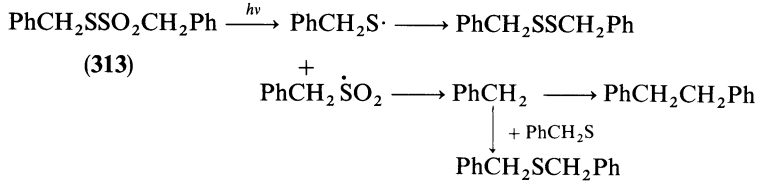


Ar = Ph or *p*-tolyl

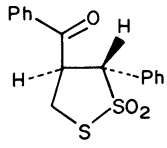
(311)



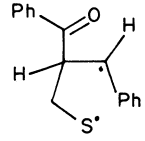
(312)



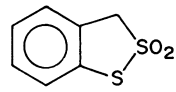
SCHEME 28



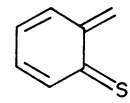
(314)



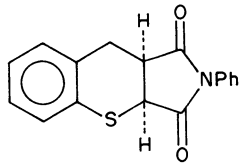
(315)



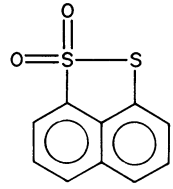
(316)



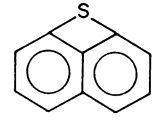
(317)



(318)



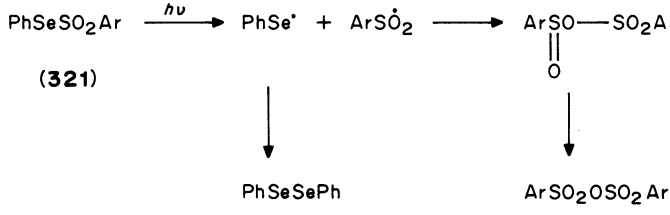
(319)



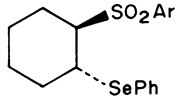
(320)

B. Sulphur–Selenium Bond Fission

Gancarz and Kice[280,286] have also studied the photochemical reactivity of the selenyl sulphones **321**. Irradiation in carbon tetrachloride affords the products shown in Scheme 29. The formation of a selenyl and a sulphur radical can be demonstrated by irradiation in cyclohexene when the adduct **322** is formed. Addition also takes place to



SCHEME 29



(322)

ArSO2CH2CH2SePh

(323)

cycloocta-1,5-diene, norbornadiene, and to simple alkenes. Irradiation of the selenyl sulphones **321** in the presence of diazomethane yields the sulphone **323**[287].

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CHAPTER **14**

Electrochemistry of sulphonic acids and their derivatives

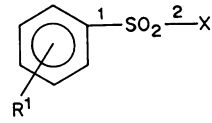
JACQUES SIMONET

Laboratoire d'Electrochimie organique, CNRS, Université de Rennes 1, France

I. INTRODUCTION

The family of sulphonic acid derivatives is obviously very wide. But rather surprisingly, electrochemical data concerning all the members of the family are rather few. These available concern mainly sulphonyl esters, sulphonyl amides and sulphonyl chlorides. Additionally, data exist also for aromatic sulphonic acids when they are strongly activated.

As shown in the course of this chapter, the electrochemical activity concerns almost exclusively the reduction of those derivatives. The reduction is also nearly always associated with a cleavage reaction (two-electron scission). The reduction is strongly favoured when the electron transition allowing the occupation of a π^* orbital is made easier. A decrease in the LUMO energy may correspond, at least, to the introduction of an aromatic ring when associated to the SO_2 or SO_3 group. In other words, the reduction of



The chemistry of sulphonic acids, esters and their derivatives
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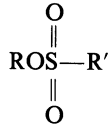
$X = OR^2$, NR^3R^4, Cl, OH is strongly favoured (and even increased if R^1 possesses an electron-withdrawing effect) while the corresponding aliphatic systems RSO_2X may be inactive (except when X = Cl since the cathodic activation of the S—Cl bond is not of the same type).

After the first electron transfer, a chemical reaction (here a scission) may occur only if the transition $\pi^* \rightarrow \sigma_1^*$ or $\pi^* \rightarrow \sigma_2^*$ is possible. In most cases, the cleavage of the C—X bond is observed with formation of the arenesulphinate ion. This reaction was exploited for deprotecting alcohols and amines.

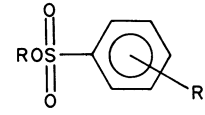
II. ELECTROREDUCTION OF SULPHONIC ESTERS

A. Direct and Indirect Reductions

While the available literature only describes the electronic activity of organic arenesulphinates, it should be assumed that esters **1** can undergo cathodic reduction only when R and/or R′ possess a rather low energy level of their LUMO. In other words, when R and R′ are fully saturated, it is rather foreseeable that **1** is totally inactive in terms of cathodic reactivity. To the best of our knowledge, *all* papers devoted to sulphonic esters deal only with the behaviour of arenesulphonates[4] and nearly all of them focus their interest on the reduction of tosylates **2** (R″ = *p*-CH_3).



(1)



(2)

The cathodic reduction of **2** leading to a more or less selective cleavage of the S—O bond, appears to be the main goal of different studies in this field because those esters are considered as forms protecting the alcohol ROH. Interest in cathodic deprotection lies mainly in the fact that alternative chemical processes (solvolysis or reduction by hydrides) lead to racemization or inversion of the R group.

From aqueous electrolytic solutions, early experiments conducted by Horner and coworkers[2,17,18] in the sulphinate cleavage reaction have displayed good regioselectivity of the electrochemical breaking of esters (Table 1). In the cases where the R group is optically active, retention of configuration can be observed. Table 2 exhibits the high optical retentions obtained by the cathodic method.

$$ROSO_2Ar \xrightarrow[H^+]{2e^-} ROH + ArSO_2^-$$

However, in non-aqueous media the cathodic cleavage of arenesulphonates is far from

TABLE 1. Electrochemical cleavage of tosyl esters[2]

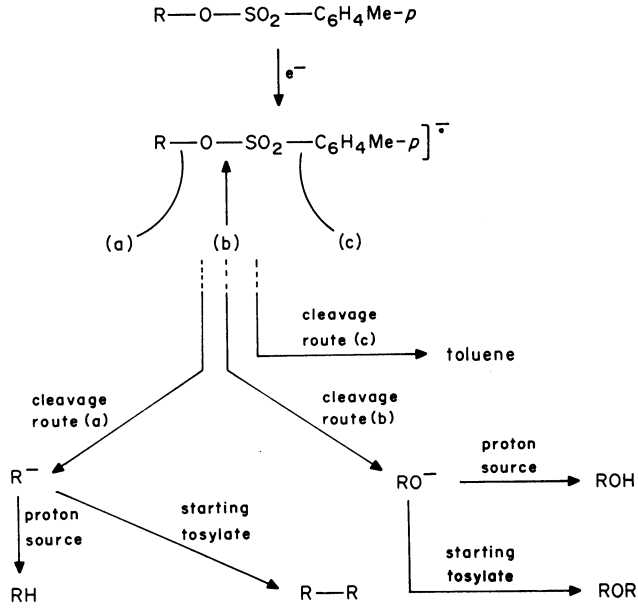
Ester	Isolated products	Yield (%)
Methyl	Toluenesulphinic acid	90
Benzyl	Toluenesulphinic acid	99
	Benzyl alcohol	85
Cyclohexyl	Toluenesulphinic acid	94
	Cyclohexanol	81
Phenyl	Toluenesulphinic acid	91

TABLE 2. Cleavage of optically active tosylates[3]

Tosyl ester of	% Yield of ROH	$[\alpha]_{546}^{21\,a}$	$[\alpha]_{546}^{21\,b}$
1-Menthol	73	−57.9	−57.2
1-Borneol (optically enriched)	95	−33.3	−33.9
Cholesterol	95	−45.7	−45.3

[a]Optical rotation of the alcohol before esterification.
[b]Optical rotation of the alcohol after cathodic deprotection.

selective. The recovery of the alcohol remains the desired process, while many side-reactions depending on the electrolysis medium and on the formation of electrogenerated nucleophiles occur. Thus, the cleavage of the S—O bond may compete with that of the C—O and C—S ones[5,6]. Toluene in more or less detectable amounts can be isolated[5]; additionally symmetrical hydrocarbons and ethers can be obtained through nucleophilic substitutions in the catholyte solution. The different routes tested with toluenesulphonates are presented in Scheme 1.



SCHEME 1

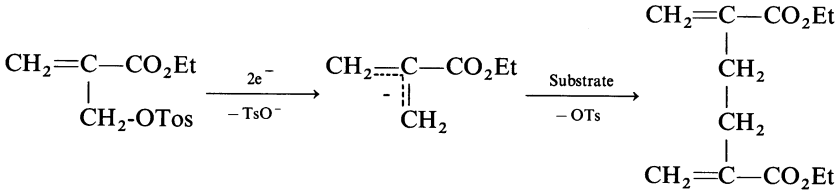
As shown by Yousefzadeh and Mann[5], the transient anion radical has a very short lifetime (less than a few milliseconds when formed in acetonitrile). The proton donor was demonstrated to be the tetrapropyl ammonium salt (propene was detectable). While the symmetrical ether ROR was formed in substantial amounts on carbon cathodes during large-scale reductions, its yield dropped dramatically when a mercury cathode was used. This intriguing difference has been explained by a change of reactivity within the electrical double layer, whose structure is probably strongly dependent upon the nature of the solid conductor.

Other examples[6] are available: *p*-nitrobenzyl tosylate leads to 1,2-di-*p*-nitrophenylethane (78%) (reduction in acetonitrile) whereas *p*-methylbenzyl tosylate gives rise to *p*-xylene (30%) besides *p*-methylbenzyl alcohol (70%) (when electrolyses are conducted in DMF).

Electrochemical data on activated sulphonates are available. Thus allyl[12] and propargyl[13] *p*-toluenesulphonates were polarographically reduced. These results permit one to estimate the two-electron reactivity (overall cathodic process) of sulphonates in relation to other potential leaving groups. For such activated R groups, tosylate would possess an electrochemical activity of the same order as chloride but less than bromide, and also surprisingly much less than a sulphonyl group.

$$\underset{-1.32\ \text{V/SCE}}{p\text{-TolSO}_2\text{CH}_2\text{C}{\equiv}\text{CH}} \qquad \underset{-1.78\ \text{V/SCE}}{p\text{-TolSO}_2\text{—O—CH}_2\text{C}{\equiv}\text{CH}}$$

The cathodic reactivity of 2-carbethoxyallyl *p*-toluenesulphonate with the formation of a transient nucleophile may furnish a nice example of the formation of a symmetrical R—R type compound (Scheme 2).



SCHEME 2

The indirect reduction of tosyl esters can be performed[7] in non-aqueous solutions. Thus, for example, the anthracene anion radical formed by cathodic reduction in DMF/TBAB (tetrabutylammonium bromide) electrolyte may reduce tosylates in solution. Similarly, the pyrene anion radical was shown[8] (Figure 1) to react also with ethyl tosylate. The redox catalysis general scheme (indirect reduction by a redox *P*/*Q* couple) where P is a reducible species and Q its stable reduced form can be written as below:

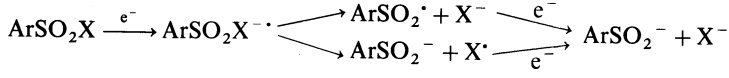
$$\text{P} + \text{e}^- \rightleftharpoons \text{Q}$$

$$\text{Q} + \text{Tosylate} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{P} + [\text{Tosylate}]^{-\cdot}$$

$$[\text{Tosylate}]^{-\cdot} \xrightarrow{k} \text{bond cleavage}$$

Saveant's group [9-11] has considerably developed the kinetic and thermodynamic potentialities of redox catalysis. Therefore, this theory can be applied to the indirect reduction of tosylates[7] and allows, by a judicious choice of *P*/*Q* couples, to displace the equilibrium k_1/k_2 to the right side, so permitting one to estimate either values of tosylate standard potentials or *k* parameters. Some of those values[7] corresponding to several tosylates are gathered in Table 3.

The indirect reduction of tosyl esters by reduced forms of organic mediators may lead[15] in certain cases to chemiluminescence and then help to determine the mode of cleavage of the S—O bond and the nature of the free radical present.



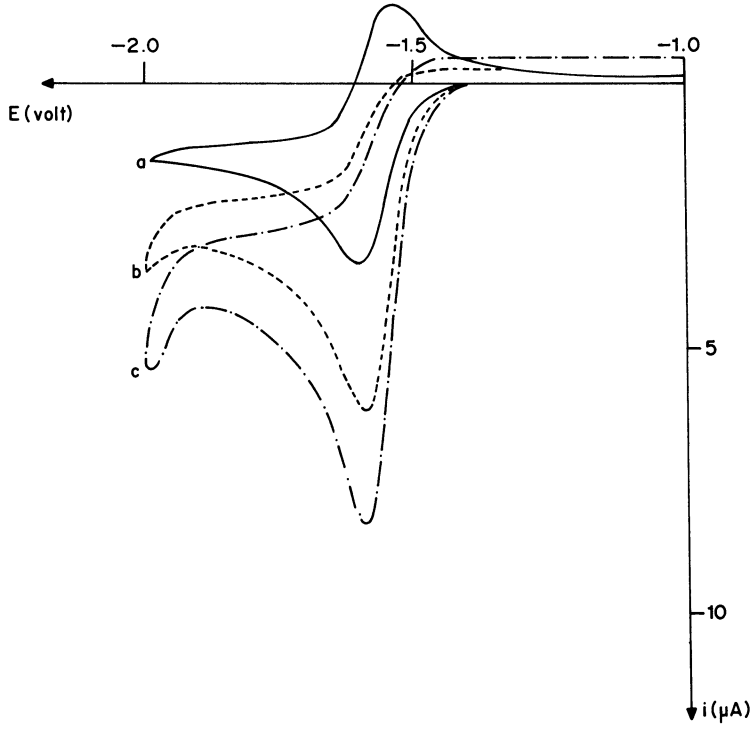
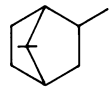


FIGURE 1. Cyclic voltammetry of pyrene[8] in the absence and presence of ethyl *p*-toluenesulphonate in dimethylformamide/Bu_4NBF_4 0.1 M as an electrolyte. Stationary mercury micro-electrode. Reference electrode: Ag/AgI/I^- 0.1 M system. Sweep rate 0.1 V s^{-1}. Curve a, pyrene alone 10^{-3} M; b, preceding solution with 10^{-3} M sulphonate; c, solution (a) with 2×10^{-3} M sulphonates[8]

TABLE 3. Thermodynamic and kinetic data from the indirect electrochemical cleavage of tosylates from non-aqueous solutions at a mercury micro-electrode[7]

R in *p*-$MeC_6H_4SO_3R$	E° vs SCE (V)	k (s^{-1})
Me	−2.36	1×10^7
Et	−2.27	3×10^5
i-Pr	−2.33	1×10^6
$CH_3OCH_2CH_2$	−2.24	2×10^5
$C_6H_5CH_2$	−2.24	2×10^5
	−2.26	1×10^5

Thus, the formation of free radicals appears to be a prerequisite of the cathodic luminescence of aryl tosylates[16] in HMPA:

$$TolSO_2 - OAr + e^- \longrightarrow TolSO_2^- + ArO^\cdot$$

$$ArO^\cdot + e^-_{Solv} \longrightarrow {}^\cdot(ArO^-)^* \longrightarrow ArO^- + h$$

In the case where the electron source is a suitable detector compound A, able to be cathodically excited, energetic limitations may produce only the triplet state as expressed

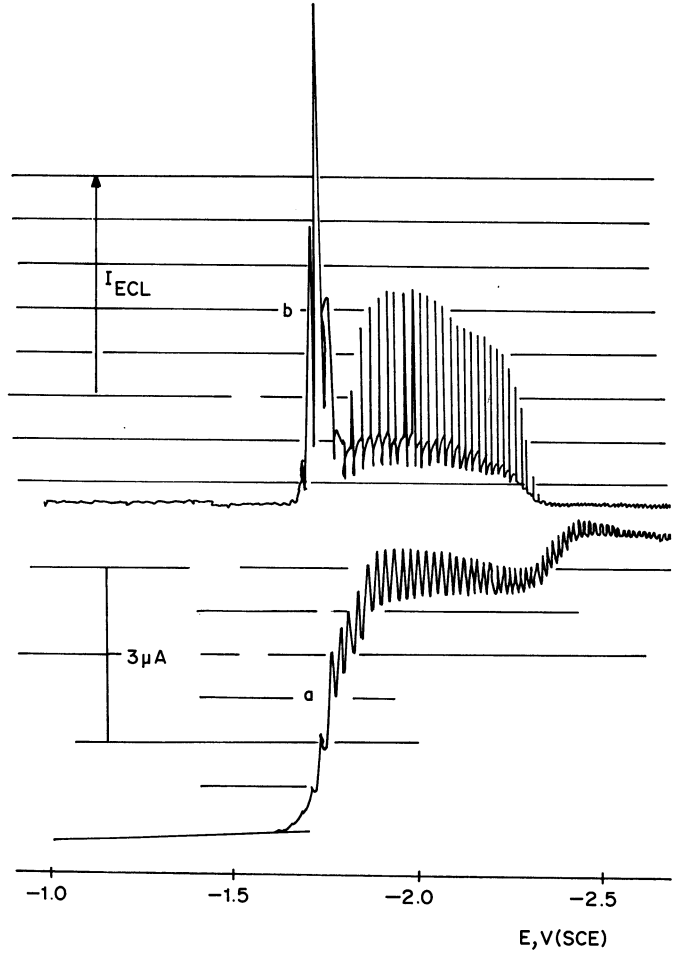


FIGURE 2. Polarogram (curve a) and corresponding 'ecl' intensity–potential curve (curve b) of a mixture of *p*-bromophenyl *p*-toluenesulphonate/diphenylacetylene (both at concentration 1 mM) in 0.1 M tetraethylammonium perchlorate/dimethylformamide as an electrolyte. (Reprinted with permission from Reference 15. Copyright (1982) Pergamon Press plc.)

below:

$$A + e^- \longrightarrow A^{-\cdot}$$

$$A^{-\cdot} + ArSO_2^{\cdot} \longrightarrow {}^3A + ArSO_2^-$$

$$A^{-\cdot} + X^{\cdot} \longrightarrow {}^3A + X^-$$

$$2\,{}^3A \longrightarrow {}^1A^* + A$$

$${}^1A^* \longrightarrow A + h$$

The electrogenerated chemiluminescence (ecl) is therefore specific of the triplet–triplet annihilation for A-type compounds. In such processes, the triplet formation, on which the ecl phenomenon is based is in competition with the expected reactions already established for redox catalysis, namely homogeneous electron exchange reactions (SET and then disproportionation reactions):

$$ArSO_2X + A^{-\cdot} \rightleftharpoons ArSO_2 - X^{-\cdot} + A$$

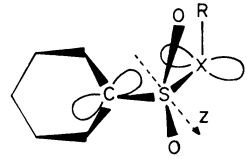
and

$$ArSO_2^{\cdot} + ArSO_2X^{-\cdot} \longrightarrow ArSO_2^- + ArSO_2X$$

Figure 2 exhibits an example of ecl for a sulphonic ester indirectly reduced by a diphenylacetylene anion radical. The occurrence of 'ecl' was also[15] established experimentally under similar experimental conditions for sulphonyl chlorides (X = Cl) and sulphonamides ($X = NR^1R^2$).

B. Structure/Cathodic Reactivity Relation

When compared to the corresponding di-oxygenated sulphur compounds like sulphones, organic sulphonates tend to be in general easier to reduce. This could be explained[19] both by a partial hybridization of the molecular orbitals of the oxygen atom bearing the aliphatic chain and a higher electron-withdrawing effect due to the SO_3 group leading to a diminished level of the LUMO of the unsaturated system (here, the aromatic ring). Therefore, a structure of sulphonates was proposed by Gerdil[19] in the general case where X is heteroatom (O or N), connected to the sulphur atom.



The effect of the R group on the reduction potentials (measured in most of the cases in buffered aqueous solution for two-electron processes implying S—O bond scission as discussed below) is rather clear and tends to support the assumption presented above: unsaturated and/or electron-attracting substituents enhance the case of reduction (Figure 3). One may note, on comparison with sulphones, a linear regression of the R group effect due to the interposition of methylene group as fully expected. However, a rather low bond index for the dianion does not appear to be a determining element for enabling the cleavage at the stage of this reduced form.

C. Cathodic Cyclizations Involving at Least One Tosylate Function

When using media of low acidity, the electrochemical reduction of *trans*-1-bromo-2-tosyloxycyclohexane leads to the corresponding epoxide[14]. The proposed mechanism

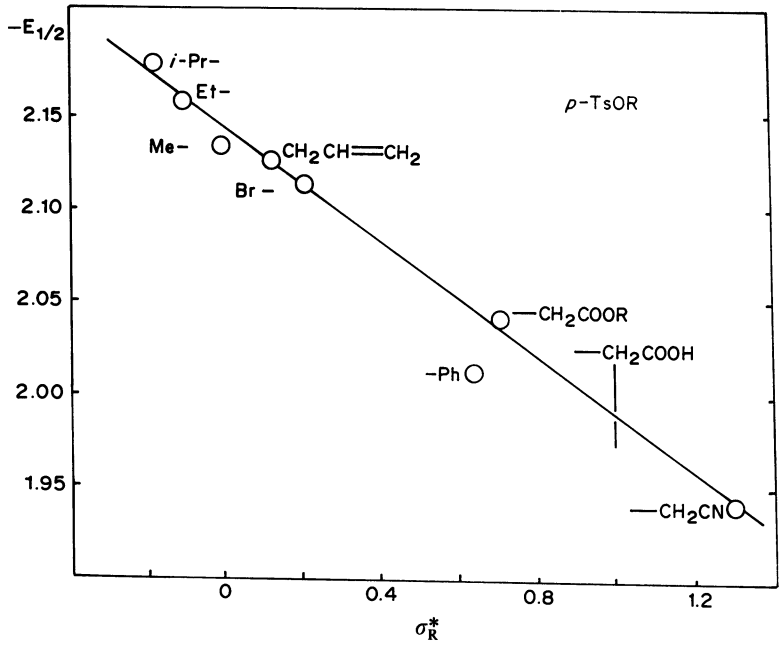
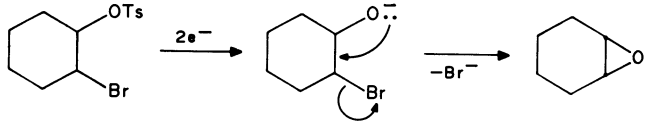


FIGURE 3. Plot of half-wave potentials (referred to Ag/AgCl/Cl^- sat) vs the polar constant σ_R^* for different tosylates (Reproduced by permission of Verlag Helvetica Chimica Acta from Reference 19)

assumes that the tosylate function is cathodically cleaved before the carbon–bromine bond:



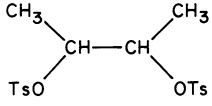
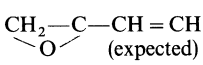
However, a similar result could obviously be obtained when assuming that the C—Br linkage is broken first.

Some α,ω-ditosylates $TsO(CH_2)_nOTs$ ($1 \leqslant n \leqslant 10$) were reduced[20] in dimethylformamide. Cyclizations were shown to occur. For $n = 2$, ethylene oxide was formed in a good yield (Table 4). When $n > 2$, the formation of five-membered ($n = 4$) and six-membered ($n = 5$) rings was confirmed. On the other hand, reductions conducted in the presence of a rather strong excess of a proton donor appear to lead directly to diols:

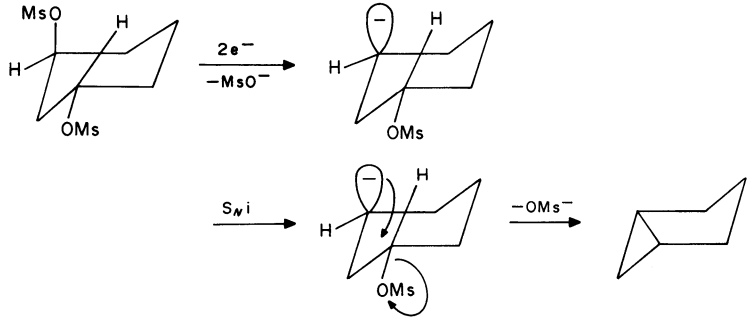
$$TsO-(CH_2)_n-OTs \xrightarrow[2\,H^+]{4\,e^-} HO-(CH_2)_n-OH + 2Ts^-$$

However, when dimesylates (MsO) are submitted to electrolysis, product distribution becomes dramatically different from that corresponding to ditosylates already described. As a matter of fact, the reduction of cyclopentane and cyclohexane 1,3-bismethanesulphonate (divided cell, Pt cathode and anode, potentiostatic electrolysis) now leads to a cyclopropane ring and not to the expected four-membered ring ether (Scheme 3).

TABLE 4. Polarographic data from solutions of DMF/Bu_4NClO_4 0.1 M and corresponding macroelectrolysis results at a mercury cathode[14]

Substrates $TsO(CH_2)_nOTs$	$E_{1/2}$ (V)[a]	Electricity consumption (F mole^{-1})	Product (yield %) (electrolysis solvent used)
$n=1$	−1.927	—	Formaldehyde (expected)
$n=2$	−2.055	1.9	Ethylene oxide (85) (acetonitrile)
$n=3$	−2.139	1.9	Not isolated
$n=4$	−2.143	1.9	Tetrahydrofuran(46) (acetonitrile)
$n=5$	−2.166	1.9	Tetrahydropyran(30) (dimethylformamide)
	−2.145	1.9	Dimethyloxirane(60) (acetonitrile)
$TsOCH_2CH{=}CHCH_2OTs$	−2.094	1.7	 (expected)

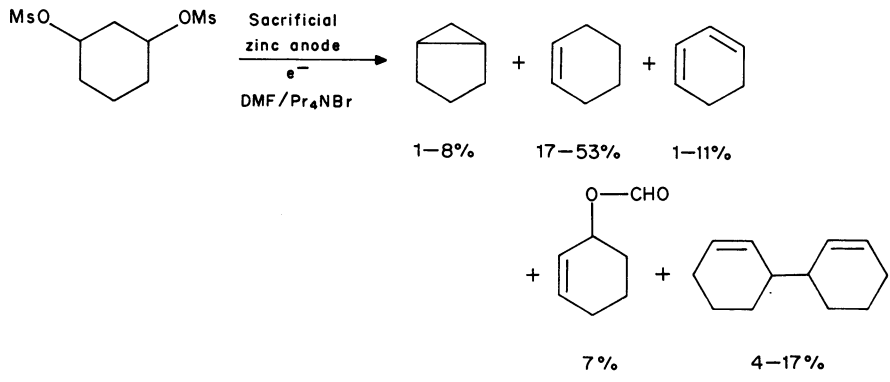
[a]Referred to Ag/AgCl/KCl sat electrode.



SCHEME 3

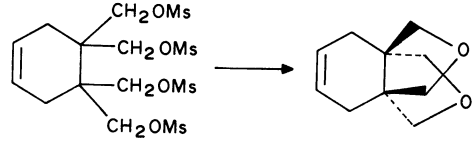
Under the other experimental conditions described by Hoffmann[21] (undivided cell, Pt cathode, sacrificial magnesium or zinc anode, galvanostatic H electrolysis), the carbon—mesyloxy bond apparently behaves cathodically like a carbon–halogen bond. Formation of 1,2-methylenecyclopentane is favoured by using a magnesium anode (yield up to 20%) contrary to the classical potentiostatic electrolysis without sacrificial anode where cyclohexene is obtained in a good yield (71%) at a platinum cathode. Scheme 4 exhibits the products obtained by reduction of a 1,3-dimesylate when using a sacrificial zinc anode. Most of the given products may result from solvolysis (by the electrolyte or or by reaction of $MgBr_2$) of the starting material.

As already mentioned, saturated monomesylates should possess a very low cathodic reactivity (absence of an electrophore permitting the first charge transfer). While possessing probably a better activity, dimesylate should only react (for the moment no



SCHEME 4

potentials are available) at very reducing potentials. Hoffmann[21] also studied the electrochemical reactivity of a tetramesylate:



The product of this reaction seems to conform to what was expected from the cathodic cleavage of the tosylates.

III. THIOSULPHONIC ESTERS

Rather similarly to organic sulphonates, the reduction of thiosulphonates proceeds via cleavage of the S—S linkage:

$$RSO_2SR' + 2e + 2H^+ \longrightarrow RSO_2H + R'SH$$

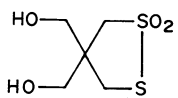
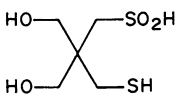
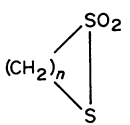
This reaction was investigated[22] (see Table 5) for a large number of thiosulphonates (R and R′ being aliphatic or aromatic) at a mercury cathode. Under such conditions the cathodic cleavage occurs at very moderate potential values in aqueous alcoholic media. The presence of a second reduction wave was reported but no assignment has so far been made. Ethanethiosulphate was reported as behaving similarly with scission of the S—S bond[25].

Half-wave potentials of some cyclic thiosulphonic esters were also reported[24,25]. Presumably, the opening of the ring according to the above-mentioned S—S bond cleavage does occur.

IV. CATHODIC CLEAVAGE OF ARENESULPHONAMIDES. ELECTROCHEMICAL DEPROTECTION OF AMINES

Arenesulphonamides may be cathodically cleaved in alkaline as well as acidic media[27,60]. The electrochemical hydrogenolysis of sulphonamides at mercury cathodes using tetramethylammonium salts as supporting electrolytes was first investigated[2]. It was then established that aromatic sulphonamides were cleaved to yield amines in high yields and therefore this cathodic reaction appeared to present an important route in the deprotection

TABLE 5. Examples of cathodic reductions of organic thiosulphonates

Substrate	Main cleavage products (first step)	Aq. solvent/electrolyte	$E_{1/2}$ (V)	Ref.
$MeSO_2SMe$	$MeSO_2H + MeSH$	25% EtOH/0.1 M TEAI[a]	−0.24 V vs Hg pool	22
$PhSO_2SMe$	$PhSO_2H + MeSH$	25% EtOH/0.1 M TEAI[a]	−0.13 V vs Hg pool	22
$EtSO_2SEt$	$EtSO_2H + EtSH$	C_6H_6, MeOH, H_2O (1/7/2) pH 1	−0.75 V vs SCE	23
$PhCH_2SO_2SCH_2Ph$	$PhCH_2SO_2H + PhCH_2SH$	C_6H_6, MeOH, H_2O (1/7/2) pH 1	−0.39 V vs SCE	23
$PhSO_2SPh$	$PhSO_2H + PhSH$	75% Dioxane, 0.005 M TMAC[b]	−0.48 V vs NCE	17
		Aq. buffer, pH 4.7	−0.53 V/SCE	24
 $n = 3$, 4 and 5	?	Diglyme, TBAP[c]	−0.83 V vs SCE ($n = 3$) −1.05 V ($n = 4$) −0.85 V ($n = 5$)	25

[a]Tetraethylammonium iodide.
[b]Tetramethylammonium chloride.
[c]Tetrabutylammonium perchlorate.

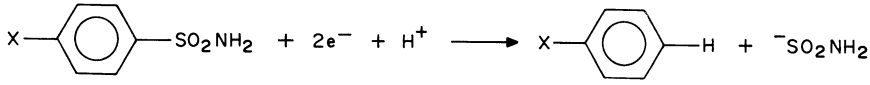
of amines.

$$ArSO_2NR^1R^2 + 2e^- + 2H^+ \longrightarrow ArSO_2H + R^1R^2NH$$

The latter reaction occurs with all types of substituents R^1 and R^2 (aliphatic or/and aromatic) since the presence of an aromatic moiety associated with the $-SO_2-$ group renders the whole class of aromatic sulphonamides electroactive. On the other hand, anilides of aliphatic sulfonic acids are not reduced under similar experimental conditions (aqueous electrolyte) as given in Reference 2. Thus the presence of the arenesulphonyl group appears then to be a necessary condition to permit the preliminary electron transfer and therefore to allow the deprotection of amines.

The nature of the amine moiety was confirmed to be of minor importance in the hydrogenolysis of arenesulphonamides[2]. Moreover, steric hindrance due to bulky substituents on the nitrogen atom does not play any role. Therefore sulphonamides possessing *N*-phenyl groups substituted in the 2,6-positions are cathodically easily converted into the corresponding amines and sulphinic acids in high yields. For example, according to Horner[2], the cathodic cleavage of *N*-[2,4,6-trimethylphenyl]-*p*-toluenesulphonamide at a mercury cathode renders possible the recovery of the expected primary amine in a very good yield (92%). Similarly, tosylamides derived from secondary amines are also satisfactorily cleaved (Table 6). Reductions in buffered aqueous solution were also carried out[6] with sulphonamides possessing an acidic NH proton. Reduction steps vanish for pH > 7.

Contrariwise, when sulphonamides possess a very strong electron-withdrawing group X, the nature of the cleavage may be dramatically changed and reduction causes the scission of the C—S bond[28]. It was claimed that an S_N2-type mechanism is involved:



$$^-SO_2NH_2 + H_2O \longrightarrow HSO_3^- + NH_3$$

with X = COOH, $COOCH_3$, CN, SO_2NH_2

TABLE 6. Cathodic reductions of various sulphonamides in methanol[2]

Tosyl sulphonamides TosN(R^1)(R^2)	Products of cleavage in tetramethylammonium salt as an electrolyte	
	Amine (%)	Toluenesulphinic acid (%)
R^1 = H		
R^2 = Hexyl	94	97
Butyl	55	97
Benzyl	64	90
Phenyl	88	87
2,4,6-Trimethylphenyl	96	95
2,6-Diethylphenyl	94	94
$R^1 \neq H$		
$R^1 = R^2$ = Phenyl	88	86
R^1 = Methyl, R^2 = Benzyl	98	96
R^1 = Phenyl, R^2 = Benzyl	95	97

The use of non-aqueous solutions (like aprotic organic solvents) permits one to determine the mode of cleavage and the mechanism of the S—N bond scission. Cottrell and Mann[30] expected that the irreversible two-electron step observed in acetonitrile would result in a fast decomposition of the dianion:

$$ArSO_2NR^1R^2 \overset{e^-}{\rightleftharpoons} ArSO_2NR^1R^2]^{-\cdot} \overset{e^-}{\rightleftharpoons} ArSO_2NR^1R^2]^{2-}$$

$$ArSO_2NR^1R^2]^{2-} \xrightarrow{\text{fast}} ArSO_2^- + {}^-NR^1R^2$$

followed by protonation of the amide anion by the solvent:

$$CH_3CN + {}^-NR^1R^2 \longrightarrow {}^-CH_2CN + HNR^1R^2$$

However, the intermediate species postulated when R^1 or R^2 were not aromatic could not be detected. On the contrary, if $R^1 = R^2 = Ph$, an ESR signal attributed to that of the transient anion radical was obtained by means of an *in situ* electrolysis in the cavity[31].

Nevertheless, more recent works dealing with the cleavage of arenesulphonamides[29,32] point to cleavage at the stage of the anion radical as a more reasonable route:

$$ArSO_2NR^1R^2 \xrightarrow{e^-} ArSO_2NR^1R^2]^{-\cdot} \xrightarrow[\text{cleavage route (1)}]{\text{fast}} ArSO_2^- + {}^{\cdot}NR^1R^2$$

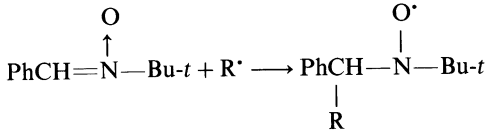
$${}^{\cdot}NR^1R^2 + e^- + H^+ \xrightarrow[\text{(solvent)}]{} NHR^1R^2$$

However, the nature of the substituents R^1 and R^2 may obviously influence the mode of scission and another way of decomposition for the intermediate anion radical is

$$ArSO_2NR^1R^2]^{-\cdot} \xrightarrow[\text{cleavage route (2)}]{\text{fast}} ArSO_2^{\cdot} + {}^-NR^1R^2$$

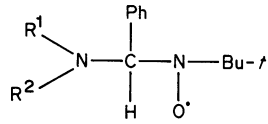
The bulky character of the Ar group does not appear[56] to change the rates of electrochemical reductions, which thus show little sensitivity to steric hindrance. The reduction products of sulphonamides added to baths for the electroplating of nickel may have an influence on the value of the internal stress of this metal[57].

An elegant way to discriminate between cleavage routes (1) and (2) appears to be the '*in situ*'[33] spin marking method. The radical produced by scission should add rapidly to a non-electroactive spin trap at the potential where the first charge transfer does occur. This radical adduct has to be very stable both chemically *and* electrochemically. One of the most-used spin markers at very reducing potential values remains for the moment *t*-butyl phenyl nitrone (BPN) (reduction potential: -1.72 V vs Ag/AgI/I^- 0.1 M electrode) leading with radicals $R^{\cdot}$ to a very stable nitroxide radical,



The fast trapping of such transient radicals generally renders the overall electrochemical reaction monoelectronic (by deactivation of the very reactive free radical into an unreactive nitroxide). With carbon radicals $R^{\cdot}$, the ESR spectra exhibit splitting of the triplet of ^{14}N (1:1:1) due to the proton in the α-position and give therefore a 6-line signal. On the contrary, in the cases when the electron is carried by a heteroatom whose spin is

different from zero, the use of BPN appears to be decisive. Thus, the formation of three characteristic multiplets that can be seen in ESR spectra for the following nitroxide



can also be observed with amino radicals from cathodic cleavage of sulphonamides (Figure 4).

The trapping process of electrogenerated radicals from sulphonamides thus allows one, when 12-line spectra are observed, to demonstrate the occurrence of cleavage route (1). (Sulphonyl radicals should lead to 6-line spectra.) It is worth noting, however, that observing 6-line spectra could be also due to a reorganization of the free radical and not to a change in the mode of cleavage. For example, the cleavage of carbazole or pyrazole tosylates leads for both to a classical 6-line ESR response. This could be due either to a

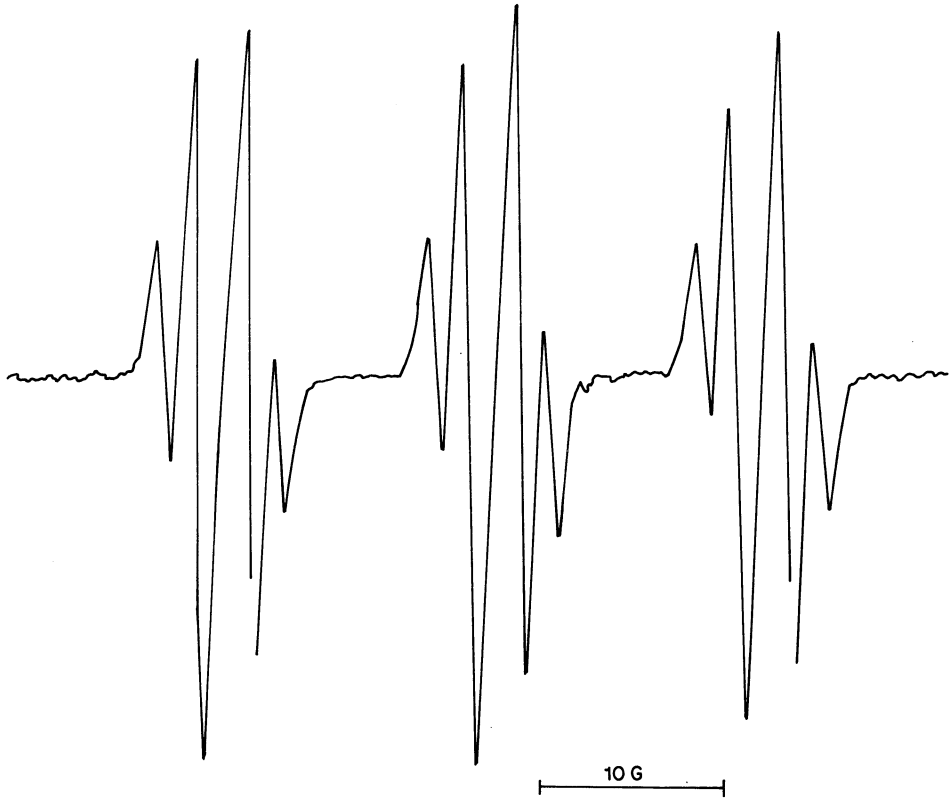
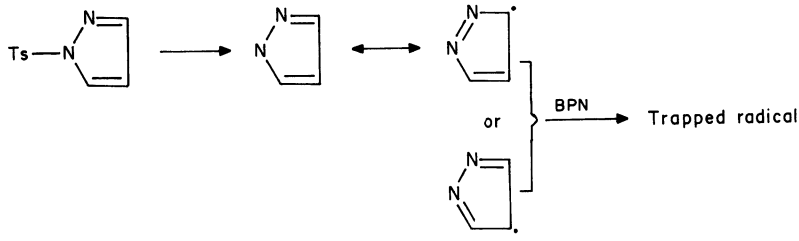


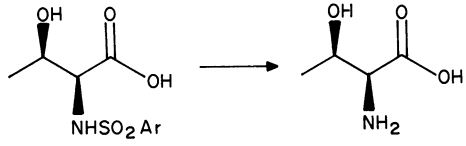
FIGURE 4. Reduction of Ph_2NTs in the presence of an excess of BPN in DMF/tetrabutylammonium tetrafluoroborate. (From Reference 34).

hydrogen atom exchange with the solvent SH (trapping of the S• radical) or to a faster trapping of the carbon radical (Scheme 5).



SCHEME 5

Because the use of aprotic media allows one to reach more reducing potentials and thus widens greatly the potentialities of the method, most recent studies on the deprotection of amines are conducted in DMF or acetonitrile, with added tetraalkylammonium electrolytes and proton donors. Often mercury cathodes are used, when strong adsorption phenomena are mentioned[35]. The reductive deprotection of threonine (cleavage of its *N*-arenesulphonyl amide) was investigated[36] both chemically and electrochemically:



It was reported that when Ar = Ph, cathodic deprotection gives a yield of 85%, whereas conventional chemical methods like sodium in ammonia of HBr/acetic acid are less efficient (yields of 55 and 40%, respectively).

Direct reductions of tosylamides were studied[29,32,57] in both aprotic and protic media in order to control and understand the role and influence of the proton donor and its concentration in the catholyte on the product distribution. Table 7 demonstrates that the absence of a proton source leads to the recovery of approximately 50% of the starting tosylamide. It appears then that amide may play the role of a proton donor toward the electrogenerated base formed by the two-electron scission. Tosylamide deactivated by loss of a proton does not suffer any other electron transfer.

$$Ph(CH_2)_2N\begin{matrix}Ts\\H\end{matrix} \xrightarrow[-Ts^-]{2e^-} Ph(CH_2)_2\bar{N}—H$$

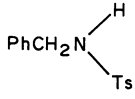
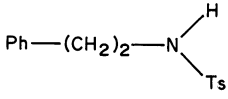
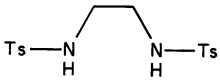
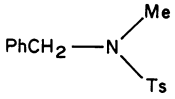
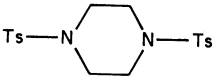
$$Ph(CH_2)_2\bar{N}—H + Ph(CH_2)_2N\begin{matrix}Ts\\H\end{matrix}$$

$$\rightleftharpoons Ph(CH_2)_2NH_2 + Ph(CH_2)_2\bar{N}—Ts$$

Moreover it was found that the amide is also deactivated by the addition of a strong base in DMF, corresponding then to the overall one-electron process (this is the case where a really aprotic DMF is used):

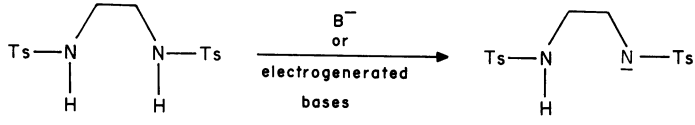
$$2Ph(CH_2)_2N\begin{matrix}Ts\\H\end{matrix} \xrightarrow[-Tos^-]{2e^-} Ph(CH_2)_2NH_2 + \underbrace{Ph(CH_2)_2\bar{N}—Ts}_{\text{electrochemically deactivated}}$$

TABLE 7. Potentiostatic electrolyses of some *p*-toluenesulphonamides in DMF/Bu_4NI 0.15 M. Working electrode: mercury pool of 10 cm^2 area. Reference electrode: Ag/AgI/I^- 0.1 M[29]

Substrate[a]	Solvent DMF	Reduction potential (V)	Ratio of moles of electron/ mole of substrate	Products (%)
	Aprotic	−1.87[c] (−2.0)	1.30	Benzylamine(30) Starting material(52)
	Protic[b]	(−2.0)	2.10	Benzylamine(84)
	Aprotic	−1.87[c] (−2.0)	1.50	2-Phenylethylamine(55) Starting material(48)
	Protic[b]	(−2.0)	2.15	2-Phenylethylamine(80)
	Aprotic	−1.89[c] (−2.2)	3.20	Ethylenediamine(20) Starting material(57)
	Protic[b]	(−1.9)	4.35	Ethylenediamine(75)
	Protic[b]	−1.86[c] (−2.0)	2.01	*N*-methylbenzylamine(78)
	Protic[b]	−1.85[c] (−2.0)	4.10	Piperazine(88)

[a]Mass of substrate: 1 to 1.5 g
[b]DMF rendered protic by addition of acetic acid (0.05 M).
[c]Peak potential from voltammetry on mercury micro electrode. Values in parentheses correspond to the applied potential.

In terms of voltammetric response, the progressive change to a protic medium and to a very basic media is exemplified (Figure 5) for the *N*,*N*′-ditosylate of ethylenediamine.



When the electrolysis medium is rendered more and more basic, one may note a splitting of the step and its shift to more cathodic values. Excesses of a strong base lead to total deactivation of the tosylamide. On the other hand, the addition of phenol permits the occurrence of a four-electron step where the two N-Ts bonds are cleaved simultaneously.

Deactivation reactions involving the N—H function were confirmed[29] by reducing *N*,*N*-ditosylates, when the transient amide can be formed even in the absence of a proton

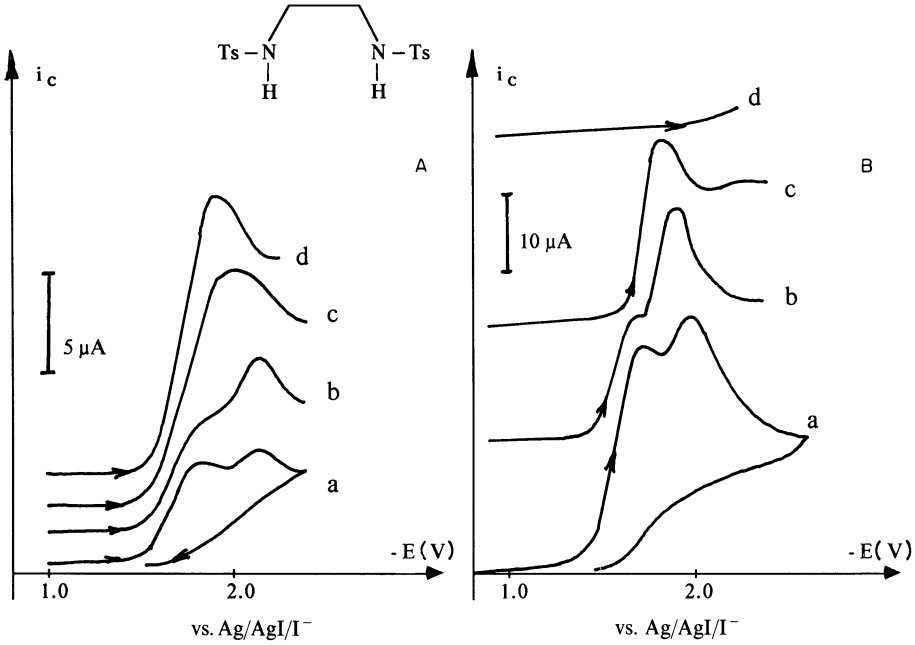


FIGURE 5. Voltammograms of ethylene diamine ditosylate (concentrations: A, 10^{-3} M and B, 5×10^{-3} M, curves a) at a mercury microelectrode. Electrolyte: DMF–Bu_4NI 0.1 M. Sweep rate: 100 m V s^{-1}. (A) Curves b, c and d: with 10^{-3} M, 9×10^{-3} M and 10^{-2} M phenol added respectively. (B) Curves b, c and d after addition of tetraethylammonium hydroxide at the concentration of 1.5×10^{-1} M, 1.65×10^{-1} M and over 2×10^{-1} M, respectively. (From Reference 32)

donor (Figure 6 and 7).

$$Ph(CH_2)_2N\begin{matrix}Ts\\Ts\end{matrix} \xrightarrow[Ts^-]{2e^-} Ph(CH_2)_2\bar{N}—Ts$$

$$Ph(CH_2)_2\bar{N}—Ts \underset{E^-}{\overset{H^+}{\rightleftharpoons}} Ph(CH_2)_2NHTs$$

$$Ph(CH_2)_2NHTs \xrightarrow[-Ts^-]{2e^-,H^+} Ph(CH_2)_2NH_2$$

In the absence of a proton source, only two electrons are transferred and the transient amide is not reducible. Only the adding of an excess of proton donor permits the second N—Ts cleavage to be obtained.

In the case of tosylates of secondary amines, the effect of bases appears to be more harmful for the stability of the amine moiety in the course of the electrolysis. Here, the deprotonation process involves a proton located in the α-position to the nitrogen atom and may lead[37] therefore to an anionic elimination. The formation of an imine and its further degradation during the work-up are the principal causes of the low yields when the deprotection process is conducted without a sufficient amount of a proton source. By

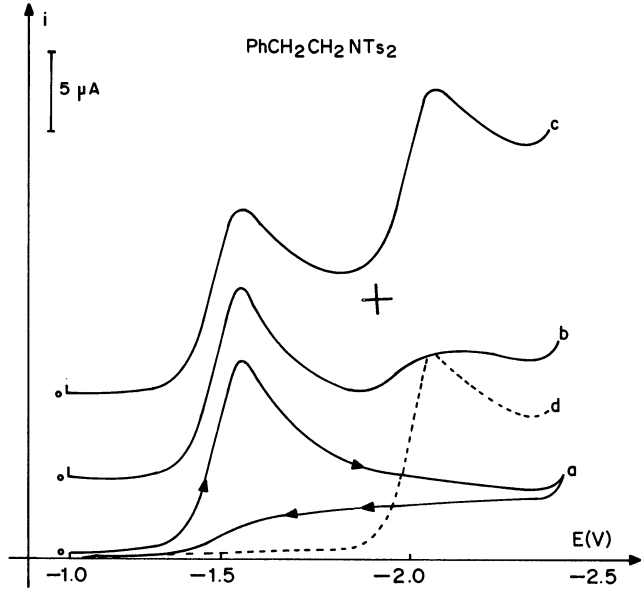
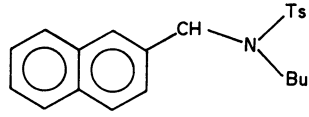


FIGURE 6. Voltammograms (stationary mercury electrode) of the *gem-N,N*-ditosyl derivative of 2-phenylethylamine (concentration: 2×10^{-3} M). Reference electrode: Ag/AgI/I^- 0.1 M. Sweep rate. 0.1 V s^{-1}. Electrolyte: DMF/Bu_4NClO_4. (a) Cathodic voltammetric response in totally aprotic solvent. (b,c) Curves in the presence of phenol as a proton donor, at the concentrations of 2×10^{-3} M and 8×10^{-3} M, respectively. (d) Voltammetry of the corresponding monotosyl derivative at the concentration of 2×10^{-3} M. (From Reference 32)

$$R^1R^2CH-\underset{\displaystyle R^3}{\underset{|}{N}}-Ts \xrightarrow[\text{(electrogenerated bases)}]{B^-} R^1R^2\bar{C}-\underset{\displaystyle R^3}{\underset{|}{N}}Ts \xrightarrow{-Ts^-} R^1R^2C{=}NR^3$$

$$\xrightarrow[\text{(work up)}]{\text{hydrolysis}} R^1R^2C=O + H_2NR^3$$

means of electroanalytical methods, the progressive accumulation of the imine in the vicinity of the microelectrode (in voltammetry) can be demonstrated when aprotic solvents are used. For example the two-electron cathodic cleavage of



occurs at a potential of − 1.83 V (Figure 8). The quasi-reversible step located at − 2.14 V is assignable to the one-electron reduction of the naphthalene moiety. However, from the

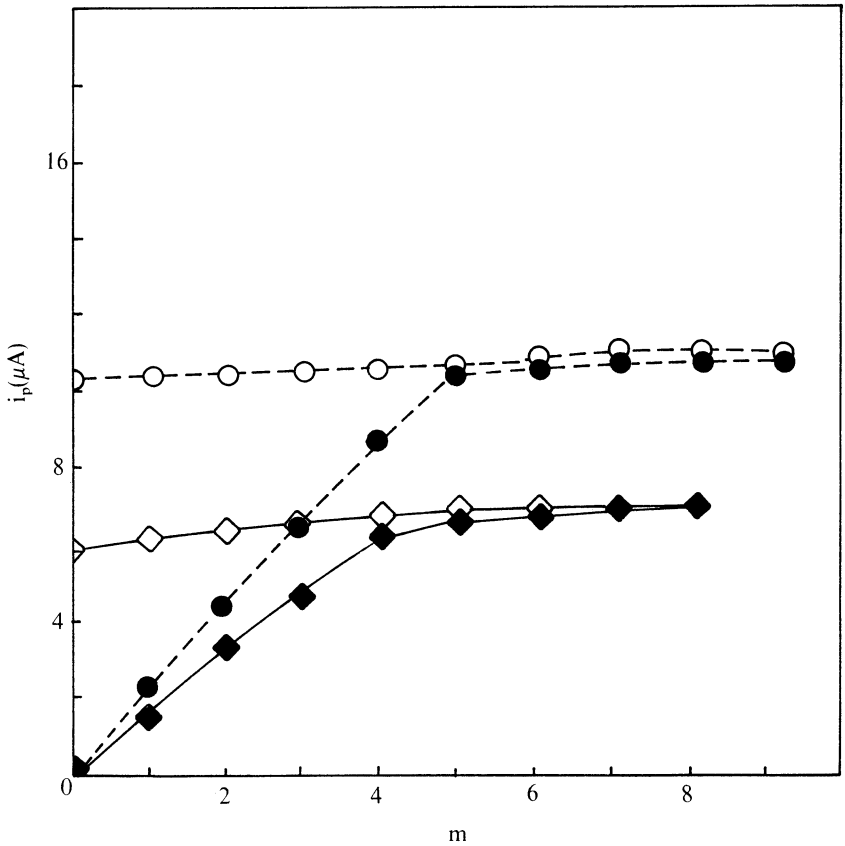


FIGURE 7. Evolution of peak currents at a stationary mercury electrode for two *gem-N,N*-disulphonamides, as a function of proton availability of the solvent (m = [PhOH]/[Substrate]). ○ and ◇ refer to first peak current, ● and ◆ to second peak current. Substrate concentrations: 10^{-3} M in DMF/Bu_4NClO_4 0.1 M. Sweep rate: 100 mV s^{-1}. (From Reference 32)

second step, a pre-peak appears progressively at about − 1.60 V and was attributed to the corresponding imine.

As a consequence of the above results, deprotection reactions have to be conducted in the presence of a proton donor strong enough to protonate efficiently the electrogenerated bases but at the same time protonation of the resulting amine should be avoided since it can be the cause of hydrogen evolution consuming both electricity and proton donor. Additionally, the proton donor has to be easily removed during the work-up. For all these reasons, phenol and acetic acid do not seem to be the best choice. On the other hand, acidic ammonium salts like Et_4NHSO_4, added progressively in the course of the electrolysis, allow[37] nearly quantitative polydeprotection reactions, even in cases considered as delicate or even non-feasible chemically. Thus the hexatosyl precursor[39] of a macrocyclic ligand shown here was cleaved nearly quantitatively[37] according to a twelve-electron reaction. The deprotection of cyclic polyamines was generalized[40] with other tetra- and

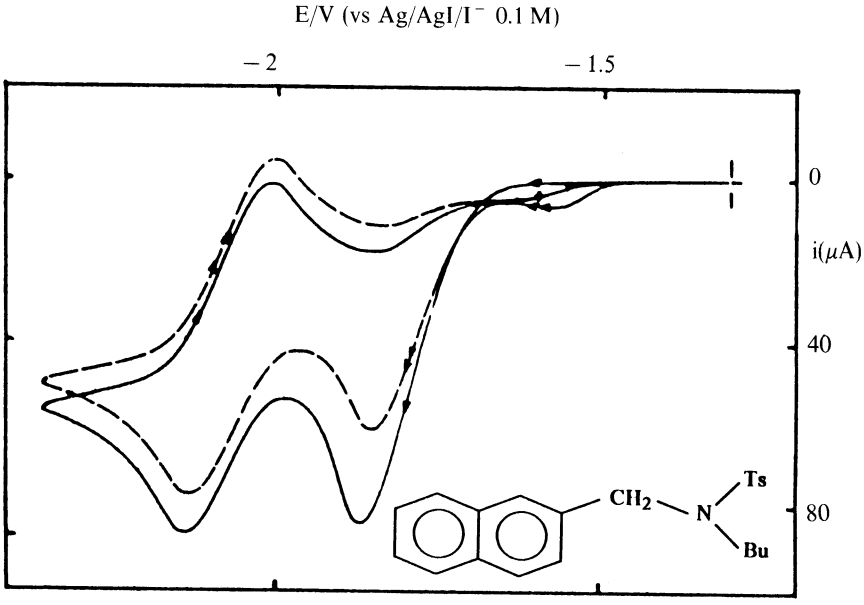
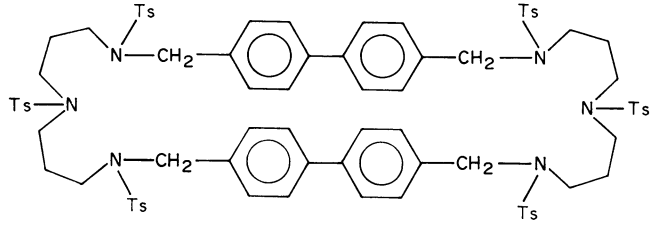
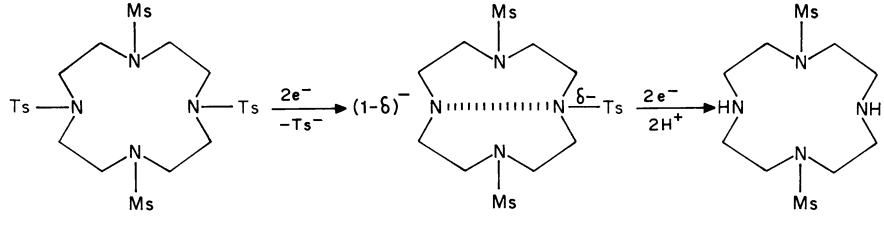


FIGURE 8. Cyclic voltammetry of the tosylamide shown in DMF/Bu_4NI 0.1 M vs Ag/AgI/I^- 0.1 M as a reference. Mercury microelectrode. Sweep rate 0.1 V s^{-1}. Curves corresponding to the first sweep (—►) and the second sweep (—► —►). (From Reference 37)



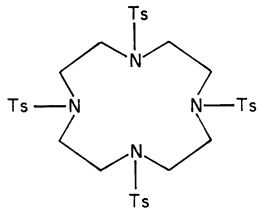
hexa-tosylates. For example, the cleavage selectivity between *N*-mesylate (Ms) and *N*-tosylate functions may be achieved in protic media (Scheme 6).



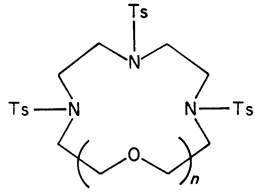
SCHEME 6

The splitting of the four-electron step was attributed[37] to a transannular effect rendering, after the first scission, the cathodic cleavage of the second N—Ts bond less easy by increasing the electron density on it.

On the other hand, the reduction of sulphonamides was also carried out indirectly with the aim of conducting deprotection processes more efficiently or for getting kinetic or thermodynamic data concerning the charge transfer and decomposition of the resulting anion radical. The first indirect deprotection of tosylamides was achieved by Simonet and coworkers[41] for the cathodic synthesis of aza and aza-oxa ligands. As a matter of fact, the classical reduction of polytosylamides like **3** or **4** appeared to be delicate owing to the Hoffmann degradation of the tetraalkylammonium salt (obligatorily used when a mercury cathode is chosen). Under such conditions, the corresponding trialkylamine is produced together with the cyclic ligand whose purification therefore becomes difficult. Alkali metal salts can be used instead, but cathode materials like mercury should be avoided because of the very easy reduction of Li^+ or Na^+ on mercury. The alternative method is to use, in dipolar aprotic solvents, electron carriers whose standard potentials are adapted to the deprotection reaction to be conducted. Thus, the electrogenerated anion of pyrene (produced in DMF/$LiClO_4$ 0.2 M as an electrolyte) is able to reduce efficiently structures such as **3** or **4**. The presence of a proton donor during direct electrolyses of complex cyclic polysulphonamides was shown to produce mainly hydrogen evolution.



(3)



(*n*=1 or 2)

(4)

Other indirect cathodic deprotection reactions of amines by removal of the arenesulphonyl group were described[56]. Ban and collaborators[42] used a new 'cooperative' system as mediator (namely anthracene with added ascorbic acid as a proton donor) and conducted complex cyclization. Therefore, such a mild deprotection process may contribute to internal rearrangement in good yield (Scheme 7). In other studies[7,38] the analytic indirect reduction of sulphonamides was carried out in order to get standard potential values concerning the first charge transfer.

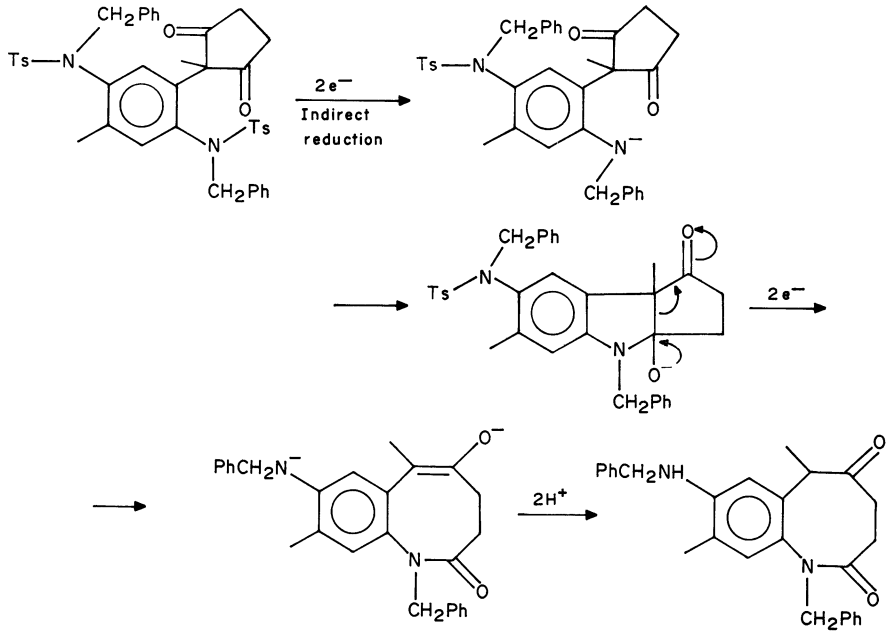
V. CATHODIC REDUCTION OF SULPHONYL HALIDES

The reduction of sulphonyl halides RSO_2X may occur whatever the (aliphatic or aromatic) nature of the R group. Disturbances may be caused either by the solvent (solvolysis with breaking of the S—X bond) or the electrode (interaction between the sulphonyl halide and the mercury). All presently available data concern exclusively the chloride (X = Cl).

Similar to other activated chloro derivatives, the reduction occurs via the two-electron cleavage of the S—Cl bond.

$$RSO_2Cl + 2e^- \longrightarrow RSO_2^- + Cl^-$$

Under well-defined experimental conditions the cathodic cleavage can therefore be considered as a source of sulphinate ions at low potential even when R is aliphatic. For example[45,46], the reductions of $MeSO_2Cl$, $CH_2{=}CHSO_2Cl$ or $PhCH{=}CHSO_2Cl$ lead



SCHEME 7

to the corresponding sulphinate ions within a potential range of -0.2 V to -0.4 V vs SCE. Solvents used were aqueous alcoholic solutions or DMF.

However, data concerning aromatic sulphonyl chlorides are much more numerous[59,61], but the results show that the product distribution is far from being selective. Sulphinic acid was already suggested to be an intermediate by Fichter and coworkers[47] at the beginning of this century. From sulphinic acid solutions, the reaction may lead directly to the thiol, and Fichter[48] proposed the following sequence:

$$ArSO_2Cl \xrightarrow[2N\ H_2SO_4/EtOH]{\text{lead cathode}} ArSO_2H \longrightarrow ArSH \xrightarrow{\text{air oxidation}} ArSSAr$$

Thiosulphonate $ArSO_2SAr$ was supposed to be formed from the disproportionation of the intermediate sulphinic acid. These results were confirmed later by other workers[49].

Other studies were performed in organic solvents. It appeared[50] (Figure 9) that the stability of arenesulphonyl chlorides was much higher in acetonitrile than in DMF. In the latter solvent, one can get in moderate yield the corresponding thioether when electrolyses were run in the presence of an electrophile:

$$ArSO_2Cl \xrightarrow[\substack{DMF\\(RX\ as\ an\ electrophile)}]{\text{Hg cathode}} ArSR$$

23–33%

On the other hand, sulphinate ion was shown to be formed in acetonitrile since adding *in situ* an electrophile (e.g. gaseous CH_3Cl) leads to the corresponding sulphone. However, thioethers and thiols are formed in this case too (Scheme 8).

The alkylation of the sulphinate seems to be in competition with the formation of the thiosulphonate, the latter affording the thiolate. In rather acidic organic solutions

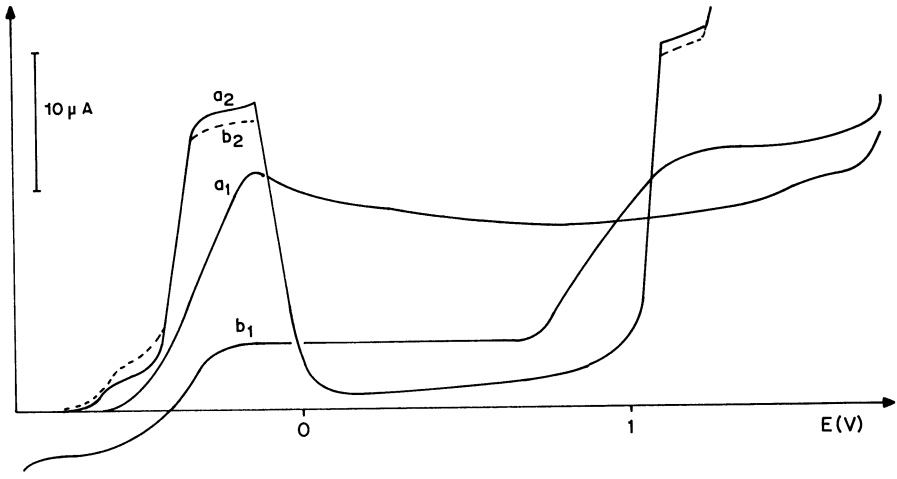
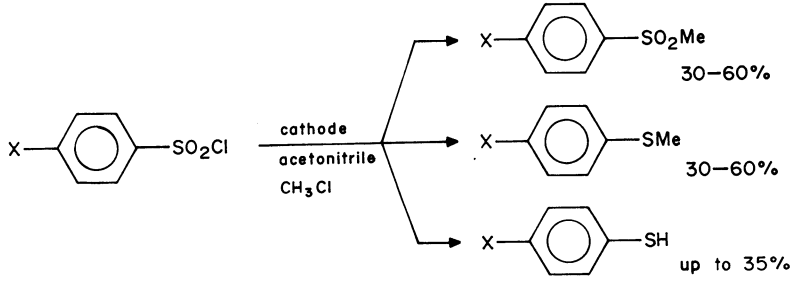


FIGURE 9. Polarographic curves of $PhSO_2Cl$ (concentration 2×10^{-3} M). Solvents: dimethylformamide (1) or acetonitrile (2). Electrolyte $LiClO_4$ 0.1 M. (a) Freshly prepared solution. (b) The same solution after a quarter of an hour. (Reproduced by permission of the Société Française de Chimie from Reference 50)



SCHEME 8

(acetonitrile containing a large excess of dry perchloric acid), the overall reaction becomes nearly hexaelectronic (Figure 10a), showing quantitative formation of thiol (Table 8).

TABLE 8. Electrolysis of 4-methoxybenzenesulphonyl chloride (2 g, in acetonitrile/$HClO_4$ 90/10 v/v with 0.3 M of added $LiClO_4$). Electrolysis potential vs $Ag/AgI/I^-$ (0.1 M)

Number of F $mole^{-1}$ passed	$ArSO_2Cl$ (%)	$ArSO_2H$ (%)	$ArSO_2SAr$ (%)	ArSSAr (%)	ArSH (%)
2.0	30	0	70	0	0
3.4	0	0	66	34	0
4.6	0	0	0	72	28
5.4	0	0	0	0	100

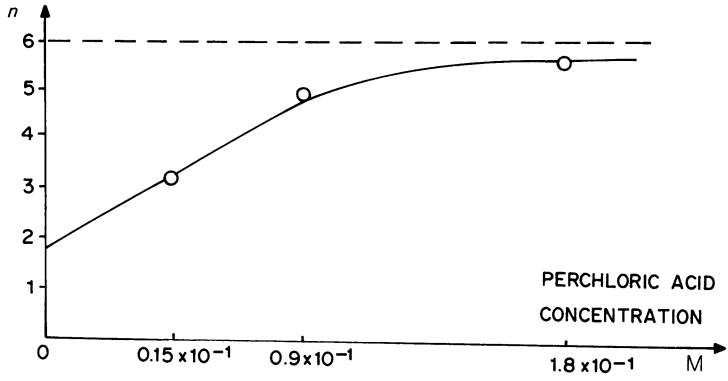


FIGURE 10a. Potentiostatic coulometries of tosyl chloride in acetonitrile/$LiClO_4$. Variation of electricity consumption (in faraday per mole) with the concentration in perchloric acid is shown. Electrolyses conducted with about 0.5 g substrate at mercury pool electrode. (Reproduced by permission of the Société Française de Chimie from Reference 50)

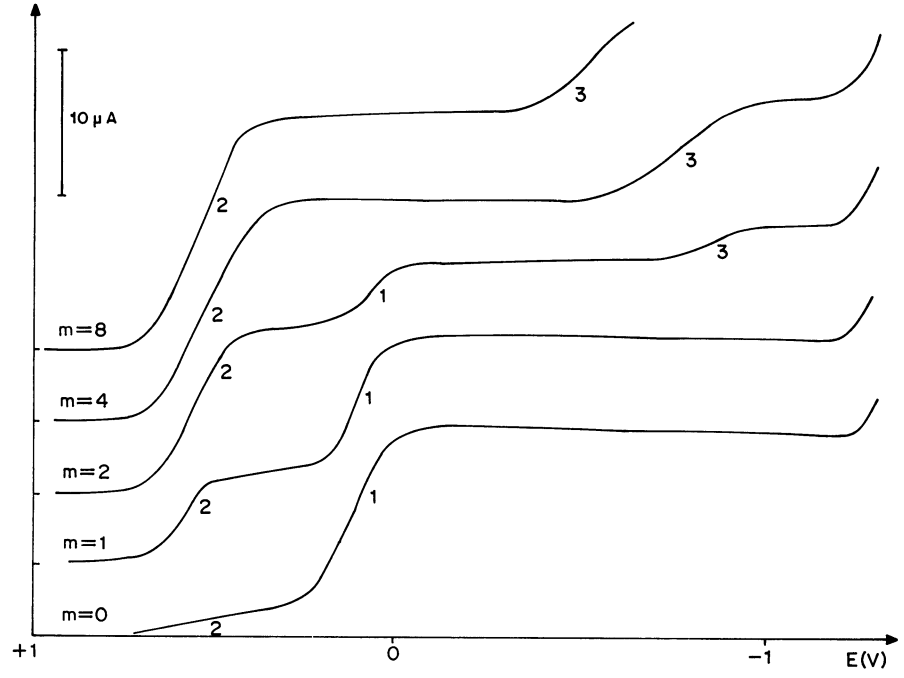
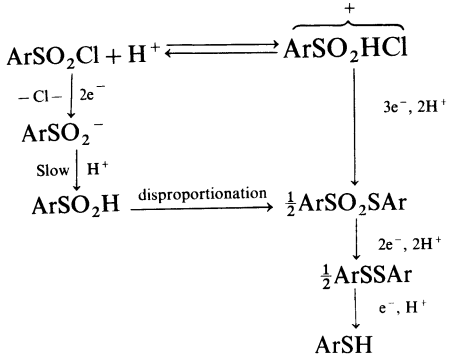


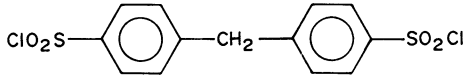
FIGURE 10b. Polarographic curves of *p*-toluenesulphonyl chloride (10^{-3} M) as a function of the solvent acidity ($m = [HClO_4]/[\text{tosyl chloride}]$). Electrolyte: acetonitrile with added 0.1 M $LiClO_4$. Reference: Ag/AgI/I^- 0.1 M (Reproduced by permission of the Société Française de Chimie from Reference 50)

The difference of reactivity between neutral and acidic solvents could only lie in the fact that the aromatic sulphonyl chloride is protonated and consequently reduced more easily in its protonated form. A potential shift of about 0.5 V for the main reduction step (Figure 10b) can be observed in the voltammetries. The general Scheme 9[51] fits the two possible routes according to the acidity of the medium.

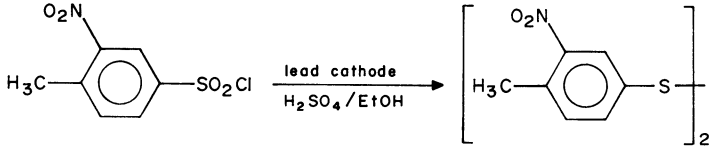


SCHEME 9

Polarographic data concerning polysulphonyl chlorides are also available[58]. The reaction also leads to the corresponding disulphinic acid.

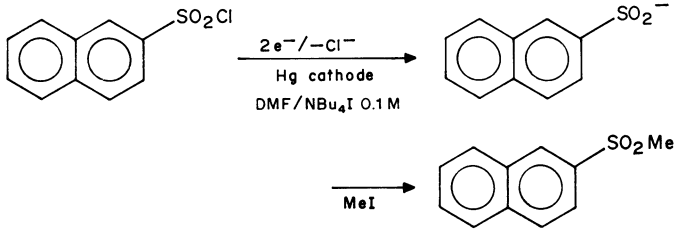


More complex sulphonyl chlorides were also reduced; again the product distribution remains dependent on the acidity of the solvent; see, for example, Scheme 10[47].



after air-oxidation of the thiol

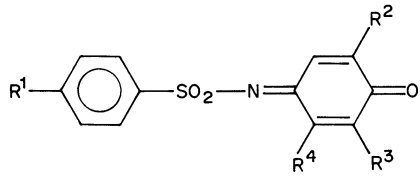
SCHEME 10



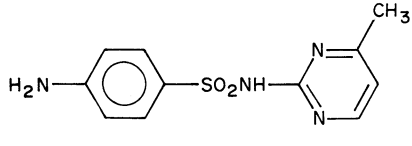
SCHEME 11

However, use of acetonitrile[45] leads to the protection of the $ArSO_2$ moiety. Scheme 11 is particularly clear when reading results exhibited in Figure 11 (the specific voltammetric response of methyl naphthyl sulphone is obtained after treatment of the electrolysis solution with methyl iodide).

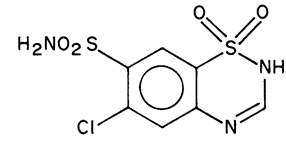
Data on sulphonamides derived from imines (e.g. *N*-arenesulphonyl benzoquinone monoimines)



are also available[43]. A correlation between the nucleophilicity of the reduction products (after electron transfer) and the electron acceptor character of the quinone imine group was established. Other sulphonamides (sulpha drugs used mainly as antibiotics and diuretics) were studied electroanalytically for their oxidation response[44]. For example, sulphamerazine (**5**) and chlorthiazide (**6**) exhibit an oxidation current at gold and platinum rotating disc electrodes. However, these electron transfer reactions appear to be due to the amino groups present in the molecule more than to the sulphonamide function itself.



(5)

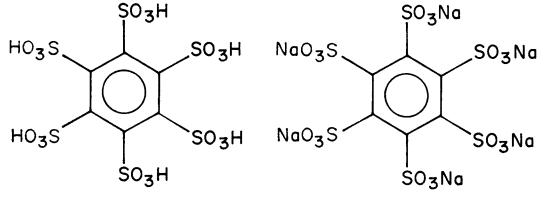


(6)

VI. CATHODIC DESULPHONYLATION OF POLYSULPHONIC ACIDS

A cathodic response in unbuffered media was reported for benzenesulphonic acid (or its sodium salt)[17] and its substituted analogs[51]. However, it is not obvious that the observed reduction steps are due to a specific activity of the sulphonic acid. More satisfactorily, these steps could be interpreted by a reduction due to the proton of the acid added to the neutral media. In such conditions, it is easy to understand that 10-camphorsulphonic acid exhibits[51] also a similar behaviour, showing a reduction wave (in water in the presence of 0.09 M of tetramethylammonium iodide) located at -1.6 V vs Ag/AgCl electrode. On the other hand, and more logically, in the absence of activation by unsaturated substituents, the absence of a specific polarographic activity was regularly noted[52].

Benzenepolysulphonic acids (1,2,4,5-tetra, penta and hexasulphonic acids) and their sodium salts were reduced polarographically[53]. The mutual activation of sulphonic groups allows one to observe for the hexa-derivative (acidic form or sodium salt) several specific steps leading to successive desulphonylations.



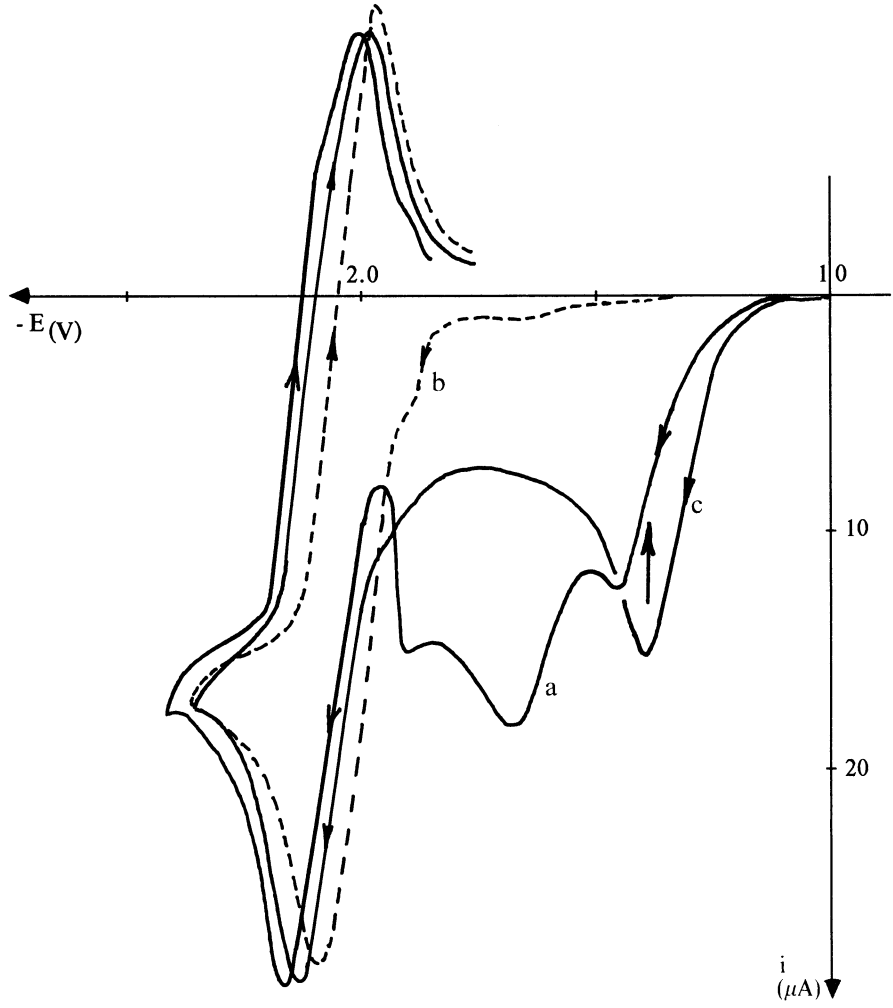
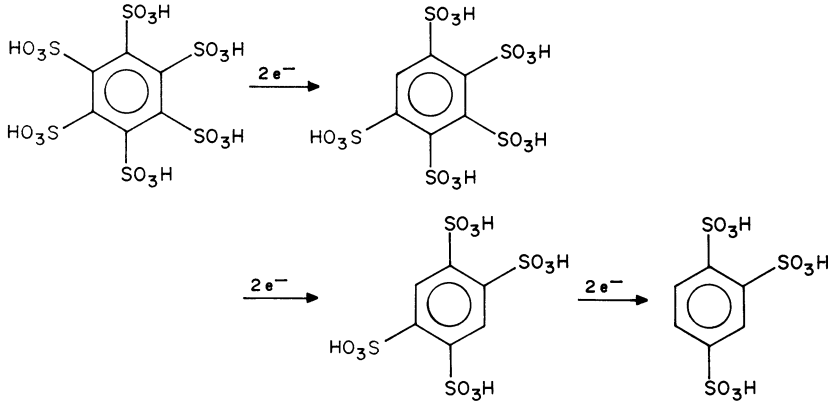


FIGURE 11. Voltammetric reduction of 1-naphthalenesulphonyl chloride (C:9.7 × 10^{-3} M) in DMF/Bu_4NI. Stationary mercury microelectrode. Curve a: 5 sweep rate: 0.1 Vs^{-1}. Curve b: after controlled potential electrolysis at −1.4 V (arrow) after 1.92 F mol^{-1} (total reduction) have passed. Curve c shows the response after adding to the preceding solution an excess of methyl iodide showing the formation of the corresponding sulphone (from Reference 45)

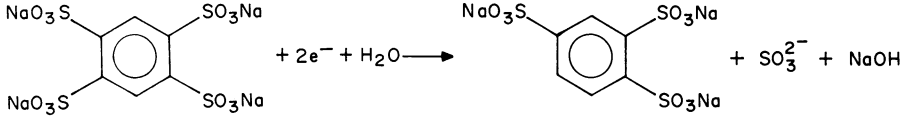
Thus, when reduced in phosphate buffer (pH ~ 8) three main steps, each consuming two electrons, are noted for the hexa-derivative (Scheme 12).

The strong electron-depletion on the ring caused by several electron-withdrawing groups allows also the reduction of sodium salts according to Scheme 13.

No further reaction was observed for the benzenetrisulphonic acid. Data reporting a similar electrochemical behaviour are available on naphthalenepolysulphonic acid[52]. Here, the transfer of one electron on the π^* orbital is obviously favoured and a specific

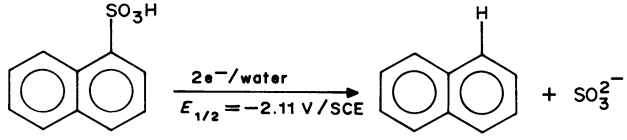


SCHEME 12



SCHEME 13

reduction was observed for 1-naphthalenesulphonic acid which may be written as follows:



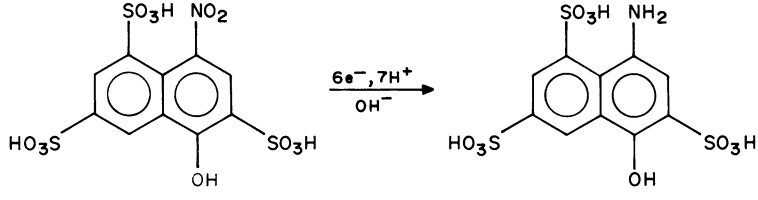
The overall two-electron mechanism is detailed[52] below and resembles a cathodic cleavage with expulsion of a leaving group:

$$C_{10}H_7SO_3^- + e^- \longrightarrow C_{10}H_7^{\cdot} + SO_3^{2-}$$

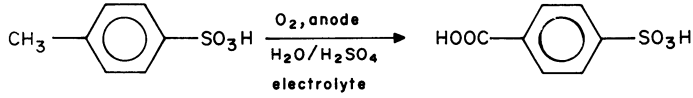
$$C_{10}H_7^{\cdot} + e^- \longrightarrow C_{10}H_7^-$$

$$C_{10}H_7^- + H_2O \longrightarrow C_{10}H_8 + HO^-$$

The electrochemical behaviour of other substituted arenesulphonic acids can be related to the cathodic or the anodic properties of substituents *prior* to the cleavage of C—S bonds as mentioned above. For example, an aromatic nitro group will be reduced[55] before the SO_3H group:



while *p*-toluenesulphonic acid can be oxidized[54] to the corresponding benzoic acid:



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CHAPTER 15

Syntheses and uses of isotopically labelled sulphonic acid derivatives and related compounds

MIECZYLAW ZIELINSKI

Isotope Laboratory, Faculty of Chemistry, Jagiellonian University, Cracow, Poland

and

MARIANNA KANSKA

Department of Chemistry, University of Warsaw, Warsaw, Poland

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I. CHEMICAL SYNTHESES OF LABELLED SULPHONIC ACID DERIVATIVES

Sulphonic acid derivatives are an important class of organic compounds in both scientific and practical chemistry[1a]. They impact on society, particularly by industrial production of sulphonates, anionic surfactants which are constituents of detergent formulations and by significant clinical applications of sulphonyl derivatives[2]. Especially, the progress made in the large-scale preparations of sulphamides and their versatile applications in medicine during the last 50–55 years[3] created the immediate need for the preparation of the corresponding isotopically labelled compounds to investigate their biodegradation and metabolic fate in animals and in the environment[4,5]. In this chapter the most suitable chemical methods from the standpoint of maximal utilization of starting radioactive materials and minimization of the radioisotope wastes, used in the preparation of isotopically labelled sulphonic acid derivatives, are described. In the case of short-lived

positronium emitters[6] the very important 'time of reaction' factor had also to be taken into account in the elaboration of synthetic schemes.

A. Syntheses of Labelled Sulphonic Acids and their Salts

1. Syntheses of ^{14}C- and ^{35}S-labelled alkanesulphonates and surfactants

Isotopic tracing of the bacterial decomposition pathways of the detergents in rivers and in water reservoirs has been a task imposed on isotope chemists by environmental protection agencies. Besides the traditional ^{14}C labelling, ^{35}S-sulphonates were also obtained, to study the desulphonation of these compounds *in vivo*.

a. Synthesis of (1-^{14}C)undecanesulphonate and (1-^{14}C)hexadecanesulphonate. Both have been synthesized (equation 1)[7] by modifying established procedures[1a,8-12] used for the production of primary alkane sulphonates[8] and for the synthesis of long-chain (1-^{14}C)alkane precursor compounds[9-12]. The ^{14}C-labelled alkyl bromides were converted to the corresponding thiols by thiourea, and after the usual work-up the resultant labelled thiol was diluted with unlabelled thiol to obtain a product of specific activity equal to at least 10 μ Ci/mg. Sodium (1-^{14}C)alkanesulphonates were obtained by oxidation. The specific radioactivities were 1.9 mCi for 1 mmol undecanesulphonate, 2.7 mCi for 1 mmol dodecanesulphonate and 5.1 mCi for 1 mmole of hexadecanesulphonate.

$$\mathrm{RBr} \xrightarrow{\mathrm{Mg}} \mathrm{RMgBr} \xrightarrow{^{14}CO_2(5\,\mathrm{m\,Ci})} \underset{80\text{–}85\%\ \text{yield}}{\mathrm{R}^{14}\mathrm{COOH}} \xrightarrow{CH_2N_2}$$

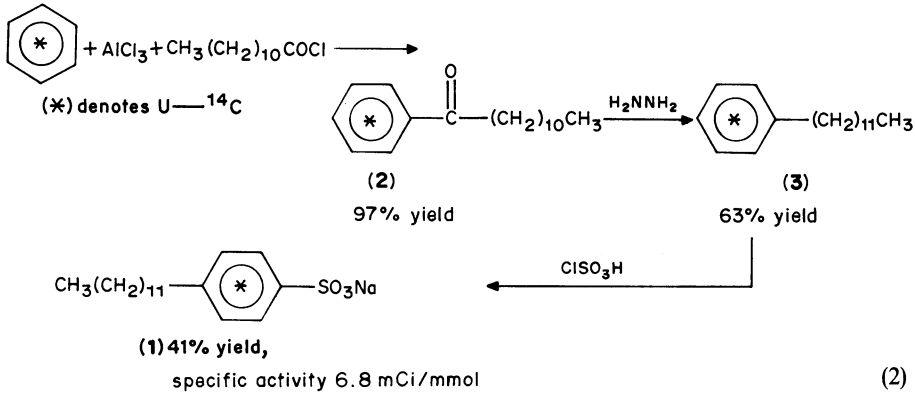
$$\mathrm{R}^{14}\mathrm{COOMe} \xrightarrow{LiAlH_4} \mathrm{R}^{14}\mathrm{CH_2OH} \xrightarrow[\text{excess}]{\mathrm{HBr}} \mathrm{R}^{14}\mathrm{CH_2Br}$$

$>90\%$ radiochemical purity — 75% radiochemical yield — 58–62% radiochemical yield

$$\xrightarrow{(NH_2)_2CS} \mathrm{R}^{14}\mathrm{CH_2SH} \xrightarrow[45\,^\circ\mathrm{C},\ 3\,\mathrm{h\ stir.}]{HNO_3(70\%)} \mathrm{R}^{14}\mathrm{CH_2SO_3H} \qquad (1)$$

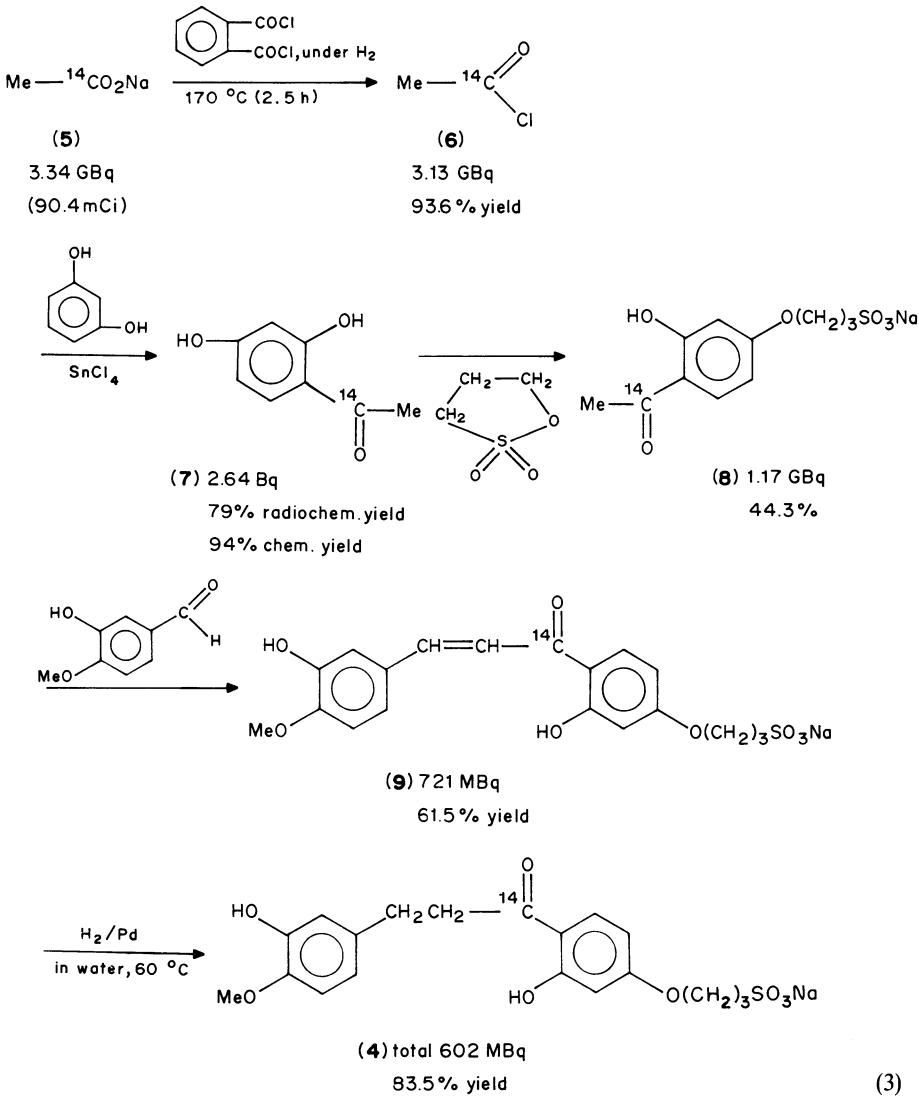
18–24% radiochemical yield

b. Synthesis of dodecane[^{35}S]sulphonate. This compound of 1.6 mCi/mmol specific radioactivity has been synthesized as above from dodecyl bromide and [^{35}S]thiourea followed by oxidation. Reverse isotope dilution analysis had shown that the synthesized ^{14}C and ^{35}S-labelled compounds were $>98\%$ radiochemically and chemically pure.



(2)

c. Synthesis of sodium p-*dodecylbenzenesulphonate-[phenyl-U-^{14}C], 'LAS'.* This anionic surfactant, **1**, has a more readily biodegradable side-chain than the earlier branched alkylbenzenesulphonates, and is synthesized now on an industrial scale. ^{14}C-labelled **1** has been needed for continued investigations of its metabolism and biodegradability. Synthesis of ^{14}C-benzene ring labelled **1** has been accomplished according to a three-step scheme (equation 2)[13], which involves acylation of benzene-*U*-^{14}C with lauroyl chloride, reduction of the resulting undecylphenyl ketone-[phenyl-*U*-^{14}C], **2**, with 85% hydrazine hydrate[14] and sulphonation of dodecylbenzene-[phenyl-*U*-^{14}C], **3**, with chlorosulphonic acid[15]. The final product **1** has been obtained with 26% overall radiochemical yield. The purity of **1**, determined by TLC, was found to be $\geqslant 98\%$.



(3)

2. Synthesis of 1-[2-hydroxy-4-(3-sulpho-1-propyloxy)-phenyl]-3-(3-hydroxy-4-methoxyphenyl)-propan-1-one-1-^{14}C sodium salt

This artificial sweetening agent **4** has been labelled with ^{14}C at the carbonyl group[16] to investigate its pharmacokinetical properties and metabolism. Its synthesis has been accomplished in five steps (equation 3). Labelled sodium(1-^{14}C)acetate, **5**, has been converted into (1-^{14}C) acetyl chloride **6**, which was used to acylate resorcinol yielding the ketone **7**. In the next step **7** reacted[17] with propane sultone to give the impure sodium salt **8**, which in turn was condensed with isovanilline to give the chalcone **9**. This, after purification, had a specific radioactivity of 8.47 mCi/mmol = 313 MBq/mmol indicating the occurrence of a normal kinetic ^{14}C isotope effect in the first and second reaction steps. The required compound **4** obtained in the last hydrogenation step had a molar activity A_f = 8.86 mCi/mmol = 327 MBq/mmol, which is slightly smaller than the calculated one A_0 = 9.04 mCi/mmol = 334 MBq/mmol. The ratio $A_f/A_0 = 0.9800$ indicates that in the ^{14}C—ONa bond rupture and in the ^{14}C—Cl bond formation in the first reaction step as well as in the ^{14}C—Cl bond rupture and in the ^{14}C—C bond formations in the second reaction step a certain ^{14}C fractionation is taking place; ^{12}C reacts faster than ^{14}C, and slightly less than 100% yields lead to some lowering of the specific activity of the final product (equation 3).

3. Synthesis of $^{13}C_2$-, [2-$^3H_2$]taurine and of [2-$^3H_2$]hypotaurine

a. Synthesis of taurine-$^{13}C_2$. An excessive amount of $^{14}CO_2$ was found in the breath of experimental rats possessing an intestinal bacterial overgrowth, after the oral administration of ^{14}C-labelled taurine[18]. To avoid the long-term deposition of radioactive amino acids into the human body protein pool in the course of a ^{14}C-labelled taurine breath test, the ^{13}C-labelled taurine **10** has been prepared for diagnostic use in human non-radioactive $^{13}CO_2$ breath test to evaluate the possible small intestine bacterial overgrowth[19] of children and reproductive-age females and gastrointestinal function in general. To avoid losses of the volatile starting materials, the 1,2-dibromoethane-$^{13}C_2$ (90%) was diluted with non-labelled 1,2-dibromoethane to obtain a 2% mixture of taurine-$^{13}C_2$ synthesized according to equation 4[20].

$$3\,Br^{13}CH_2{}^{13}CH_2Br + 1\,NaHSO_3\ (87\,mmol) \xrightarrow{EtOH/H_2O,\ 4\,h\ reflux}$$

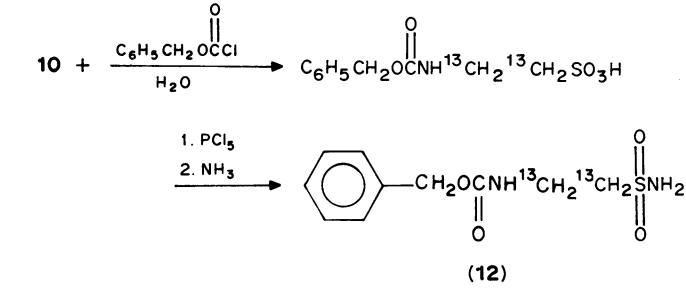
$$5.2\,mol\ 1,2\text{-dibromoethane-}{}^{13}C_2 + 260\,mol\ 1,2\text{-dibromoethane}$$

$$2\,Br^{13}CH_2{}^{13}CH_2Br + Br^{13}CH_2{}^{13}CH_2SO_3Na \xrightarrow[1\ week\ standing]{NH_4OH(58\%)} H_2N^{13}CH_2{}^{13}CH_2SO_3H$$

81.24% yield of 2% $^{13}C_2$ (**11**) — 79.82% yield, m.p. > 300 °C (**10**) (4)

The overall yield was 65.6%. The amount of ^{13}C incorporated into the non-volatile **10** has been determined by derivatization of the important volatile *N*-carbobenzyloxytaurine amide **12** according to equation 5[21] and direct introduction of the vapours of volatile derivative **12** into the ion source of the mass spectrometer.

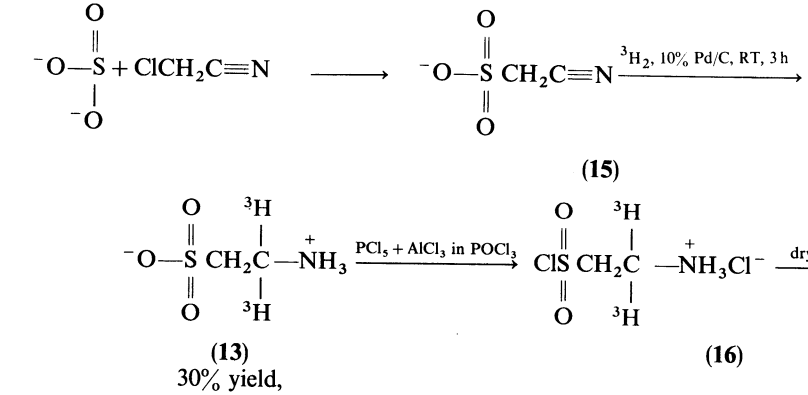
b. Synthesis of [2-$^3H_2$]-2-aminoethanesulphonate and [2-$^3H_2$]aminoethanesulphinate. Both these compounds, **13** and **14** respectively, of high specific tritium activity have been prepared[22] to investigate their metabolic origin, fate and function[23a]. The position of tritium at $C_{(2)}$ enables one to follow the kinetics of possible transamination of taurine **13** and hypotaurine **14** in mammalian tissue by simply detecting the appearance of



(5)

(12)

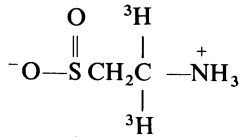
tritiated water in boty fluid. Synthesis of **13** and **14** has been carried out according to equation 6, which involves preparation of cyanomethylsulphonate **15** from sodium sulphite and chloroacetonitrile, reduction of **15** with tritium gas using a palladium/charcoal catalyst, conversion of taurine **13**, diluted with non-labelled taurine, to its sulphonyl chloride **16** and reduction of **16** to **14** with powdered zinc. Specific activity of the isotopically diluted product **14** was 100 mCi/mmol. Treatment of **14** with dilute hydrogen peroxide gave taurine **13**. In a similar manner, ^{14}C- and ^{35}S-labelled taurine and hypotaurine have been synthesized from the correspondingly labelled taurine precursors.



(15)

(13)
30% yield,
sp. act. 13.7Ci/mmol

(16)

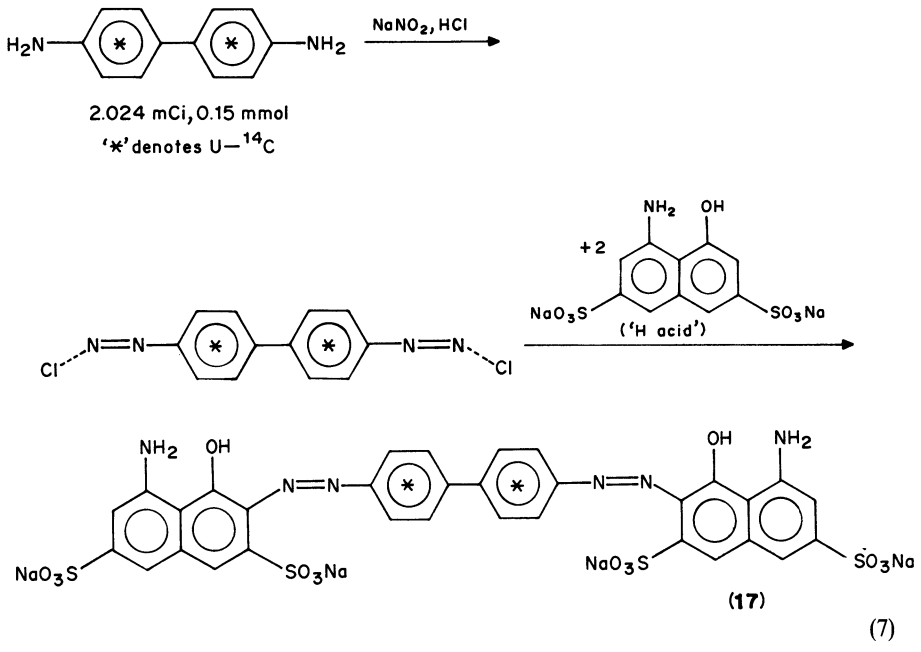


(6)

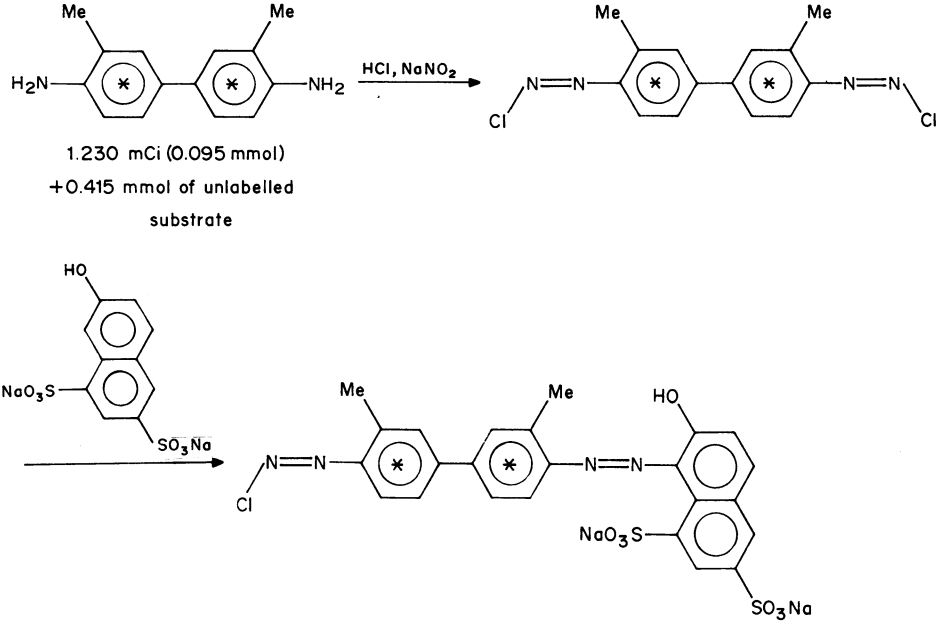
(14) 90% conversion

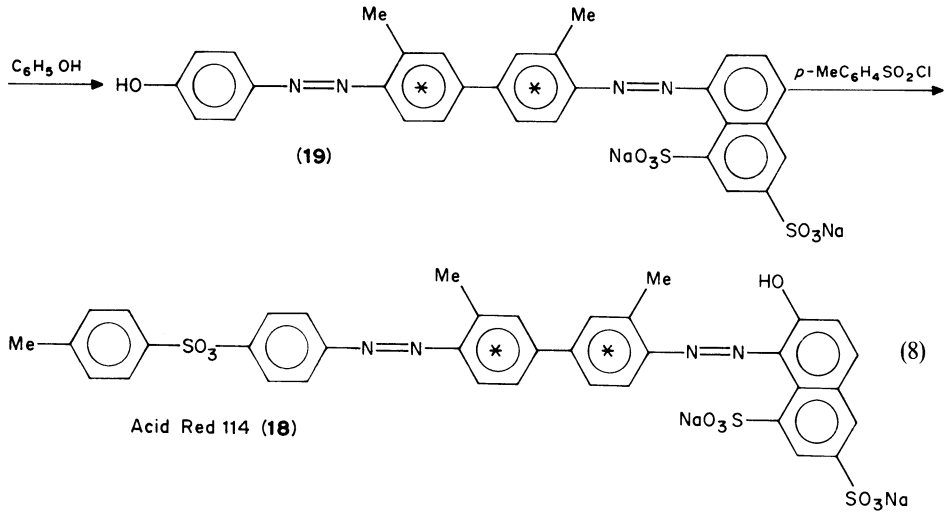
4. Synthesis of ^{14}C-labelled bis-azo biphenyl dyes

^{14}C-labelled *Direct Blue 6* (**17**) and *Acid Red 114* (**18**), bis-azo biphenyl dyes, possible human carcinogens[23b], needed in order to study their distribution and biological transformations in animals, have been prepared[24] from uniformly ring-labelled ^{14}C-benzidine and ^{14}C-3,3′-dimethylbenzidine according to equations 7 and 8. **17** has been prepared by reacting the diazotized benzidine with two equivalents of H acid under basic conditions to insure the occurrence of the attack of the electrophilic species at the *ortho*


NaNO2, HCl
2.024 mCi, 0.15 mmol
'*' denotes U—14C
+2
('H acid')
(17)

(7)


HCl, NaNO2
1.230 mCi (0.095 mmol)
+0.415 mmol of unlabelled
substrate

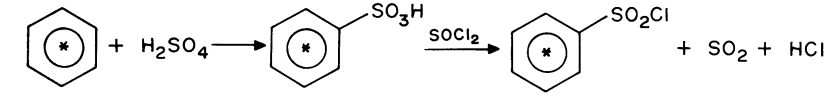


(8)

position to the hydroxyl group. **18** has been prepared by a similar sequence of reaction. The derivative **19** esterified with *p*-toluenesulphonyl chloride gave ^{14}C-labelled Acid Red 114 (**18**) in 67% yield.

5. Synthesis of O-ethyl-S-phenyl-^{14}C(U)-ethylphosphonodithioate

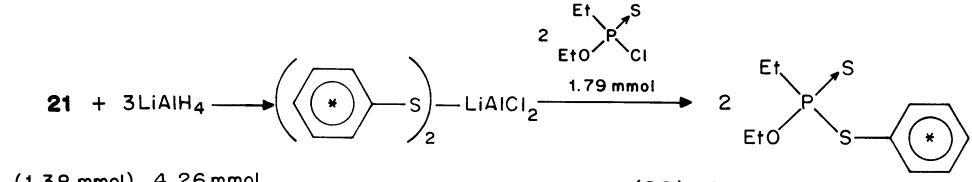
^{14}C uniformly labelled benzenesulphonic acid **20** and ^{14}C(U)benzenesulphonyl chloride **21** have been synthesized according to equations 9 and used in the production of compound **22**, a soil insecticide[25]. ^{14}C(U) benzene was sulphonated with excess of 100% sulphuric acid. The intermediate product **20** reacted with thionyl chloride producing ^{14}C(U)benzenesulphonyl chloride **21**. The latter, treated with lithium aluminium hydride, gave the dithiophenyl lithium aluminium dichloride complex[26] which in turn, reacted with *O*-ethyl-ethylphosphonochloridothioate yielding **22**, in 95% radiochemical purity.



2.13 mmol (**20**) (**21**) 97% yield

sp. act. 4.7mCi/mmol

(9a)



(1.38 mmol) 4.26 mmol

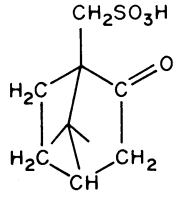
(**22**) 1.08 mmol, 78% yield

5,2 mCi, sp. act. 4.65 mCi/mmol

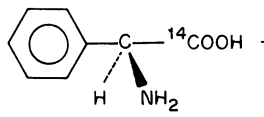
(9b)

6. Synthesis of 6-(D-α-aminophenylacetamido-1-^{14}C)-penicillanic acid

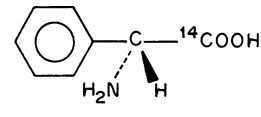
D-Camphorsulphonic acid **23** has been used to separate the **24** -D form from the D,L-α-aminophenylacetic acids–1-^{14}C mixture. The former was used in a four-step synthesis[27] of one of the most useful semisynthetic antibiotics, ampicillin (**25**).



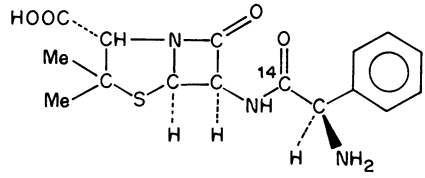
(23)



(24)-L



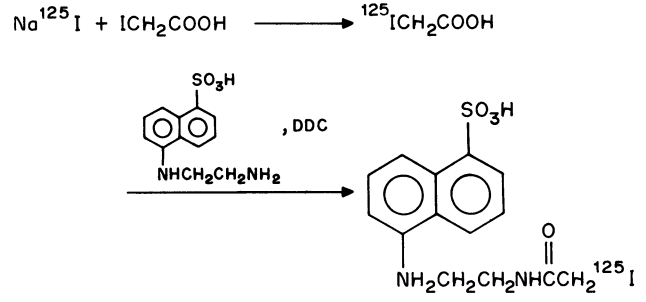
(24)-D



(25)

7. Synthesis of [5-^{125}I]iodoacetamidoethyl aminonaphthalene-1-sulphonic acid

This compound **26**, [^{125}I]IAEDANS, a potential radiopharmaceutical for imaging of infarcted myocardial tissue, entrapped within positively charged liposomes has been prepared[28] beginning with sodium ^{125}I iodide (equation 10), modifying the general procedure of Hudson and Weber[29]. Kinetic studies have shown that in acetonitrile solvent the reversible ^{125}I exchange between [^{125}I]iodide and iodoacetic acid reaches equilibrium at 35 °C already after about 22 minutes. The condensation of [^{125}I]iodoacetic acid with *N*-(aminoethyl)-5-naphthylamine-1-sulphonic acid (1,5-EDANS) was catalysed by dicyclohexylcarbodiimide (DDC). The authors[28] investigated the effect of time, temperature, light, concentrations of reagents, etc. on the yield of **26**, its stability and incorporation efficiency (entrapment efficiency) into liposomes. This synthetic route could accommodate also the use of sodium [^{123}I]iodide ($T_{1/2}$ = 13.3 h) having a much shorter half-life than ^{125}I $T_{1/2}$ = 60 d) but possessing superior imaging characteristics for external detection.

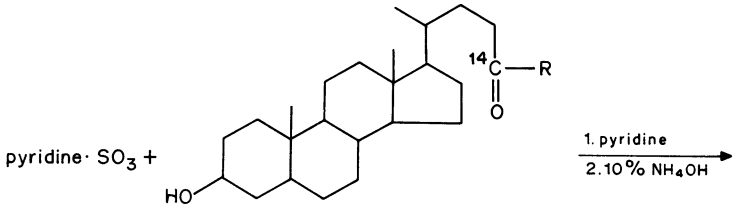


(10)

(26) 30–40% radiochem. yield

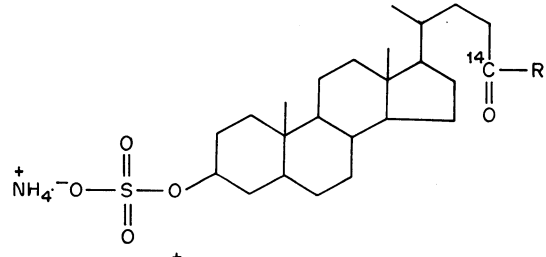
8. Synthesis of sulphate esters of ^{14}COOH-lithocholic and taurolithocholic acids

^{14}C-labelled lithocholic acid sulphates, **27**, found in both human and animal bile[30,31], have been synthesized in a one-step[32] sulphonation procedure (equation 11) to study the metabolic processes caused by human intestinal microflora and to make possible the identification of new mutagenic/carcinogenic products. Fecal bile lithocholic acid enhances liver and colon tumorigenesis.



(**28**) (**a**) R = OH, lithocholic acid
(**b**) R = $NHCH_2CH_2SO_3^-Na^+$
taurolithocholate

(11)



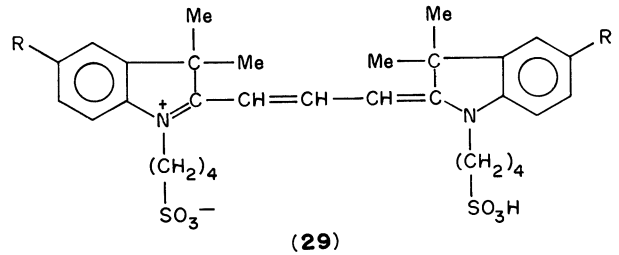
(**27**)(**a**) R = $O^-\overset{+}{N}H_4$, sulpholithocholate, diammonium salt
(**b**) R = $NHCH_2CH_2SO_3^-\overset{+}{N}H_4$, sulphotaurolithocholate, diammonium salt

[^{14}COOH]sulpholithocholic acid sulphate esters have been prepared using commercially available sulphur trioxide·pyridine complex as the sulphonating reagent and [^{14}COOH]lithocholic acid, **28a** (actually 50 μCi) produced by Amersham. All procedures have been carried out under yellow fluorescent light. The yield of product **27a** was 90%, radiochemical purity 98%, specific activity 0.30 mCi/mmol and melting point 183–185 °C.

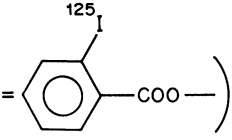
[^{14}COOH]-sulphotaurolithocholate has been prepared in a similar manner using commercial [^{14}COOH] taurolithocholate, **28b**. The specific activity of the isolated crystals **27b** was 0.36 mCi/mmol, purity 97–98% and melting point 190–191 °C (literature value, 189–190 °C).

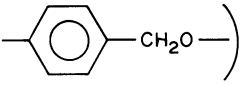
9. Synthesis of ^{125}I- and ^{14}C-labelled indomonocarbocyanines

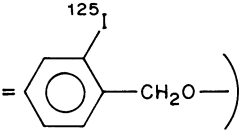
Colorants **29** A, B and C, useful in studies of the mechanism of hepatic cell functions[33], have been labelled with ^{125}I following equations 12–14[34]. Cyanine **29** A has been obtained by condensing 2-^{125}I-benzoic acid chloride with cyanine dihydroxy-5,5′ (**30**, equation 12). **29** B and C have been prepared by condensing dihydroxycyanine **30** with ^{125}I-labelled *p*-iodo- and *o*-iodo-benzyl bromides **31** (equation 13).



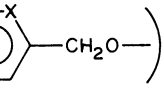
(29)

cyanine 'A': cyanine, 5,5'-bis(2-iodobenzoate) (R = )

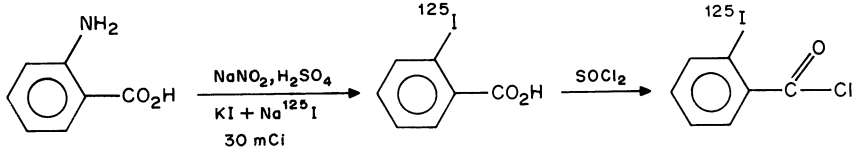
cyanine 'B': cyanine, 5,5'-bis(4-iodobenzyloxy) (R = )

cyanine 'C': cyanine, 5,5'-bis(2-iodobenzyloxy) (R = )

cyanine D: cyanine, 5,5'-dimethoxy (R = $^{14}CH_3O-$)

cyanine E: cyanine, 5,5'-dibenzyloxy (R = )

'X' denotes ^{14}C label



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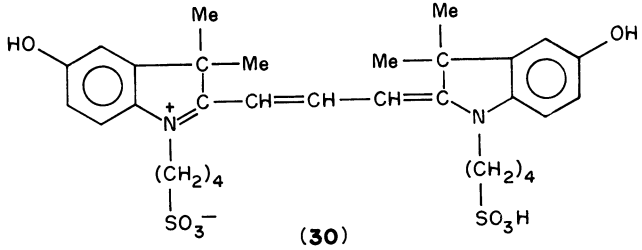


(30)

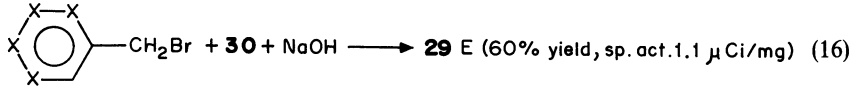
$$o\text{- and } p\text{-}H_2NC_6H_4CH_3 \xrightarrow[KI + Na^{125}I\ (51\ mCi)]{NaNO_2,\ HCl} o\text{- and } p\text{-}^{125}IC_6H_4CH_3 \xrightarrow[CCl_4]{NBS} o\text{- and } p\text{-}^{125}IC_6H_4CH_2Br$$

(31) (13)

$$\mathbf{31} + \mathbf{30} + NaOH \longrightarrow B(\text{sp. act. } 9\ \mu Ci/mg) \text{ or } C(\text{sp. act. } 5\ \mu Ci/mg) \quad (14)$$

^{14}C-labelled indomonocarbocyanines 'D' and 'E', needed for metabolism studies of these colorants, have been prepared by condensing $^{14}CH_3I$ or ^{14}C-benzyl bromide with **30** as before (equations 15 and 16).

$$^{14}CH_3I + \mathbf{30} + NaOH \longrightarrow \mathbf{29}\ D\ (45\%\ \text{yield, sp. act. } 1.5\ \mu Ci/mg) \quad (15)$$

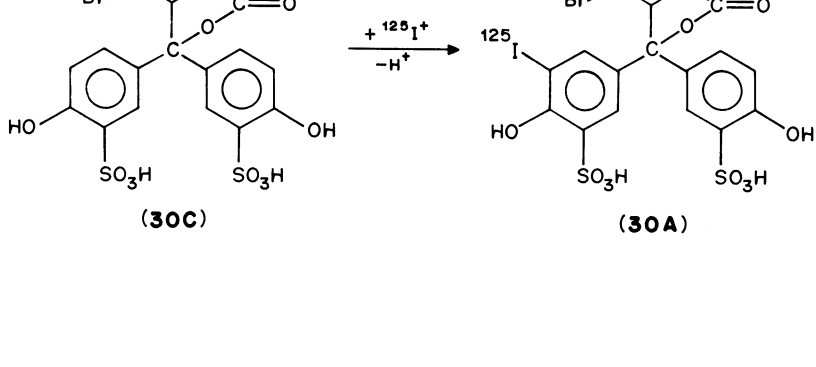


1.265 mCi (16)

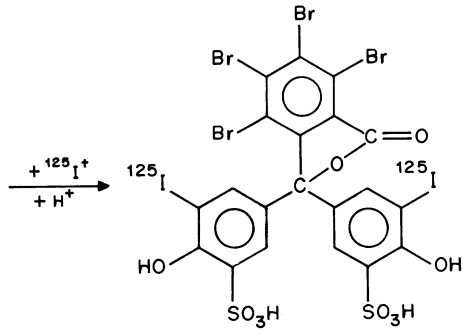
10. Separation of the ^{131}I-labelled S-sulphonated A and B insulin chains and of ^{125}I-labelled aromatic sulphonic acids

a. ^{131}I-labelled S-sulphonated 'A' and 'B' insulin chains. These have been separated[35a] by thin-layer chromatography on silica gel 'G' or on Amberlite IR-120 resin plates with an elution mixture consisting of n-butanol saturated with a very dilute aqueous solution of formic acid at pH = 4.6. The spots corresponding to A and B chains were localized by autoradiography and by recording the radioactivity in the course of scanning the plates with an automatic device.

b. Separation of ^{125}I-labelled bromosulphane. Paper chromatography has been used[35b,35c] to identify and separate the mono-^{125}I (**30A**) and di-iodo-^{125}I substituted (**30B**) bromosulphanes obtained usually in the course of electrophilic radioiodination (substitution) of bromosulphane **30C** (equation 16a). Many uniformly ^{14}C-labelled compounds, including sulphanilic acid, have been produced by Bubner and Mittag[35d].



(30C) **(30A)**



(308) (16a)

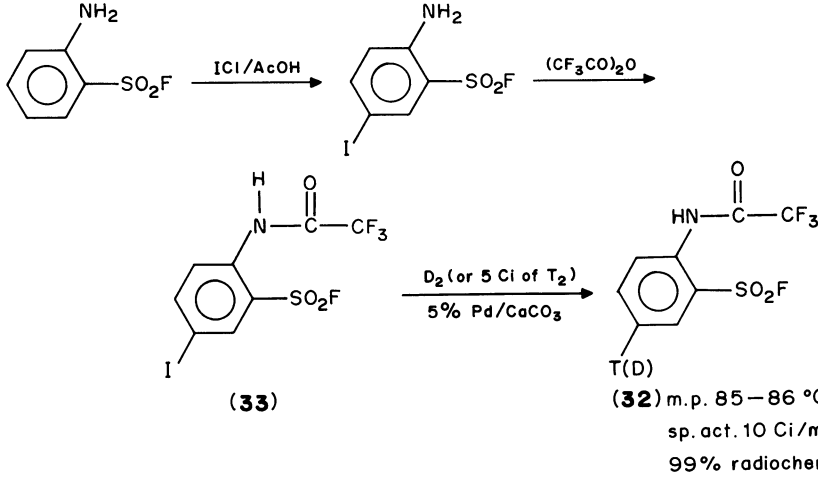
11. Synthesis of ^{35}S-labelled sulphonic acids by means of electrical gaseous discharges

Synthesis of ^{35}S-labelled sulphonic acids by treatment of hydrocarbons with $^{35}SO_2$ in electrical microwave gaseous discharges is considered[36] as a more efficient general method of synthesis of radioactive sulphonic acids than the syntheses taking place under self-β-radiation of ^{35}S or in the flux of radiation of other radionuclides with longer half-lives. Silent discharges[37] and Tesla discharge[38] have also been applied to speed up the labelling procedures. RSO_2Cl compounds are produced on an industrial scale by irradiating mixtures of the hydrocarbons with Cl_2 and SO_2 with gamma rays. When R = cyclohexyl radical, the radiation yield of the RSO_2Cl is of the order of 10^6.

B. Synthesis of Isotopically Labelled Sulphonyl Halides

*1. Synthesis of tritium and deuterium-labelled 2-trifluoroacetamidobenzene-sulphonyl fluoride (**32**)*

Tritium or deuterium labelled **32** of high specific activity, considered as a potent elastase inhibitor, has been prepared[39a] by synthesizing 5-iodo-2-trifluoroacetamido-



(33) (17)

(**32**) m.p. 85–86 °C
sp. act. 10 Ci/mmol
99% radiochem. purity

benzenesulphonyl fluoride **33** and its deiodination with deuterium or with carrier-free tritium gas, catalysed by palladium on $CaCO_3$ (equation 17). The product **32** was diluted with benzene to a concentration of 0.4 mCi/ml^{-1} and stored at 6–10 °C. The 2-trifluoroacetamido[5-^{2}H]benzenesulphonyl fluoride **32**-D was isolated in 45% yield. Deuterium incorporation into **32** as indicated by mass spectrum was the following: $d_0 = 9.77\%$, $d_1 = 90.04\%$ and $d_4 = 0.20\%$. Probably small incorporation of solvent hydrogen into **32**-D, caused by the palladium catalyst, took place. No deuterium scrambling into other positions was noticed by ^{2}H-NMR, which showed only one aromatic deuterium singlet.

2. *Synthesis of ^{14}C-labelled sulphonyl chlorides*

Isotopically labelled sulphonyl halides are highly reactive intermediates used in many synthetic schemes (see, e.g., Section I.A.5, **21**).

a. Synthesis of ^{18}F-fluorobenzenesulphonyl chloride. The ^{18}F-labelled compound **33A** is an important precursor of different S-containing compounds such as sulphonate esters, sulphones, sulphinic acids, thiols, antibacterials, enzyme inhibitors containing sulphonamido groups or proteins. These have been synthesized[39b] according to three reaction schemes (equation 17a–c).

$$p\text{-}O_2NC_6H_4SO_2Cl \xrightarrow[\substack{110\,^\circ C,\ 20\,min\\ \text{in platinum vessel}}]{Cs^{18}F \text{ in DMSO}} p\text{-}O_2NC_6H_4SO_2{}^{18}F \quad (17a)$$

$$+\ p\text{-}^{18}FC_6H_4SO_2Cl\ (5\%\ \text{radiochem. yield by HPLC})$$

(33A)

$$^{18}FC_6H_5 \xrightarrow{ClSO_3H} {}^{18}F\text{-}C_6H_4\text{-}SO_2Cl \quad (17b)$$

(33A)

$$p\text{-}(O_2N)_2C_6H_4 \xrightarrow{^{18}F^-} p\text{-}^{18}FC_6H_4NO_2 \xrightarrow{Pd/C,\ H_3PO_2}$$

$$p\text{-}^{18}FC_6H_4NH_2 \xrightarrow[2.\ SO_2,\ Cl^-]{1.\ NaNO_2\text{·}HCl} \mathbf{33A}\ (10\text{–}30\%\ \text{radiochem. yield}) \quad (17c)$$

$$^{18}F\text{-}C_6H_4\text{-}SO_2Cl \xrightarrow[100-110\,^\circ C,\ 15\ min]{NH_3\ conc.} {}^{18}F\text{-}C_6H_4\text{-}SO_2NH_2 \quad (17d)$$

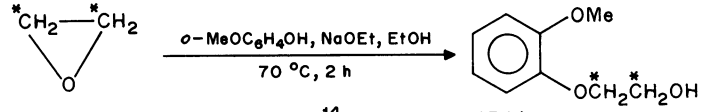
(33B)

Treatment of *p*-[^{18}F]fluorobenzenesulphonyl chloride with concentrated ammonia solution gave *p*-[^{18}F]fluorobenzenesulphonamide **33B** (equation 17d). Similarly, treatment of *p*-[^{18}F]fluorobenzenesulphonyl chloride with 5-amino-1,3,4-thiadiazole-2-sulphonamide gave 5-(*p*-[^{18}F]fluorobenzenesulphonamido)-1,3,4-thiadiazole-2-sulphonamide.

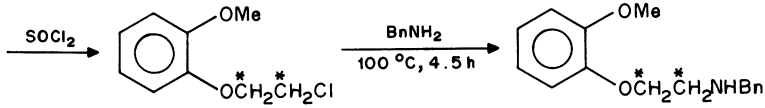
C. Syntheses of Isotopically Labelled Sulphonamides, Sulphonimides and Sulphonimines

1. Synthesis of ^{14}C-labelled 5-[1-hydroxy-2-[2-(o-methoxyphenoxy)-ethylamino]ethyl]-2-methylbenzenesulphonamide hydrochloride (YM-09538)

[^{14}C]YM-09538 (**34**), a novel α- and β-adrenergic blocking agent, required for metabolism and pharmacokinetic studies, has been prepared[40] according to equation 18. [U-^{14}C]ethylene oxide (**35**) reacted with guaiacol yielding 2-(*o*-methoxyphenoxy) [1,2-^{14}C]ethanol (**36**) in 92% yield. **36** with thionyl chloride gave **37** which in turn with

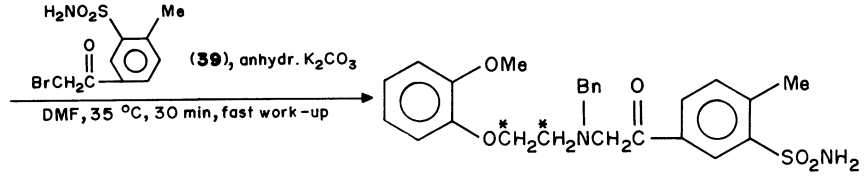


(**35**) 20 mCi '*' denotes ^{14}C label (**36**) 92% yield

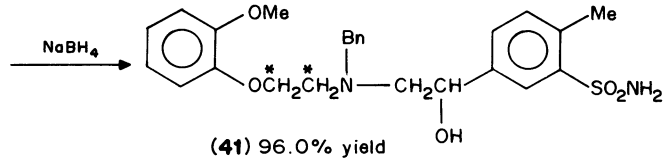


(**37**) 98.5% yield (**38**) 96.6% yield

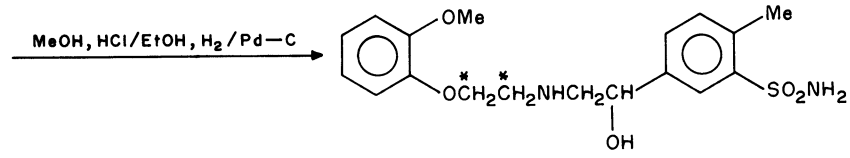
radiochem. purity 99%



(**40**) 92.7% yield



(**41**) 96.0% yield



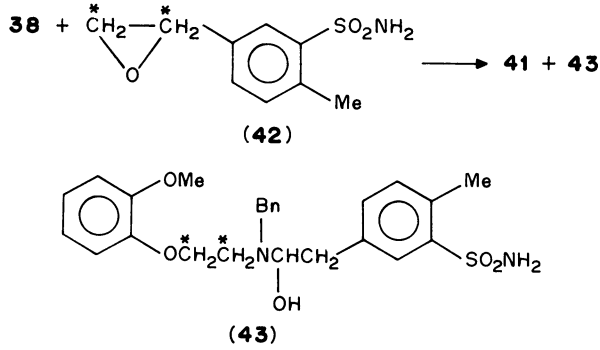
(**34**) 76.7% yield

sp. act. 4.76 mCi/mmol

radiochem. purity >99%

Bn = $CH_2C_6H_5$ (benzyl) (18)

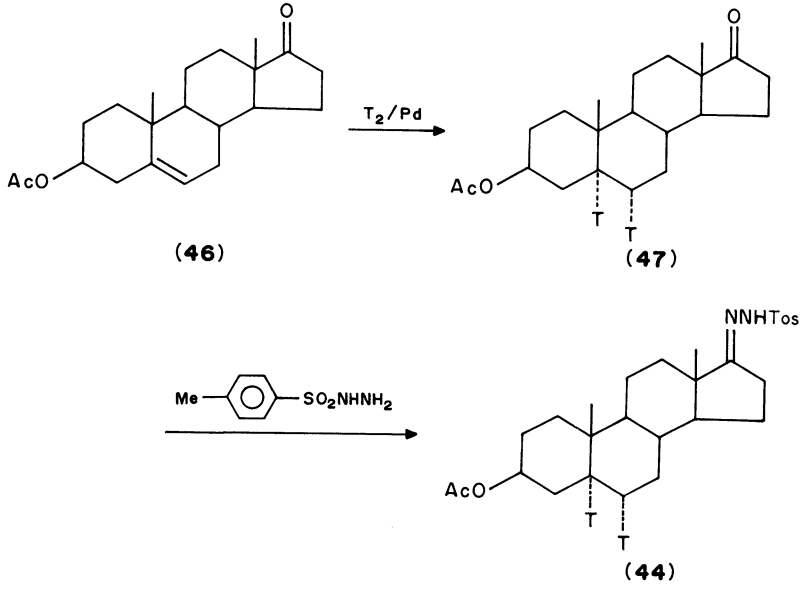
benzylamine gave the labelled *N*-benzyl-2-(*o*-methoxyphenoxy) [1,2-^{14}C]ethylamine (**38**). Heating **38** with **39** yielded 5[N-benzyl-*N*-[2-(*o*-methoxyphenoxy) [1,2-^{14}C]ethyl] aminoacetyl]2-methylbenzenesulphonamide (**40**). Reduction of the latter gave 5-[1-hydroxy-2-[*N*-benzyl-*N*-[2-(*o*-methoxyphenoxy)[1,2-^{14}C]ethyl]aminoethyl]-2-methylbenzenesulphonamide (**41**). Removal of the benzyl group of **41** by hydrogenolysis provided [^{14}C]YM-09538 (**34**) in an overall radiochemical yield of 50.6% based on [^{14}C]ethylene oxide. Direct reaction of **38** with epoxide **42** yields an isomeric mixture of aminoalcohols **41** + **43**, difficult to separate (equation 19).

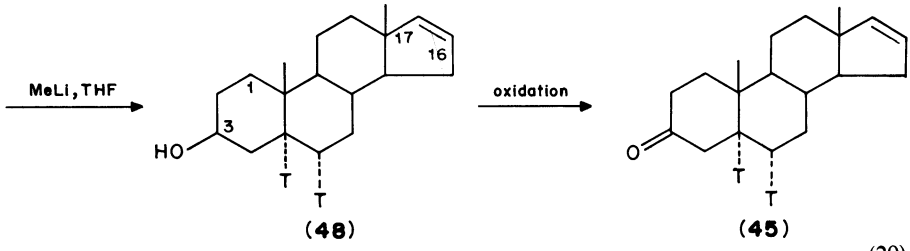


(19)

2. Synthesis and application of [5α, 6α-^{3}H]-5α-androst-16-en-3-one

Tritium-labelled 3β-acetoxy-[5α,6α-^{3}H]-5α-androstan-17-tosylhydrazone (**44**) has been prepared as an intermediate in a four-step synthesis[41] of the hormone [5α,6α-^{3}H]-5α-androst-16-en-3-one (**45**), starting from 3β-acetoxyandrost-5-en-17-one (**46**, equation 20). Product **45** has been applied in radioimmunoassay determinations of 5α-androstenone in biological systems.

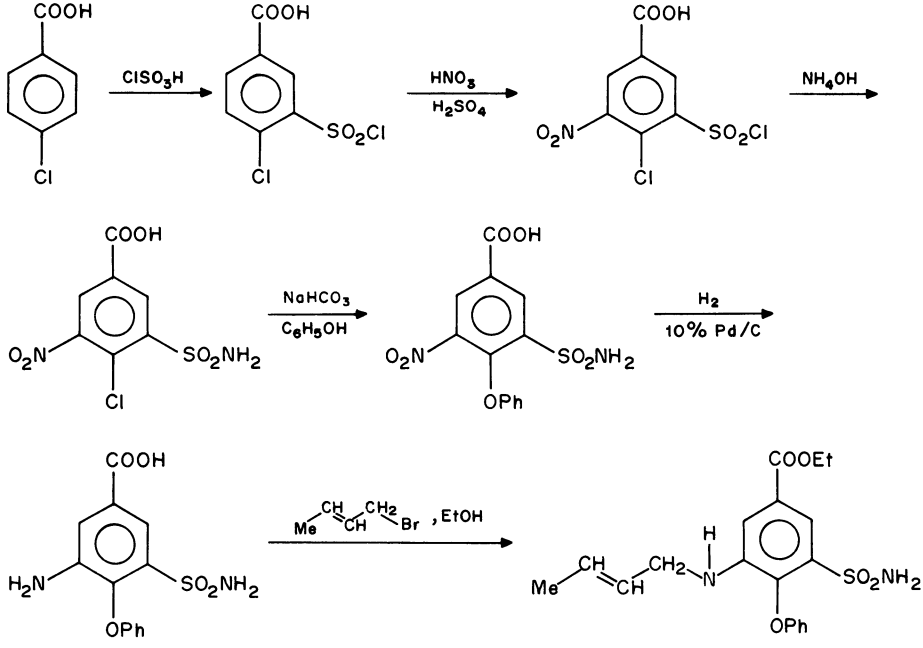


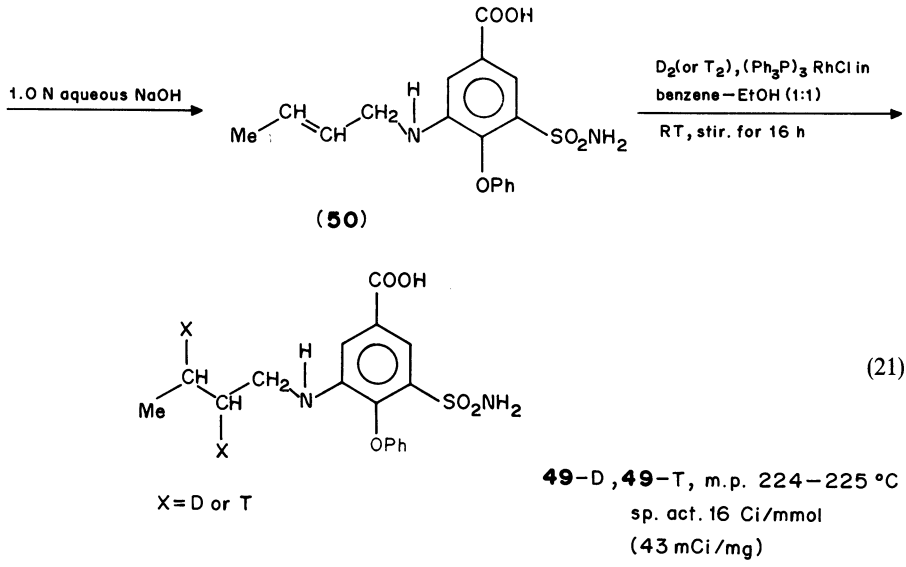


(20)

3. *Synthesis of tritiated bumetanide*

[*N*-Butyl-2,3-$^2H_2$]bumetanide (**49**-D) and [*N*-butyl-2,3-$^3H_2$]bumetanide (**49**-T), diuretics inhibiting, similarly to furosemide, Na^+, K^+ and Cl^- contransport through biological membranes, has been isotopically labelled[42] in the *N*-butyl side-chain by reduction of 3-[N-(1-but-2-enyl)amino]-4-phenoxy-5-sulphamylbenzoic acid (**50**) with carrier-free tritium or deuterium gas (equation 21). Homogeneous rhodium-catalysed isotopic hydrogen reductions have been accompanied by smaller label scrambling than has been observed in the heterogeneous palladium-catalysed deuterium reductions. Mass spectrometric data indicated that the deuterated product **49**-D contained: $d_0 = 3.13\%$, $d_1 = 11.67\%$, $d_2 = 69.11\%$, $d_3 = 12.31\%$, $d_4 = 2.96\%$ and $d_5 = 0.82\%$. 5.0 Ci(0.086 mmol) of carrier-free tritium gas have been used in the synthesis of **49**-T. After removal of all labile tritium from **49**-T by subsequent back exchanges with absolute ethanol and chromatography on silica gel plates, 352 mCi of the purified product **49**-T of 99% radiochemical purity were obtained. The tritiated bumetanide **49** dissolved in absolute ethanol was stored at 5 °C to minimize its decomposition caused by the β-radiation of the tritium.

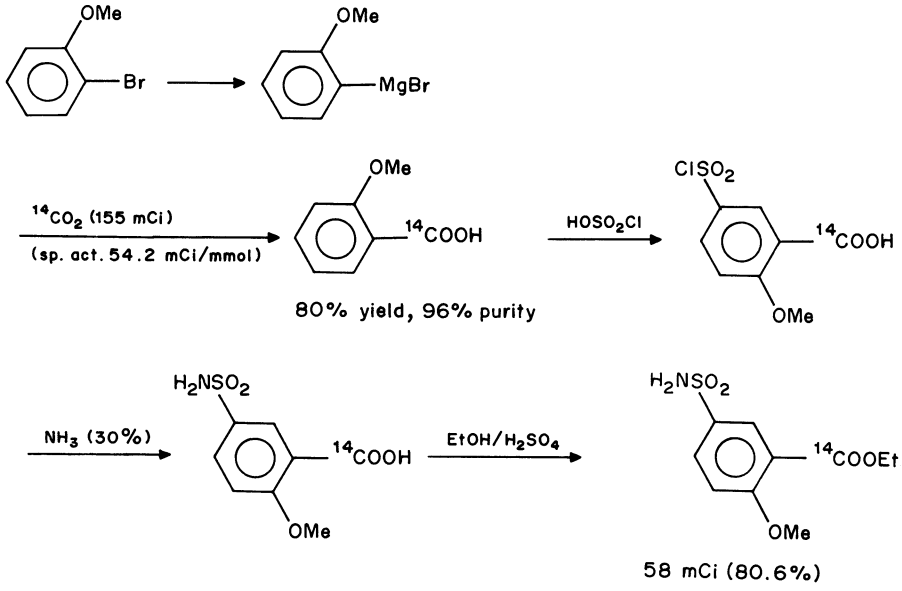


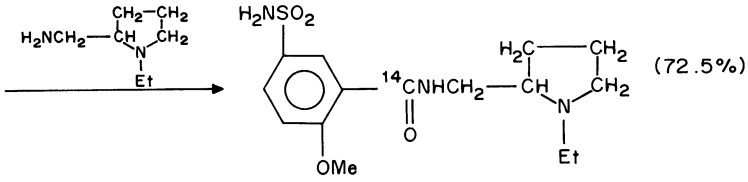


(21)

4. Synthesis of carbonyl-^{14}C labelled 'sulpiride' {N-[(ethyl-1-pyrrolidinyl-2)methyl]methoxy-2-sulphamoyl-5 benzamide}

Compound **51** the drug 'sulpiride' (Dogmatil®) clinically defined as 'regulator of comportment', possessing anti-depressing properties[43], has been labelled with carbon-14 in the carbonyl group in a five-step synthesis[44a] (equation 22). The final overall radiochemical yield with respect to $Ba^{14}CO_3$ of the pure product **51** was **22%**, with a radiochemical purity of 99.5%.



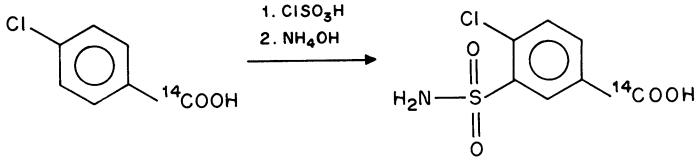


(22)

(**51**) 42 mCi

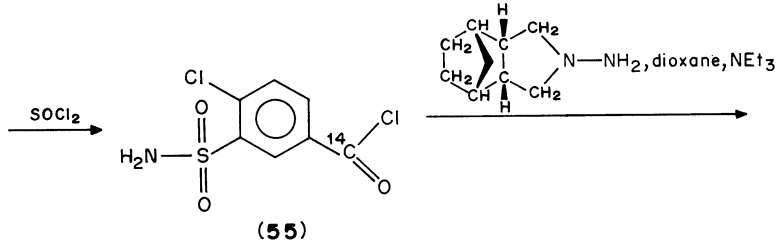
*5. Synthesis of ^{14}C-labelled 4-chloro-3-sulphamoyl-N-(3aα, 4α,5,6,7α,7aα-hexahydro-4,7-methano-isoindolin-2-yl)benzamide (**52**)*

Compound **52** an effective anti-hypertensive drug, has been synthesized[44b] for biotransformation studies from *p*-chlorobenzoic acid–carbonyl-^{14}C (**53**) in three steps modifying the methods of Sturm[45], Hoefle[46] and coworkers (equation 23). The intermediate 4-chloro-3-sulphamoylbenzoic acid–carbonyl-^{14}C (**54**) with thionyl chloride yielded the acid chloride **55**, which with 2-amino-3aα, 4α,5,6,7aα-hexahydro-4,7-methano-isoindoline gave the carbonyl-^{14}C labelled compound **52**. The UV spectra of **52** and of the unlabelled **52** as well as the R_f value on TLC of the single radioactive peak and of the fluorescent spot of unlabelled authentic specimen of **52** coincided.

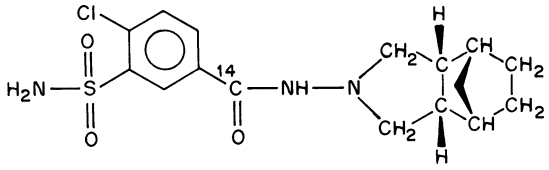


(**53**) 46.8 mCi

(**54**) 53% yield



(**55**)

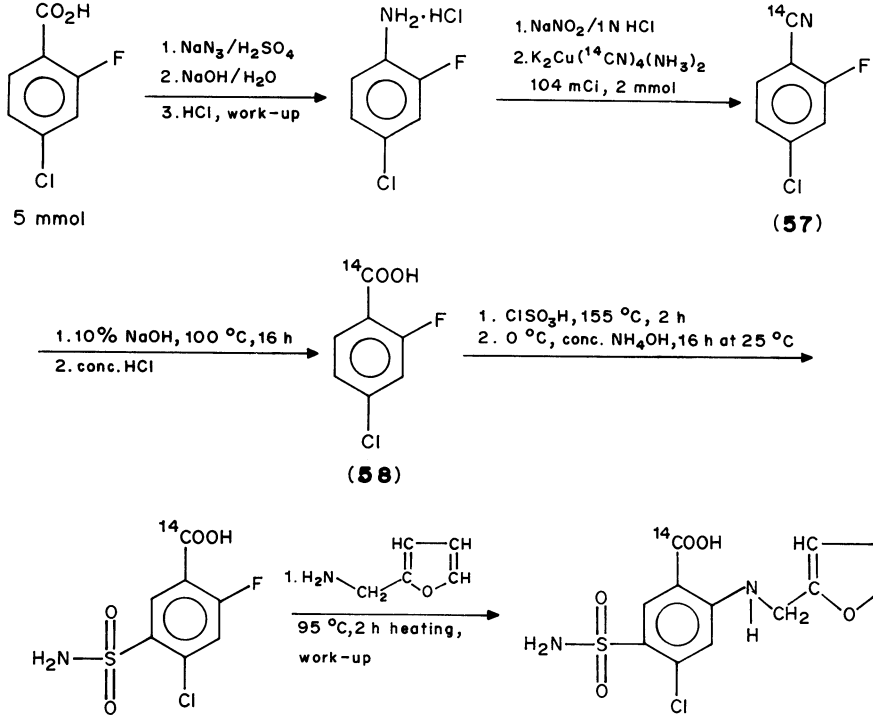


(23)

(**52**) colourless needles
13.9% yield
sp. act. 31.7 μCi/mg

6. Synthesis of ^{14}C-, deuterium- and tritium-labelled furosemide and its derivatives

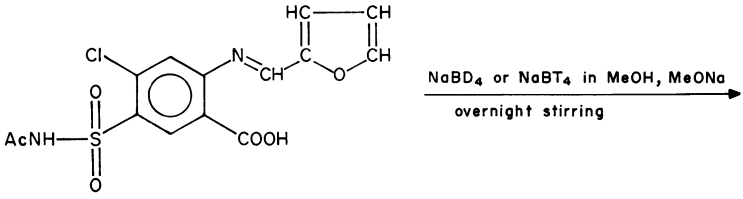
a. Synthesis of carboxyl-^{14}C furosemide. 4-Chloro-*N*-furfuryl-5-sulphamoylanthranilic-7-^{14}C acid (**56**) has been labelled with ^{14}C in the carboxyl group avoiding conventional carbonation reactions[47] following an elaborate scheme (equation 24)[48] which includes Schmidt reaction followed by a modified Sandmeyer reaction requiring only a moderate excess of cyanide-^{14}C for the synthesis of 4-chloro-2-fluorobenzonitrile-7-^{14}C (**57**), hydrolysis of the latter to the 4-chloro-2-fluorobenzoic-7-^{14}C acid (**58**), amidation of **58** and selective replacement of fluorine with furfurylamine[49,50a]. ^{35}S-labelled furosemide[50b] has also been synthesized and applied in metabolic studies.



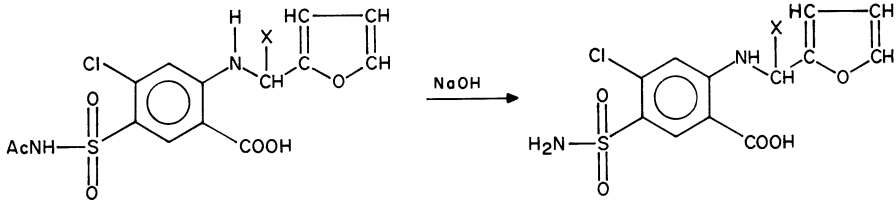
(24)

b. Synthesis of 2-furanylmethyl-α-^2H and -^3H furosemide. Furosemide, 2-[(2-furanylmethyl)amino]-4-chloro-5-(aminosulphonyl)benzoic acid (**59**), an important diuretic used in the treatment of congestive heart failure and in renal insufficiency, has been labelled[51] with deuterium and tritium at the 2-furanylmethyl α-position by reduction of *N*-[(2-furanylmethyl)imino]-4-chloro-5-(*N*-acetylaminosulphonyl)benzoic acid (**60**) with sodium ^2H- or ^3H-borohydride, followed by hydrolysis of the acetyl group with 2NNaOH (equation 25). Using tritiated sodium borohydride (0.45 mmol, sp. act. 55 mCi/mmol, diluted with carrier sodium borohydride) tritium-labelled **59** was obtained in 25% yield, based on the starting imine **60** with specific activity 9.32 mCi/mmol and radiopurity

> 99%. The imine **60** used for preparation of **59** has been formed by reacting 2-amino-4-chloro-5-(*N*-acetylaminosulphonyl)benzoic acid with 2-furancarboxaldehyde.



(**60**) 0.105 mmol in MeOH

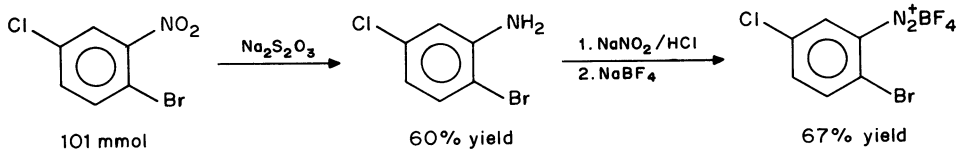


X=D or T

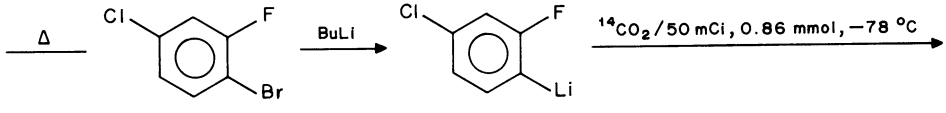
(**59**) m.p. 207 °C (d)
0.0364 mmol
(34.7% yield)

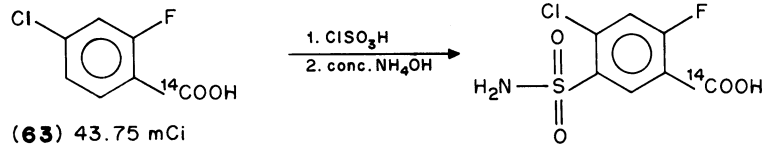
(25)

*c. Synthesis of 4-chloro-*N*-furfuryl-5-butoxymethylenesulphamoylanthranilic acid-[$^{14}CO_2H$]FFBu-^{14}C,* (**61**). FFBu-^{14}C (**61**), the labile pro-drug of the diuretic furosemide **62**, has been prepared in 20% yield according to equation 26[52]. Purified samples of **61** are always contaminated with traces of **62** and the conversion of **62** into **61** is rather low. Hence the high-yield synthesis of **62** in equation 26 is especially valuable.



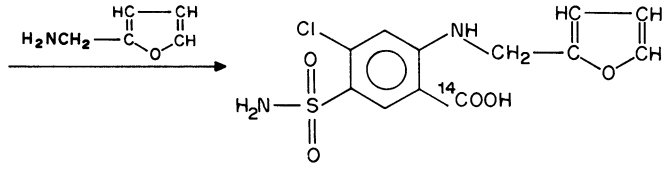
101 mmol — 60% yield — 67% yield



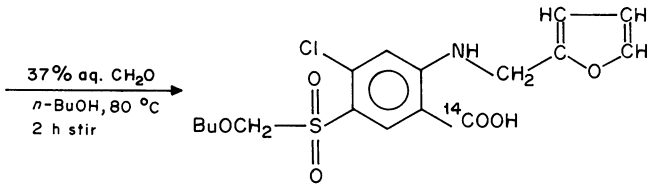


(**63**) 43.75 mCi
87.5% radiochem. yield,
99% radiochem. purity

(**64**) 25 mCi
sp. act. 6.52 mCi/mmol



(**62**) 22.6 mCi
90% yield based on **64**
> 95% purity



(**61**) 3.86 mCi, sp. act. 6.65 mCi/mmol
20% yield based on 19 mCi of **62**

(26)

7. Synthesis of 4-ethylsulphonyl-1-naphthalenesulphonamide-^{15}N (ENS)

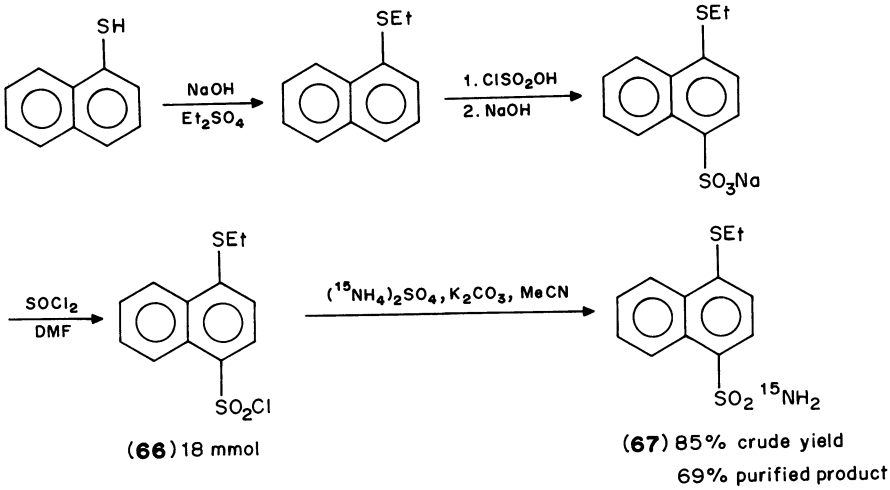
The compound ENS (**65**), promoting experimental bladder carcinogenesis, has been labelled with nitrogen-15 according to a five-step reaction sequence (equation 27)[53] in 50–60% overall yield, which is better than in earlier reaction schemes[54]. 4-Ethylthio-1-naphthalenesulphonamide-^{15}N (**67**) has been prepared in good yield by using ammonium sulphate as a source of ammonia involving *in situ* generation of $^{15}NH_3$. **65** has also been prepared according to the alternatives scheme (equation 28)[55], but in this case the final yield was only 33%, mainly because of the formation of a by-product having the sulphonimide structure **68**.

8. Synthesis of (R)- and (S)-amphetamine-d_3

By modifying the procedure of Karrer and Ehrhardt[56], who converted the ethyl ester of (*R*)-(+)-phenylalanine to (*S*)-(+)-amphetamine in 5% overall yield, (*R*)-(−)- and (*S*)-(+)-2-amino-1-phenylpropane-3,3,3-d_3 (**69**) has been synthesized[57] in 32.8% overall yield, 99% isotopic purity and >99% enantiomeric purity according to the reaction scheme (equation 29) which involves (*R*)-3-phenyl-2-(4-toluenesulphamoyl)propyl-1,1-d_2 4-toluenesulphonate, (*R*)-**70**, and (*S*)-*N*-(1-methyl-d_3-2-phenethyl)-4-toluenesulphonamide, (S)-**71**, as the important intermediates. The sulphonamide **71** was cleaved to the parent amine **69** with naphthalene radical anion without racemization of the asymmetric centre adjacent to the nitrogen. The deep-green solution of naphthalene anion radical had been prepared by treating a solution of naphthalene in THF with small pieces of sodium under nitrogen.

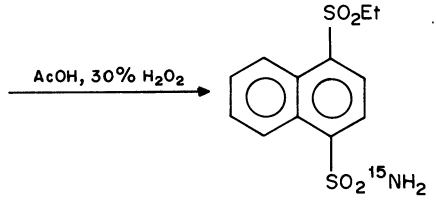
9. Synthesis of ^{35}S- and ^{14}C-labelled famotidines

3-[[2-[(Diaminomethylene)amino]-4-thiazolyl]methyl] [^{35}S]thio]-N^2-sulphamoyl-propionamidine, [^{35}S]famotidine (**74a**) and [thiazole-4-^{14}C]famotidine (**74b**), a new



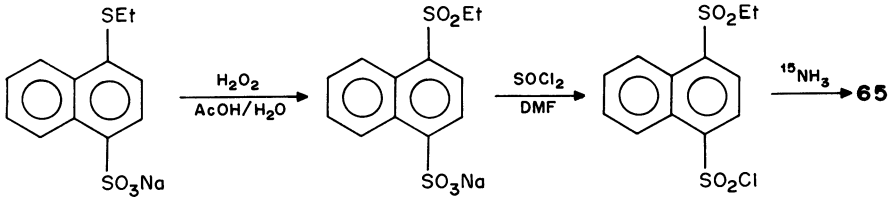
(**66**) 18 mmol

(**67**) 85% crude yield
69% purified product



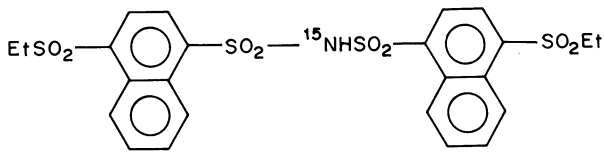
(**65**) m.p. 199–200 °C
81% yield

(27)

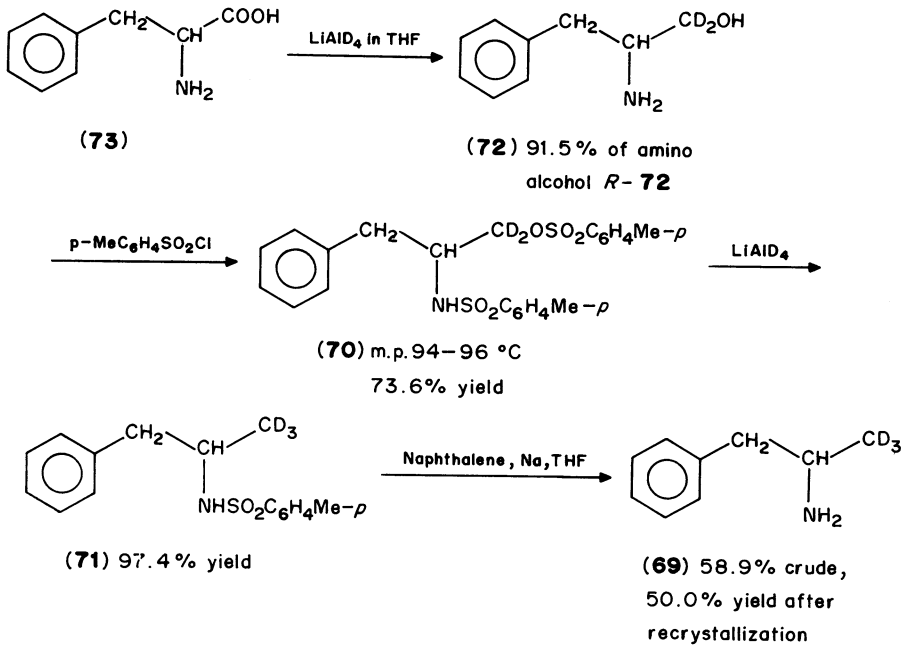


80% yield (not isolated)

(28)

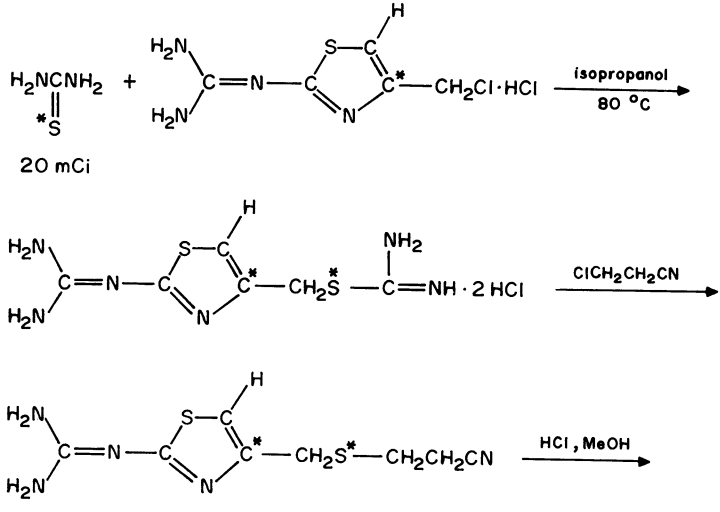


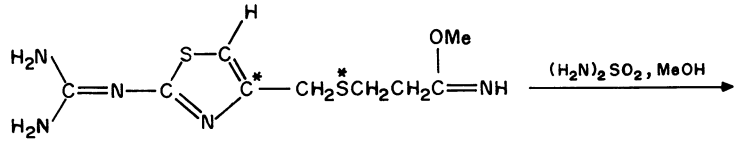
(**68**)



(29)

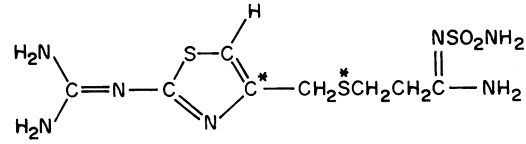
potent histamine H_2 receptor antagonist, have been ^{35}S- and ^{14}C-labelled[58] according to a four step procedure (equation 30) using commercial [^{35}S]thiourea and 4-chloromethyl-2-[(diaminomethylene)amino][4-^{14}C]thiazole hydrochloride. A high molar ratio of sulphamide: **75a** in the last step was necessary to decrease the formation of the bis-thiazole compound **75b**, but difficulties in the isolation of pure **74** necessitated the use of 5 equivalent moles only of the sulphamide, ensuring 70% yield of the desired product **74**.





(75a) crystals

(30)

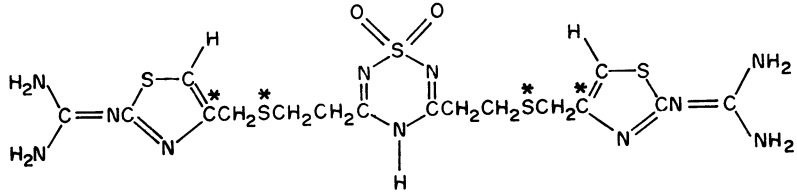


(74a,b)

(a) ^{35}S-labelled at S*, sp. act. 45.7 μCi/mg, 23.6% overall radiochem. yield

(b) ^{14}C-labelled at C*, sp. act. 47.6 μCi/mg, 59.9% overall radiochem. yield

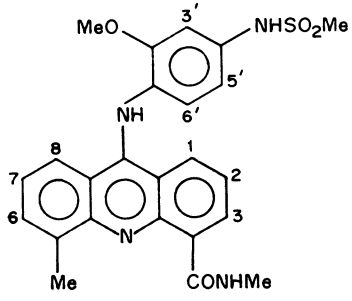
Radiochemical and chemical purity about 98–99% for both **74a** and **b**.



(75b)

10. Synthesis of deuterium, tritium and carbon-14 labelled 'CI-921'

a. Synthesis of deuterium- and tritium-labelled 9-[[2-methoxy-4-[(methylsulphonyl) amino]phenyl]amino]-N,5-dimethyl-4-acridinecarboxamide ('CI-921'). CI-921 (**76**), a potent antitumor derivative, more effective than amsacrine **77** against murine solid tumors,

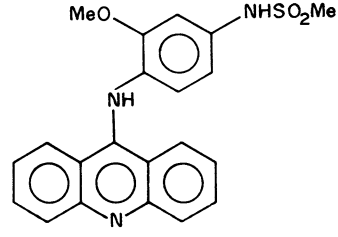


(76)(a) ^{2}H-labelled

(b) ^{3}H-labelled

(c) ^{14}C-labelled free base

(d) ^{14}C-labelled isethionate salt

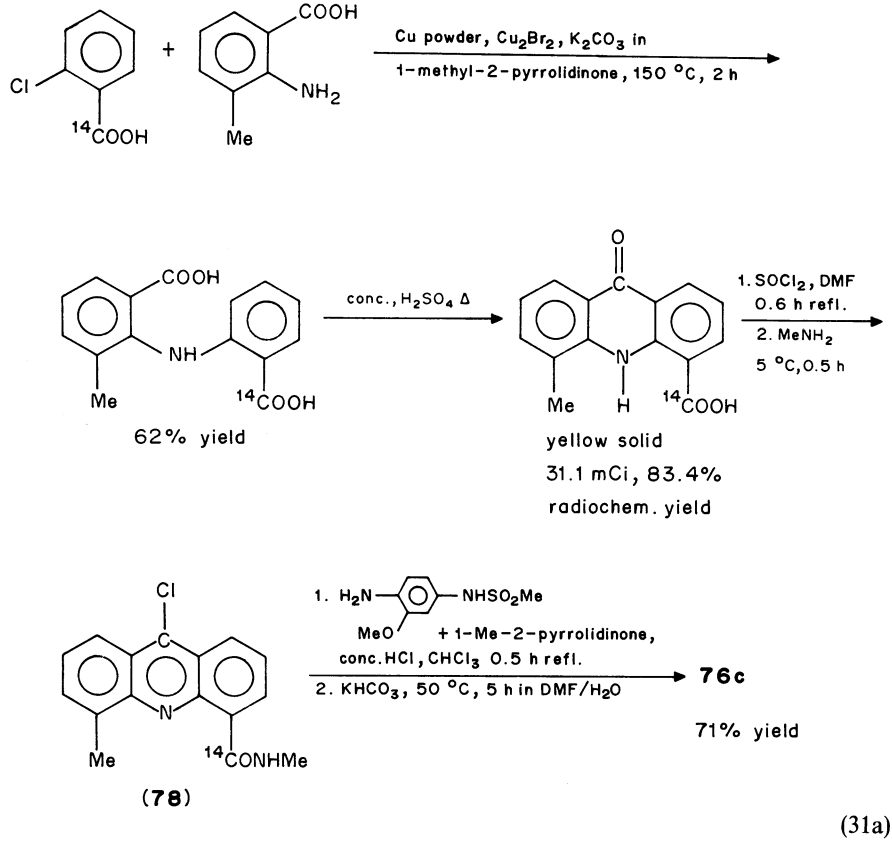


(77)

has been labelled with deuterium, tritium and carbon-14 for preclinical toxicology studies[59]. Partial deuterium labelling of **76** has been achieved by heating the free base of **76** with acetic acid, D_2O, and platinum black in a sealed vial during 18 hours at 80 °C. NMR (at 300 MHz) and mass spectroscopic investigation of the deuterated **76** showed that deuterium incorporates predominantly in the 7 (68% deuterium), 2(68%) and 6(58%) positions, which are sterically the least hindered. In positions 3,1,8,6′ and (3′,5′) the atom % of deuterium were as follows: 13,3,0,29 and 13%. **76** contained on average 2–3 deuterium atoms per molecule.

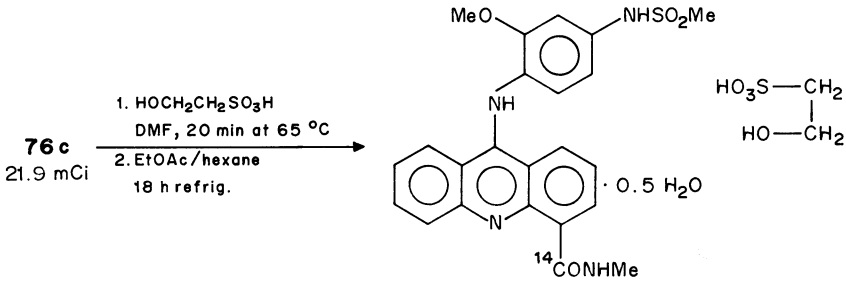
Tritium-labelled CI-921 (**76b**) has been obtained in an exchange reaction with tritiated water and unlabelled **76**, catalysed by platinum black in HOAc. Any labile tritium has been removed in vacuo using MeOH as a solvent. The product had, after preparative silica-gel plate chromatography of **76b** and after TLC of the formate salt of **76b**, a specific activity of 4.2 Ci/mmol, with radiochemical purity greater than 99%. The tritiated salt of high specific activity had, after converting it to the free base and dilution with the 2-hydroxyethanesulphonate salt of unlabelled CI-921 and purification, a final specific activity of 59.3 mCi/mmol.

b. 9-[[2-Methoxy-4-[(methylsulphonyl) amino]phenyl]amino]-N,5-dimethyl-4-acridine-carboxamide-^{14}C,2-hydroxyethane sulphonate (1:1), hemihydrate. (**76d**) has been prepared following the reaction scheme in equation 31 using 60.5 mCi of 2-chlorobenzoic-



(31a)

carboxy-^{14}C acid as the starting material. The free base **76c** has been obtained by addition of *N*-(4-amino-3-methoxyphenyl)methanesulphonamide to the acridyl chloride amide **78** and converting the hydrochloride salt with $KHCO_3$ to the free base **76c** (21.9 mCi, 411 mg, 70.4% radiochemical yield from acridone). **76c** has been converted to isethionate salt **76d** (equation 31b) with 60.7% yield and radiochemical purity greater than 99%.



76d, 13.3 mCi
m.p. 268–270 °C (dec.)
sp. act. 26.9 mCi/mmol

(31b)

*11. Synthesis of N-2,2,2 ($^2H_3$)ethyl-p-toluenesulphonamide (**79**) and N-2,2,2 ($^2H_3$) ethyl-N-nitroso-p-toluenesulphonamide (**80**)*

The deuterated compounds **79** and **80** have been prepared[60] in the course of synthesis of 2,2,2($^2H_3$)diazoethane **81** (equation 32). The latter is a very useful reagent for the synthesis of deuterated ethyl esters and is generated in excellent yield from **80**, which is more stable[61] and less toxic than other precursors[62,63]. **80** has been prepared in three steps from trideuterioacetonitrile in 71.3% overall yield. It is possible to suppress the formation of

$$CD_3CN \xrightarrow{LiAlH_4/Et_2O} CD_3CH_2NH_3{}^+Cl^-$$

82% yield, m.p. 99–107 °C colourless, hygroscopic plates

$$\xrightarrow[2.\ TosCl/1,4\text{-dioxane}]{1.\ NaOH/H_2O} TosNHCH_2CD_3 + [Tos_2NCH_2CD_3]$$

(**79**) 92.5% yield mp. 64 °C (**82**) mp 114–116 °C

$$\textbf{79} \text{ in } AcOH/H_2O \xrightarrow{NaNO_2/H_2O,\ 0\,^\circ C} \underset{ON}{Tos}\!\!>\!\!N—CH_2CD_3$$

(10/1, v/v) (**80**) 94% yield m.p. 42–43.5 °C

$$\xrightarrow{KOH/ROH,\ 0\text{–}5\,^\circ C} CD_3CHN_2 + TosOR \qquad (32b)$$

(**81**) R = Me or Et

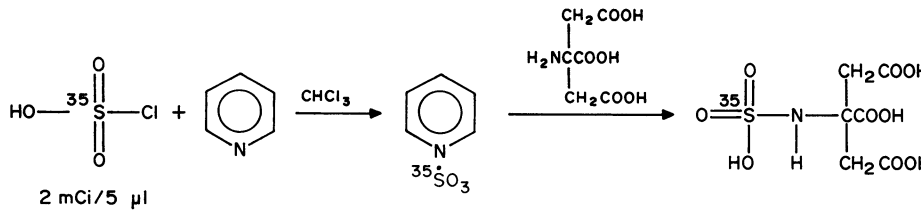
bistosylate **82** by choosing optimal reaction conditions. Fast alkaline decomposition of **80** at $-4\,^{\circ}C$ gives, after co-distillation, the ether/hexane solution of **81**, which when stored for five weeks at $-80\,^{\circ}C$ retains 75–80% of its initial concentration. Pure crystals of **80** show no decomposition after six months storage in the dark at 4 °C but heated above its melting point it undergoes denitrosation. Above 82 °C ethylene is formed in a violent decomposition.

$$CD_3CHN_2\ (\mathbf{81}) \xrightarrow{RCO_2H} RCO_2CH_2CD_3 \qquad \xrightarrow[D_2O/DO^-]{RCO_2D} RCO_2CD_2CD_3 + RCO_2CHDCD_3 \tag{33}$$

Reaction 33 carried out in HTO/TO^- is also a route for the introduction of tritium into the methylene group of esters. Diazoethane readily exchanges (1 min) its 1-H with $NaOD/D_2O$ solution at 4 °C. Reaction of partially deuterated CH_3CDN_2 with *p*-$O_2NC_6H_4CO_2D$ gave (1-^{2}H)-ethyl and (1,1-$^2H_2$)-ethyl 4-nitrobenzoate.

12. Synthesis of N-[^{35}S]sulpho-2-amino tricarballylate, 'SAT'

The compound 'SAT' (**83**), inhibitor of calcification *in vitro*, was required for pharmacokinetic studies *in vivo* to evaluate its therapeutic potential in prevention and treatment of kidney stones. It has been produced in high purity in a rapid and simple two-step synthesis (equation 34)[64,65].



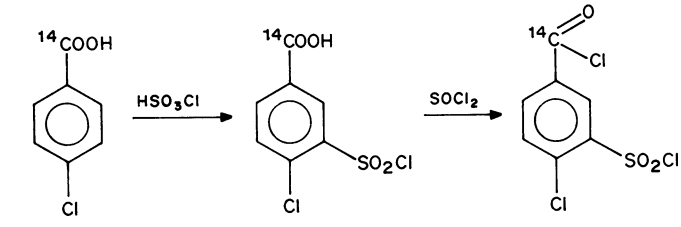
(34)

Chloro-[^{35}S]sulphonic acid (**84**) and pyridine were reacted at 0 °C in a standard scintillation vial, sealed with a rubber cap at stirring. The solid pyridine-[^{35}S]sulphur trioxide (**85**) was coupled with 2-amino tricarballylate to give radio-labelled ^{35}S-SAT (**83**). The low yield of **83** in the second step of the synthesis was assumed to be caused by steric hindrance around the amino group of 2-amino tricarballylate.

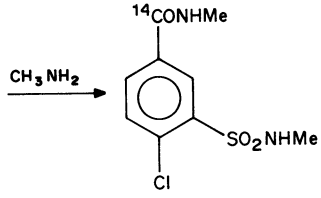
13. Synthesis of ^{14}C-labelled derivatives of 4-chloro-3-sulphamoylbenzoic acid

*a. 4-Chloro-*N*-methyl-3-(methylsulphamoyl)benzamide(carbonyl-^{14}C),* **86** has been prepared according to equation 35[66].

b. 4-Chloro-3-sulphamoylbenzoic acid 2,2-dimethylhydrazide (carbonyl-^{14}C), 'CI-546(carbonyl-^{14}C) (**91**), has been obtained according to equation 36[66].

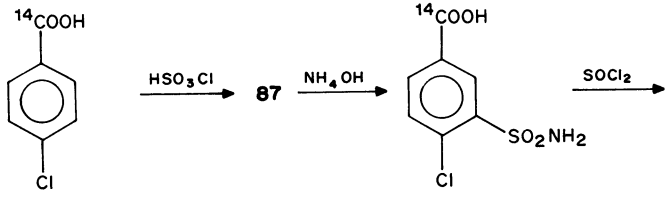


7.15 mCi, 1.65g (87) (88)



(86) (35)

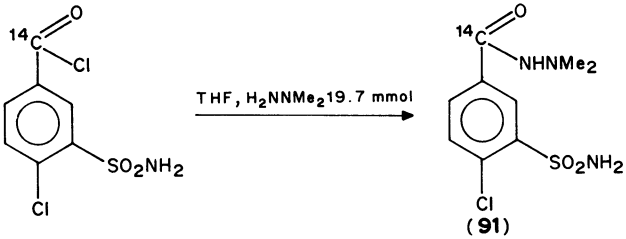
'Cl–456 (carbonyl–^{14}C)'
1.21 g, 40.8% yield
sp. act. 2.14 Ci/mg
tot. act. 2.92 mCi



7.15 mCi
1.65 g
(10.5 mmol)

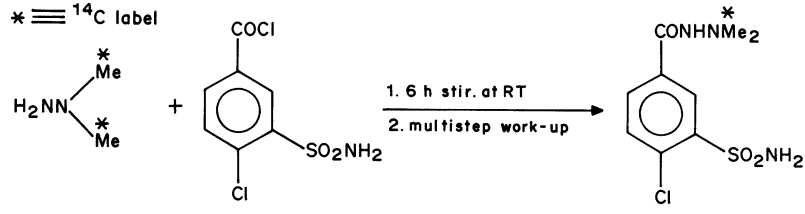
(89) 2.4 g
dry product

(36)



(90) (91)
sp. act. 4.71 μCi/mg

c. 4-Chloro-3-sulphamoylbenzoic acid 2,2-dimethylhydrazide (methyl-^{14}C), code number 'Cl-546(Methyl-^{14}C), **92**', has been synthesized by reacting an excess of non-labelled **90** with unsymmetrical dimethylhydrazine-^{14}C ('UDMH'-^{14}C), and subsequent multistep work-up (equation 37)[66]. Weight and ^{14}C yields of **92** based on UDMH-^{14}C were 58% and 44%, respectively.

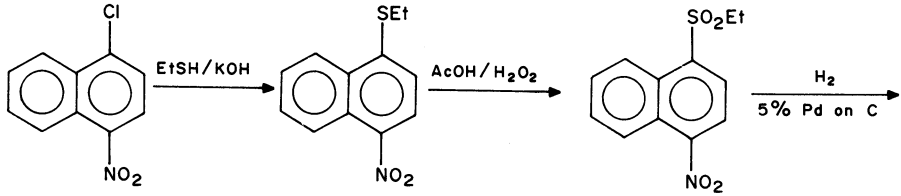


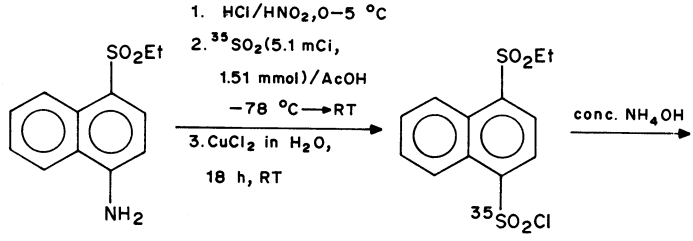
3.6 mmol (946 μCi ^{14}C) in 3.6 mmol triethylamine

5.4 mmol in THF

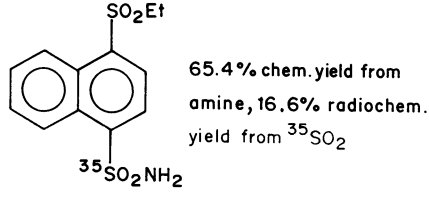
(**92**) 580 mg, m.p. 191—193 °C, sp. act. 0.71 μCi/mg

(37)





(**94**) (**95**)



(**93**) sp. act. 2.57 mCi/mmol

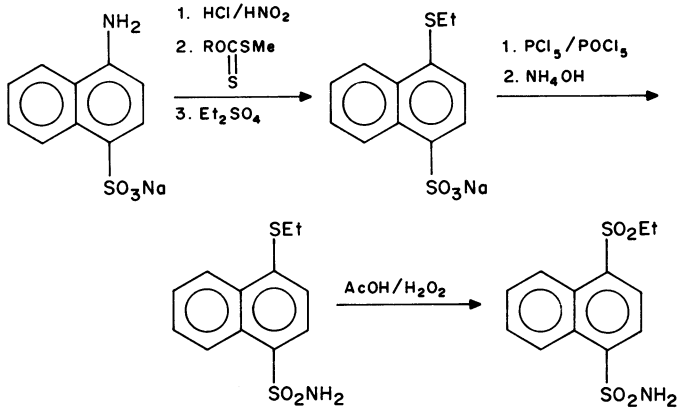
(38)

All three derivatives **86**, **91** and **92**, possessing diuretic and antihypertensive activity, have been prepared for use in drug metabolism studies.

*14. Synthesis of 1-ethylsulphonylnaphthalene-4-(^{35}S)sulphonamide (**93**)*

Low chemical yields of non-labelled **93** are obtained according to the method of Brimelow and Vasey[67]. **93** has therefore been synthesized[68] according to equation 38 in which the ^{35}S label is introduced into **93** as a sulphonamide group at a late stage.

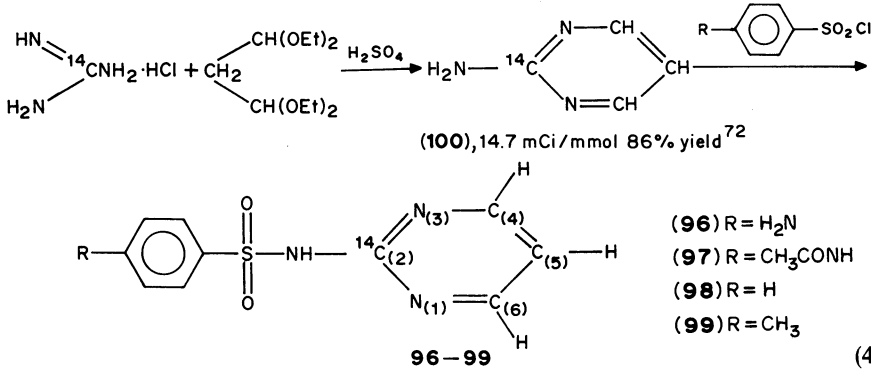
In the above method an excess of sulphur dioxide–^{35}S had to be applied, but the ^{35}S isotope is relatively cheap and the procedure of equation 38 is more economic than that based on xanthate (equation 39)[67], which is characterized by the low 7.5% chemical yield on the semimolar scale. Compound **93** has a response already at a single oral dose, but induces in rats and mice bladder cancer at repeated administration.



(39)

15. Synthesis of [^{14}C]-labelled sulphadiazines

*a. Sulphadiazine **96** and its three derivatives.* (N^4-acetylsulphanilamido)-2-pyrimidine (**97**), (benzenesulphonamido)-2-pyrimidine (**98**) and (*p*-toluenesulphonamido)-2-pyrimidine (**99**) labelled with ^{14}C in the pyrimidine moiety have been synthesized[69] according to the general scheme in equation 40 by condensing amine **100** with the appropriate sulphochloride. Product **96** was found to concentrate in the Yoshida tumor tissue of rats[70].



(40)

The hydrochloride of guanidine -^{14}C which was used has been obtained by heating at 165 °C a mixture of barium cyanamide-^{14}C with ammonium nitrate[71] (equation 41).

$$Ba^{14}CO_3 \longrightarrow BaN^{14}CN \xrightarrow[165\,^\circ C]{NH_4NO_3} \begin{matrix} HN \\ H_2N \end{matrix} \!\!>\!\!= {}^{14}CNH_2 \cdot HCl \qquad (41)$$

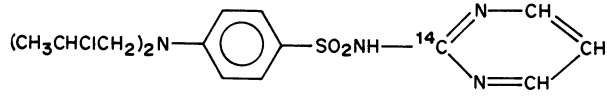
b. Synthesis of N_4-di(2-chloropropyl)sulphadiazine(pyrimidine ^{14}C-2) (**101**, 'CB 1932 ^{14}C'). The growth inhibitor of the Yoshida and Walker 256 tumors [70] has been labelled with ^{14}C for cancer research (equation 42)[73]. The crude product **101** was contaminated with 15% of **100**. After purification 3.5 mCi (63% radiochem. yield) of radiochemically pure product **101** has been isolated. Its chemical purity was better than 99%.

(100)

5.5 mCi (0.33 mmol) $(CH_3CHClCH_2)_2N$—C$_6$H$_4$—SO_2Cl (0.5 ml)

purified by vac. subl. ⟶

at 90 °C



(42)

(101) 4.9 mCi

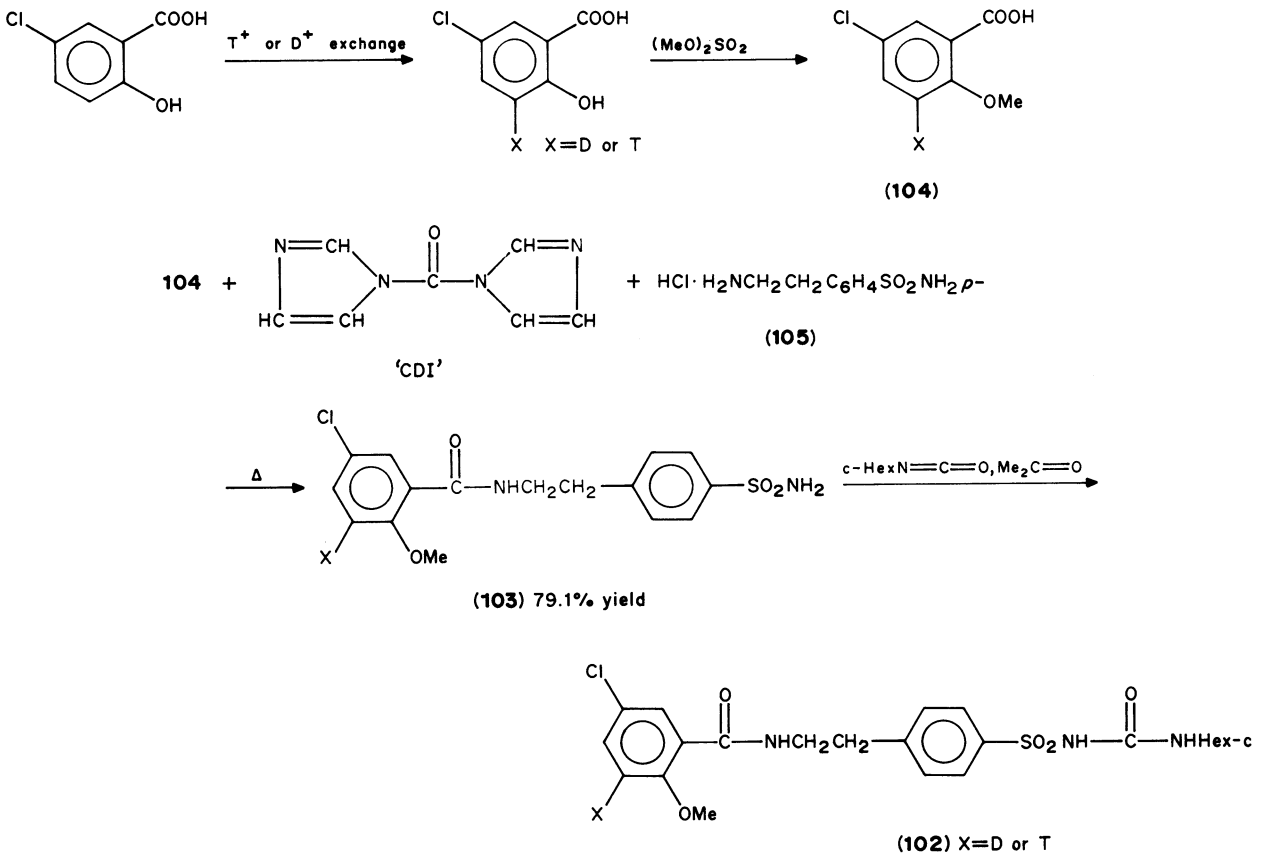
16. Synthesis of carbon-14 and tritium labelled glyburide

N-{4-[2-(5-chloro-2-methoxybenzamido)ethyl]phenylsulphonyl}-N'-cyclohexylurea (**102**), a potent oral hypoglycemic agent, has been labelled[74] with tritium and deuterium in the C_3 position of the 5-chloro-3-methoxybenzoyl portion of the molecule and with carbon-14 in the C_2 position of the 2-phenylethylamine moiety of compound **102** in the sequence of reactions shown in equations 43 and 44.

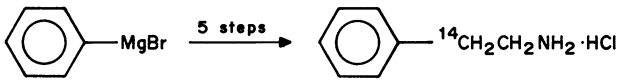
a. 4-[2-(5-chloro-2-methoxy-3-tritiobenzamide)ethyl]benzenesulphonamide (**103**) was obtained (equation 43) by reacting **104** with carbonyl diimidazole ('CDI') and treating the reaction mixture with 4-(2-aminoethyl)benzenesulphonamide hydrochloride (**105**). The isolated product **103** had m.p. 210–213 °C and specific activity 8.21 mCi/mmol. **103** reacted with cyclohexylisocyanate in acetone yielding **102** (m.p. 171–173.5 °C, sp. act. 8.50 mCi/mmol).

b. 2-Phenylethylamine-2-^{14}C hydrochloride (**106**-^{14}C) has been obtained from 150 mCi of $Ba^{14}CO_3$ by synthesizing benzoic acid (carboxyl-^{14}C), reducing it with $LiAlH_4$ to benzyl alcohol-α-^{14}C which, in turn, was converted to benzyl bromide-α-^{14}C. Treatment of the bromide with KCN yielded phenylacetonitrile-2-^{14}C, which by diborane reduction gave **106**.

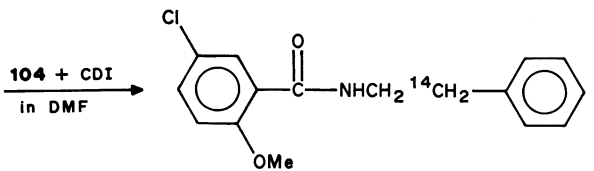
N-(5 chloro-2-methoxybenzoyl)-2-phenylethylamine-2-^{14}C (**107**) was prepared by reacting non-labelled **104** with CDI in DMF and treating directly the reaction mixture with **106**. Subsequent chlorosulphonation and sulphonamide formation gave (5-chloro-2-methoxybenzamido)ethyl-1-^{14}C benzenesulphonamide (**103**-^{14}C), which after condensation with cyclohexyl isocyanate yielded the carbon-14 labelled, radiochemically pure glyburide (**102**-^{14}C).


Cl
COOH
OH
T+ or D+ exchange
X X=D or T
(MeO)2SO2
OMe
(104)
104 +
N=CH
CH=N
HC=CH
CH=CH
'CDI'
+ HCl·H2NCH2CH2C6H4SO2NH2 p-
(105)
Δ
NHCH2CH2
SO2NH2
c-HexN=C=O, Me2C=O
(103) 79.1% yield
SO2NH
NHHex-c
(102) X=D or T

(43)

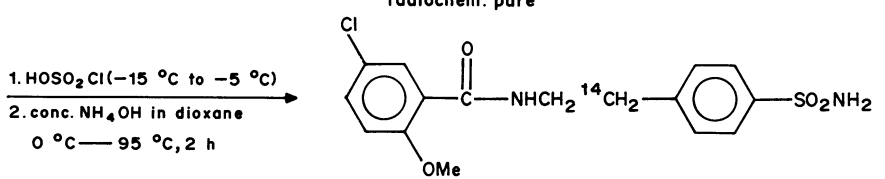


(106) sp. act. 3.28 mCi/mmol



(107) 97% yield

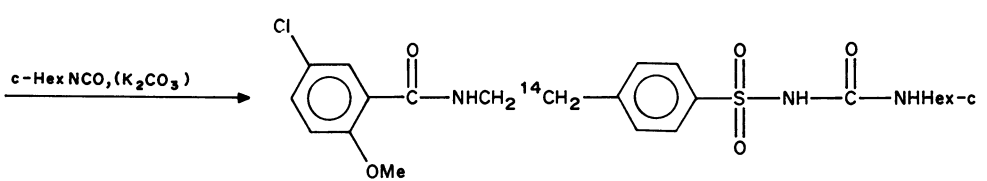
radiochem. pure



(44)

(103—^{14}C) 63.5% yield

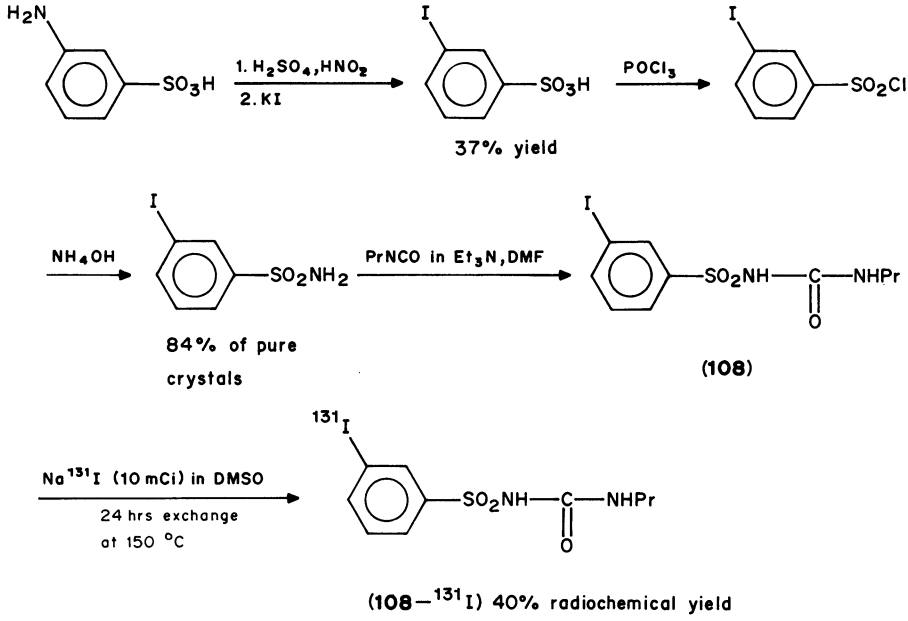
m.p. 211—213 °C, sp. act. 3.27 mCi/mmol



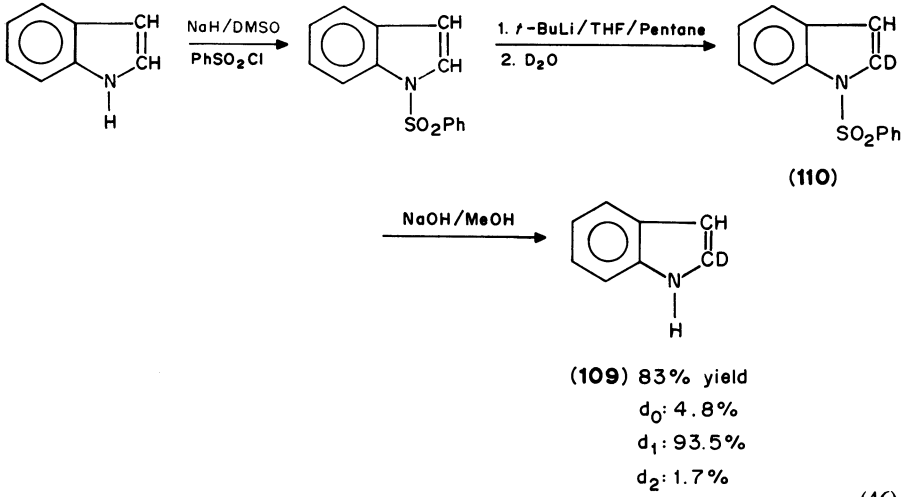
(102—^{14}C) 60.2% yield, sp. act. 3.66 mCi/mmol

17. Synthesis of N-3-iodo (^{131}I) benzenesulphonyl-N'-propylurea

This compound also called *m*-Iodopropamid (**108**), has been synthesized[75] according to equation 45 in order to investigate its stability and tissue distribution. **108**-^{131}I was found



(45)



(46)

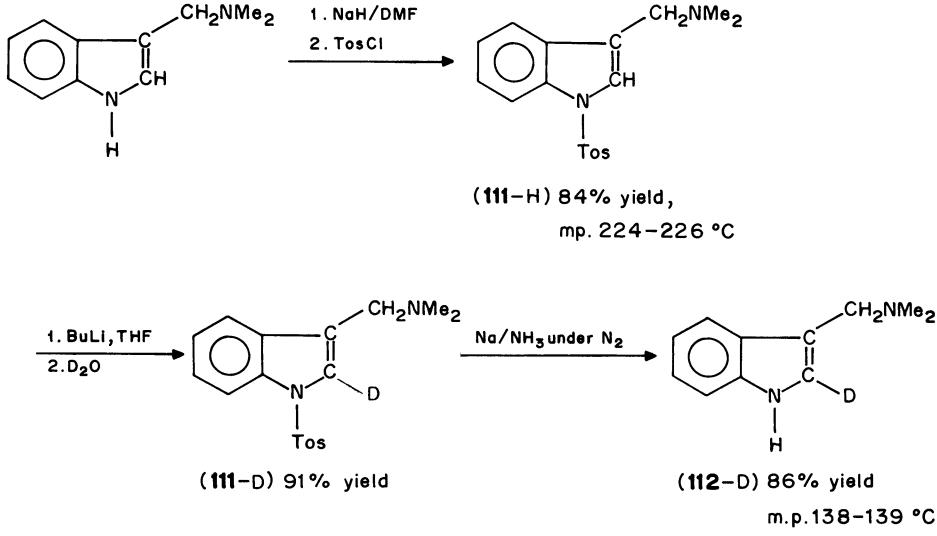
to be chemically stable and undergoes much less *in vivo* de-iodination than the *p*-isomer, but its concentration in the pancreas is, contrary to expectations, not significant but it concentrates mainly in the blood, intestines and in the liver.

18. Synthesis of (2-D)indole

By exploring different exchange[76] and chemical methods of synthesis of biologically active indoles labelled with deuterium in different positions of the pyrrole moiety and of the benzene ring, indole-(2-D), **109**, has been prepared[77] according to equation 46, which involves deuterium-labelled *N*-benzenesulphonyl-indole-2-D (**110**) as an intermediate[78].

19. Synthesis of 1-(o-toluenesulphonyl)-3-(dimethylaminomethyl) indole-2-D

This compound, **111**-D, has been synthesized[79] in the course of preparation of deuterium-labelled 3-(dimethylaminomethyl)indole-2-D, **112**-D (equation 47), utilizing

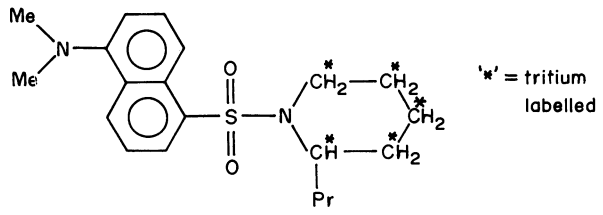


(47)

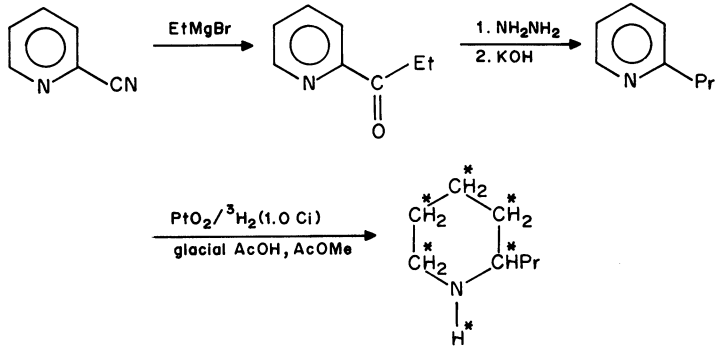
the blocking and activating properties of the *p*-toluenesulphonyl group[80]. Facile lithiation, deuteration and removal of the *p*-toluenesulphonyl group yielded product **112**-D containing more than 95% of deuterium in the 2-position. Tritium can be introduced into the 2-position of 3-substituted indoles in a similar manner.

20. Synthesis of tritium-labelled 1-N-dimethylaminonaphthalene-5-sulphonyl-d,l-coniine-^3H (Dns-coniine ^3H)

This compound, **113**, has been obtained[81] following the procedure of Seiler and Wiechmann[82], using *d*, *l*-coniine **114**. The latter was tritium-labelled in the ring by catalytic hydrogenation of 2-propylpyridine (equation 48)[83,84].



113

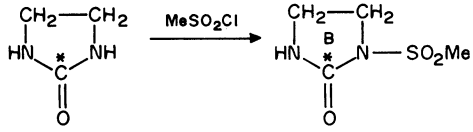


(48)

(114) 54% yield
sp. act. 385.0 mCi/mmol

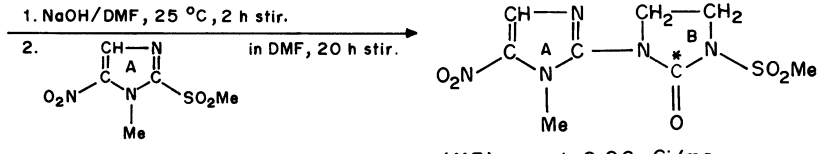
21. Synthesis of imidazolidinone-2-^{14}C, 'Go 10213'

a. Synthesis of ring B carbonyl-^{14}C. This compound **115**, has been synthesized[85] (equation 49) from 2-[^{14}C]-2-imidazolidinone (**116**) and methanesulphonyl chloride



(116)
'*' = position of ^{14}C label

(117) 6.92 mCi
60% yield



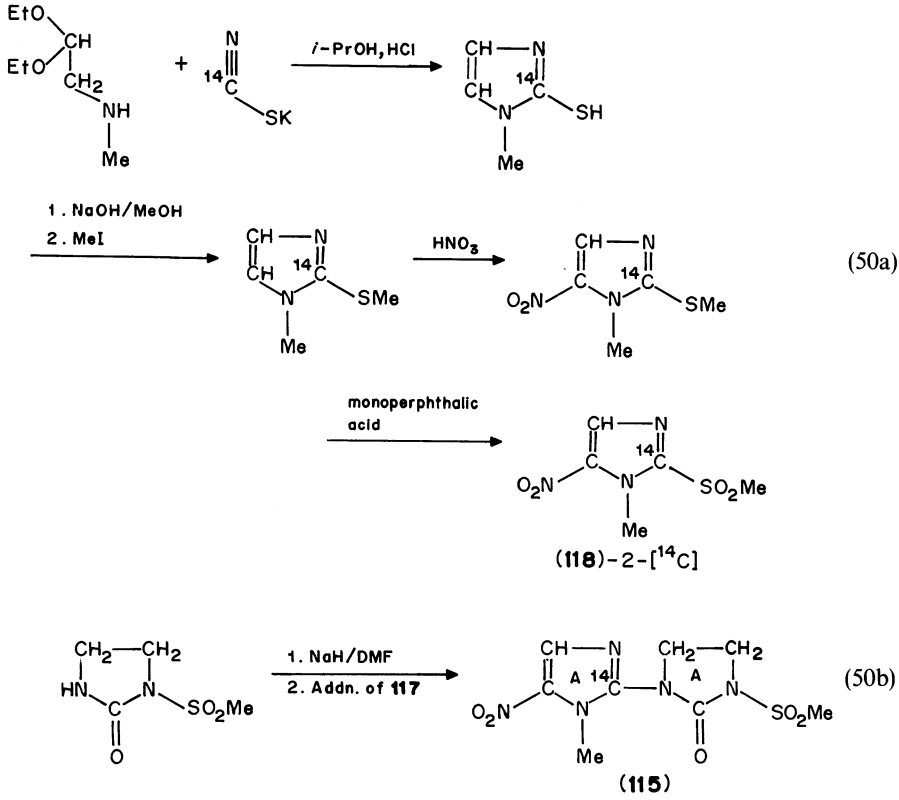
(118)

(115) sp. act. 6.06 μCi/mg
radiochem. purity>99%

(49)

which gave ^{14}C-*methanesulphonylethyleneurea*, [^{14}C] MSEU-**117**, sp. act. 10.84 μCi/mg in 60% yield. Condensation of the sodium salt of **117** with 2-methanesulphonyl-1-methyl-5-nitroimidazole **118** afforded pale yellow crystals of the imidazolidinone-2-^{14}C, Go 10213 (**115**), in 80.5% radiochemical yield.

b. Synthesis of ^{14}C*-labelled 1-methanesulphonyl-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-imidazolidinone.* The compound, antiamoebic-antitrichomonal agent Go 10213, **115**, has been labelled[86] with ^{14}C at the 2-position of the 5-nitroimidazole ring for pharmacokinetic and metabolism studies following the synthetic sequence in equations 50a and b. Starting with a mixture of potassium [^{14}C]thiocyanate (10 mCi, sp.



(50a)

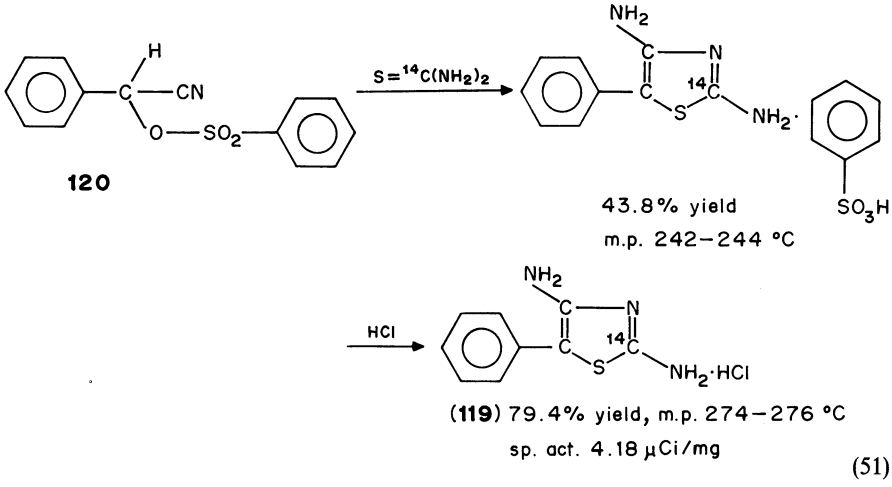
(50b)

act. 2.8 mCi/mmol) with inactive potassium thiocyanate the labelled [2-^{14}]-Go 10213 was obtained in 22% overall yield, sp. act. 1.34 mCi/mmol, radiochem. purity > 99%, m.p. 186–187 °C (equation 50b).

22. Synthesis of ^{14}C*-labelled 2,4-diamino-5-phenylthiazole hydrochloride ('amiphenazole',* ***119****)*

In the course of synthesis of compound **119**[87] possessing analeptic properties and used in the management of respiratory depression caused by narcotic analgesics[88] the

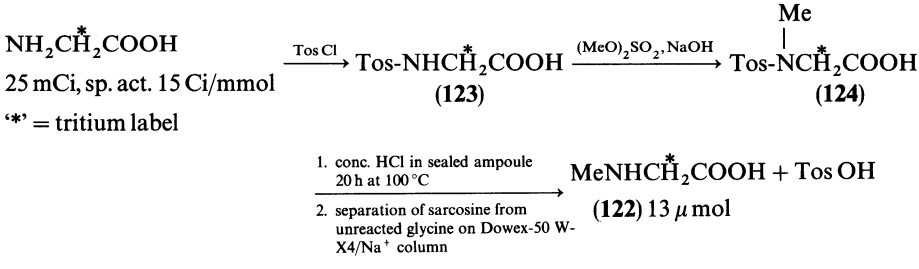
benzenesulphonate salt of **119** was obtained by condensng α-benzenesulphonylbenzyl cyanide **120** with ^{14}C-thiourea. **119** was obtained in 34.5% overall yield and 32.8% radiochemical yield. Using ^{35}S-thiourea in the reaction scheme in equation 51, the ^{35}S label can be introduced into **119**.



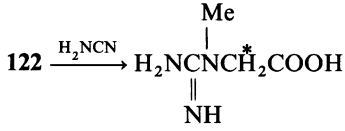
(51)

23. Synthesis of [2-^{3}H]creatine

Tritium-labelled creatine **121** with high specific activity, 309 mCi/mmol, needed to investigate its transport into the cells from the extracellular medium and for biological interactions, has been synthesized[89,90] according to equations 52a and b using



(52a)



(52b)

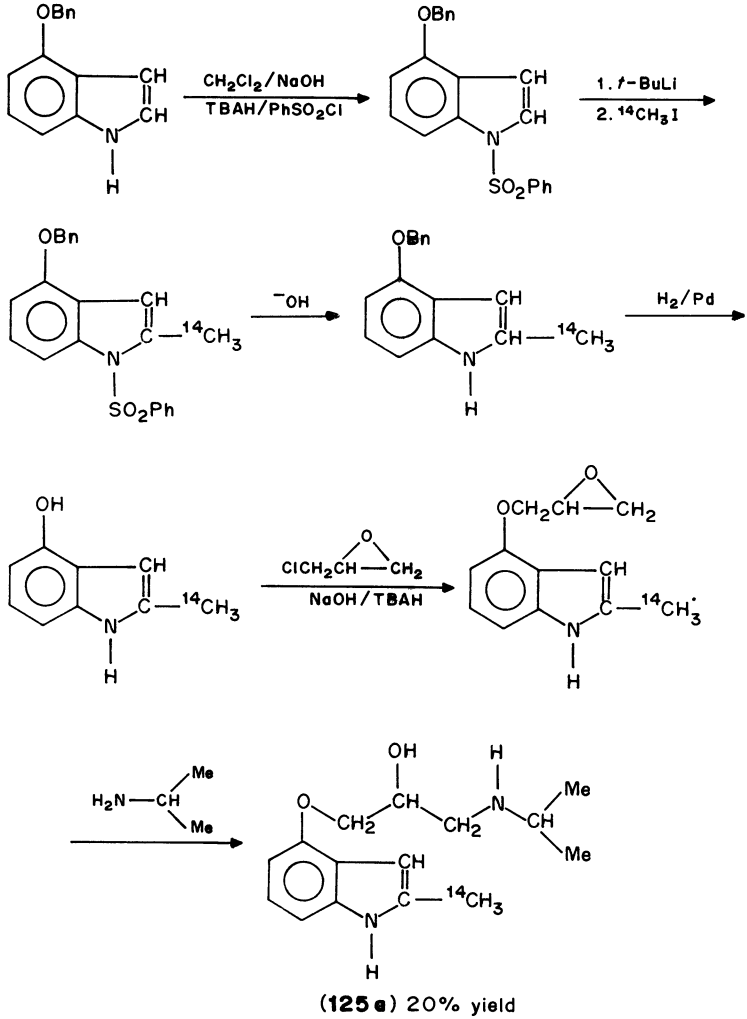
(121)

10% yield, 100% radiochem. purity, sp. act. $2.5 \cdot 10^8$ cpm μmol

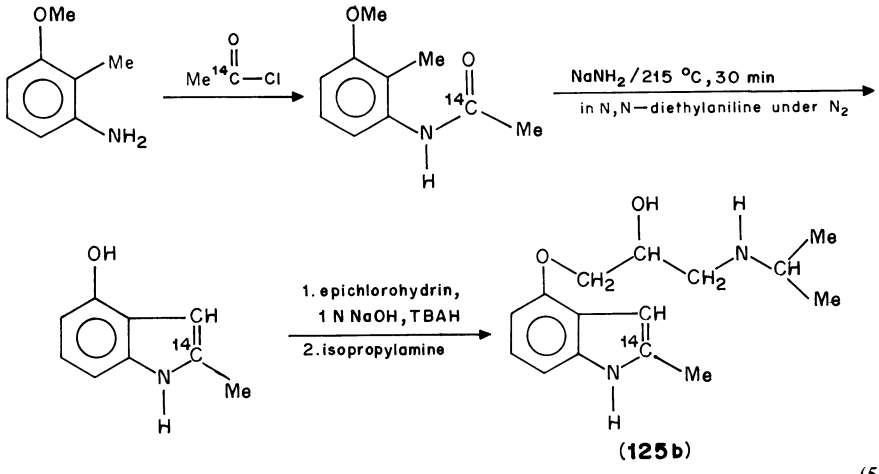
[2-^{3}H]sarcosine **122** and tritium-labelled sulphonic acid derivatives **123** and **124** as the intermediate compounds.

24. Synthesis of 2-[^{14}C]methyl mapindolol

4-(2-Hydroxy-3-isopropylaminopropoxy)-2-[^{14}C]methyl indolesulphate, **125a**, a potent β-adrenoceptor blocking agent with antihypertensive mode of action, needed for pharmacological studies, has been prepared according to the reaction scheme in equation 53, where benzenesulphonyl chloride is used to protect the nitrogen in the course of the selective lithiation and methylation of the indole at carbon-2 with ^{14}C methyl iodide[91]. In the case of the (2-^{14}C) product **125b**, which was obtained in 69% yield according to equation 54, the specific activity was 2.06 GBq(55.8 mCi) per mmol and the radiochemical purity was 97.9%.



(53)



(54)

25. Synthetic application of p-*toluenesulphon-di[*^{14}*C]alkylamides*

These compounds, **126** and **127**, were found to be stable and very suitable as intermediates for the synthesis of ^{14}C dialkylamines (equations 55 and 56)[92].

$$\mathrm{TosNH_2} \xrightarrow{2\mathrm{R\overset{*}{I}}} \mathrm{TosN\overset{*}{R}_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{HX}} \mathrm{HN\overset{*}{R}_2} \qquad (55)$$

(126)

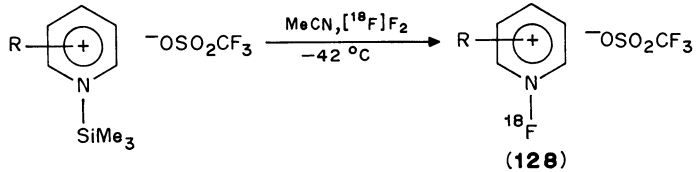
$$\mathrm{R^* = {}^{14}CH_2R \text{ or } CH_2{}^{14}CH_2R}$$

$$\mathrm{TosNHR^1} \xrightarrow{\mathrm{\overset{*}{R}^2I}} \mathrm{TosNR^1\overset{*}{R}^2} \xrightarrow[\mathrm{H_2O}]{\mathrm{HX}} \mathrm{HNR^1\overset{*}{R}^2} \qquad (56)$$

(127)

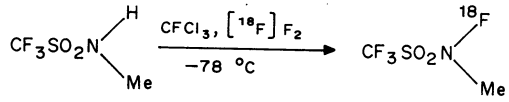
26. Synthesis of ^{18}*F-labelled* N-*fluoro compounds as electrophilic labelling reagents*

The new [^{18}F]>N—F labelling reagents, namely *N*-fluoropyridinium triflates (**128**), *N*-fluoro-*N*-methyl trifluoromethanesulphonamide (**129**), *N*-fluoro-*N*-ethylperfluorooctanesulphonamide, *N*-fluoro-*N*-methyltoluenesulphonamide (**130**, **131**) and *N*-fluorobis(trifluoromethanesulphone)imide (**132**), have been prepared in moderate to good yields by treating various >NR(R = H, $SiMe_3$) compounds with molecular [^{18}F]F_2 in the micro-scale (50–500 μM) diluted to 1–2% with neon (equations 57–61)[93]. The [^{18}F]F_2 has been produced in the ^{20}Ne(d,α)^{18}F nuclear reaction. $2.96 \cdot 10^9$ Bq of ^{18}F were diluted with $4 \cdot 10^{-4}$ M F_2 in a typical run. The substrate to [^{18}F]F_2 ratio was about 0.75–0.9. The radioactive gas mixture was bubbled through a solution of the substrate.



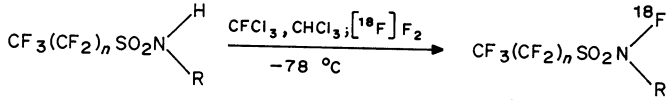
(57)

R=H; F; 2,4,6-Me_3; 3,5-Cl_2



(58)

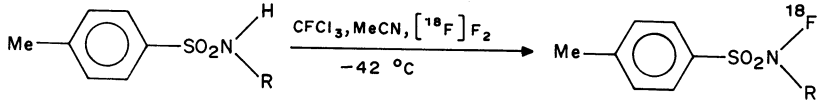
(129)



n=3, R=Me; n=7 R=Et

(59)

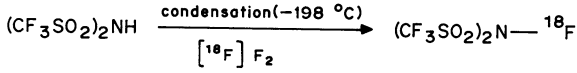
(130)



R=Me, Pr, $CH_2CH_2CHMe_2$, c-Hex

(131)

(60)

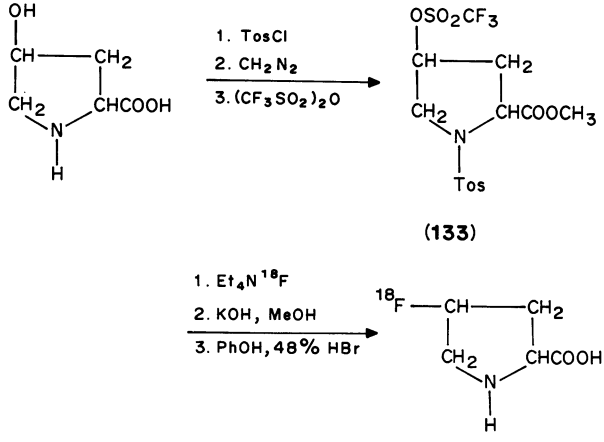


(61)

(132)

27. Synthesis of N-*tosyl*-O-*trifluoromethanesulphonyl*-L-*4-hydroxypyroline methyl ester (**133**)*

Triflate **133** has been used[94] in the course of the synthesis of 4-[^{18}F]fluoroproline **134** according to the reaction scheme in equation 62. Positron-emitting [^{18}F]fluorine ($t_{1/2}$ = 109.7 min), a very attractive isotope used for labelling radiopharmaceuticals, has been



(133)

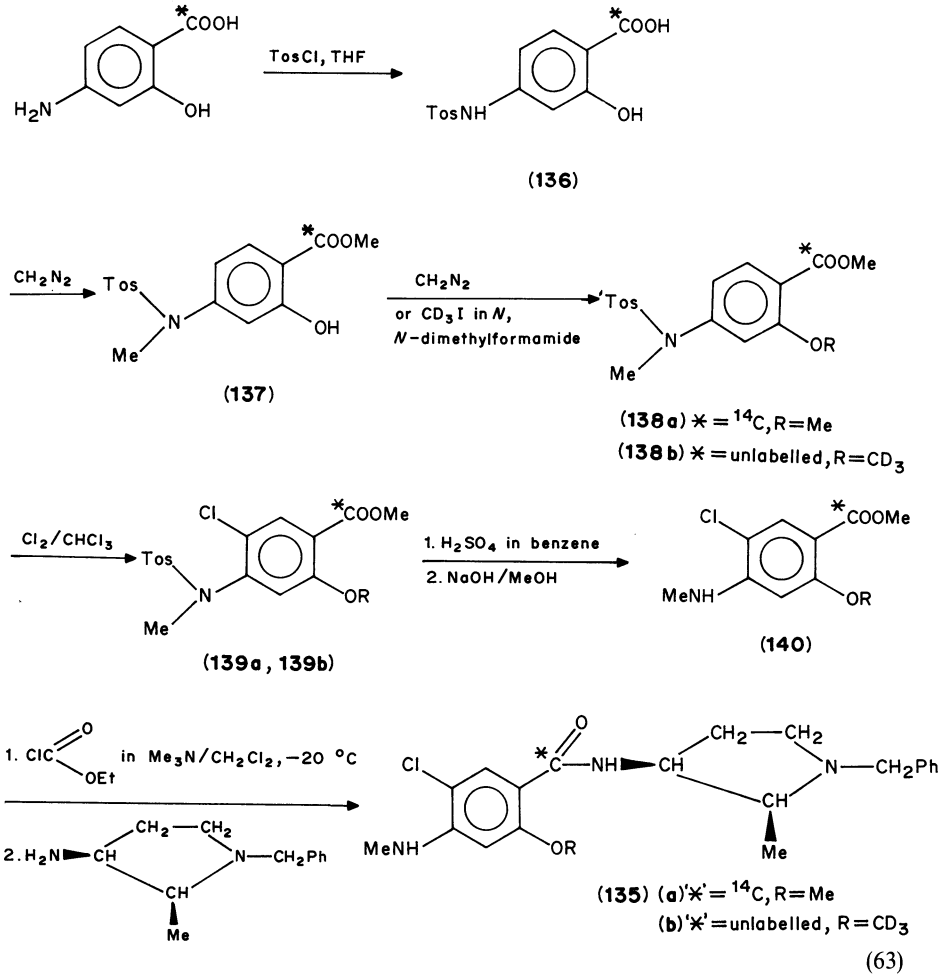
(62)

(134)

produced by irradiating Li_2CO_3 in quartz ampoules for 20 min with 5.10^{13}n $cm^{-2}s^{-1}$ thermal neutron flux in a nuclear reactor and applied for the preparation of $Et_4N^{18}F$[95,96].

28. *Synthesis of ^{14}C and deuterium-labelled YM-09151-2*

In the course of synthesis of ^{14}C and deuterium-labelled *N*-[(2*RS*, 3*RS*)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-(methylamino)benzamide (**135**), a potent drug in the treatment of psychosis, the following ^{14}C- and deuterium-labelled[97] tosylamide derivatives have been prepared (equation 63): 2-hydroxy-4-tosylamido-carbonyl-^{14}C benzoic acid (**136**); methyl 2-hydroxy-4-(*N*-methyl-*N*-tosylamido)benzoate (**137**); methyl 2-methoxy-4-(*N*-methyl-*N*-tosylamido)[carbonyl-^{14}C]benzoate (**138a**); methyl 2-(methoxy-d_3)-4-(*N*-methyl-*N*-tosylamido)benzoate (**138b**) and methyl 5-chloro-2-methoxy-4-(*N*-methyl-*N*-tosylamido)[carbonyl-^{14}C]benzoate (**139a**) as well as the 2-(methoxy-d_3) compound (**139b**). The overall radiochemical yield of **135a** in the six-step



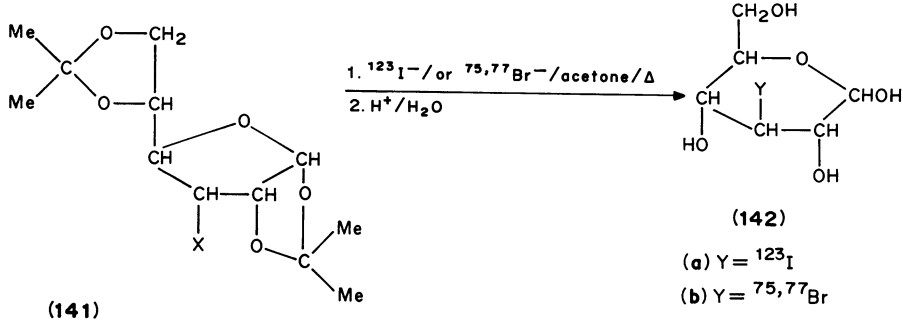
(63)

synthesis was 79.1%, sp. act. 21.18 mCi/mmol. **135b** has been prepared in 60.8% overall yield calculated on the basis of iodomethane-d_3, as also shown in equation 63.

D. Synthesis of Isotopically Labelled Sulphonate Esters and Sulphates

1. Synthesis of D-*glucose derivatives labelled with positron emitters* $^{75,77}Br$ *and with a single photon emitter* ^{123}I

1,2:5,6-Di-isopropylidene-3-tosyloxy-D-allose (**141a**) and 1,2:5,6-di-isopropylidene-3-trifluoromethanesulphonyloxy-D-allose (**141b**) have been synthesized[98a] and applied for fast preparation of D-glucose derivatives **142a,b** labelled with isotopes[98b–f] prepared in cyclotrones, such as ^{75}Br ($t_{1/2} = 101$ min), ^{77}Br ($t_{1/2} = 57$h) and ^{123}I ($t_{1/2} = 13.3$ h). These isotopes are easier to handle chemically than ^{18}F ($t_{1/2} = 109.7$ min) and ^{11}C ($t_{1/2} = 20.3$ min), which are suitable only for use in institutions having their own cyclotron. The tosylate **141a** used in the reaction scheme shown in equation 64 has been prepared in 80% yield (m.p. 113 °C) from 1,2:5,6-di-isopropylidene-D-allose and *p*-toluenesulphonyl chloride. The triflate **141b**, possessing a better leaving group X, has been prepared in 60% yield from trifluoromethanesulphonic anhydride and the same allose but it had to be stored at −20 °C, since it is not stable at RT. Removal of the sulphonate groups and halogenation afforded the radioactive [^{123}I]-3-deoxy-3-iodo-D-glucose (**142a**) and [^{75,77}Br]-3-deoxy-3-bromo-D-glucose (**142b**) in 73% (1.6 mCi) and 68% (1.1 mCi) radiochemical yields, respectively. The derivatives **142a,b** have been applied for studies in biodistribution and regional glucose metabolism in the brain and in the heart of mammals using positron emission computed tomography (PECT) and single photon emission computed tomography (SPECT)[102,103]. Only D-glucose and some of its analogues are unidirectionally transported by the hexose carrier at the blood-brain barrier (BBB).

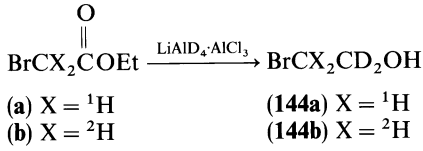


(64)

2. Synthesis of 2-bromo[1,1-$^2H_2$*]ethanol 4-methylbenzenesulphonate (**143a**) and 2-bromo[1,1,2,2-*$^2H_4$*]ethanol 4-methylbenzenesulphonate (**143b**)*

Both these compounds, **143a** and **b**, needed to investigate the mechanism of biosynthesis of the plant growth hormone ethylene, have been prepared according to the reaction scheme in equation 65[99]. **144a** and **b** have been prepared by reduction of unlabelled or deuterated ethyl bromoacetate with lithium aluminium deuteride–anhydrous aluminium chloride. Subsequently, **143a** and **143b** have been synthesized with 4-methylbenzene-

sulphonyl chloride. **143**, on reaction with ethyl isocyanoacetate and sodium hydride, gave deuterium-labelled 1-aminocyclopropane-1-carboxylic acid, which was utilized to study the ^{1}H- and ^{13}C-NMR spectra of its different derivatives.



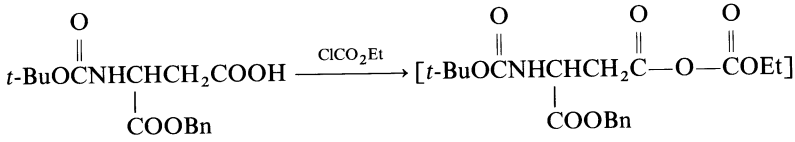
(**a**) X = ^{1}H (**144a**) X = ^{1}H
(**b**) X = ^{2}H (**144b**) X = ^{2}H

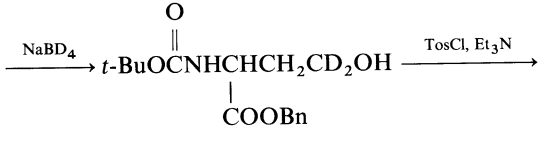
(65)

(**143**) (**a**) X = ^{1}H
(**b**) X = ^{2}H
(90–93% yield, m.p. 11.8 °C for **143a**)

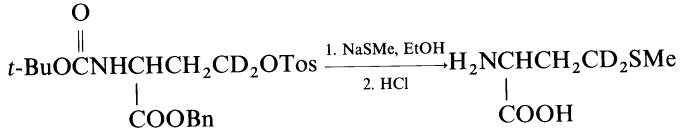
3. *Synthesis of* L-*[4,4-$^{2}H_2$]methionine*

The deuterium-labelled tosylate **145** has been isolated as a clear viscous oil in the course of synthesis of L-[4,4-$^{2}H_2$]methionine **146** (equation 66) starting with *N*-*t*-BOC-L-





(**147**)



(**145**) 84% yield

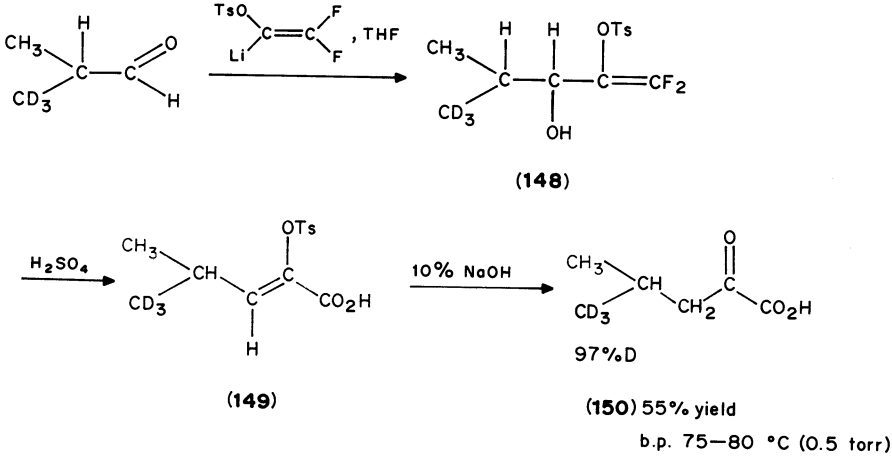
(**146**)
70% yield, m.p. 275–277 °C

(66)

aspartic acid α-benzyl ester and using $NaBD_4$ as a source of deuterium[100]. The final product **146** has been utilized to study the mechanism of biosynthesis of 1-amino-cyclopropane-1-carboxylic acid[99] and other natural products.

4. Synthesis of stable isotope labelled α-ketoacids

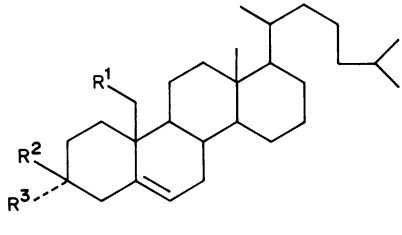
The deuterated unsaturated tosyloxy carbinol **148** and the unsaturated tosyloxy acid **149** have been involved[101,102] in the synthetic scheme (shown in equation 67) to produce 4-[D_3]methyl-2-oxopentanoic acid (α-ketoisocaproic acid), **150**, a compound of biomedical interest. [1-^{13}C]-4-methyl-2-oxopentanoate has also been produced in 45–60% yield to measure $^{13}CO_2$ in breath[101].



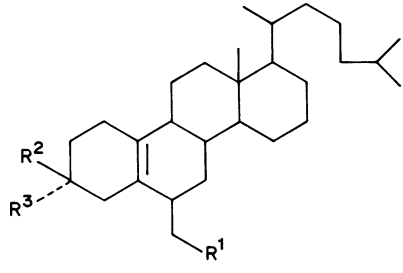
(67)

*5. Synthesis of 6β-[^{131}I]iodomethyl-19-norcholest-5(10)-en-3α-ol (**151**)*

This adrenal scanning agent has been synthesized[103] by homoallylic rearrangement of **152**, [^{131}I]-19-iodocholest-5-en-3α-ol. The synthesis involved treatment of the 19-



(**153**) R^1=OH, R^2=H, R^3=OAc
(**154**) R^1=OTs, R^2=H, R^3=OAc
(**155**) R^1=I, R^2=H, R^3=OAc
(**152**) R^1=I, R^2=H, R^3=OH

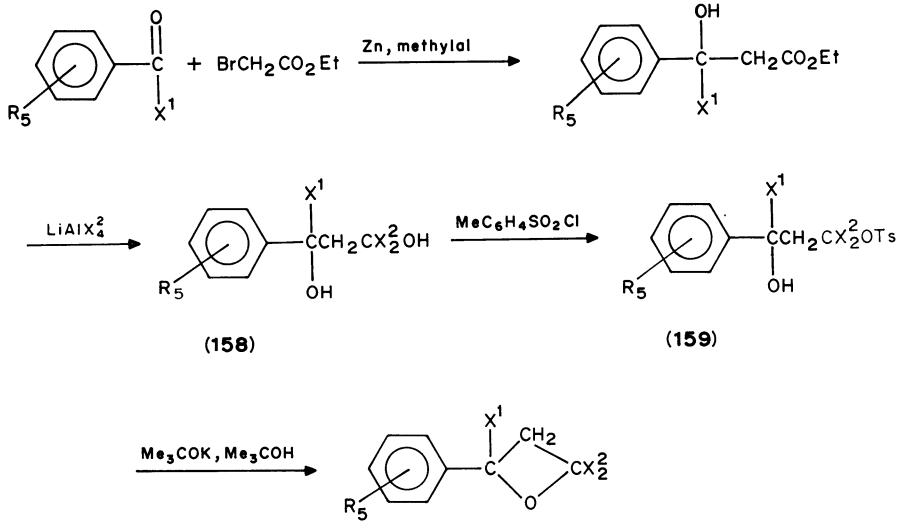


(**156**) R^1=I, R^2=H, R^3=OAc
(**151**) R^1=I, R^2=H, R^3=OH

hydroxy-3α-acetate (**153**) with *p*-toluenesulphonyl chloride, displacement of the tosylate **154** (obtained in 56% yield) by iodide leading to **155** and hydrolysis of the latter to yield the 19-iodo-3α-ol **152**. Subsequent reflux of **152** in acetonitrile yielded **151** in 52% overall yield from **155**. **152**-^{131}I and **151**-^{131}I were obtained from the non-labelled compounds with Na^{131}I.

6. *Syntheses of ^{13}C- and deuterium-labelled 2-phenyloxetanes*

Within the framework of studies of the mechanism of fragmentation of 2-phenyloxetane by electron bombardment in the ion source of a mass spectrometer 2-phenyloxetanes labelled with stable isotopes were needed[104]. 2-Phenyloxetanes, **157**, labelled with $^{2}_{1}$H (and ^{13}C) in different positions have been synthesized according to four-step reaction schemes shown in equations 68 and 69[105]. In the first step, isotopically (D- or ^{13}C) labelled benzaldehyde has been coupled with ethyl bromoacetate in the presence of Zn and dimethoxymethane. The deuterated 3-phenyl-3-hydroxypropionate obtained has been reduced with lithium aluminium hydride. In the next step the primary alcohol group of the deuterated phenyl propanediol **158** has been tosylated. Cyclization of the monotosylates **159** yielded ^{13}C- or deuterium-labelled 2-phenyloxe-oxtanes **157**.

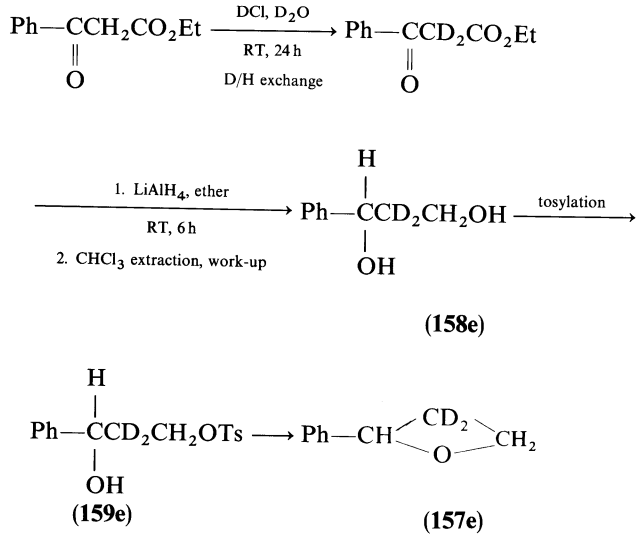


(158) (159)

(68)

The following deuterium-labelled monotosylates and oxetanes have been obtained: (**a**) R = D,X^1 = X^2 = H; (**b**) R = H,X^1 = D, X^2 = H; (**c**) R = X^1 = H, X^2 = D; (**d**) R = H, X^1 = O,X^2 = D. The 3,3-dideuterio-2-phenyloxetane (**157e**) has been prepared according to equation 68, but using the dideuterio derivative **158e**, which was then tosylated and cyclized to **157e** (equation 69).

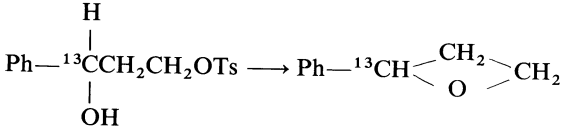
The [13C]-labelled phenyl-2 oxetane, **157f**-^{13}C, and its precursor **159f**-^{13}C have been



(158e) (69)

(159e) (157e)

also synthesized according to the reaction sequence in equation 68, but starting from ^{13}C-labelled benzaldehyde prepared in turn from ^{13}C-benzoic acid.



(159f–^{13}C) (157f–^{13}C)

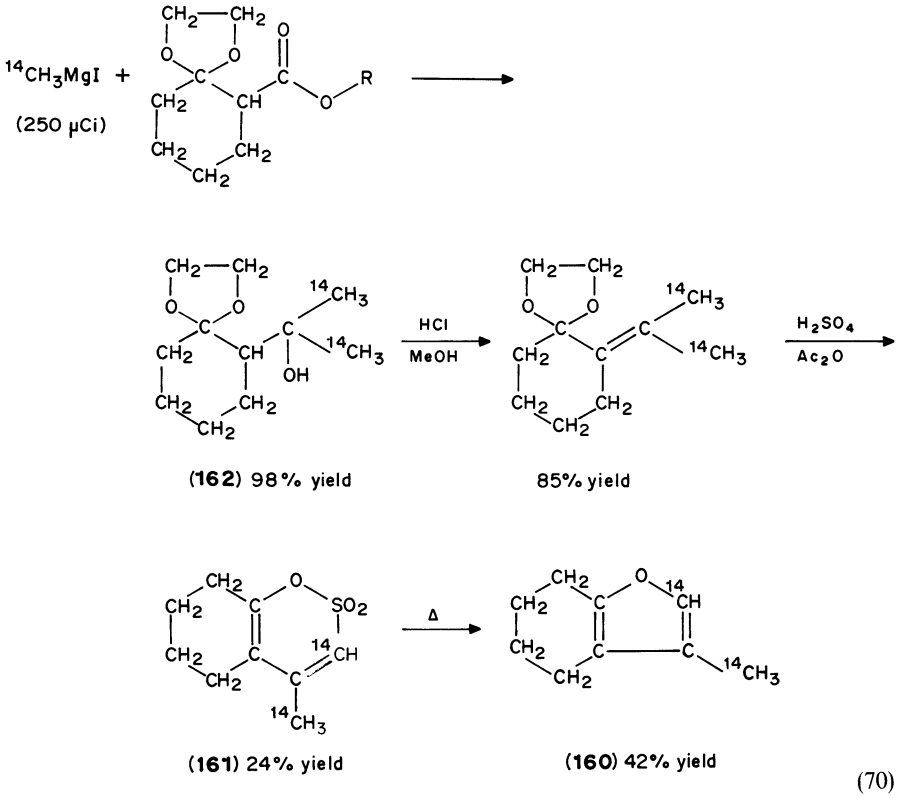
($^{13}C = 90.2\%$; $^{12}C = 9.8\%$)

7. *Synthesis of ^{14}C- and ^{13}C-labelled furan derivatives*

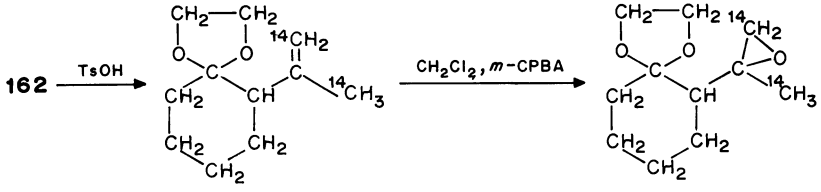
A facile synthetic scheme (equation 70) for preparation of radio-labelled 3-methyl-4,5,6,7-tetrahydrobenzofuran (**160**) has been elaborated[106] to help the identification of the products of metabolism of physiologically toxic furan derivatives[107,108]. It involves the preparation of the ^{14}C-labelled sulphonate **161** and its subsequent thermal decomposition in rather moderate yields. Much higher yields of **160** were obtained by treating the alcohol **162** with *p*-toluenesulphonic acid, epoxidation of the alkene **163** with *m*-chloroperbenzoic acid and cyclization of the epoxide intermediate **164** to furan **160** with excellent yield. This method can be applied equally well to the synthesis of ^{13}C-labelled 3-substituted furans using $^{13}CH_3I$ as the starting labelled compound (equation 71).

8. *Synthesis of deuterium enriched (+)-propoxyphene*

In the synthetic scheme (equation 72) leading to the production of [benzyl-d_7]-(+)-propoxyphene, (**164b**) and [*N*,*N*-dimethyl-d_6]-(+)-propoxyphene (**164c**), the *threo*-(+)-3-



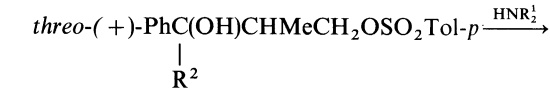
(70)



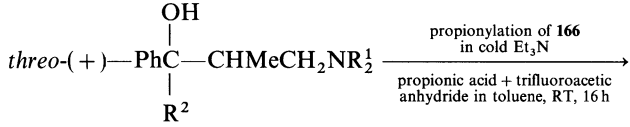
pentane, 2M HCl

160 83% yield
sp. act. 20.26 μCi/g
colourless liquid
b.p. 69–71 °C (10 mm)

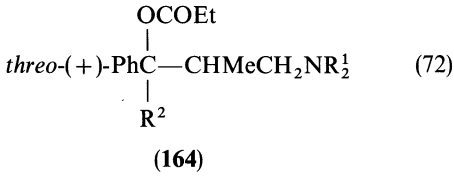
(71)



(165)



(166)



(164) (72)

Propionate (**a**) $R^1 = Me$, $R^2 = CH_2C_6H_5$
Propionate (**b**) $R^1 = Me$, $R^2 = CD_2C_6D_5$
Propionate (**c**) $R^1 = CD_3$, $R^2 = CH_2C_6H_5$

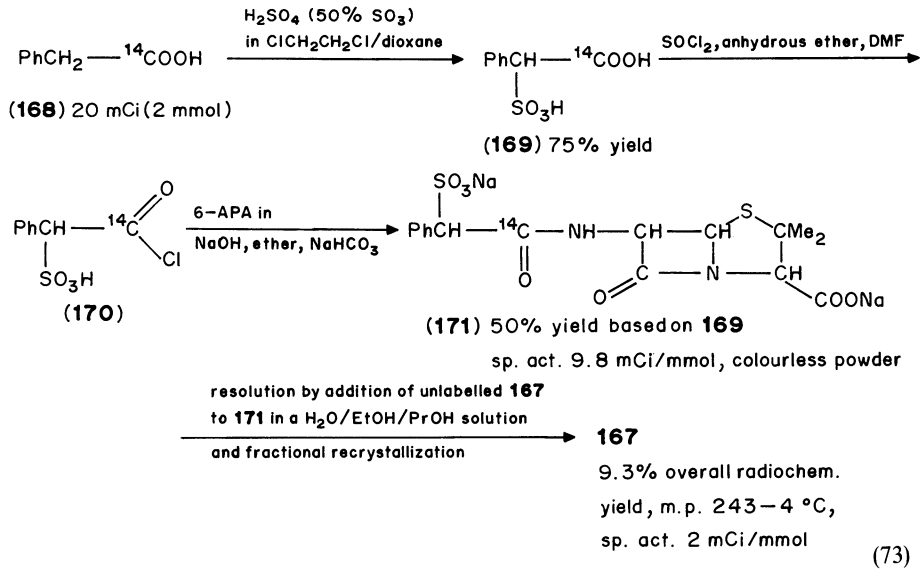
Propoxyphene is a widely used analgesic.

hydroxy-2-methyl-3,4-diphenyl-n-butyl *p*-toluenesulphonate **165** has been used as the starting compound[109].

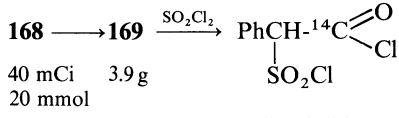
9. *Synthesis of sulphocillin-^{14}C and SP-421-^{3}H, ^{14}C*

Disodium D(−)-6-(2-phenyl-2-sulphoacetamido-1-^{14}C)penicillanate (**167**), a semi-synthetic penicillin showing a broad antibiotic spectrum against Gram-positive and negative bacteria, and which is more stable in aqueous solution than carbenicillin and relatively non-toxic, has been ^{14}C-labelled[110] according to the scheme in equation 73 by sulphonation of phenylacetic acid-1-^{14}C (**168**), converting the product to 2-phenyl-2-sulphoacetyl chloride-1-^{14}C (**170**), reacting the latter with 6-aminopenicillanic acid (6-APA). The final step was separation of the diastereoisomeric mixture of 6-(2-phenyl-2-sulphoacetamido-1-^{14}C) penicillanate (**171**) by fractional crystallization into two isomers.

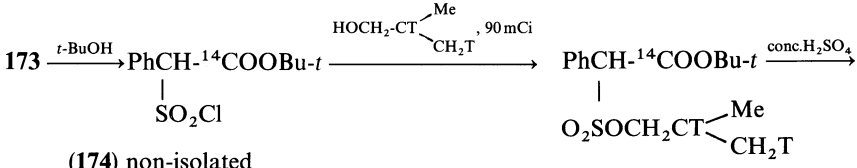
Doubly labelled (^{3}H and ^{14}C), **172**, 6-(2-isobutyl-β,γ-$^{3}H_2$-sulpho-2-phenyl-acetamido-1-^{14}C) penicillanic acid, was synthesized as shown in equation 74. 2-Chlorosulphonyl-2-phenylacetyl chloride-1-^{14}C (**173**) was obtained from **169** with thionyl chloride. Selective esterification of **173** with an equimolar amount of *t*-butanol at low temperature in the presence of pyridine gave the ester **174**. Subsequent esterification of **174** with isobutanol-2,3-$^{3}H_2$ produced *t*-butyl 2-isobutyl-β,γ-$^{3}H_2$-sulpho-2-phenylacetate-1-^{14}C (**175**). Cleavage of the *t*-butyl group in **175** afforded 2-isobutyl-β,γ-$^{3}H_2$-sulpho-2-phenylacetic acid-1-^{14}C (**176**). The latter was converted into the corresponding acetyl chloride-1-^{14}C (**177**) and condensed with trimethylsilyl 6-aminopenicillanate (6-APA-$SiMe_3$). This gave the final product **172** in 34% yield based on isobutanol-2,3-$^{3}H_2$ and 17% yield based on **168**, with specific activity 9 mCi/MMol (^{3}H) and 2 mCi/mmol (^{14}C) and 98% purity, as found by radiochromatography and by the isotope dilution method.



(73)

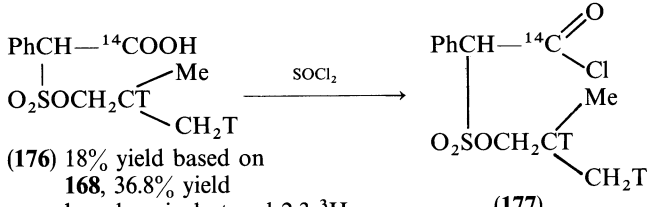


(173) 3.17 g, 63% yield based on **168**



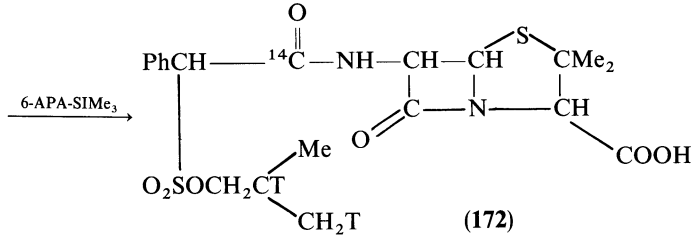
(174) non-isolated

(175) 36% yield based on **168**



(176) 18% yield based on **168**, 36.8% yield based on isobutanol-2,3-$^3H_2$

(177)

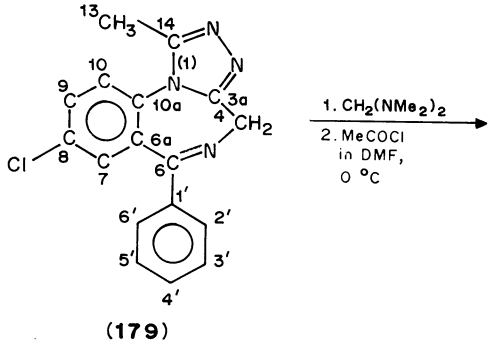


(172)

(74)

*10. Synthesis of ^{13}C- and ^{14}C-labelled 'Alprazolam', 8-chloro-1-(2-dimethylamino)-ethyl-6-phenyl-4H-S-triazolo [4,3-a] [1,4] benzodiazepine (**178**) and of its tosylate (**178** los OH)*

Compound **178**, 'Alprazolam', considered as an agent of possible clinical interest, has been ^{14}C and ^{13}C-labelled for biotransformations in test animals and man using $CH_3{}^{14}COOH$ and $^{13}CH_3COOH$ as starting isotopic molecules. The metabolites of **178** retain the intact triazolo ring[111]. [1-^{14}C]acetic acid was used to introduce the ^{14}C label into the $C_{(1)}$ triazole ring position and [2-^{13}C]acetic acid to introduce ^{13}C into the side-chain to distinguish the two side-chain methylene carbons by ^{13}C NMR and follow their metabolic fate. The tosylate of **178** has been obtained[112] in the last step (equation 75) by treating ^{14}C or ^{13}C-labelled **179** with an excess of bis(dimethylamino)methane and acetyl chloride and subsequent treatment of the purified free base **178** with *p*-toluenesulphonic acid. The yield of **178**-^{13}C was 67.5%.



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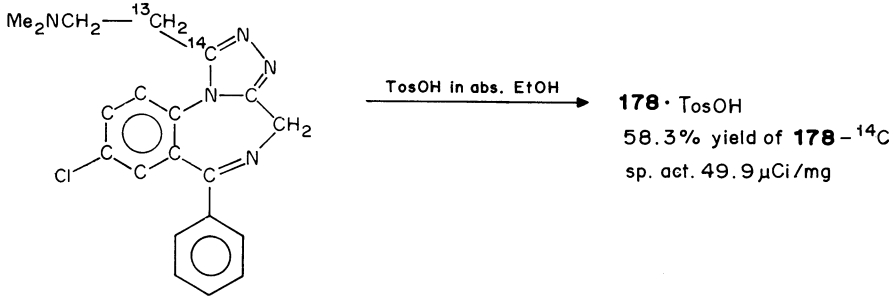


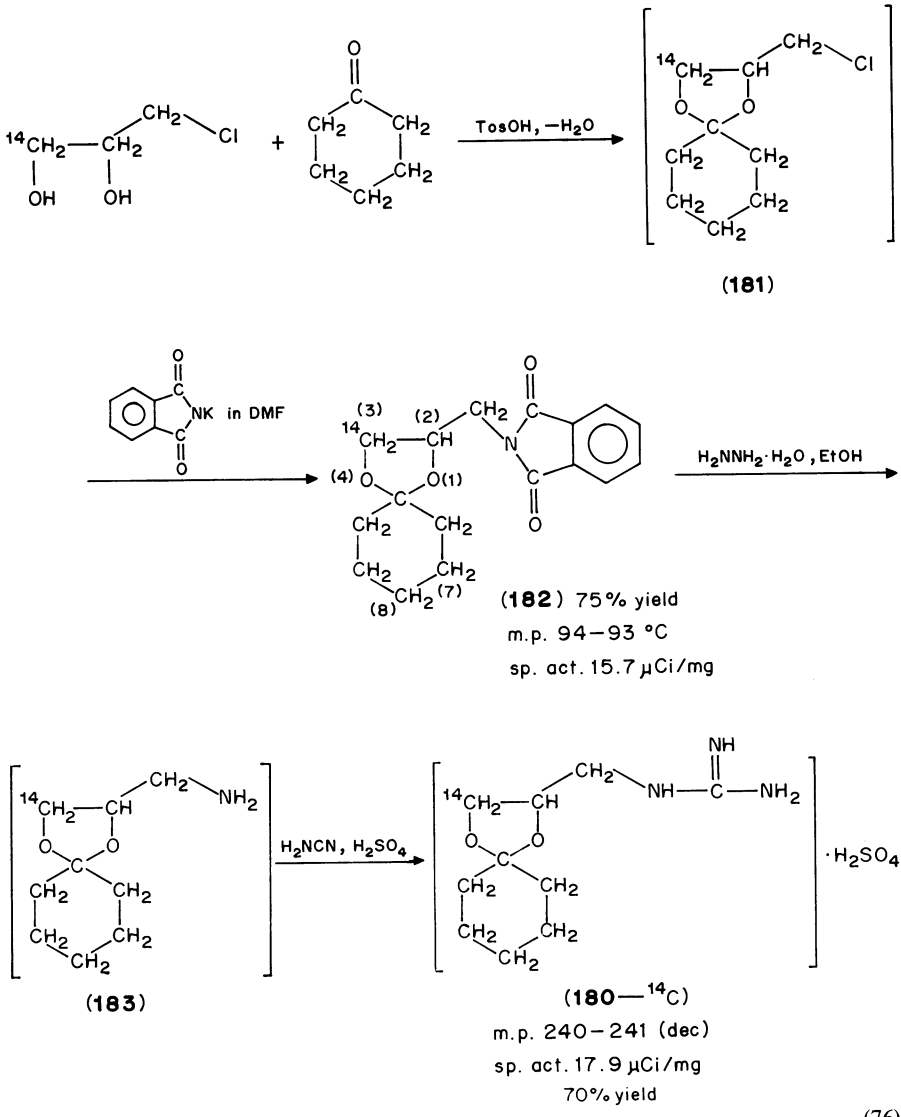
(178)

(75)

11. Synthesis of ^{14}C- and tritium-labelled guanadrel sulphate

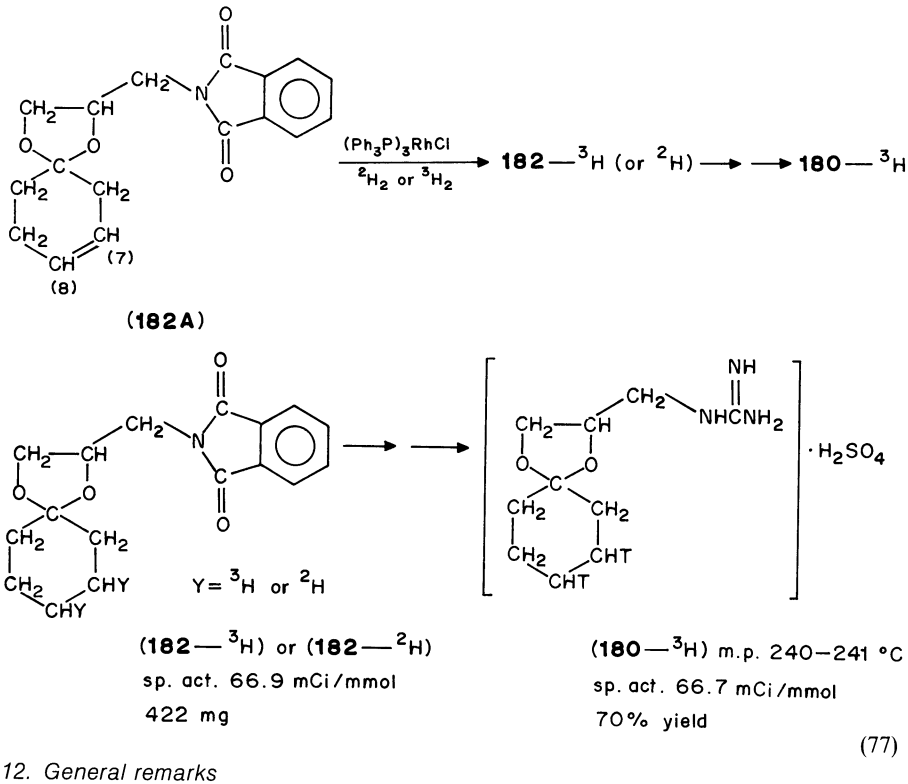
This compound, **180**, an antihypertensive drug of clinical utility, has been labelled with carbon-14 in the propanediol[113] portion of the molecule and with tritium in the cyclohexanone portion of **180** to enable the investigation of metabolic transformations of both labelled fragments in test animals and man. (1,4-Dioxa[3-^{14}C]spiro[4,5]dec-2-ylmethyl)guanidine sulphate[113] (**180**-^{14}C) has been prepared in the four-step reaction

sequence shown in equation 76 involving 2-phthalimidomethyl-1,4-dioxa[3-^{14}C]spiro[4,5]decane (**182**). The phthalimido group of the latter has been removed and the amine **183** obtained yielded with cyanamide the ^{14}C-labelled guanadrel sulphate **180**-^{14}C.



(76)

Tritium has been introduced into non-labile 3- and 4- positions[113] of the cyclohexanone ring by reducing with tritium gas the double bond of the intermediate **182A**, obtained from 1,4-dihydroxycyclohexane, and converting **182**-^{3}H into (1,4-dioxa[7,8-^{3}H]spiro[4,5]dec-2-ylmethyl)guanidine sulphate (**180**-^{3}H); see equations 76 and 77.



(77)

12. General remarks

The examples presented in Sections IA–ID clearly demonstrate the general utility of sulphonic acid derivatives in the syntheses of isotopically labelled compounds. Sulphonate esters possessing the excellent anionic leaving sulphonate group are especially useful. Numerous labelled sulphonic acid derivatives have been directly applied to solve scientific, industrial and medical problems. The kinetic deuterium and tritium isotope effects, which limit to a certain degree the tracer applications of deuterium- and tritium-labelled sulphonic acid derivatives, are discussed in Section III.

II. BIOCHEMICAL SYNTHESES AND APPLICATIONS OF LABELLED SULPHONIC ACID DERIVATIVES

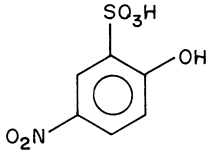
A. Biochemical Studies with ^{35}S-labelled Sulphates

Sulphur-containing compounds play a crucial role in the functioning of all living organisms. The transport of the simple ^{35}S-labelled sulphates and their utilization by animals are discussed in this section.

1. Investigation of the contraluminal sulphate transport in the proximal tubule of rat kidney

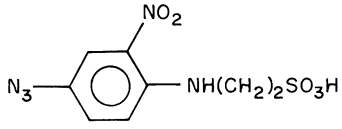
The effect of various sulphate esters and sulphonate compounds on the 4-second contraluminal $^{35}SO_4^{2-}$ influx into renal cortical tubular cells has been investigated[114a]

and it has been found that only sulphate monoesters, possessing one negative charge remaining on the sulphate, but not sulphate diesters, interact with the sulphate counter transport system,[114b] inhibiting $^{35}SO_4^{-2}$ influx. Sulphonate compounds interact with the contraluminal sulphate carrier if they contain OH or NH groups, as in **184–186**, in the close vicinity, participating in hydrogen bond formation with the sulphate carrier.



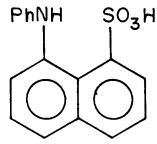
(184)

2-hydroxy-5-nitro-benzenesulphonic acid



(185)

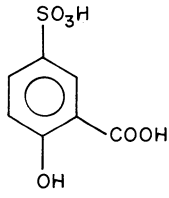
N-(4-azido-2-nitrophenyl)-2-aminoethane-1-sulphonic acid



(186)

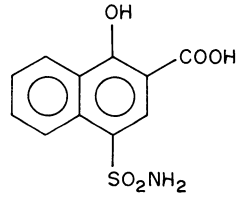
8-anilinonaphthalene 1-sulphonic acid

The effect of di- and tricarboxylates, disulphonates and of compounds which have both a carboxy- and a sulphonate group, on the contraluminal sulphate transport system has also been studied[115] and it has been noted that methane- and ethane-disulphonate and benzene-1,3-disulphonate as well as aliphatic dicarboxylates with closely positioned —COO^- groups, and also oxalate and maleate but not malonate, hydroxymalonate or citrate, interact with the ^{35}S-sulphate transporter and inhibit contraluminal $^{35}SO_4^{2-}$ influx. Aromatic dicarboxylates and disulphonates possessing $-COO^-$ and/or SO_3^- charged groups in the 1,3-position, e.g. **187**, reveal also the inhibitory potency.



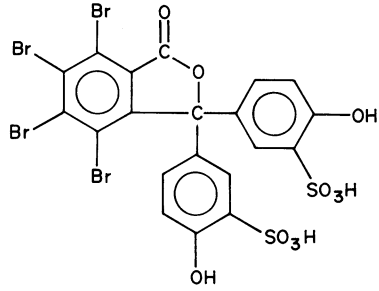
(187)

3-carboxy-4-hydroxy-benzenesulphonic acid



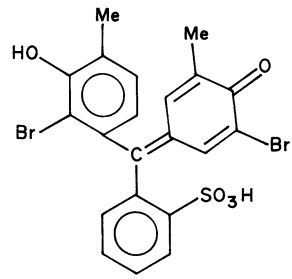
(188)

Further studies[116] have shown that salicylate ($\equiv$ 2-hydroxybenzoate) analogues or corresponding naphthalene compounds, for instance 1-naphthol-4-sulphamoyl-2-carboxylate (**188**), are also strong inhibitors of the contraluminal influx of $^{35}SO_4^{2-}$ into proximal tubular cells if they possess —COOH,—SO_3H or other electronegative or electrically charged groups in position 5, participating directly in the interaction of these compounds with the $^{35}SO_4^{2-}$ transport system during the 4-second contact time. Addition of a second OH group to the salicylate molecule in the 5 or 3 position does not induce interaction with the ^{35}S-sulphate transport system. The specific inhibitory effect of phenolphthaleins, e.g. **189**, sulphonphthaleins, e.g. **190**, and other sulpho dyes, sulphamoyl compounds, diuretics **191** and **192**, and diphenylamine-2-carboxylate derivatives on the contraluminal ^{35}S-sulphate transport in the proximal tubule of the rat kidney has also been investigated[117], and the final conclusion has been reached that the numerous accumulated results support the hypothesis of a multiple organic anion transport system.



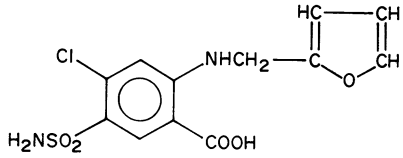
(189)

bromsulphalein



(190)

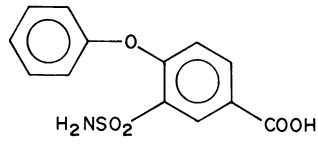
bromocresol purple



(191)

furosemide

3-sulphamoyl-4-chloro-6-(2-furyl-methylamino) benzoic acid



(192)

3-sulphamoyl-4-phenoxybenzoic acid

2. Utilization and turnover of ^{35}S-sulphate in animals

By giving rabbits intramuscular injections, each containing 3 mCi of carrier-free sodium ^{35}S-sulphate, it has been established[118], by isolating sulpholipids from the brain and measuring their weak beta radiation 108 hours later, that exchange is taking place between the sulphate group of the sulpholipids in the brain central nervous system and the labelled free sulphate.

Dziewiatkowskii[119] had successfully demonstrated that after intraperitoneal administration of carrier-free sodium ^{35}S-sulphate to young albino rats, the sulphate sulphur is converted to cystine sulphur. It has been suggested that bacteria in the intestinal tract are responsible for the synthesis of ^{35}S-cystine. Samples isolated from the internal organs contained the highest concentration of ^{35}S. The major portion of ^{35}S retained by the rat after administration of $Na_2{}^{35}SO_4$ appears as ester sulphate in mucopolysaccharides[120]. The turnover of *^{35}S-cerebroside sulphate* (galactose sulphate) in brain, kidney, liver, spleen and heart of the rat and in a mast cell tumor of the mouse has been investigated[121].

It has been found that injected ^{35}S-sulphate reaches maximal incorporation into rat brain cerebroside sulphate only 2 days after injection, and its activity remains practically constant and undergoes only very slow turnover. After 32 days the level of cerebroside sulphate activity was still 3/4 of that found on the second day after injection[98c]. In liver, spleen and heart the maximum incorporation of ^{35}S into cerebroside sulphate was reached after 12 hours and after 4 days the radioactivity virtually disappeared in these organs.

However, in the kidney the maximum incorporation had been attained 24 hours after injection, and the radioactivity was still present on the 32nd day. In the brain the ^{35}S-substance sedimented with mitochondria; in the kideny with microsomes and in the liver it was found in the soluble fraction. No cerebroside sulphate has been observed in rat blood cells or plasma.

Metabolism of sulphate and sulphur amino acids in Blattella germanica. The observation that cockroach and Japanese beetle are utilizing sulphate sulphur for synthesis of methionine and cystine had induced Block and Henry[122] to investigate the metabolism of various compounds labelled with ^{35}S. Injected $Na_2{}^{35}SO_4$ had incorporated into cystine, methionine, glutathione and sulphite but only a small amount of ^{35}S-taurine was formed by xenic *Blattella* in contrast to chick embryo. This indicates that taurine is formed in this insect not directly from sulphate but via cysteine. Reduction of sulphate to sulphite occurs in the cockroach. Intracellular symbionts are responsible for converting ^{35}S-sulphate into ^{35}S-methionine–^{35}S-cystine. Injected cystine-^{35}S and cysteine-^{35}S were converted by xenic and aposymbiotic *Blattella* to glutathione, sulphate and taurine but to methionine + methionine sulphoxide in xenic *Blattella* only. ^{35}S-Cysteic acid underwent decarboxylation to ^{35}S-taurine and partial oxidation to ^{35}S-sulphate. Most of the injected ^{35}S-taurine was excreted unchanged, but in the presence of intestinal bacteria some taurine-^{35}S was degraded to sulphate-^{35}S, which was then used by the xenic insect for the synthesis of cystine, cysteine, glutathione and methionine. ^{35}S-methionine and ^{35}S-sulphoxide were not converted to cysteine, glutathione and taurine in large extent. Radioactive sulphur from administered ^{35}S-methionine sulphone has not been detected in any separated compound. It has also been concluded that cysteic acid is not a significant intermediate in *Blattaria*, since it had not been found in extracts of cockroaches after feeding or injection of the above-mentioned ^{35}S-labelled materials.

It has been suggested that ^{35}S-cystine and ^{35}S-methionine are converted in the cockroaches to sulphate according to at least two pathways (equations 78 and 79) from

$$\underset{\underset{\text{methionine sulphoxide}}{\underset{\underset{O}{\|}}{CH_3{}^{35}SCH_2CH_2CH(NH_2)COOH}}}{\rightleftharpoons} \underset{\text{methionine}}{CH_3{}^{35}SCH_2CH_2CH(NH_2)COOH} \longrightarrow$$

$$H^{35}SCH_2CH_2CHNH_2COOH \xrightarrow[\text{(serine)}]{HOCH_2CH(NH_2)COOH}$$

homocysteine

$$HO_2CCHCH_2CH_2{}^{35}SCH_2CH(NH_2)COOH \qquad (78)$$

$$\underset{\text{(193) cystathionine}}{\underset{|}{NH_2}}$$

$$\longrightarrow \underset{\text{cysteine}}{H^{35}SCH_2CH(NH_2)COOH} \longrightarrow \underset{\underset{\text{cysteinesulphinic acid}}{\text{(194)}}}{HO^{35}\overset{\overset{O}{\|}}{S}CH_2CH(NH_2)COOH} \longrightarrow$$

$$\underset{\underset{\underset{\text{(195)}}{\underset{\text{pyruvic acid}}{\underset{\beta\text{-sulphinyl}}{\underset{\underset{O}{\|}}{\underset{\underset{O}{\|}}{HO^{35}S\text{-}CH_2CCOOH}}}}}}}{} \longrightarrow \underset{\text{sulphite}}{{}^{35}SO_2} + CH_3COCOOH \longrightarrow \underset{\text{sulphate}}{{}^{35}SO_4{}^{2-}}$$

which the first (equation 78) is the principal one (79). Already in 1952) Boström and Åquist[123] discovered that ^{35}S-sulphate administered to adult white rats by intraperitoneal injections incorporates not only into mucopolysaccharides containing ester sulphates and to chondroitin sulphuric acid of coastal cartilage, but also into taurine, $NH_2CH_2CH_2{}^{35}SO_3H$, isolated from liver. Methionine and cystine isolated from liver did not contain or contained very little ^{35}S from inorganic sulphate.

$$\begin{aligned}\text{methionine} &\longrightarrow (\text{homocysteine}) \longrightarrow (\text{cystathione}) \longrightarrow \\ \text{cysteine} &\longrightarrow (\text{cysteinesulphinic acid}) \longrightarrow (\text{2-aminoethanesulphinic acid}) \\ &\longrightarrow \text{taurine} \longrightarrow ? \longrightarrow \text{sulphate} \\ &\quad (\mathbf{10})\end{aligned} \tag{79}$$

Chicks utilize inorganic ^{35}S-sulphate in the synthesis of taurine. Dietary cholic acid and its derivatives (bile acids)[124] conjugate with taurine in the chicks liver, pass into the gall bladder and increase the volume of the bile fluid. Cholic acid feeding therefore stimulates the incorporation of sulphate-^{35}S into taurocholate while supplementation of taurine to the diet diminishes the amount of ^{35}S present in chick bile fluid. Carrier-free $H_2{}^{35}SO_4$ administered orally to young chicken is converted[125] after activation and reduction into taurine without passing via cysteine, that is, via total reduction of sulphate-sulphur into the HS group of cysteine, followed by oxidation. The presence of an optimum level of inorganic sulphate in the diet enhances the synthesis of taurine more than additions of organic sulphur. Thus, only small amounts of ^{14}C-taurine were found in the chick after injection with cystine-3-^{14}C. Taurine is probably formed by the conjugation of activated sulphate and a carbon acceptor possibly containing an amino group. Good incorporation of ^{14}C into taurine and taurocholate was found after injection of ^{14}C-labelled amino acids into the chicks. It has been observed also that addition of cystine to the diet lowered the total amount of taurine in the liver and the concentration of taurocholate-^{35}S in the bile fluid caused by enzyme repression or feedback. Taurine, after attainment (2–3 h) of a quasi-equilibrium level, undergoes conversion to isethionate, $HOCH_2CH_2SO_3^-$. Probably taurine is an intermediate in the conversion of sulphate-sulphur to amino acid sulphur in hens. Cysteine may also be formed from taurine through a mercaptoethylamine intermediate.

Tracer experiments[126] with $Na_2{}^{35}SO_4$ added to the diet of chicken have revealed that sodium sulphate improves growth, feed efficiency, and is capable of stimulating normal feather development even when the sulphur amino-acid content in the diet is too low to support optimal growth. About 20% of sulphur from $Na_2{}^{35}SO_4$ retained by chickens was found to be incorporated into body taurine.

Chapeville and Fromageot[127] also found that an aqueous sodium ^{35}S-sulphate solution injected under the shell of chicken eggs and incubated during 36 hours has been utilized by the chicken embryos, *in vivo*, to produce large quantities of ^{35}S-labelled taurine and other radioactive sulphur compounds identified by autoradiography. ^{35}S of the labelled sulphate added to embryo homogenates *in vitro* has also been incorporated into various radioactive sulphur compounds (differing from these produced *in vivo*). The ^{35}S-labelled organic molecules produced *in vitro* reinjected into incubated chicken embryos *in vivo* have not been transformed into ^{35}S-labelled taurine. This has been interpreted as an indication that the C—^{35}S bond in organic compounds produced *in vitro* is 'biologically stable'.

Growing chicken[128] and hens[129] utilize sulphate sulphur for cystine synthesis. Biological radio-tracer experiments[130] with $Na_2{}^{35}SO_4$ (10 μCi) have shown that over 65% of the ^{35}S administered to a 24-hour-old embryo is incorporated into taurine of the chick. No radioactive cystine, methionine or cysteic acid was detected in the hydrolysate obtained from the embryo and only a small portion of total taurine-^{35}S occurs as taurocholic acid. The embryo is unable to utilize sulphate sulphur for cystine synthesis.

The incorporation of ^{35}S-sulphate into cystine by growing chicken probably takes place via microorganisms in the intestinal lumen, or there may be an enzyme system in the chicken for this synthesis which is not present in the embryo. The findings of Machlin and coworkers[128–130] have been confirmed by Lowe and Roberts[131]. Already within 30 minutes after injection of ^{35}S-sulphate the radioactivity was detected in taurine and in other organic substances but not in cystine, methionine or glutathione. Incubation of the homogenate of chick embryo with ^{35}S-sulphate in the presence of pyruvate and acetate resulted in the formation of several ^{35}S-labelled organic compounds but not taurine. Addition of coenzyme A (Co-A), ATP and diphosphopyridine nucleotide (DPN) to the incubated mixture increased the rate of incorporation of ^{35}S into organic compounds.

By injecting intravenously ^{35}S-labelled sulphite into sterilized rabbits[132] (to eliminate the eventual interference of intestinal bacteria), it has been established that ^{35}S-sulphite but not ^{35}S-sulphate is utilized for the synthesis of ^{35}S-cysteinesulphinic acid, which undergoes subsequent reduction to ^{35}S-cysteine in the organism. Cysteinesulphinic acid is also a precursor of the ^{35}S-taurine. A comparison of specific ^{35}S activities of taurine isolated from bile and that of cysteine isolated at the same time indicates that decarboxylation of cysteinesulphinic acid and its subsequent oxidation is a faster process than the reduction to cysteine. Oxidation of cysteine to cysteinesulphinic acid is a reversible process. Incorporation of inorganic ^{35}S-sulphite into organic sulphur compounds should proceed at a higher rate in young animals. The study [132] has excluded direct exchange between ^{35}S-labelled free sulphite and the sulphinyl group of cysteinesulphinic acid, **194**.

Incubation of embrionic calf liver with ^{35}S-labelled sodium sulphite, sodium pyruvate and sodium glutamate at 38 °C under nitrogen resulted in formation of ^{35}S-cysteinesulphinic acid[133,134]. ^{35}S-hypotaurine has also been isolated, but taurine-^{35}S and cystine-^{35}S have not been found. In the presence of serine, the yield of ^{35}S-cysteinesulphinic acid was smaller. Organic ^{35}S compounds without amino groups have also been formed in the same experiment. In the conditions employed in this bioexperiment cysteinesulphinic acid is not reduced to cystine-^{35}S, although such reduction was found possible *in vivo*.

B. ^{18}O Study of the Microbial Desulphonation of Naphthalene- and Benzenesulphonic Acids

Certain bacteria present in sewage are able to desulphonate sulphonated aromatic compounds and utilize their sulphur for growth. A *Pseudomonas sp.* and *Arthrobacter sp.* can desulphonate 16 aromatic compounds but are unable to use them as a carbon source. *Pseudomonas sp. strain S-313* converted 1-and 2-naphthalenesulphonic acids, 5-amino-1-naphthalenesulphonic acid, benzenesulphonic acid and 3-aminobenzenesulphonic acid to 1-and 2-naphthol, 5-amino-1-naphthol, phenol and 3-aminophenol, respectively. The oxygenolytic mechanism of the cleavage of the C—S bond has been studied[135] by growing the cultures in the presence of $^{18}O_2$, and examining the products by GC–MS. It was shown that oxygen of the ^{18}OH groups in the naphthols and phenols obtained in the biodegradation experiments with $^{18}O_2$ is derived from molecular oxygen (equation 80).

$$1\text{-NaphSO}_3\text{H} \xrightarrow[\textit{Pseudomonas}]{^{18}O_2} 1\text{-NaPh}^{18}\text{OH} \qquad (80)$$

Substrate/product kinetic curves have been presented by the authors[135] for the growth of *Pseudomonans sp. strain S-313* with 5-amino-1-naphthalenesulphonate as the sulphur source in a succinate-containing medium in the presence of $^{16}O_2$ only. However MS-identification of the 5-amino-1-naphthol product was presented both for cultures grown in

the presence of $^{16}O_2$ ($M^+ = 159$) as well as in the presence of $^{18}O_2$ ($M^+ = 161$). No dioxygenase is involved in this C—S bond cleavage. Desulphonation by a monooxygenase of broad substrate specificity is postulated as the most probably mechanism of transformation (equation 80) and will be further tested.

C. Biochemical Studies with Labelled Sulphonates

1. *Biodegradation of [^{35}S] sulphonic acids by cyanobacteria*

The possible role of cyanobacteria in the biodegradation of sulphonic acids has been investigated[136] using the cyanobacterial strains *Anabaena variabilis* and *Plectonema 73110*. The growth of several cyanobacteria has been examined with [^{35}S]taurine and [^{35}S]ethanesulphonate [137] as the only source of sulphur. Not all cyanobacteria tested were able to utilize sulphonates. Comparison of the uptake rates for [^{35}S]ethane sulphonate, [^{35}S]taurine and [^{35}S]sulphate by *Anabaena variabilis*(+) and *Synechococcus 6301* (−) confirmed the view that the ability to utilize sulphonates depends on the presence of an active sulphonate transport system[137]. *Synechococcus 6301* is unable to utilize sulphonic acids for growth[138] under all conditions tested, though same sulphate uptake was found in sulphur-starved cultures. Uptake of [^{35}S]-labelled ethanesulphonate, [^{35}S]taurine and [^{35}S]sulphate was found to be present in *Anabaena variabilis* grown under taurine, ethanesulphonate or S-limited conditions. Sulphate-[^{35}S] uptake in such conditions was about 8 times higher than ethane[^{35}S]sulphonate uptake. Sulphate-grown cultures did not transport ethanesulphonate or taurine. The optimum uptake of ^{35}S taurine in *Anabaena variabilis* in the 5.0–11.5 pH range was found to be at pH 6.5. Taurine transport was independent of Na^+ concentration, but phosphate buffer increased it markedly. The specific 'sulphonic acid permease' action is not influenced by the presence of HO, HS, NH_2 or HOOC groups in sulphonic acid molecule or by its chain length, although this has been found in *chlorella fusca*. [^{35}S]sulphonic acids readily enter normal metabolic pathways in *Anabaena variabilis*. After growing in the presence of [^{35}S]ethanesulphonate and [^{35}S]taurine the following [^{35}S]-labelled compounds have been isolated: cysteine, methionine, glutathione, sulphate and sulpholipids. ^{35}S-labelled volatile thiols and sulphide detected in intact cells indicate that the degradation of sulphonic acids proceeds via reduction to thiols followed by the C—S bond cleavage. Cyanobacteria playing role in the biodegradation of sulphonic acids contribute to the conservation of the proper sulphur cycle in nature by utilization of the sulphonates produced and released in nature.

2. *[^{35}S]sulphonate uptake in* Chlorella fusca

Detailed kinetic studies[137] of the [^{35}S]ethanesulphonate uptake[139] and metabolism in *Chlorella fusca* have shown that [^{35}S]sulphonate uptake in this green alga depends linearly on time during the first 90 minutes and depends strongly on pH and on temperature. Optimum values with maximal rates of uptake were found at pH 7.8 and at about 33 °C. The Arrhenius plot at 18–33 °C gave an activation energy of 41.3 kJ mol^{-1}. Lack of exchange of internal ^{35}S-labelled ethanesulphonate with external compounds of natural isotopic composition indicates a rapid metabolism of the [^{35}S]ethanesulphonate within the alga. A large variety of sulphonates as well as sulphoacetate added to the medium were able to compete with the ethanesulphonate uptake, indicating that the specificity of the ^{35}S uptake system in *Chlorella fusca* is limited to the sulphonate group only. Cysteine, methionine, cysteic acid, alanine and valine present in the ^{35}S-labelled ethanesulphonate (ES) medium increased the ES uptake to 140–145% of the control. The effect of various inhibitors on ES uptake in *Chlorella fusca* has also been studied. Some uncouplers (e.g. 2,4-

dinitrophenol) were found to be very effective metabolic inhibitors. *p*-Chloromercuribenzyl sulphonate, PCMBS, the non-penetrating reagent reacting with SH groups on the outer surface of the cell membrane, also caused extensive inhibition of ES. Phenylmethylsulphonyl fluoride, blocking irreversibly serine hydroxyl groups by sulphonation[140], had a large negative effect. Polyvalent cations stimulated ^{35}S-sulphonate uptake, apparently by reduction of the surface potential which favours the accumulation of anions at the membrane–solution interface. Phosphate was found to be the most effective compound stimulating[^{35}S]ES uptake, independently of its corresponding cation. This indicates that the activity of ES permease is regulated by a phosphorylation/dephosphorylation mechanism involving permease itself or closely related membrane proteins. Identification of the radioactive products formed from ES showed that 96.1% of the radioactivity was taken up as water-soluble compounds. Sulphate is the main and very likely the first degradation product of ES in *Chlorella fusca* but 10% ES, 4% glutathione and 2% cyst(e)ine and methionine as well as sulpholipids were also found in this fraction. The entry of [^{35}S]ES into *Chlorella fusca* may involve both transport and metabolism, as has been postulated in the case of taurine uptake in *Staphylococcus aureus M*.

A new ninhydrin-reactive substance, *N*-(1-carboxyethyl)taurine (**196**) has been isolated from three species of marine red algae. It had the same m.p. and R_f values as the crystals obtained by reacting α-bromopropionic acid with taurine[141].

$$HO_3SCH_2CH_2NHCHCOOH$$
$$\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\quad CH_3$$

(196)

3. *Uptake of [1,2-^{14}C]taurine in encapsulated* Staphylococcus aureus *strain M*

Using [1,2-^{14}C]taurine[142,143], a novel uptake system (including transport and metabolism) for taurine has been discovered[143] in the prokaryote, encapsulated *Staphylococcus aureus*, which previously was found to contain 2-aminoethanesulphonate as a component of capsular polysaccharide[144]. Radioactive taurine in the growth medium was taken up and rapidly metabolised by a variety of encapsulated and unencapsulated *S. aureus strains*. Detailed radiobiological studies have revealed[143] that [^{14}C]taurine is ingested according to a highly specific Na^+-dependent system differing from the other amino acid transport systems in *S. aureus* described previously. The [^{14}C]taurine uptake by the whole cells strongly depend upon NaCl concentration and is stimulated by the presence of glucose in the medium. This means that the endogenous metabolism supporting taurine uptake is augmented by the exogenous energy source present in glucose. The [^{14}C]taurine uptake has its maximum at 37 °C, while it is negligible at 0 °C and also 60 °C. The taurine uptake was constant at pH values between 6 and 8. Addition of excess of unlabelled taurine to cells grown on [1,2-^{14}C]taurine showed lack of back-exchange of ingested [^{14}C]taurine. Addition of hypotaurine and 3-amino-1-propanesulphonic acid to the assay mixture slightly decreased the uptake of taurine, but agents inhibiting the Na^+-linked transport system decreased the taurine uptake very strongly. Saturation kinetics of the taurine uptake indicates that it is a carrier-mediated process. Taurine is metabolised rapidly upon its entry into the cell cytoplasm to a trichloroacetic acid-soluble form. Strong inhibition of taurine uptake by sodium *p*-chloromercuribenzoate indicates the involvement of protein SH groups in the process. It is suggested that taurine incorporating into surface molecules in *Staphylococcus* strains may be also a staphylococcal nutrient, which is present in the body of warm-blooded animals, the natural environment of staphylococci.

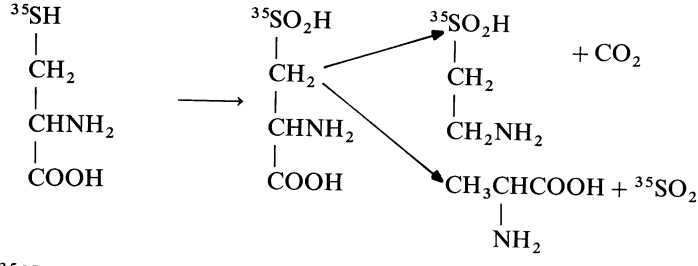
4. The metabolism of ^{35}S-labelled amino acids by liver in cystinosis and by brain in aminoaciduria

a. The intracellular depositions of poorly soluble crystalline cystine found in infant tissues in the course of examinations and diagnosis of cystinosis lead to the suggestion that a specific enzyme defect in cysteine–cystine metabolism leads to storage of the resultant excess of cystine in the tissues and consequent naphrotoxic effects. Infusion of [^{35}S]cystine to cystinosis patients[145] demonstrated the complete oxidation of the ^{35}S-amino acid, as shown by the appearance of ^{35}S-labelled urinary inorganic sulphate and normal urinary excretion of inorganic sulphate by cystinosis patients. Studies *in vitro*[146] using autopsy samples of cystinotic liver have showed that most processes involving cysteine, cystine and cysteic acid proceed in livers taken from cystinosis patients in the same way as in normal liver.

b. Aminoaciduria is associated with pathologic conditions such as mental retardation and convulsive diseases. [^{35}S]Methionine, [^{35}S]cystine and [^{35}S]taurine have been used to investigate the metabolism of sulphur in rat brain[147]. It has been found that ^{35}S of these amino acids incorporates into cystathione, cysteine, cysteinesulphinic acid, cysteic acid, hypotaurine, taurine and sulphate. Conversion of [^{35}S]taurine to [^{35}S]isethionic acid has also been observed. The conclusion has been drawn that the brain possesses enzyme systems analogous to those of the liver for the metabolism of sulphur amino acids.

5. The mechanism of [^{35}S]taurine formation from [^{35}S]-cysteine in rats

The *in vivo* mechanism of ^{35}S-taurine formation from ^{35}S-cysteine in the rat has been studied by Awapara and Wingo[148]. Ten minutes after injection, large amounts of ^{35}S cysteine and traces of sulphate-^{35}S were found only in the liver. After 20 minutes small amounts of 2-aminoethanesulphinic-^{35}S acid were also found (equation 81). Taurine began to appear in the liver 30 minutes after the injection. Two hours after administration, analyses for [^{35}S]taurine, alanine, [^{35}S]cysteic acid and 2-aminoethanesulphinic acid were carried out in liver, kidney, heart and spleen of the rats. [^{35}S]Cysteic acid had been detected only when large amounts of ^{35}S-labelled cysteine were injected. It has been suggested that the degradation of [^{35}S]cysteine *in vivo* proceeds in rats according to equation 81. Formation of 2-aminoethanesulphinic acid and its oxidation to taurine is a preferred pathway. Much less [^{35}S]sulphate than 2-aminoethanesulphinic-^{35}S acid and taurine-^{35}S had been found one hour after incorporation of ^{35}S-labelled cysteine.



(81)

The [^{35}S]cysteinesulphinic acid, included in the scheme in equation 81, has been identified unambiguously by Chapeville and Fromageot[149] in the liver and kidney of seven-week-old rats injected with [^{35}S]cystine hydrochloride and sacrified 15 minutes later. [^{35}S]Taurine and [^{35}S]sulphate have also been detected, and the [^{35}S]cysteinesulphinic acid has been oxidized subsequently by performic acid to [^{35}S]cysteic acid.

6. *Absorption of injected [^{35}S]taurine by tissues of rat organs*

Taurine was found in varying concentrations in all organs of rats and other animals investigated[150]. Heart and some other organs contain large amounts of taurine while liver, where taurine is produced, retains the smallest amount. Awapara[151] injected [^{35}S]taurine into the tail vein of rats and reached the conclusion that the level of taurine in the urine depends upon the amount of sulphur amino acids in the diet, whereas its concentration in the tissues is independent of the diet. Taurine-^{35}S is absorbed from blood by all organs studied, but at different rates. Thus 15 minutes after injection the concentrations of ^{35}S-taurine found in different organs were as follows: kidney > spleen > liver > heart > intestine > muscle. However, after 7 days the distribution was heart > spleen > muscle > intestine > kidney > liver, and after 12 days it was heart > muscle > spleen > intestine > kidney > brain > testis > liver. The concentration of ^{35}S-taurine in the heart increases slowly: the taurine already present in the heart is very slowly replaced by dietary taurine or taurine formed from sulphur amino acids. After reaching a maximum after 3 days the concentration of ^{35}S-taurine in the heart is practically constant during the subsequent 4–7 days after the injection.

The kinetics of [^{35}S]taurine exchange between plasma blood and tissues of different organs of rats has also been investigated by Boquet and Fromageot [152]. These authors confirmed the observations of Awapara[151] and came to the conclusion that a half-life of 12–13 days is characteristic for taurine turnover in normal rats. The smallest rate of turnover of taurine in muscle has been confirmed. The rate of endogenous biosynthesis of taurine was found to be about 35 μmoles per 100 g per 24 h. [^{35}S] Taurine is removed directly through the kidney or indirectly after catabolism, leading to the appearance of taurine sulphur in the urine as sulphate or partly as isethionic acid. The degradation of taurine [^{35}S] by intestinal micro-organisms is certain, but the role of the intestinal tissue itself needs further clarification. Fecal excretion of sulphur derived from taurine plays a secondary role. These results are valid if the radioactivity injected is $\lesssim 10\,\mu$Ci per single rat. Administration of higher ^{35}S activities caused an increase in the rate of [^{35}S] taurine excretion due to internal radiation effects.

7. *Oxidation of [^{35}S]methionine to $^{35}SO_4^{2-}$ and [^{35}S] taurine in X-irradiated rat*

Besides sulphate and urea, increased urinary excretion of taurine by X-irradiated rats has been observed in several studies[153,154]. The metabolism of ^{35}S methionine in X-irradiated rats was investigated[155], since it had appeared that the excessive excretion of taurine might be the result of the alteration of the metabolism of sulphur-containing compounds. One of two specially pretreated groups of rats was sham-irradiated, while the second group has been uniformly irradiated at a rate of 25 r min^{-1}. After having been exposed to 600 r of total body X-irradiation, all rats were injected intraperitoneally with [^{35}S]-L-methionine (20 μmol, 0.739 μCi), and the amount of [^{35}S]sulphate and [^{35}S]taurine was determined in the rat urine collected during 24 hours. Comparison of measurements of the total amount, total activity and specific activity of [^{35}S] taurine and [^{35}S]inorganic sulphate in the irradiated rats and in the control group as well as supplementary results obtained on liver slices from X-irradiated rats had demonstrated that increased oxidation of [^{35}S]methionine as a result of extrahepatic catabolism related to adrenal activity is the main source of excessive inorganic [^{35}S]sulphate. [^{35}S]taurine derived from [^{35}S]methionine increased 1.34 times, while total urinary taurine increased 2.33 times in X-irradiated rats in comparison with the control group and the specific activity of taurine decreased 1.755 times. The above results have been interpreted as indicating that excess of taurine found in the urine of X-irradiated rats is derived from sources other than the oxidation of methionine. There are no biokinetic measurements

which would enable the evaluation of the rate ratios of taurine formation from its ^{35}S-labelled precursor and from its inactive precursor[156].

8. Dietary influences on the disposition of [^{35}S]taurine and [^{35}S]taurocholate in the rat

Taurine had been considered for a long time[157] as the biologically inactive end-product of cystine metabolism. Intraperitoneal injections of [^{35}S]taurine in rats and subsequent metabolic studies[158,159] have established that the urinary excretion of [^{35}S]taurine depends on the magnitude of the dose administered. There is a definite renal threshold for taurine and therefore in non-tracer experiments, which required large dosages, high proportions of taurine had been excreted. The urinary excretion of [^{35}S]taurine was influenced by the preliminary diet. Animals fed with low protein diet excreted less ^{35}S-labelled organic sulphur in the urine and incorporated more ^{35}S. Rats which had been fed with cystine or were injected with cysteic acid excreted more [^{35}S]taurine. No radioactivity was found in cystine isolated from acid hydrolysates of rat tissue. The radioactivity in protein-free extracts was identified as [^{35}S]taurine. Taurine-^{35}S, prepared as shown in equation 82[158], has been used for biosynthesis of taurocholate-^{35}S. Both [^{35}S] taurine and [^{35}S] taurocholate were used in metabolism and excretion studies in normal rats[158]. Rats fed diets low in organic sulphur excreted lesser amounts of bile acid and retained larger amounts of ^{35}S in the tissue. Most of the activity was found in the musculoskeletal system of the animals and in the kidney.

$$HBr\cdot H_2NCH_2CH_2Br + Na_2{}^{35}SO_3 \longrightarrow HBr\cdot H_2NCH_2CH_2{}^{35}SO_3Na \quad (82)$$

m.p. 304–307 °C

9. Metabolism of [^{35}S]hypotaurine in rats and mice

[^{35}S]Hypotaurine has been prepared[160,161a] according to reaction 83. [^{35}S]Hypotaurine was injected intraperitoneally into male mice and rats. 30 minutes after the injection, besides [^{35}S]hypotaurine, [^{35}S]taurine and [^{35}S]sulphate were detected in the serum and in the urine of the experimental animals. Since sulphate is formed from taurine at a slower rate, the above findings indicate that the metabolism of [^{35}S]hypotaurine in the rat organism is confined to the two reactions leading to [^{35}S]sulphate and [^{35}S]taurine formation. The preferential conversion of [^{35}S]hypotaurine to [^{35}S]sulphate raises the possibility that $H_2NCH_2CH_2{}^{35}SO_2H$ is a necessary intermediate[161b] in the oxidation of [^{35}S]cysteine, with cystamine and [^{35}S]cysteamine leading to [^{35}S]sulphate as the end-product (compare equation 81).

$$(H_3\overset{+}{N}CH_2CH_2\ {}^{35}S)_2 + Hg^{++} + Cl^- \xrightarrow[RT]{H_2SO_4} H_3\overset{+}{N}CH_2{}^{35}SO_2H + H_3\overset{+}{N}CH_2CH_2{}^{35}SHgCl \quad (83)$$

m.p. 170 °C, 23% yield
sp. act. 4 mCi per mg of S

10. New sulphonic acid urinary metabolites, thiotaurine and quinaldylglycyltaurine

Awapara[162a] observed an unknown ^{35}S-cystine metabolite in the organs of rats. Cavallini and coworkers[162b] have shown that this new metabolite is thiotaurine, $NH_2CH_2CH_2SO_2SH$ (**197**), which appears in the urine of rats fed a diet supplemented

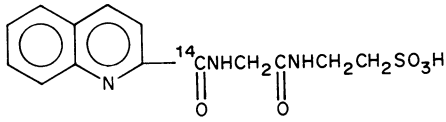
with L-cystine. The presence of aminoethylthiosulphonate in excretion has been documented by comparing the chromatogram of synthetic thiotaurine with that of biosynthesized thiotaurine. Cyanolysis of the eluted compound and direct cyanolysis of the urine (equation 84) had also confirmed the occurrence of thiotaurine in the urine of experimental rats. Pure crystalline thiotaurine has been prepared in reaction 85.

$$H_2NCH_2CH_2SO_2SH + CN^- \longrightarrow H_2NCH_2CH_2SO_2H + SCN^- \quad (84)$$

$$H_2NCH_2CH_2SO_2H + S_8 \xrightarrow[2\,h\ boiling]{0.2\ N\ NaOH,\ EtOH} H_2NCH_2CH_2SO_2SH \quad (85)$$

1 mmol 1.5 mmol 0.7 mmol

A new, strongly acidic product, quinaldyl(carboxyl-^{14}C)glycyltaurine (**198**), a sulphonic acid urinary metabolite, has been discovered[163] and its chemical structure established by subcutaneous injections and oral administrations of quinaldic acid–carboxyl-^{14}C to hungry cats. Hydrolysis of **198** demonstrated the presence of glycine, taurine, quinaldic acid and quinaldylglycine in the hydrolysate.



(198)

11. [^{35}S]Isethionic acid in urine of human subjects as catabolite of [^{35}S]taurine

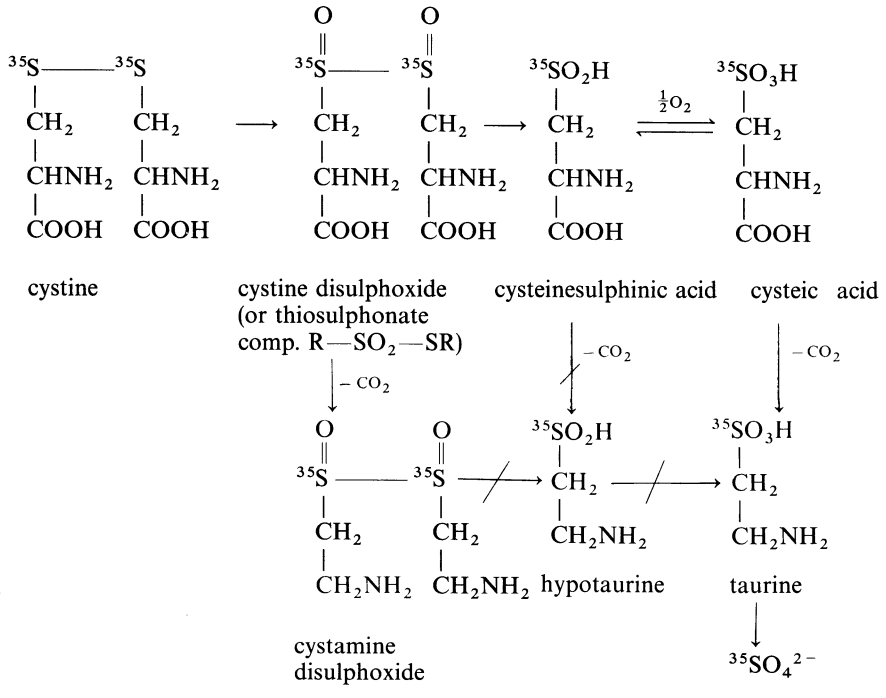
Oral administration of [^{35}S]taurine and of [^{14}C]taurine to fasting normal and mongoloid human subjects resulted in the appearance of [^{35}S]-2-hydroxyethanesulphonic acid and of C-14 isethionic acid in the urine specimens[164a]. Bioexperiments with [^{14}C]taurine indicate that the [^{35}S]isethionic acid, $HOCH_2CH_2{}^{35}SO_3H$ (**199**), is the product of direct degradation of [^{35}S]taurine and not the result of indirect reincorporation of [^{35}S]sulphate found also in the urine. The identification of [^{35}S]-**199** was greatly facilitated by application of anion exchange column chromatography. The biomedical significance of isethionic acid, found in nervous and other human tissues, is under prompt investigation. It has been suggested that **199** is a regulator of irritability in the dog heart[164b].

Bacterial extracts from sewage mud containing bacteria which can grow on taurine as the sole source of carbon, nitrogen and sulphur were found[165] to form sulphoacetaldehyde, **200**.

12. The metabolism of ^{35}S-labelled cysteine, cystine and methionine by chicken embryo

The aerobic metabolism of cystine-^{35}S by chicken embryo, investigated[166] both *in vivo* and *in vitro*, resulted in the formation of cystinedisulphoxide-^{35}S (*in vitro* only), [^{35}S] cystinesulphinic acid, [^{35}S] cysteic acid, [^{35}S]taurine and sulphate-^{35}S. Hypotaurine has been detected neither *in vivo* nor *in vitro*. This indicates that, contrary to what had been observed in mammalian liver, hypotaurine is not the precursor of taurine in chicken embryo (equation 86). The enzyme decarboxylase, which effectively decarboxylates [^{35}S]cysteic acid, does not act on cysteinesulphinic acid. Sulphate-^{35}S may be produced also by the desulphination of cysteinesulphinic acid (equation 87) or from some other

metabolite of cystine.



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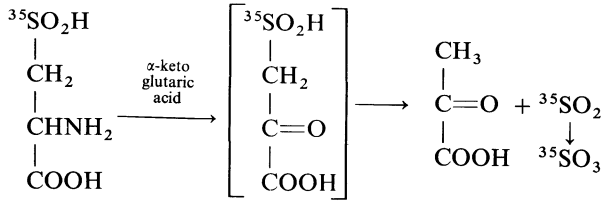


(87)

β-sulphinylpyruvic acid

Chick embryo utilizes ^{35}S-sulphate for the synthesis of ^{35}S-taurine, but the amount of sulphate-sulphur present in the unincubated egg is insufficient to furnish S necessary for the taurine synthesized. Injection[167] of L-methionine-^{35}S or of L-cysteine·HCl-^{35}S into the egg white, and determination of the distribution of ^{35}S in the chick hatched from the incubated egg revealed that with [^{35}S]cysteine 10% of the administered ^{35}S is located in the chick as taurine, 12% as sulphate, 1.3% as methionine and 49% as cystine. With methionine-^{35}S 9.1% was recovered as taurine, 10% as sulphate, 43% as cystine and 35% as methionine. These findings indicate that methionine is converted to cystine during embryonic development, but significant amounts of cysteine-^{35}S were incorporated also into methionine. Possibly, trans-sulphonation from methionine to cysteine is reversible to some extent in the chick embryo, similarly to what has been found in young rats[168].

Interestingly, 84–85% of the sulphate produced has been utilized for tissue synthesis (e.g. protein-bound forms and cartilaginous tissue formed during the last few days of incubation and thus ^{35}S-sulphate is not merely an excretory product.

Enzymatic decarboxylation[169] of L-cysteic acid-^{35}S (equation 86) by the tissues of chicken embryo has been investigated by Fromageot and coworkers[170]. Enzyme preparations from liver appeared to be the most active, and the authors determined [^{35}S]taurine as well as unreacted ^{35}S-cysteic acid, ^{35}S-β-sulphonylpyruvic acid and ^{35}S-sulphate. The reaction is inhibited by L-cysteine sulphinic acid, by DL-α-methylcysteic acid, $CH_2ICOONa$, NaCN and by hydroxylamine. The enzyme is activated by pyridoxal phosphate.

13. Enzymic decarboxylations of [1-^{14}C]cysteinesulphinic acid and [1-^{14}C]cysteic acid in mammalian tissues

[1-^{14}C]cysteinesulphinic acid ($CySO_2H$) and [1-^{14}C]cysteic acid ($CySO_3H$) have been prepared starting with DL-[1-^{14}C]cystine[171–175]. The [^{14}C]-labelled $CySO_2H$ and $CySO_3H$ have been decarboxylated in the presence of enzyme-containing tissue extracts prepared from liver and brain of adult male albino rats[176]. Linear relations have been found between the rate of $^{14}CO_2$ production from L-[1-^{14}C]$CySO_2H$ and the time and between the amounts of [^{14}C]O_2 produced and the concentrations of the enzymes at constant time. The influence of pH on the decarboxylations has been also investigated and optima were determined at various pH values for different enzymes and substrates. The ratio of $CySO_2H$- to $CySO_3H$-decarboxylase activity was constant and equal to 7.1 in agreement with previous values[177], showing that decarboxylation of $CySO_2H$ to hypotaurine is a preferred pathway in mammalian tissues. It has been further established that the decarboxylation of one of the amino acids was competitively inhibited by the other and approximately linear Lineweaver–Burk[178] plots, v^{-1} versus $[S]^{-1}$ (where v is the rate of evolution of [^{14}C]O_2 and [S] is the number of moles of [^{14}C]$CySO_2H$ or [^{14}C]$CySO_3H$), of the decarboxylations have been obtained*.

The apparent Michaelis (K_m) and inhibition (K_1) constants have been estimated from the above plots. K_m values are approximately the same as the K_1 values for each amino acid (K_m corresponds to the dissociation constant of the enzyme–substrate complex, K_1 to the enzyme–inhibitor complex; $K_1 \cong K_m$ both for L-$CySO_3H$ and for L-$CySO_2H$ suggests that the same enzyme catalyses the decarboxylation of both amino acids accepting both substrates.) The apparent K_m values for [^{14}C]$CySO_2H$ and [^{14}C]$CySO_3H$ are about 10 times lower in liver than in brain. K_m for L-[^{14}C]$CySO_2H$ is about three times lower than K_m for L-[^{14}C]$CySO_3H$ in decarboxylations catalysed by rat-liver and two times lower in decarboxylations catalysed by rat-brain preparations. The accumulated experimental observations strongly suggest that a single enzyme, L-cysteine sulphinate carboxy-lyase, catalyses the decarboxylation of [^{14}C]$CySO_3H$ and [^{14}C]$CySO_2H$ both in rat liver and in rat brain. Differences in the characteristics of the enzymic activity in liver and in brain indicate that tissues of these organs contain different enzymes catalysing the same reaction.

*Linear Lineweaver–Burk plots[178] correspond to enzyme reactions described by the kinetic equation

$$\frac{1}{v} = \frac{1}{v_{(max)}} + \frac{K_S}{v_{(max)} \cdot [S]}$$

where $K_S = [E][S]/[ES]$, $[E] + [ES] = \text{constant}$, [S] is varied and v^{-1} is plotted against $[S]^{-1}$.

14. Metabolism of ^{35}S-sulphur amino acids in invertebrates

The metabolism of ^{35}S-labelled sulphur amino acids in marine and fresh water invertebrates has been studied and reviewed by Awapara and coworkers[179,180]. The general conclusion drawn from these studies was that the metabolism of sulphur-bearing amino acids in two molluscs studied is qualitatively the same as in mammals. Taurine, which serves as an osmoregulator in marine molluscs, is formed either by decarboxylation of cysteic acid (in *Rangia cuneata*) or by oxidation of hypotaurine (in *Mytilus edulis*), derived from cysteinesulphinic acid by decarboxylation. In *Arenicola cristata* only the terminal reactions are different. Methionine and cysteine sulphur incorporates into taurocyamine by transamidation between taurine and arginine.

III. GENERAL PHYSICAL AND CHEMICAL APPLICATIONS OF LABELLED SULPHONIC ACIDS AND THEIR DERIVATIVES

A. Isotopic Tracer Studies

1. ^{33}S Nuclear magnetic resonance study of sodium sulphonates

A linear relationship has been found[181] between the ^{33}S chemical shift of $-{}^{33}SO_3^-$ in sodium sulphonates, $R^{33}SO_3Na$, and the ^{13}C chemical shift of the carboxylic carbon in the corresponding sodium carboxylates, RCOONa (equation 88).

$$\delta(^{33}S) = -390.3_7 + 2.129_6\delta(^{13}C) \tag{88}$$

The validity of this correlation has been established for R = Me, Et, Pr, Bu, $CH_2{=}CH$, Ph, *p*-Tol, *m*-$NH_2C_6H_4$, $NaOOCCH_2$, H_2NCH_2, *m*-$NO_2C_6H_4$, 1-Naph, 2-Naph and *p*-ClC_6H_4. The ^{33}S 'SCS' (substituent-induced chemical shift) of $-{}^{33}SO_3^-$ is almost two times more sensitive to substituent effects than ^{13}C 'SCS' in carboxyl groups. Additional data are required for detailed interpretation of all ^{33}S SCS, but the established parallelism clearly indicates that ^{15}N, ^{17}O and ^{33}S chemical shifts are susceptible to the same kinds of electronic and steric influences as ^{13}C shifts upon alkyl substitution. Particularly, substitution of a hydrogen atom by a Me group in $CH_3{}^{33}SO_3Na$ resulted in deshielding of a 9.8 ppm (β effect), while substitution of a methyl hydrogen in $EtSO_3Na$ by Me caused a shielding 'γ effect' of 2 ppm. The more remote δ deshielding effect is of 1.2 ppm only. The upfield shift of (^{33}S) (large negative values relative to Na_2SO_4 external reference standard) observed in the case of unsaturated sodium sulphonates is explained by electron release from the conjugated π system to the ^{33}S sulphur atom.

2. ^{15}N NMR study of sulphonamides, sulphinamides and sulphenamides

The ^{15}N-NMR spectra of 11 sulphonamides ($R^1R^2NO_2Y$), 10 sulphinamides (R^1R^2NSOY) and 7 sulphenamides (R^1R^2NSY) have been determined, analysed and used to reveal the factors governing the electronic distribution of the nitrogen–sulphur bond and the hybridization of the nitrogen atom[182]. δ^{15}N (in ppm relative to $MeNO_2$) of the series examined obeys the following equation:

$$\delta^{15}N(R^1R^2NSOY) > \delta^{15}N(R^1R^2NSO_2Y) > \delta^{15}N\ (R^1R^2NSY)$$

Differences between the chemical shifts of sulphur compounds R_2NX and of the corresponding secondary amine R_2NH are decreasing in the following order:

$$\Delta\delta^{15}N(\text{sulphinamides}) > \Delta\delta^{15}N(\text{sulphonamides}) \gg \Delta\delta^{15}N(\text{sulphenamides})$$

By changing substituents R^1 and R^2, while keeping substituent X constant in $R^1R^2N—X$, it has been shown that increase in the size of R causes the nitrogen-15 signals to shift towards low fields as ^{15}N hybridization is passing from sp^3 hybridization to hybridization closer to sp^2. Thus these changes in $\Delta\delta^{15}N$ provide information about hybridization changes at the nitrogen atom.

In the case X = SCl, $\Delta\delta^{15}N$ depends only a little on R, which means that the geometry of the nitrogen atom hardly depends on the substituent.

In the case $X = SO_2Y$, $\Delta\delta^{15}N$ depends in a significant manner on the size or R, changing for instance from 54.7 to 34.2 ppm in going from Et_2NSO_2Ph to *i*-Pr_2NSO_2Ph. Crowding at the sulphur atom causes the nitrogen atom to be tetrahedral (pyramidal sp^3 structure).

In the case X = SOCl, changes in $\Delta\delta^{15}N$ are found to lie between the changes observed for R_2NSCl and for sulphonamides. This indicates that the geometry of the nitrogen atom is intermediate between that characteristic for R_2NSCl and for R_2NSO_2Cl. Electronegativity alone of the substituent X cannot explain the results, since this would require

$$\Delta\delta^{15}N(\text{sulphonamides}) > \Delta\delta^{15}N(\text{sulphinimides}) > \delta^{15}N(\text{sulphenamides})$$

To explain the experimental findings it has been necessary to admit that there are $p\pi$–$d\pi$ interactions between p-orbitals of the substituent and d-orbitals of sulphur. This $p\pi$–$d\pi$ overlap in sulphinamides should be relatively small between oxygen and sulphur and thus the $p\pi$–$d\pi$ overlap between the nitrogen and the sulphur is more pronounced. The $p\pi$–$p\pi$ interaction is weaker between nitrogen and SO_2Cl than between nitrogen and SOCl. Electronegativity and $p\pi$–$d\pi$ interactions taken together seem to explain the experimental data. This reasoning is supported by the values of $^1J_{PN}$ and those of the free enthalpy ΔG of the barrier for rotation involving S–N and P–N in the investigated RRNX compounds. The percentage of sp^3 hybridization decreases in the three series of compounds in the sequence:

$$\%sp^3(\text{sulphonamides}) > \%sp^3(\text{sulphinamides}) > \%sp^3(\text{sulphenamides})$$

The ΔG values decrease in the order:

$$\Delta G_{(\text{sulphenamides})} > \Delta G_{(\text{sulphinamides})} > \Delta G_{\text{sulphonamides})}$$

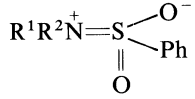
Halogen exchange in pronounced in sulphenamides and indicates the existence of a planar cation $R^1R^2N{=}S^+$, in which $p\pi$-$d\pi$ interactions between nitrogen and sulphur should be strongest and supports the above rule.

In a subsequent study[183] a linear correlation (equation 89) has been established by Dorie and Gouesnard between experimental chemical shifts $\delta^{15}N_{exp}$ and $\delta^{15}N$ chemical shifts calculated using equation 90.

$$\delta^{15}N_{exp} = 0.92\delta^{15}N_{calc} - 19 \tag{89}$$

$$\delta^{15}N_{calc(R^1R^2NR^3)}\text{ppm/NH}_3 = \sum_i [\delta^{15}N_{(H_2NR^i)} - \delta^{15}N_{(NH_3)}] \tag{90}$$

Relation 89 has been tested using ^{15}N-containing compounds $R^1R^2NR^3$ in which $R^3 = SO_2Ph$ or $R^3 = SO_3NH_4$. The departure from relation 89 by about 53 ppm towards high field, observed in the case of $(p\text{-}MeC_6H_4SO_2)_2NOH$, was taken as evidence of the specific diamagnetic effect of the hydroxyl group on the nitrogen which stabilizes the structure

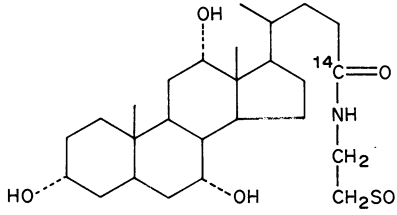


(91)

responsible for the high field shift [$\delta^{15}N_{calc} = (95.5 \times 2) + 115$ ppm = 306 ppm; hence equation 89 gives the value $0.92 \times 306 - 19 = 262.52$ ppm while the experimentally found chemical shift is $\delta^{15}N = 209.1$ ppm with respect to NH_3, which gives the departure 262.52–209.5 = 53.02].

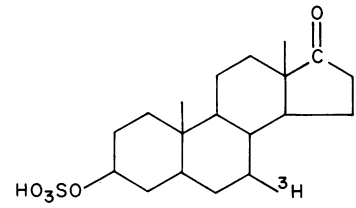
3. Direct specific activity determination of ^{14}C- and tritiun-labelled [24-^{14}C]taurocholic acid and [7-^{3}H]dehydrosterone sulphate by 'fast atom' bombardment (FAB) and field desorption mass spectrometry

[24-^{14}C]taurocholic acid (**201**) and [7-^{3}H]dehydroepiandrosterone sulphate (**202**) in [$^{2}H_5$]glycerol matrix have been used[184] to interpret the partial negative ion FAB spectra of these unlabelled compounds and to show that FAB and field desorption mass spetrometry enable one to determine quickly the specific radioactivity and label distribution within highly labelled biochemicals. The minimal specific radioactivities detectable by this method are about 20 MBq/mmol and 10 GBq/mmol for compounds labelled with ^{14}C and with tritium, respectively, with 1% and 5% accuracy. The use of mass spectrometry minimizes interferences from labelled impurities.



(**201**)

s.p. act. 1.80 GBq/mmol

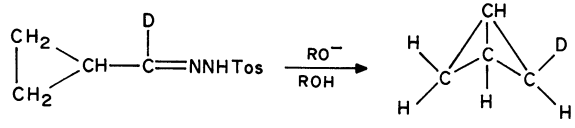


(**202**) *ca* 80 ng

sp. act. 1.129 TBq/mol

4. Deuterium study of the conversion of cyclopropanecarboxaldehyde tosylhydrazone to bicyclobutane

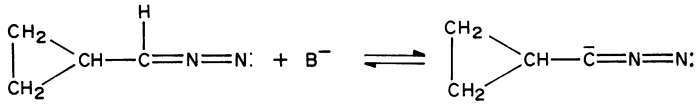
The mechanism of bicyclobutane (**203**) formation in the thermal decomposition of cyclopropanecarboxyaldehyde tosylhydrazone (**204**) in the presence of alcohols has been investigated using deuterium-labelled substrate **204**-d and deuterium-containing solvent (equation 91)[185]. In the presence of a limited amount of base, **203** contained 92% of one deuterium, practically all in *exo* position, but in the presence of excess of base **203** contained significantly less deuterium. Thermal decomposition of **204**-d in ethylene glycol-d_2 gave also **203**. Decomposition of unlabelled **204** in a deuterium-labelled solvent with a deficiency of base did not lead to incorporation of deuterium into the product. It has been suggested that, as with other tosylhydrazones[186], the decomposition of **204**-d involves the loss of *p*-toluenesulphinic acid and formation of diazomethylcyclopropane (**205**), which in



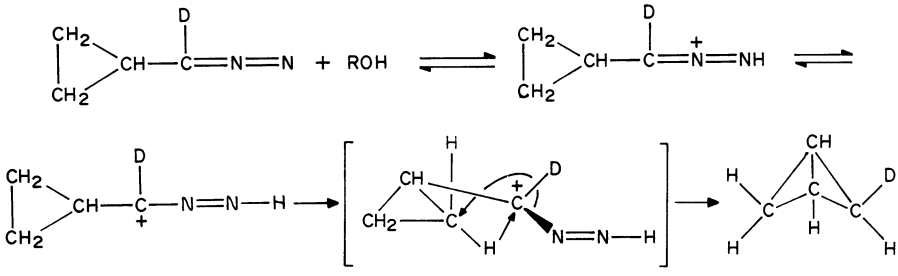
(91)

(**204**–d) (**203**)

turn undergoes a facile base-catalysed hydrogen exchange (equation 92). In the presence of alcohols (providing protons) the decomposition of **204**-d proceeds according to equation 93.



(205) (92)



(203) (93)

5. Deuteration and sulphonation of azulenes

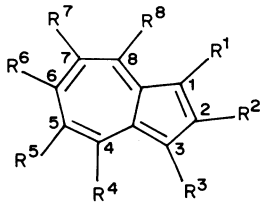
The deuteration with $CF_3CO_2{}^2H$ and sulphonation either with $(^2H_8)$dioxane·SO_3 or with $(^2H_3)$ nitromethane·SO_3 of series of azulenes (**206**), guaiazulene and bis(3-guaiazulenyl)methane (**207**) has been investigated[187] by NMR but the proposed mechanism (equation 94), involving the formation of stable σ-complexes (**208**) in the sulphonation of 4,6,8-trimethylazulene, has not been corroborated by studying deuterium kinetic isotope effects in the sulphonation of the perdeuterated analogues of **206** and **207**. Reaction of **207** with $CF_3CO_2{}^2H$ leads to three dications due to deuteration at the positions 1 + 1′, 1 + 3′ and 3 + 3′ in a ratio 17/44/39%. Strong acids, such as $HF{\cdot}BF_3$, FSO_3H or $FSO_3H{\cdot}SbF_5$, are used in studies of σ-complexes of aromatic hydrogen exchanges[188].

6. ^{18}O tracer and deuterium isotope effect study of the mechanism of oxygenation of organic sulphur compounds

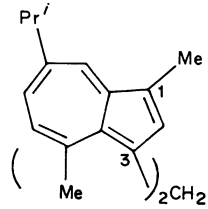
Electrophilic and nucleophilic mechanisms of the oxygenation of organic sulphur compounds, both chemical and enzymatic one-electron transfer oxygenation, accompanied by C—S bond cleavage taking place along with S-oxygenation, and the hypervalent σ-sulphurane mechanism (equation 95) have been reviewed by Oae[189]. The one-electron transfer oxidation mechanism has been supported by the lack of incorporation of ^{18}O from $H_2{}^{18}O$ medium into the sulphoxide produced[190].

On oxidation of the sulphide $PhSCH_3$[191a] in [^{18}O]-labelled phosphate buffer solution, only 1.3% of the $H_2{}^{18}O$ used has been incorporated into the produced sulphoxide

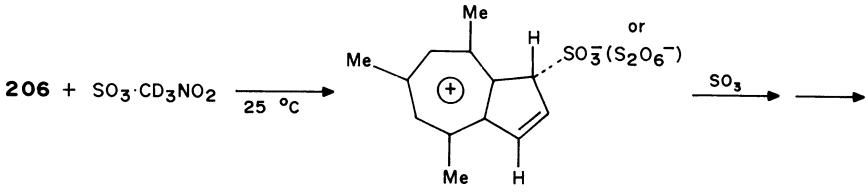
$$\begin{matrix} PhSCH_3 \\ \| \\ {}^{18}O \end{matrix}$$



(206) R^i = H, Me, Bu^t, Pr^i, CHO or Ph

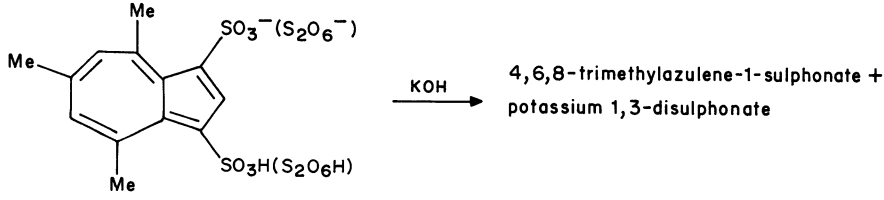


(207)



(208)

(94)



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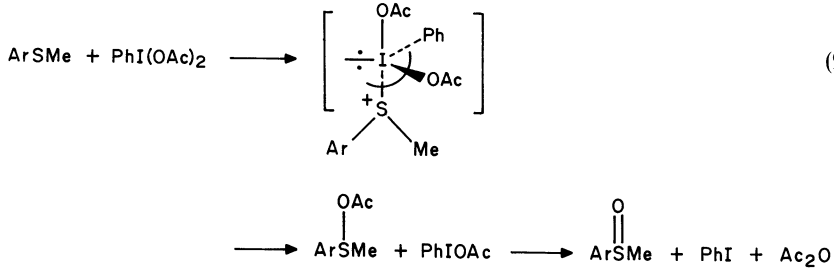


in the case of oxygenation with cytochrome P-450 and 4.7% in the case of Fenton's system. These data indicate that in the cytochrome oxygenation the substrate is tightly coordinated to the active site and the amount of heavy water molecules around this enzyme site is too small to compete with the 'oxenoid' located in the vicinity of the enzyme-bound substrate, which becomes the main source of oxygen so that the ^{18}O incorporation into the sulphide cation radical, $R^1R^2S^{+\cdot}$ is even smaller than in Fenton's system[191b,c]. It has been suggested that the enzymatic oxygenation of sulphides is taking place according to equation 96.

$$\mathrm{ArSCD_2X} \xrightarrow[\mathrm{O_2,\ NADPH,\ D_2O}]{\text{P-450}} \left[\mathrm{ArS^{+}CD_2X}\right] \xrightarrow{\downarrow[O]} \mathrm{ArS(=O)CD_2X} \quad \text{(S-oxygenation)}$$

$$\left[\mathrm{ArS^{+}CD_2X}\right] \longrightarrow \mathrm{ArSCDX(OD)} \longrightarrow \mathrm{ArSD} + \mathrm{ODCX} \quad \text{(S-dealkylation)}$$

(electrophilic attack by active oxygen bound to the heme iron) (96)

In the case of oxidation of phenacyl phenyl sulphide, $PhSCD_2COPh$, with hepatic rabbit liver microsomes at 36 °C in H_2O, only a small deuterium kinetic isotope effect, $k_H/k_D = 1.2$, has been found. In the reaction with Fenton's reagent, $k_H/k_D = 1.3$.

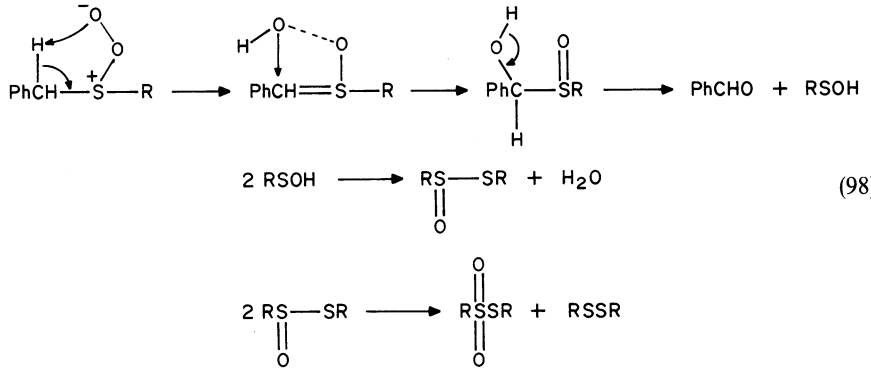
Oxidation of disulphides[192] with cytochrome P-450 proceeds according to equation 97. The mechanism of enzymatic S-oxygenation of thioanisole derivatives has also been studied[192]. Relatively large deuterium isotope effects ($k_H/k_D \approx 3.2$–5.1) have been found in the O-demethylation of the anisoles, $p\text{-}CD_3OC_6H_4OCH_3$ and $p\text{-}(CD_3O)_2C_6H_4$.

$$\mathrm{-S-S-} \xrightarrow[\mathrm{NADPH/O_2}]{\text{P-450}} \mathrm{-S(=O)-S-} \longrightarrow \mathrm{-S(=O)_2-S-} \qquad (97)$$

Oxidative cleavage of the C—S bond of the alkyl phenyl sulphide, $PhSCHR^1R^2$ (**209**), and formation of the ketone

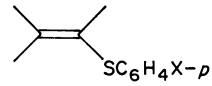
$$\mathrm{R^1-C(=O)-R^2}$$

and of the disulphide PhS—SPh has been observed when oxygen gas has been bubbled[190] into a methanol solution of **209** in the presence of *N,N'*-ethylenebis(benzoylacetoniminato)cobalt(II). In the case of a similar reaction of $PhSCH_2CN$ (**210**), carried out in MeOD, the recovered sulphide **210** contained 70% of deuterium at the α-methylene carbon after 50% conversion. According to Corey and Ouannes[193] the oxidation of benzyl alkyl sulphides with singlet oxygen proceeds as shown in equation 98.

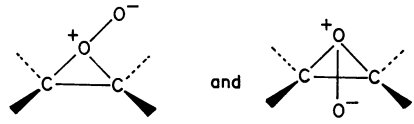


(98)

A tracer study of the mechanism of the rearrangement of thiolsulphinate with acetic anhydride using ^{13}C and ^{18}O has been carried out by Oae and coworkers[194]. A deuterium isotope effect study of the mechanism of the reactions of singlet oxygen with allylic and vinylic sulphides,



has been presented by Clennan and coworkers[195]. The formation of highly reactive perepoxide transient compounds



has been invoked to rationalize the determined small kinetic deuterium isotope effects.

B. Isotope Effect Studies with Labelled Sulphonic Acid Derivatives

Secondary deuterium isotope effect studies of solvolytic substitutions and eliminations of organic sulphonates have been reviewed by Shiner[196] and by Sunko and Borčić[197]. In the present section, more recent works are described and general remarks on deuterium secondary isotope effects are made.

1. Secondary deuterium isotope effects in trifluoroacetolysis of isopropyl p-toluenesulphonate

Rates of trifluoroacetolysis of undeuterated (Me_2CHOTs) and of deuterium-labelled isopropyl tosylates have been measured[198]. An α-deuterium isotope effect, $(k_H/k_D)_\alpha = 1.22 \pm 0.02$, has been found for isopropyl-α-d (Me_2CDOTs) at 25 °C. In the case of $(CD_3)_2CHOTs$ the secondary β-deuterium isotope effect equals $(k_H/k_D)_\beta = 2.12 \pm 0.1$. Values $\Delta H = 18.5 \pm 1$ kcal/mol and $\Delta S = -17 \pm 4$ e.u. were estimated for the undeuterated tosylate. α-Deuterium isotope effects are usually interpreted as depending on the geometry of the transition state, while β-deuterium isotope effects serve as a measure of the charge development in the transition state of solvolytic reactions. Secondary deuterium isotope effects are larger when using trifluoroacetic acid (which has low nucleophilicity and high ionizing power) than in the acetolysis of isopropyl tosylate where $(k_H/k_D)_\alpha = 1.12$ has been found[199]. The conclusion has been reached that the transition state in trifluoroacetic acid has greater carbocation character than in the acetic acid medium.

2. Methyl-d_3 isotope effects and α-methyl hydrogen rate effects in solvolytic reactions

Replacement of a hydrogen at the reaction centre by methyl[200] increases the rate of carbonium ion reactions by a factor of 10^6. This has been interpreted as the result of predominant hyperconjugative stabilization of a tertiary carbocation relative to a secondary ion in the solvolysis. Secondary β-deuterium isotope effects in solvolytic reactions also arise predominantly through a hyperconjugative mechanism[201]. Sunko and coworkers[202] confirmed the common origin of both effects, and found a linear

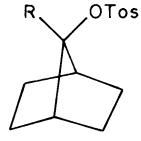
correspondence between the α-Me/H and α-CH_3/CD_3 rate ratios and established[203] a free energy-relationship (equation 99) for a variety of compounds including *p*-bromobenzenesulphonates ('brosylates' = OBs), but in the case of certain tosylates a deviation from the linear plot (equation 99) has been noted. In the solvolysis of the neopentyl derivative ($Me_3CCHROBs$) in 50 vol% aqueous ethanol, ($k_{CH_3}/k_H \cong 10^{3.73}$, and both $(k_{CH_3}/k_{CD_3})_{obs}$ and (k_{CH_3}/k_{CD_3}) calculated from equation 99 were found to be 1.206. In the case of solvolysis of 7-norbornyl tosylates (**211**) the predicted value of (k_{CH_3}/k_{CD_3}) was 1.49, while the observed ratios were 1.94 in AcOH, 2.11 and 2.00 respectively in 97% and 80% aqueous trifluoroethanol, and 1.84 in 80 vol% aqueous ethanol. These deviations from the values predicted by equation 99 have been analysed within the framework of the scheme in equation 100, which takes into account[203] the contribution to the isotope effects both from partial rate-determining elimination in the tight ion-pair step, R^+X^-, and at the solvent-separated ion-pair stage $R^+ \| X^-$. Some elimination occurs at the rate-determining step k_{5E}, but more elimination product arises (k_{6E}) from the solvent-separated ion pair formed after the rate-determining step since the relatively low basicity of the counter-ion in the case of 7-methylnorbornyl tosylates reduces the elimination from the tight ion pair. Even so, only approximate agreement was reached between the experimental values of the (k_H/k_{d_3}) ratios and the new values $(k_H/k_{d_3}) \cong 1.67$–2.52, calculated by using equation 100. It has been concluded that equation 99 holds for all reactions where the formation of the tight ion pair (k_1) or of the solvent separated ion pair (k_2) is the rate-determining step in both the hydrogen and α-methyl compound. S_N2 reactions for which CH_3/H and α-CH_3/CD_3 effects are small do not obey equation 99. The carbocation derived from **211** shows an unusually large electron demand.

$$\log(k_{\alpha\text{-}CH_3}/k_{\alpha\text{-}CD_3}) = 0.02024 \log(k_{\alpha\text{-}CH_3}/k_{\alpha\text{-}H}) \tag{99}$$

$$RX \underset{}{\overset{K}{\rightleftharpoons}} R^+X^- \xrightarrow{k_2} R^+ \| X^- \xrightarrow{k_{6S}} \text{alcohol} + \text{ether} \tag{100}$$

$$\downarrow k_{5E} \qquad \downarrow k_{6E}$$

olefin olefin



(**211**) R=H,CH_3,CD_3

3. *β-Deuterium isotope effect in the solvolysis of 2-cyano-2-propyl trifluoromethanesulphonate* (**212**)

An experimental kinetic study has shown that the influence of the α-cyano group on the rate of solvolysis of 2-propyl sulphonates, namely the $k_{(HCMe_2OTs)}/k_{(NCCMe_2OTs)}$ ratio (extrapolated from 80–170 °C temperature interval to 25 °C) in 100% 2,2,2-trifluoroethanol buffered with 2,6-lutidine, is only 3.5×10^3. This is considerably smaller than the retardation factor expected on the basis of the Taft polar substituent constant. To evaluate the possibility that the investigated methacrylonitrile formation reaction proceed by a rate-limiting concerted E2 elimination, the effect of α-deuterium substitution on the rate of

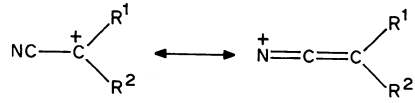
solvolysis of compound **212** has been measured[204] in the temperature interval 35–65 °C and the value extrapolated for 25 °C (equation 101).

$$N{\equiv}C{-}CMe_2OSO_2CF_3$$

(212)

$$k_{CH_3}/k_{CD_3} = [k_{(N-CC(CH_3)_2OTf)}/k_{(N-CC(CD_3)_2OTf)}]^{1/2}$$
$$= (3.86 \times 10^{-5}\,s^{-1}/1.77 \times 10^{-5}\,s^{-1})^{1/2} = 2.1808^{1/2} = 1.477 \qquad (101)$$

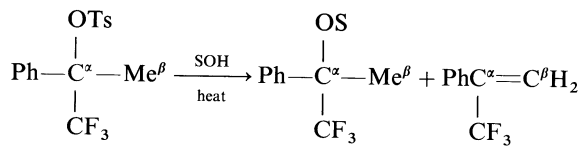
$\Delta H^{\neq}$ (kcal/mol) and $\Delta S^{\neq}$ (e.u.) are equal to 21.4 ± 0.5 and -8.9 ± 1.6 in the case of **212** and 20.3 ± 0.2 and -12.0 ± 0.7 in the case of $N{\equiv}CC(CD_3)_2OTf$. The obtained value 1.48 is close to the ratio 1.46 found in trifluoroacetolysis of 2-propyl *p*-bromobenzenesulphonate[198] ($2.12^{1/2} = 1.456$) and to the ratio 1.54 for the CD_3 isotope effect observed in the solvolysis of 2-trifluoromethyl-2-propyl *p*-toluenesulphonate[205]. These small values eliminate the possibility of a rate-limiting concerted elimination, since CH_3/CD_3 isotope effects in E2 eliminations are in the range 2–8[196]. S_N2 solvolysis without nucleophilic solvent assistance has also been ruled out by comparing the solvolyis of highly hindered 1-cyano-1-cyclooctyl tosylate which undergoes solvolysis without nucleophilic solvent assistance, with the solvolysis of cyclooctyl tosylate. The (H/CN) ratio has been found to be 1.87×10^3, a value close to the ratio found in the case of the 2-propyl system. The experimental kinetic data concerning the effect of the α-cyano group can be explained by assuming that the destabilizing inductive effect of the cyano group is balanced by mesomeric effect stabilizing the cationoid structures **212a**



(212a)

4. β-Deuterium isotope effect in the solvolysis of 1-trifluoromethyl-1-phenylethyl tosylate (**213**)

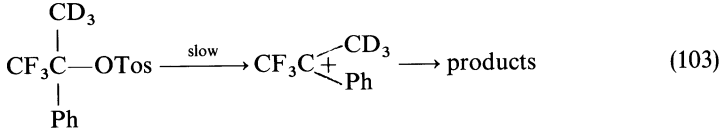
The kinetic study of the effect of electron-withdrawing substituents on the formation of carbocation intermediates is an area of continuous activity of numerous research groups. Tidwell and coworkers[205,206] investigated the influence of the CF_3 substituent on the solvolysis of tosylates (equation 102) in solvents of different ionizing power and nucleophilicity and found a linear free-energy relationship (with slope $m_{OTs} = 1.01$, correlation coefficient 0.986) between rate constants of compound **213**, $-\log k_{(CF_3CMePhOTs)}$, and the rate constants of 2-adamantyl tosylate, $-\log k_{(2\text{-}AdOTs)}$, in the same solvent at 25 °C. **213**-CH_3 and **213**-CD_3 have been prepared from the alcohols obtained by reactions of $PhCOCF_3$ with MeMgI or with CD_3MgI.



(102)

(213-CH_3) **(214)** **(215)**

The k_H/k_{CF_3} ratio, $k_{(PhCHMeOTs)}/k_{(PhCCF_3MeOTs)}$, is 2×10^5 in 100% EtOH. Salt addition ($NaClO_4$, NaCl, NaOAc, NaN_3) caused a modest (13 to 25%) increase in the rate of solvolysis of **213**-CH_3. Thus in 80% EtOH the value $k_{obs} = 1.33 \times 10^{-4}\,s^{-1}$ without $NaClO_4$ increased to $1.67 \times 10^{-4}\,s^{-1}$ in 0.06 M $NaClO_4$ at 65.8 °C. After 10 half-lives only the product of substitution by solvent (**214**) and of elimination (**215**) were observed by NMR. The isotope effects, k_{CH_3}/k_{CD_3}, corresponding to the rate of solvolysis of **213**-CH_3 and **213**-CD_3 (equation 103), range from about 1.54 to 1.77 in the less ionizing and more nucleophilic solvents ($k_{CH_3}/k_{CD_3} = 1.57$ in HOAc at 77.4 °C and 1.63 in 80% EtOH at 55.7 °C) to values of 1.22 to 1.34 in more ionizing solvents ($k_{CH_3}/k_{CD_3} = 1.28$ in CF_3COOH at 25 °C), since more polar solvents stabilize better the developing carbenium ion centre and reduce the demand for the hyperconjugative stabilization by the CH_3 group, while elimination is more pronounced in the less ionizing solvents.



(103)

(**213**-CD_3)

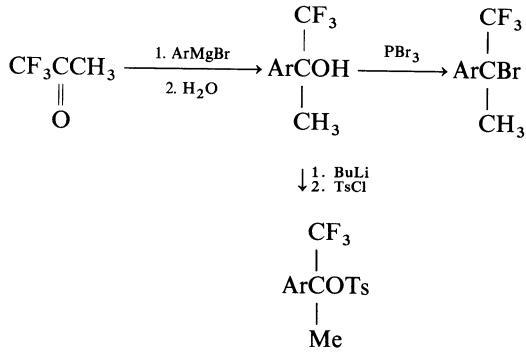
The linear free-energy relationship indicates that **213** reacts similarly to AdOTs by rate-limiting carbenium ion formation through the S_N1/E1 mechanism illustrated by equation 103. The substitution/elimination products can be formed from all intermediate species shown in equation 103a.

(103a)

The ion $PhC^{+}(CF_3)Me$ is relatively stable and can be observed by NMR. The adamantyl derivatives and **213** react by the same mechanism in which k_1 is the slowest rate-limiting ionization step. The salt effect is more pronounced in the case of CF_3CMe_2OTf and increases the rate by about 120% or 128% and 190% upon addition of 0.06 M NaOAc and NaN_3, respectively[206a]. The precision of the rate determinations was only ± 5%, therefore the observed, rather small temperature dependence of the secondary isotope effect cannot serve as an indirect measure of the vibrational structure of the transition state. Only the gross changes in the CH_3/CD_3 isotope effect caused by changes of solvent composition are used as a reliable tool indicating charge development and solvent participation in the transition state. Replacement of CF_3COOH by 80% EtOH decreases the rate of solvolysis of **213**-CH_3 by a factor of 6×10^4 and increases the isotope effect by a factor of 2.4. Similar rate decelerations (by a factor of 10^6) and deuterium isotope effect increases (by a factor of 2.0) have been observed in these solvents for phenylethyl chlorides.

In the solvolysis of cyclopentyl brosylate the increase in the isotope effect $k_{(H)}/k_{(\beta-d_4)}$ with increasing solvent ionizing power has been interpreted as evidence for a rate-limiting elimination in the more polar solvent[207]. Investigation of a much larger number of substituents is needed to understand the effect of electron-withdrawing α-substituents on solvolytic reactions.

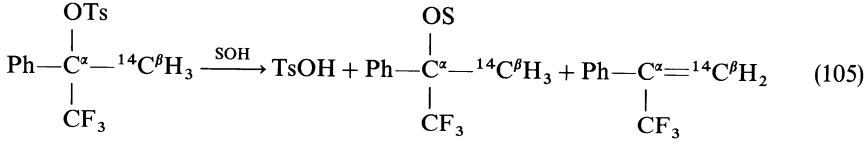
The solvolysis of nine 1-aryl-1-(trifluoromethyl)ethyl tosylates and 1-aryl-1-(trifluoromethyl)ethyl bromides obtained in the reaction in equation 104 has also been studied by K. T. Liu and coworkers[208].



(104)

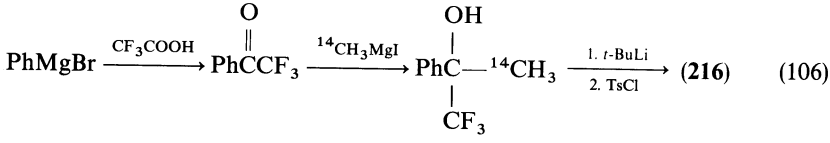
5. Kinetic ^{14}C isotope effect in the solvolysis of 1,1,1-trifluoro-2-phenyl-2-propyl-3-^{14}C-p-toluenesulphonate (**216**)

The investigation of the ^{14}C isotope effects in the reaction of equation 105 has been undertaken by Guo and Fry[209] using **216** labelled with carbon-14 in the beta position (equation 106). ^{14}C-labelled **216** has been synthesized according to equation 106.



(105)

(216)



(106)

(217)

The solvolytic reaction 105 has been carried out in glacial acetic acid at 75 °C. 10–20% of alkene were found in the reaction products by spectral analysis. The ^{14}C-labelled ester was reconverted to tosylate for the radioassay. The ^{14}C kinetic isotope effect, k/k^{β}, has been estimated by measuring the specific activity 'R_{ro}' of the reactant tosylate, 'R_{rf}' of the unreacted tosylate recovered at the fraction of reaction f, and the specific activity 'R_p' of the product ester derivatized as the tosylate. All three 'R' values were determined by liquid scintillation counting. The overall mean magnitude of k/k^{β}, obtained from four experiments, was 1.008 ± 0.024. This value corresponds to formation of the substitution product. $^{14}C^{\alpha}$ kinetic isotope effect measurements in this system would be necessary to corroborate previous conclusions concerning the rate constants specified by equation 103a, drawn from deuterium kinetic isotope effect studies. Guo and Fry[209] are inclined to interpret their ^{14}C kinetic isotope effect result as arguing against rate-determining carbenium ion formation and as implying the $S_N1/E1$ mechanism.

6. Deuterium isotope effects in alkyl sulphonate solvolyses in dimethyl sulphoxide

Deuterium isotope effects upon S_N2 solvolyses of various alkyl sulphonates in DMSO have been studied by Bowerox and Shiner[210]. Deuterium magnetic resonance (DMR) has been used to characterize the products of the solvolysis. Alkyl sulphoxonium salts reacted at 25 °C yielding unrearranged alcohol, alkene and ketone. The α-carbon undergoes in DMSO an identity exchange reaction at a higher rate than the decomposition reactions α- and β-deuterium isotope effects in the solvolyses of pinacolyl sulphonates in solvents with a wide range of ionizing power and nucleophilicity were about 1.155 and 1.205, respectively. Deuterium isotope effects in the solvolysis of cyclooctyl sulphonates have also been studied. All *trans*-5-d_1 isotope effects were between 1.14 and 1.15, while β-d_4 effects varied from 1.36 to 1.76. Stereospecific labelling demonstrated that the bulk of the elimination is *syn* in nature; elimination of the *cis*-β-proton is also important.

7. General remarks

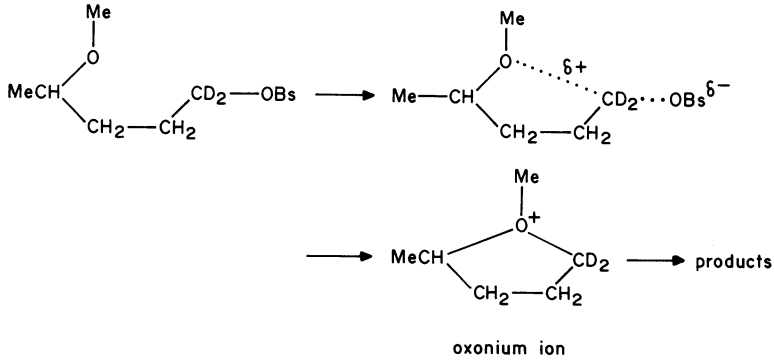
The examples quoted in this section of secondary deuterium isotope effect studies carried out during the two decades which have passed since the appearance of the two leading reviews[196,197] on this subject, illustrate the current trend in the isotope chemistry of sulphonate esters. The researchers try to avoid direct interpretation of the results in terms of vibrational frequencies and of force fields characterizing the isotopic substrates and transition states of solvolytic reactions of sulphonate esters. So far the calculations of kinetic isotope effects are based on statistical theories of reaction rates[1b,211,212] which require knowledge of the complete set of normal vibrations of the reacting isotopic molecules. Such data are seldom available for the initial states of the substrates and physically reasonable set of vibrations must be generated by constructing the proper force field for the transition state of the reaction. In the case of secondary deuterium isotope effects, changes of the force field and of the vibrations in the plane perpendicular to the reaction coordinate are important.

The substitution of hydrogen by deuterium at the reaction centre (secondary α-isotope effects) and at the position adjacent to it (secondary β-isotope effect) causes a rate deceleration of about 10–20% per deuterium atom at 25 °C. Gamma and more remote secondary deuterium isotope effects are negligible. These secondary deuterium isotope effects have therefore been explained qualitatively as indicating that phenomena such as rehybridization, hyperconjugation, inductive effects and nonbonding interactions cause the changes of the force field at the reaction centre in the transition state or stabilize the charge distribution and the structure of the transition state. α-Deuterium secondary isotope effect $[k_H/k_D = (k_H/k_{\alpha\text{-}D_2})^{1/2} = 1.15]$ in S_N1 reactions, caused by sp^3–sp^2 rehybridization taking place in the rate-determining step, are reproduced[197] by reducing to half the transition state H—C—X bending force constant (from 0.6 mdyn/Å to 0.3 mdyn/Å). Thus the secondary α-deuterium kinetic isotope effect is a measure of the change of the bending force constant between α-CH(α-CD) and the leaving groups. The force field of sulphonate esters in the ground state is analogous to the force field corresponding to H—C—F motion.

Secondary β-deuterium isotope effects are associated with the interaction of the empty *p*-orbital of the carbenium ion centre with the adjacent σ-carbon–hydrogen/deuterium bond. Small inductive effects are operating in the opposite direction. Release of steric strain is not considered to be associated with isotope effects in these reactions.

The influence of neighbouring group participation, by formation of bridged intermediates, causes (e.g. in the case of solvolysis of the primary brosylate) almost complete disappearance of secondary deuterium isotope effects, since the transition state resembles

in this case more an oxonium ion than a carbenium ion (equation 107) and has been discussed by Sunko and Borčić[197].



(107)

Room temperature data are usually discussed and compared in this section, but determinations for one reaction carried out at room temperature had to be compared quite often with data for a second reaction extrapolated from higher temperatures. Temperature dependence determinations of secondary deuterium isotope effects are not very reliabe, although statements about 'temperature independence' of these effects are frequent. Meanwhile, the temperature-dependent part makes the largest contribution to the calculated secondary isotope effect. A full discussion of abnormal temperature dependence of secondary β-deuterium isotope effects and of normal secondary α-deuterium isotope effects is given by Shiner[196]. The inductive, hyperconjugative and steric influences on the vibrational force constant changes taking place in the course of motion of the reacting molecules along the reaction coordinate from the reactants to the transition state as well as the nature of electronic effects on stretching frequency changes are discussed Thornton and Thornton[213,214].

The above brief outline indicates that secondary deuterium isotope effect studies provide a powerful supplementary isotopic technique, shedding new light on obscure kinetic problems encountered in nucleophilic solvolytic substitution reactions with sulphonate esters[215–217].

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CHAPTER 16

Directing and activating effects in reactions involving sulphonic acids and derivatives

T. WILLIAM BENTLEY

Department of Chemistry, University College of Swansea, Swansea, SA2 8PP, Wales, UK

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I. INTRODUCTION

A. Scope of Review

Reactions of sulphonate esters have played an important role in the development (over the past forty or more years) of many of the fundamental concepts on which modern organic chemistry is based, e.g. reaction mechanisms, neighbouring group participation, non-classical carbocations, kinetic isotope effects, solvent effects on reactivity and linear free-energy relationships[1], as well as the application of force fields (molecular mechanics) to calculate steric strain and to predict reactivity[2,3]. As research continues in all of these areas, newer aspects are also being investigated, e.g. applications of Marcus theory to group transfer. These topics are too broad to cover in detail in this chapter.

Emphasis will be given to recent developments in quantitative aspects of mechanisms and reactivity. It is now widely accepted that the substituent effects (both directing and activating) observed in organic chemistry are combinations of factors including 'intrinsic reactivity' observed in the gas phase. A major challenge is to show how intrinsic reactivity is modified in solution by solvation effects and by mechanistic changes. This had led to increased interest in solvation effects, which will be referred to as appropriate. Although some data are available for gas-phase acidities (Chapter 6), this chapter will be concerned exclusively with reactivity in solution.

Useful background material was presented recently in the sister publication on sulphonyl groups[4], e.g. the first two sections, surveying sulphur bonding and introductory material on the Hammett equation, are also relevant to this chapter.

Literature coverage is up to mid-1989.

B. Abbreviations

Trivial names and abbreviations commonly used for sulphonate esters are shown in Table 1. Other, less well known abbreviations will be defined in later sections as required.

II. NUCLEOPHILIC SUBSTITUTION

A. Activating Effects for C—O Cleavage in Sulphonate Esters

1. Comparisons with other esters

The most important activating effect of sulphonic acids and their derivatives is the activation of alcohols by conversion to sulphonate esters (e.g. tosylates, equation 1). In a subsequent step, the sulphonate anion (e.g. OTs^-) can then either be displaced by

TABLE 1. Trivial names and abbreviations for sulphonate esters

Formula	Name	Trivial name	Abbreviation
$4\text{-}BrC_6H_4SO_2OR$	*p*-Bromobenzenesulphonate	Brosylate	ROBs
CH_3SO_2OR	Methanesulphonate	Mesylate	ROMs
$4\text{-}NO_2C_6H_4SO_2OR$	*p*-Nitrobenzenesulphonate	Nosylate	RONs
$4\text{-}CH_3C_6H_4SO_2OR$	*p*-Toluenesulphonate	Tosylate	ROTs (or ROTos)
$CF_3CH_2SO_2OR$	2,2,2-Trifluoroethanesulphonate	Tresylate	ROTr[a]
CF_3SO_2OR	Trifluoromethanesulphonate	Triflate	ROTf

[a]Unfortunately the abbreviation Tr is also widely used for the triphenylmethyl (trityl) group, which is often attached to OH groups.

TABLE 2. Relative rates of nucleophilic displacement of various ester leaving groups

Leaving group (X)	Relative Rates		
	equation 2[a]	equation 3[b]	equation 4
Cl	1.0	1.0	1.0[c]
OAc	0.027	1.4×10^{-6}	
$OCOCF_3$		2.5	0.7[d]
$OPOPh_2$		3.8×10^{-3}	
$OPO(OEt)_2$	0.70[e]		
OTs	8.6	3.7×10^{4}	4.4×10^{5} [f]
N(Me)Ts	4.4×10^{-8} [e]		

[a]Data from Reference 5.
[b]Data from Reference 6.
[c]Data from Reference 7.
[d]Calculated from data in Reference 8.
[e]*p*-Tolysulphonyl group instead of phenylsulphonyl in equation 2.
[f]Data from Reference 9.

another nucleophile or eliminated to give an alkene. One of the major advantages of sulphonates, compared with other esters, is their high reactivity as leaving groups (nucleofuges, Table 2). As relative rates depend on the reaction, several model reactions (equations 2–4) have been chosen here for illustration. Elimination from sulphones (equation 2) has been examined for an extraordinarily wide range of leaving groups, including the highly unreactive N(Me)Ts group (Table 2).

$$ROH + TsCl \longrightarrow ROTs + HCl \quad (1)$$

$$PhSO_2(CH_2)_2X \rightleftharpoons PhSO_2\bar{C}\bar{H}CH_2X \longrightarrow PhSO_2CH{=}CH_2 + X^- \quad (2)$$

$$PhCHXCH_3 \longrightarrow \text{solvolysis in 80\% v/v ethanol/water at 75° C} \quad (3)$$

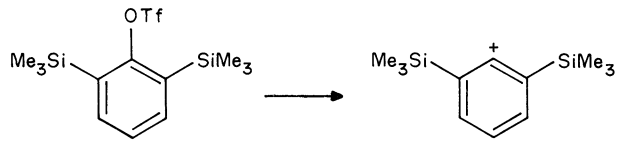
$$\text{1-Adamantyl-X} \longrightarrow \text{solvolysis in 80\% v/v ethanol/water at 25° C} \quad (4)$$

Considering only those leaving groups for which negative charge develops on oxygen, tosylates are much more reactive than acetates, trifluoroacetates, diphenylphosphinates (and other alkyl derivatives[6]) and phosphates (Table 2). Differences in relative rates are less marked in strongly acidic media, because sulphonates are protonated less readily than other esters[10].

The chloride leaving group was used as a convenient reference point for Table 2. Tosylate/halide rate ratios depend on a wide range of factors, including solvents (e.g. hydrogen bonding in protic vs. dipolar aprotic solvents[11] and low polarity solvents[12]) and differences in susceptibilities to SET pathways (e.g. ROTs < RCl < RBr < RI[13,14]). Iodides may react with thiophenoxide ion over 100 times faster than tosylates (see Section II.A.3).

2. *Substituent effects on the reactivity of sulphonate esters*

Many synthetically useful procedures have been developed[15] since it was established[16,17] that the reactivity of sulphonate esters (ZSO_2OR) depends strongly on the substituent (Z); for instance, because triflates ($Z = CF_3$) are much more reactive than tosylates, they permit solvolytic generation of aryl cations (**2**) from activated aryl esters (**1**)[18], nucleophilic aromatic substitution catalysed by metal complexes (equation 5)[19,20]



(1) (2)

and nucleophilic vinylic substitution[15,21].

$$ArOTf + {}^{-}CN \longrightarrow ArCN + {}^{-}OTf \quad (5)$$

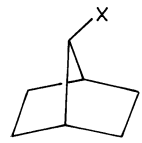
Solvolytic reactions provide much of the kinetic data available on substituent effects for reactions of alkyl sulphonates (ZSO_2OR), although exactly comparable results for a wide range of sulphonate leaving groups (ZSO_3^-) are rarely obtained. To compare data at a common temperature, extrapolations of rate data from higher or lower temperatures are usually made using the Arrhenius equation; this introduces significant uncertainties especially when the extrapolation is over a wide temperature range, but such calculations are widely accepted. Substituent effects on representative solvolytic reactions are expressed as relative rates in Table 3.

The very high reactivity of triflates can be seen from the OTf/OTs rate ratios (Table 3). As well as depending on Z, relative rates depend on the solvent and, to a lesser extent, on the alkyl group (R). Solvent effects can be illustrated by solvolyses of 2-adamantyl sulphonates at 25 °C; the OTf/OTs rate ratio of $> 10^5$ in ethanol (Table 3) is reduced to 2.9×10^4 in acetic acid[36]. Because the triflate anion is very weakly basic, it appears that rates are lower in strongly hydrogen bonding solvents[37]. This effect is most apparent for solvolyses in trifluoroacetic acid, for which OTf/OTs rate ratios are 1.9×10^3 for 2-adamantyl[36] (at 25 °C) and 780 for ethyl[38] (at 50 °C). A small dependence on the alkyl group (R) is shown by variations in the OTf/OTs rate ratios for acetolysis. For seven substrates examined[39], ratios varied from 2×10^4 for R = Me[16] to 2×10^5 for R = 7-norbornyl (**3**)[39].

TABLE 3. Relative rates of solvolytic reactions of alkyl sulphonates ZSO_2OR

Alkyl group (R)	Solvent	OTs/OMs	OBs/OTs	OTr/OTs	OTf/OTs
1-Ad[a]	EtOH[b]	1.8	5.6	82	8.0×10^5
2-Ad[a]	EtOH[c]		5.6	105	3.9×10^5
i-Pr	80% EtOH[d]	1.14[e]	4.8[f]	67[g]	
c-C_4H_9	AcOH[h]	0.70	3.6		
Et	AcOH[i]				3.0×10^4
Me	Water[j]	1.51	2.49[f]		1.6×10^4

[a]Ad = Adamantyl.
[b]Data at 25 °C from References 22 and 23.
[c]Data at 50 °C from References 23–25.
[d]Solvent is % v/v ethanol/water at 25 °C; tosylate data from Reference 26.
[e]Value at 50 °C from Reference 27.
[f]Brosylate data at 25 °C from Reference 28.
[g]Tresylate data at 25 °C from Reference 29.
[h]Data at 50 °C from Reference 30.
[i]Data at 25 °C from References 31 and 32.
[j]Data extrapolated to 0 °C from Reference 33, except for triflate data from Reference 34 (solvent at 0.3 °C contained 2% dioxan) and Reference 35 (solvent was 95% D_2O/5% CF_3CO_2D).



(**3**), X = OTf, OTs

Substituent effects of various fluoro-substituted sulphonates have been investigated. Fluorosulphonates (Z = F, more properly referred to as fluorosulphates[17]) are slightly less reactive (*ca* 3-fold) than triflates[34,35,40–42], whereas perfluorobutanesulphonates (nonaflates, Z = C_4F_9) are slightly more reactive (*ca* 2-fold)[16,43]. Tresylates have reactivity in between tosylates and triflates[41] (Table 3), and pentafluorobenzenesulphonates[44] are more reactive (*ca*-20-fold) than tresylates[22,24].

Sulphonate leaving groups incorporating trimethylammonium cations have also been studied. 2-Adamantyl [2]betylate (2-$AdOSO_2CH_2CH_2NMe_3^+$) solvolyses at the same rate as 2-adamantyl tresylate[45], showing that the substituent effect of the $CH_2NMe_3^+$ group is the same as a CF_3 group, i.e. one NMe_3^+ group has the same effect as three fluorines. It has been shown[46] that [0]betylates (**4**), in which the NMe_3^+ group is directly attached to sulphur, are about 10^5 times more reactive even than triflates! Their reactivity is so high that their formation has to be inferred from decomposition products (equation 6). Even with this super leaving group, unsubstituted phenyl cations are not produced under typical solvolytic reaction conditions, whereas they are formed from diazonium ions; hence, nitrogen is a superior leaving group compared with [0]betylates[47].

$$Me_2NSO_2OR + MeOSO_2F \longrightarrow \underset{\textbf{(4)}}{[Me_3N^+SO_2OR\ FSO_3^-]} \longrightarrow ROSO_2F + Me_3N^+SO_3^- \qquad (6)$$

Reactivities of brosylates, mesylates and tosylates are similar (Table 3), and show relatively small variations with solvent and alkyl group (R). Tosylate/mesylate rate ratios vary from 0.5 to 2.0 in S_N1 solvolytic reactions of adamantyl sulphonates[48]. Slightly higher ratios may be observed for S_N2 reactions in dipolar aprotic solvents, e.g. second-order rate constants for nucleophilic substitution in n-octyl sulphonates by thiocyanate anion show tosylate/mesylate rate ratios increasing from 0.7 in methanol to 1.5 in chlorobenzene and in cyclohexane, and to 4.4 in DMSO[12].

Brosylate/tosylate rate ratios can be considered in the broader context of reaction series in which the substituents (Z) may be a wide range of *meta*- and *para*-substituted benzene derivatives. Hammett ρ values for thirty such solvolytic reaction series have been tabulated[23], the highest observed ρ values are *ca* 1.8, for ethanolyses of 1- and 2-adamantyl sulphonates. Dependence on the alkyl group (R) is shown by the decrease in ρ to 1.55 for ethanolyses of *i*-propyl and to 1.3 for ethyl and methyl sulphonates. Lower ρ values (and lower OBs/OTs rate ratios—Table 3) are observed for more strongly hydrogen-bonding solvents.

Nosylates are both more reactive and more hydrophilic than brosylates and tosylates[49–51]. However, all of these sulphonates are very sparingly soluble in water and deviations from the Beer–Lambert law are observed even when solutions have been sonicated and appear to be homogeneous; mesylates are more readily soluble in water[10]. Nosylates have higher melting points than other monosubstituted benzenesulphonate derivatives (e.g. R = Me, Et, *i*-Pr[52]). For high precision kinetic studies of *i*-propyl sulphonates, including ^{14}C isotope effects, the β-naphthalenesulphonate group was chosen[53].

Attempts have been made to correlate some of the rate data for a wide range of activating substituents. An unusual plot (vs. σ_m) for solvolytic alkyl-oxygen cleavage of Z-SO_2OR appeared to give a satisfactory correlation ($\rho = 10.3$) for substituents ranging from Z = Me to Z = CF_3[41], but only one of the substituents contained a benzene ring (Z = *p*-tolyl) and the rate data were from diverse sources including different solvents. Correlations with σ^*[54] and σ^-[55] have also been reported. Recognising that a purely inductive effect of the substituent Z could not explain the greater reactivity of triflates than fluorosulphonates[56], the σ^* parameter was modified[46] to incorporate a small resonance contribution. Using this approach, both solvolytic and anionic nucleophilic substitutions (e.g. see Table 4) were correlated; satisfactory results were obtained for dimethyl sulphate (Z = OMe, R = Me) and reasonable predictions were made for the highly reactive [0]betylates (**4**)[46].

For convenient kinetic studies of relatively reactive substrates, it may be useful to employ sulphonates significantly less reactive than tosylates, e.g. 2,4,6-trimethoxybenzenesulphonates and pentamethylbenzenesulphonates in aqueous ethanol are about 8-fold less reactive than tosylates[57,58]. The effect of steric crowding around the sulphur atom appears to be small, because rates of acetolyses of a range of secondary and tertiary alkyl 2,4,6-trimethylbenzenesulphonates and 2,4,6-tri-isopropylbenzenesulphonates (Tps) differ by < 50%[59], the largest rate retardation was for *t*-$Bu_2CHOTps$, which was 16-fold less reactive than the corresponding tosylate.

Rate-retarding effects of *ca* 10^5 were observed in hydrolyses of sodium alkyl sulphates in basic solution[60], where Z is the strongly electron-donating substituent O^-. Primary substrates showed second-order kinetics, but first-order rate constants were obtained for secondary alkyl substrates; e.g. for *i*-propyl at 100 °C, the (interpolated) rate constant is 3.0×10^{-6} s^{-1} for the sulphate salt, whereas for hydrolysis of *i*-propyl tosylate the (extrapolated) rate constant is 0.76[33].

A chiral leaving group, camphor-10-sulphonate, revealed small but significant rate differences between solvolyses of optical isomers of 2-octyl derivates the results are surprising because three carbon atoms separate the two chiral centers[61].

3. *Comparisons of alkyl sulphonates with other powerful alkylating agents*

A comparative table, published elsewhere[17], and showing a wide range of functional groups, gave the following order of methylating power towards neutral molecules: $Me_2SO_4 < Me_3O^+ < MeOSO_2F$ and $HC(OMe)_2^+ < Me_2Cl^+$. Kinetic data provide additional quantitative comparisons (Table 4).

For alkylation of triethylamine in acetonitrile at 0 °C (equation 7)[54], ethyl fluorosulphate reacts 1.5×10^5 times faster than ethyl tosylate and 2.3×10^4 times faster than diethyl sulphate. Similarly, for methylation of *p*-nitrophenoxide in sulpholane at 42 °C (equation 8)[55], methyl triflate reacts 1.6×10^5 times faster than methyl tosylate and 3.6×10^3 times faster than dimethyl sulphate (excluding the statistical correction). These OTf/OTs rate ratios of *ca* 10^5 are of similar magnitude to those recorded for solvolytic reactions (Table 3); even higher OTf/OTs rate ratios of 1.4×10^6 have been reported for ethylation of the sodium enolate of ethyl acetoacetate[42].

$$EtX + Et_3N \longrightarrow Et_4N^+X^- \quad (7)$$

$$MeX + p\text{-}O_2NC_6H_4O^- \longrightarrow p\text{-}O_2NC_6H_4OMe + X^- \quad (8)$$

Comparing methyl triflate with other powerful alkylating agents, it solvolyses much faster than methyl perchlorate: 90-fold faster in water at 0 °C, 60-fold faster in methanol at −23 °C and over 20-fold faster in acetonitrile at 0 °C to give the nitrilium ion (MeC≡

TABLE 4. Second-order rate constants ($M^{-1} s^{-1}$) for nucleophilic displacement of alkylating agents (RX)

X	Equation 7[a]	Equation 8[b]	Equation 9[c] 0.3 °C	Equation 9[c] −23.5 °C	Equation 11[b,d]
I		0.105			5.7×10^4
OTs	1.2×10^{-6}	0.0196			4.3×10^2
OSO_2OR	7.4×10^{-6}	0.85			1.0×10^4
$OClO_3$			5.1×10^{-3}		
OSO_2F	1.7×10^{-1}	1100	3.5×10^{-2}		2.8×10^6
OSO_2CF_3		3100	8.6×10^{-2}[e]	6.8×10^{-3}	6.4×10^6
$^+OMe_2$		>5000[f]		7.7×10^{-2}	1.9×10^8

[a]In acetonitrile at 0 °C; kinetic data from Reference 54.
[b]In sulpholane at 42 °C; kinetic data from Reference 55.
[c]In acetonitrile; kinetic data from Reference 34.
[d]For Z = H.
[e]At −0.1 °C.
[f]Rates too fast to measure.

NMe^+)[34]. Also, in reactions with benzenesulphonate anion in acetonitrile (equation 9)[34] (Table 4), methyl triflate reacts over 17-fold faster than methyl perchlorate.

$$MeX + PhSO_3^- \ ^+NBu_4 \longrightarrow MeOSO_2Ph + X^- \ ^+NBu_4 \qquad (9)$$

In the following discussion of reactions of trimethyloxonium ion, statistical corrections have been made for the three methyl groups. Relative rates compared with methyl triflate depend on the reaction conditions, and there are significant differences between solvolytic reactions and reactions with anionic nucleophiles. Hydrolysis at 4 °C in 95% D_2O (containing 5% TFA) showed that trimethyloxonium borofluoride was 3.6-fold less reactive than methyl triflate[35], in agreement with the above qualitative order of methylating power. However, rates are almost identical for methylation of substituted phenyl methyl sulphides in sulpholane at 30 °C (equation 10)[62]. Also, the trimethyloxonium ion reacts 4 times faster in methanol at −23 °C and 1.6-fold faster in acetonitrile at 0 °C[34]. In reactions with anionic nucleophiles (equations 8, 9 and 11; Table 4), the trimethyloxonium ion reacts faster (up to 25-fold for the reaction shown in equation 11, $Z = NO_2$[55]), presumably because of the favourable cation–anion interactions[62].

$$ZC_6H_4SMe + MeX \longrightarrow ZC_6H_4SMe_2 \ ^+X^- \qquad (10)$$

$$ZC_6H_4S^- + MeX \longrightarrow ZC_6H_4SMe + X^- \qquad (11)$$

Extending equation 7 to the methylation of other amines in sulpholane at 30 °C, it has been shown that methyl triflate reacts faster than dimethyl sulphate by factors of 9.9×10^3 (with dimethylaniline), 3.6×10^3 (3-nitro-*N*,*N*-dimethylaniline) and 4.4×10^3 (pyridine)[62], ignoring the statistical factor of two in favour of dimethyl sulphate. The above results (and others given in Table 4) show that dimethyl sulphate is relatively unreactive, i.e. 10^3–10^4 times less reactive than methyl triflate. Also, dimethyl sulphate hydrolyses only *ca* 15-fold faster [33] (statistically corrected for the methyl groups) than methyl mesylate (Z = Me, R = Me). In terms of the modified σ^* correlation, discussed in Section II.A.2[46], there are competing inductive and resonance effects of similar magnitudes for the substituent Z = OMe in sulphonate esters (ZSO_2OR).

Interestingly, alkyl chlorosulphates have about the same reactivity as fluorosulphates towards alkylation of tetrahydropyran in nitrobenzene[63]. Methyl 2,4,6-trinitrobenzenesulphonate decomposes rapidly in sulpholane at room temperature, showing that it is more reactive than methyl triflate[64]. An even more powerful methylating agent is $MeOSO^+$, formed from methyl chlorosulphite with antimony pentafluoride in thionyl chloride[65]. Discussion of a quantitative scale of 'methylating power' (M_Y, see equation 21) is included in the following section.

B. Nucleophilicities of Sulphonate Anions

1. Applications of the Swain–Scott equation

Nucleophilicities relative to a standard solvent can be quantified by the Swain–Scott equation (12)[66], in which k and k_0 are the second-order rate constants for reactions of the nucleophile and solvent respectively, and s is a measure of the sensitivity of the substrate to nucleophilicity n. By this definition, the nucleophilicity of the solvent is zero. For all reactions examined, there will be competition between attack by solvent (present in large excess) and reaction with added anionic nucleophiles. Hence, only n values well above zero can be obtained with satisfactory reliability. In the original work[66], the solvent was water and all but one of the substrates were neutral; s was defined as 1.0 for methyl bromide and was calculated to be 0.66 for ethyl tosylate; the lowest reliable n value reported was 1.9 for picrate anion, but a value of < 1 for p-tosylate anion was reported[66] in a footnote.

$$\log(k/k_0) = sn \tag{12}$$

In the results summarized in Table 5, no allowance has been made for variations in s values, so trends in the rows of results are significant but direct comparisons should *not* be made between the absolute values for individual anions shown in each column of results.

A more sensitive alternative procedure for measuring the relative nucleophilicities of anions is based on reactions of triethyloxonium ions in ethanol at 0 °C[68]. The probable cause of the greater sensitivity is cation–anion interactions, which make nucleophilic attack by anions (equation 13) relatively more favourable than attack by solvent (equation 14). The results (Table 5) show that tosylate anion is less nucleophilic even than nitrate ion.

$$Et_3O^+ + {}^-O_3SAr \longrightarrow EtO_3SAr + Et_2O \tag{13}$$

$$Et_3O^+ + EtOH \longrightarrow 2Et_2O + H^+ \tag{14}$$

Substituent effects on the reactions of arenesulphonates with trimethyloxonium ion (equation 13) in acetonitrile[70] (and with methyl triflate[71]) show $\rho = -1.1$, e.g. p-methoxybenzenesulphonate anion reacts about 15-fold faster than p-nitrobenzenesulphonate

TABLE 5. Nucleophilicity (n, equation 12) of tosylate anion in comparison with other anions

Reference substrate	I^-	NCS^-	Br^-	Cl^-	NO_3^-	TsO^-
CH_3Br[a]	5.04	4.77	3.89	3.04	1.03[b]	< 1
Et_3O^+[c]	4.59	4.21	4.21	3.67	2.91	2.23
$4\text{-}NO_2C_6H_4CH_2OSO_2CF_3$[d]	3.64	3.64	2.89	2.21	1.28	0.92

[a]Relative to water ($n = 0$) at 25 °C; data from Reference 66.
[b]Data from Reference 67.
[c]Relative to ethanol ($n = 0$) at 0 °C (equations 12 and 13); data from Reference 68.
[d]Relative to water ($n = 0$) at 25 °C; data from Reference 69.

anion. Hence n values in ethanol for a whole range of arenesulphonate anions may now be accessible via equation 13.

Because of the convenience of modern HPLC techniques with UV detection, it is tempting to obtain relative rate data from product ratios. Nucleophilic selectivities towards *p*-nitrobenzyl triflate (Table 5) showed that the tosylate anion was a stronger nucleophile than water[69]. In studies related to chemical carcinogens and mutagens, logarithms of selectivities of alkyl sulphonates towards attack by 4-(*p*-nitrobenzyl)pyridine or by water gave S_{NBP} values, which were correlated successfully with s values[72].

2. *Applications of the Marcus equation*

An alternative measure of nucleophilicity has recently been derived from Marcus theory[73], originally applied to electron transfer and to proton transfer, and more recently extended to methyl transfer[74,75] and other group transfers[76,77]. Before useful predictions can be made, this theory requires an input of experimental data (both kinetic and thermodynamic). The required kinetic data may be obtained from equation 15, in which the attacking nucleophile and the leaving group are the same. This is referred to as an identity reaction, and can be studied using appropriate isotopic labels, e.g.[35] S[78].

$$ArSO_3^- + MeO^*SO_2Ar \longrightarrow MeOSO_2Ar + Ar^*SO_3^- \tag{15}$$

The other data required are equilibrium constants; these have been measured relative to the benzenesulphonate anion as reference[75] (equation 16), from which any other desired equilibrium constants can be calculated.

$$PhSO_3^- + MeOSO_2Ar \rightleftharpoons ArSO_3^- + MeOSO_2Ph \tag{16}$$

Following the general terminology of Lewis and coworkers[75], rate constants for the identity reactions (equation 15) of nucleophiles X^- are referred to as k_{XX} and of nucleophiles Y^- are referred to as k_{YY}; corresponding reference equilibrium constants for substrates MeX and MeY (equation 16) are K_{Xr} and K_{Yr}. For the general reaction (equation 17)

$$X^- + MeY \longrightarrow Y^- + MeX \tag{17}$$

the rate constant k_{YX} is given by equations 18 and 19:

$$\log k_{YX} = \tfrac{1}{2}\log (k_{YY}/K_{Yr}) + \tfrac{1}{2}\log (k_{XX}/K_{Xr}) \tag{18}$$

$$\log k_{YX} = M_Y + N_X \tag{19}$$

where M_Y is given by equation 20 and N_X is given by equation 21. These two equations show that M_Y is a property only of the alkylating agent (MeY), and the name 'methylating power' has been suggested[75]; similarly N_X, named 'nucleophilic power', is a property only of the nucleophile (X^-)[75]. Values of N_X for sulphonates (Table 6) show their low nucleophilicities compared with iodide ion, and the further effect of electron-withdrawing substituents, e.g. making triflate a very weakly nucleophilic anion. The order of methylating power M_Y is as expected from earlier results (Table 4).

$$M_Y = \tfrac{1}{2}\log (k_{YY}/K_{Yr}) \tag{20}$$

$$N_X = \tfrac{1}{2}\log (k_{XX}/K_{Xr}) \tag{21}$$

Comparing equation 19 with the Swain–Scott equation 12, the M_Y term replaces the $\log k_0$ term and the single N_X term replaces the dual sn term. The selectivity term (s), a property of the methylating reagent, appears to be constant presumably because all of the reactions considered are methyl transfers.

TABLE 6. Nucleophilic power of X^- nucleophiles (N_X, equation 21) and methylating power (M_Y, equation 20) for sulphonates (MeY) in sulpholane at 35 °C[a]

X^-	N_X	MeY	M_Y
$CF_3SO_3^-$	−4.2	CF_3SO_3Me	2.28
FSO_3^-	−4.1	FSO_3Me	2.14
$C_6F_5SO_3^-$	−4.1	$C_6F_5SO_3Me$	1.82
$MeOSO_3^-$	−2.9	$(MeO)_2SO_2$	−0.84
$4\text{-}ClC_6H_4SO_3^-$	−2.6	$4\text{-}ClC_6H_4SO_3Me$	−1.86
$PhSO_3^-$	−2.3	$PhSO_3Me$	−2.32
$MeSO_3^-$	−2.2	$MeSO_3Me$	−2.73
(I^-)	(1.3)	(MeI)	(−0.92)

[a]Data from Reference 75.

3. *Nucleophilic reactions of strongly nucleofugal groups*

Sulphonate anions are generally regarded as relatively weak nucleophiles, but it has recently been realized that this is not always so. To observe the product of attack by a weak nucleophile (e.g. triflate), it is necessary to suppress the subsequent reactions of the highly reactive product by appropriate choice of solvent (e.g. reactions of silver salts with alkyl halides are carried out in hexane)[23]. It is then possible to establish that typical weak nucleophiles may react with short-lived cations or in S_N processes having transition states with high carbocation character[79]. Perchlorates are reported to be relatively nucleophilic even in acetic acid[79], contrary to the accepted interpretation of the special salt effect[1a].

Within a substrate-reagent ion pair of [2] betylates (**6**), the sulphonate anion (**5**) reacts in refluxing toluene to give the ester (**7**):

$$\underset{\textbf{(5)}}{R'SO_2O^-} + \underset{\textbf{(6)}}{ROSO_2CH_2CH_2NMe_3^+} \longrightarrow \underset{\textbf{(7)}}{R'SO_2OR} + {}^-OSO_2CH_2CH_2NMe_3^+$$

If the sulphonate anion also contains a hydroxyl group (as in **8**), nucleophilic attack by the anion may be preferred, i.e. in this situation the sulphonate anion may be more nucleophilic than the hydroxyl group[80,81].

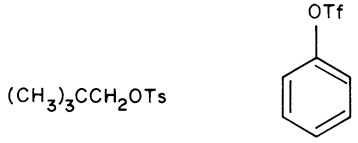
$$\underset{\textbf{(8)}}{HOCH_2(CH_2)_nSO_2O^-}$$

C. Nucleophilic Attack at Sulphur

1. *Competing pathways: S—O vs. C—O cleavage in sulphonate esters*

Nucleophilic attack with C—O cleavage of esters is a very useful reaction in organic synthesis, and usually predominates over the competing process of S—O cleavage. However, under some circumstances, S—O cleavage may be the major reaction pathway. From the earlier literature which has been reviewed[82], it appears that S—O cleavage may occur when C—O cleavage becomes less favourable for steric reasons. For example, in reactions of neopentyl tosylate (**9**), where the methylene group is hindered by the *t*-butyl group, methoxide ion cause S—O cleavage[83]. Likewise, in sulphonate esters of phenols, where direct S_N2 reaction with C—O cleavage is prevented by the aromatic ring, S—O cleavage takes place, e.g. attack of 3M methoxide ion on phenyl triflate (**10**) occurs readily

at 35 °C[84]. S—O cleavage has also been observed in vinyl sulphonates[85]. Both polarizability and steric effects in the attacking nucleophile may also be important[82]; less polarizable nucleophiles (e.g. methoxide[84], fluoride[86] appear to favour S—O cleavage. Another factor for mesylate esters could be the acidity of the methyl group in the presence of strongly basic nucleophiles (cf. chapter on sulphenes).



(9) (10)

2. *Mechanisms of sulphonyl transfer*

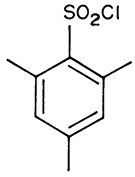
According to the Marcus treatment (Section II.B.2) observed rates depend on appropriate equilibrium constants and on the rates of identity reactions, and there is then no clear-cut distinction between the attacking nucleophile and the leaving group. Hence, terminology like methyl transfer and sulphonyl transfer are becoming popular as alternatives to established concepts of nucleophilic substitution. As recent reviews[87,88] give detailed accounts of the mechanisms of sulphonyl transfer, including mechanisms of nucleophilic substitution for sulphonyl halides and other derivatives of sulphonic acids, detailed discussion of these topics will not be repeated here.

By comparison with corresponding carboxylic acid chlorides, sulphonyl chlorides are less activated in S_N1 reactions. Available evidence is consistent with concerted bimolecular nucleophilic displacements at the sulphonyl group[87], whereas corresponding reactions of carboxylic acid chlorides may occur by S_N1 processes[89–91]. Typical sulphonyl chlorides form oxygen-bonded donor–acceptor complexes with SbF_5[92], and only exceptionally stabilizing groups such as *p*-methoxyphenyl give long-lived sulphonyl cations[93]. In contrast, acylium cations are readily formed and can be isolated as stable salts[94]. Mechanisms for bimolecular nucleophilic displacements at the sulphonyl group include addition to the sulphonyl group (the S_AN mechanism)[87].

3. *Activating effects in carbohydrates and in polynucleotide synthesis*

The challenging problems of selectivity in reactions of polyhydroxy compounds have stimulated interest in a range of aromatic sulphonyl chlorides and sulphonamides. In the phosphodiester approach for the synthesis of internucleotide bonds[95–97], a condensing agent is required to activate a phosphomonoester selectively in the presence of a secondary alcohol. Although in the original work dicyclohexylcarboxiimide was preferred over TsCl[98], later studies showed that TsCl, mesitylenesulphonyl chloride (**11**)[99] and triisopropylbenzenesulphonyl chloride (**12**)[100] were useful condensing agents. These reagents were later applied to other problems in organic synthesis.

Contrary to the reactions of carboxylic acid derivatives, the *ortho*-methyl groups in **11** provide little steric hindrance to nucleophilic attack at sulphur, judging from studies of competition between S—O and C—O cleavage[101] and of rates of sulphonylation of 2′,3′-di-*O*-benzoyluridine (**13**)[100]. Following a kinetic study[101] of the reaction in methanol of piperidine with nitrophenyl esters of TsOH and mesitylenesulphonic acid, the effect of the *ortho*-methyl group was described as 'miserable'; unusually, this qualitative description is more graphic than the kinetic data, which show rate decreases up to 8-fold attributed mainly to electronic effects. In contrast, **12** appears to be significantly more sterically-hindered, because it reacts with **13** about 10-times more slowly than **11** or TsCl[100].



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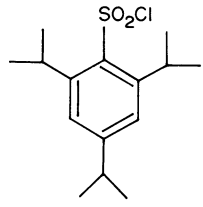

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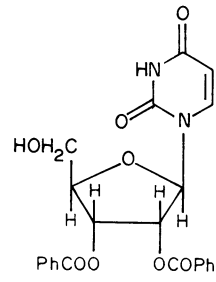
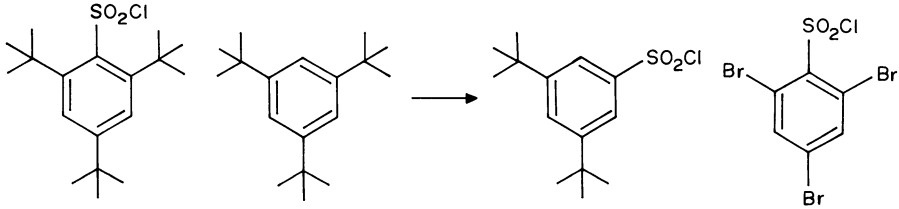


(13)

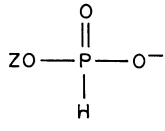
These steric effects have been exploited in synthetic routes in which a primary alcohol reacts with **12** in preference to a secondary alcohol. Yields are very high when there is only one primary OH group competing with one secondary OH group[102,103], but are satisfactory even for sulphonylation of the three primary OH groups of sucrose in competition with five secondary OH groups[104]. An even more selective sulphonylating agent would be tri-*t*-butylbenzenesulphonyl chloride (**14**). Unfortunately, this has not yet been synthesized; sulphonylation of 1,3,5-tri-*t*-butylbenzene (**15**) proceeds with loss of a *t*-butyl group to give **16**[105–107].



(14) (15) (16) (17)

As expected, **12** reacts more slowly than **11**, not only in initial condensations but also in subsequent reactions[100]. Even for C—O cleavage, the electronic effects of the three alkyl groups reduce the rate of nucleophilic displacement[59] (see also Section II.A.2). To increase the reactivity whilst retaining the steric effects, it has been suggested that 1,3,5-trihalobenzenesulphonyl chlorides (e.g. **17**) might be suitable[106].

The sulphonyl chloride **12** is also one of the condensing agents used for the synthesis of nucleoside hydrogenphosphonate diesters by reaction of a nucleoside hydrogen phosphonate monoester **18** (e.g., Z = 5′-*O*-dimethoxytritylthymidin-3′-yl) with a suitably protected nucleoside[108]; the desired phosphodiester is then formed by a mild oxidation of the hydrogenphosphonate to phosphate. The monoester **18** may be oxidized by **12** in a redox process, recently studied by ^{31}P NMR spectroscopy, in which **12** is reduced to derivatives of the corresponding thiophenol (**19**)[109]. Mesitylenedisulphonyl chloride (**20**)



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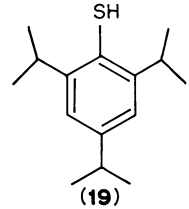

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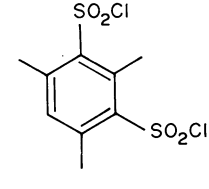
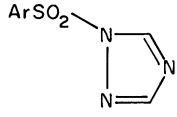


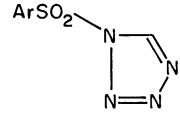
(20)

has also been used as an activating group for the synthesis of deoxyribonucleoside 3'-hydrogen phosphonates via an oxidative phosphonylation process[110].

For the synthesis of oligonucleotides by the phosphotriester method[111], **12** is a superior condensing agent to dicyclohexylcarbodiimide and mesitylenesulphonyl chloride (**11**)[112]. However, under the reaction conditions for dinucleotide synthesis (e.g. pyridine at 0 °C), **12** sulphonylates primary hydroxyl groups to a significant extent (*ca* 20%)[112]. This side-reaction is much reduced if the less reactive aryl sulphonyltriazole derivatives (**21**, where Ar = Ph, tolyl, mesityl or *p*-nitrophenyl) are used as condensing agents[112]. The surprisingly high reactivity of these heterocyclic leaving groups is shown by the tetrazole derivatives (**22**, Ar = mesityl or 2,4,6-tri-isopropylphenyl), which react faster than **12** to activate the phosphate anion (RO)(R'O)POO^- in triester synthesis[113,114].



(**21**)



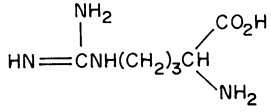
(**22**)

4. Activating effects of sulphonyl protecting groups in peptide synthesis

Sulphonyl is a well-known protecting group for amines, and the resulting sulphonamide can be cleaved either by acid or base[115]. Under acidic conditions, the sulphonamide group would first be protonated (equation 22) and the protonated substrate would then be solvolysed by nucleophilic attack at sulphur (equation 23, where R'OH is the solvent)[116]. Alternatively, if the alkyl group R (equation 22) is capable of forming a relatively stable carbocation (e.g. R = *t*-butyl or cinnamyl), R—N bond may be cleaved[116]. Typical sulphonamide protecting groups are benzenesulphonamides or toluenesulphonamides[115], but more electron-rich groups are required to protect the guanidino group in arginine (**23**) during peptide synthesis[115]. As deprotection (equation 23) is carried out in polar, weakly nucleophilic media (e.g. trifluoroacetic acid, containing thioanisole which acts mainly as a carbocation scavenger), nucleophilic solvent assistance is probably very low and positive charge will develop on the sulphur. Reaction rates increase if the substituents in the aromatic ring help to stabilize a positive charge on sulphur, e.g. even hydrolysis in pure water at 25 °C of mesitylenesulphonyl chloride (**11**)[117] occurs 26 times faster than that of benzenesulphonyl chloride[33,118]. As trifluoroacetic acid is much less nucleophilic than water[119], greater rate differences should be observed during deprotection.

$$ArSO_2NHR + H^+ \longrightarrow ArSO_2\overset{+}{N}H_2R \qquad (22)$$

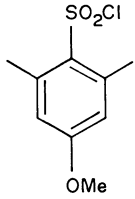
$$ArSO_2\overset{+}{N}H_2R + R'OH \longrightarrow ArSO_2OR' + R\overset{+}{N}H_3 \qquad (23)$$



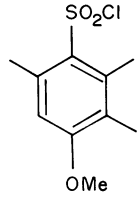
(**23**)

Various more strongly activated protecting groups have recently been investigated to increase the rate of deprotection of arginine (**23**). The protected compounds are synthesised

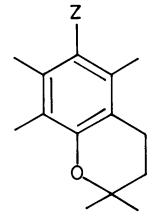
from the following sulfonyl chlorides: 4-methoxy-2,6-dimethylbenzenesulphonyl (Mds) chloride (**24**)[120], 4-methoxy-2,3,6-trimethylbenzenesulphonyl (Mtr) chloride (**25**)[121] and the pentamethyl chroman (Pmc) sulfonyl chloride (**26**, Z = SO_2Cl)[122]. Following observations that the tetramethyl derivative was less reactive than the dimethylated Mds group (**24**), the trimethylated Mtr group was synthesized[121]. Resonance between the oxygen lone pair of the methoxyl and the phenyl ring is inhibited in the tetramethyl derivative[121]. Steric inhibition of resonance in 2,6-dialkylanisoles and phenols accounts for the observation of their electrophilic substitution at the 3-position in sulphonations[123] and in Friedel–Crafts alkylations[124]. The Pmc group was designed to maximize this resonance interaction in a tetra-alkylated ring; an X-ray crystallographic analysis of the anilide (**26**, Z = SO_2NHPh) showed that the C—O bond was at an angle of only 4° out of the plane of the aromatic ring[122]. Deprotection of arginine containing peptides occurs readily in trifluoroacetic acid to give trifluoroacetate salts of the peptides and the parent chroman (**26**, Z = H)[122], and addition of 10% thioanisole is reported to lead to a small improvement in the reaction rate[122]. The Pmc group is removed more readily than the Mtr group, and is well suited to automated syntheses by solid-phase strategies[125].



(**24**)



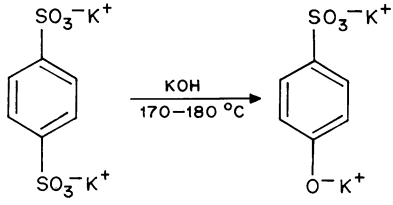
(**25**)



(**26**)

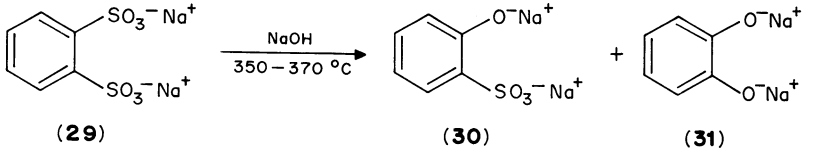
D. Nucleophilic Aromatic Substitution

Nucleophilic displacements of sulphonic acid salts by nucleophiles (e.g. hydroxide or cyanide) are well-known reactions discovered over a century ago. Conflicting and inconsistent literature reports led to a study of benzenedisulphonic acids, which illustrate activating effects. Under *relatively* mild reaction conditions (170–180 °C), potassium benzene-1,4-disulphonate (**27**) reacts with potassium hydroxide to give potassium 1-phenolate-4-sulphonate (**28**) in 88% yield (equation 24)[126]. At higher temperatures (330–340 °C), **28** is still the major product (70% yield) but phenol (15%) is also formed. Neither dihydroxybenzenes nor isomers of **28** were formed, and the sodium salt of **28** was stable at 400 °C. In these reactions, the *para* sulphonic acid group ($SO_3^-K^+$) is probably an activating group in **27** and the phenolate anion in **28** is likely to be deactivating.



(**27**) (**28**) (24)

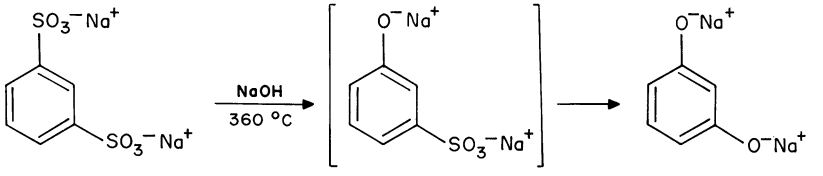
Similarly, sodium benzene-1,2-disulphonate (**29**) reacts at 350–370 °C to give mainly the disodium salt of phenol-2-sulphonic acid (**30**), but about 20% of the catechol salt (**31**) is also formed (equation 25)[126].



(**29**) (**30**) (**31**)

(25)

In marked contrast to the above results, sodium benzene-1,3-disulphonate (**32**) reacts with sodium hydroxide at temperatures up to 360 °C to give the resorcinol salt **34** in over 80% yield along with some phenol[126]. Presumably the intermediate phenol-3-sulphonate salt **33** is no longer deactivated by the phenolate anion (equation 26).



(**32**) (**33**) (**34**)

(26)

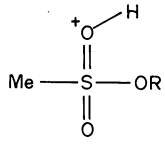
None of the above reactions led to rearranged products[126]. Labelling experiments using ^{14}C and ^{18}O showed that the alkaline fusion of benzenesulphonic acid was also a direct displacement[127].

III. ACIDITY AND BASICITY

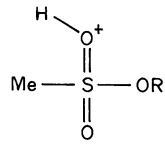
The acidity of sulphonic acids and their derivatives is such an important topic that a separate chapter (Chapter 6) is devoted to it; they are such strong acids that the benzenesulphonate anion is only half protonated in *ca* 70% w/w sulphuric acid/water[128]. Also, many important reactions occur by deprotonation of a C—H bond next to the SO_2 group (e.g. see Chapter 17). In this section the basicity of sulphonic acids and their derivatives will be discussed briefly.

Protonation of alkane- and arenesulphonic acids (RSO_3H) occurs in fuming sulphuric acid to give $RSO_3H_2^+$, but complexation with sulphur trioxide also occurs to give ($RS_2O_6H^+$)[128]. Both sulphonates and sulphonic acids are protonated cleanly in a mixture of FSO_3H and SbF_5 ('magic acid') in SO_2ClF at low temperatures (−60 °C), and cleavage processes can then be studied by temperature-dependent proton NMR spectroscopy[129]. Protonated methanesulphonic acid shows two sharp singlets in a ratio of 60/40 for the methyl group, indicating the formation of two isomers (possibly **35** and **36**, R = H). As higher homologues show only one isomer, there may be a preference for steric reasons. Protonated methyl mesylate also gives two signals, assigned to **35** and **36** (R = Me).

Protonated sulphonates and sulphonic acids are all activated towards cleavage reactions, but rates of decomposition depend strongly on the substituents. Protonated methanesulphonic acid (**35**, **36**, R = H) is probably dehydrated at 10 °C to give the sulphonylium cation **37**, which reacts with fluoride ion to give the observed product, a

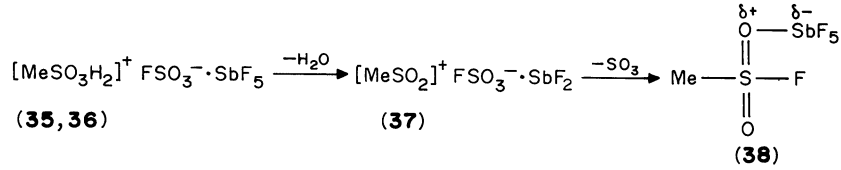


(35)



(36)

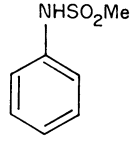
complex of methanesulphonyl fluoride **38** (equation 27)[129]. Protonated methyl mesylate is stable up to 20 °C, but then decomposes in an analogous process via alkoxy–sulphur cleavage to the sulphonylium cation **37**. Methyl benzenesulphonate, and benzene and toluenesulphonic acids also behave similarly, except that the protonated sulphonic acids are too unstable to be observed even at −60 °C. In contrast, ethyl mesylate and higher homologues decompose by alkyl–oxygen cleavage[129].



(35,36) (37) (38) (27)

Protonation of sulphonate esters in aqueous sulphuric acid mixtures appears to increase the rates of S_N1 reactions in solvent compositions of about 60% w/w or more, although the extent of protonation of substrates was estimated to be only 1% (increasing, but still less than 30% protonation, in 98% sulphuric acid)[10]. Solvolyses of primary alkyl sulphonates have been examined in sulphuric acid and in fluorosulphuric acid, containing 1 M potassium fluorosulphate[130,131]; under these conditions, it was roughly estimated[130] that ethyl tosylate would be only about 0.1% protonated.

For these and several other reactions in strongly acidic media, protonation of the substrate is probably unimportant, e.g. solvolysis of benzenesulphonyl bromide ($PhSO_2Br$) even in 99.98% sulphuric acid[132]. Rates of S_N2 reactions are probably more dependent on solvent nucleophilicity[10]. Also, electrophilic aromatic substitutions on protonated substrates are expected to be disfavoured, e.g. methanesulphonanilide (**39**) is half protonated in 84% sulphuric acid, but sulphonation reactions in 80–99.8% sulphuric acid are explained (see below) without postulating protonation of the substrate[133].



(39)

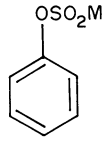
IV. ELECTROPHILIC AROMATIC SUBSTITUTION

Much of the data available on electrophilic aromatic substitution comes from detailed studies of sulphonation over many years[134]. Remarkably precise product yields (e.g. ±0.3%, usually determined by NMR analysis of mixtures) are sometimes reported, and it would be interesting to compare these results with those now available independently

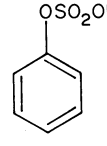
from reversed-phase HPLC; as lower detection levels may be obtained by HPLC, the range of data on partial rate factors could then be extended.

Directing and activating effects can be seen in the sulphonation of methanesulphonanilide (**39**)[133]. Partial rate factors (f) for sulphonation by $H_3SO_4^+$ in 77.8% sulphuric acid are: $f_o = 55 \pm 25$; $f_p = 610 \pm 200$; also in 96.1% sulphuric acid, for sulphonation by $H_2S_2O_7$: $f_o = 2.5 \pm 1.2$; $f_p = 41 \pm 15$ (the *meta* product was not detected). An average σ_p^+ value of -0.29 for the $NHSO_2Me$ substituent was calculated from the results in the two solvents. Errors in these measurements arise partly from the need to calculate the percentage of unprotonated substrate and partly from uncertainty in the rate constant for sulphonation of benzene by $H_3SO_4^+$.

The preference for *para* substitution is even stronger for sulphonation of phenyl mesylate (**40**), which gives 100% *para* product in 90.4% sulphuric acid[135]. In this case, the substituent OSO_2Me is strongly deactivating; phenol reacts $> 10^4$ times faster, but gives 48% *ortho*-product, so sulphonation of **40** cannot be preceded by hydrolysis to phenol. As sulphonation of potassium phenyl sulphate ($K^+PhOSO_2O^-$) in *ca* 80% sulphuric acid occurs via phenol, and the sulphate (studied at higher concentrations of sulphuric acid) is much less reactive, it seems unlikely that under these conditions phenol is sulphonated via the sulphate. The following partial rate factors have been calculated[136] for sulphonation of unprotonated substrates via the $H_2S_2O_7$ mechanism at 25 °C: phenol, $f_o = 80 \pm 20$, $f_p = 180 \pm 50$; phenyl mesylate (**40**), $f_p = 0.005 \pm 0.001$; methyl phenyl sulphate (**41**), $f_p = 0.002 \pm 0.0005$.



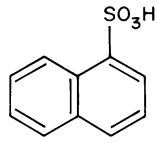
(**40**)



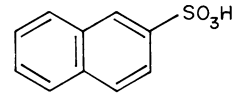
(**41**)

Sulphonic acid ($—SO_3H$) and related substituents ($—SO_3Z$) are well-known deactivating and *meta*-directing groups; e.g. nitration of benzenesulphonyl chloride in a mixture of oleum and nitric acid gave 89% *meta*-nitro product (isolated yield)[137]. For nitrations in sulphuric acid of the sulphonic acids, $Ph(CH_2)_nSO_3H$, the reacting species (mainly the sulphonate anion) are deactivated even for $n = 3$[138]. From partial rate factors for sulphonations of $Ph(CH_2)_nOSO_3H$, it was concluded that for $n \geqslant 2$ the electronic effects of $-(CH_2)_nOSO_3H$ and $-(CH_2)_nSO_3H$ were about the same[139]. The yields of *ortho*-isomer formed in the nitrations of benzenesulphonic acid decrease from 35% in 83.9% sulphuric acid to 21% in 98.5% sulphuric acid, suggesting that some of the reaction may proceed via the undissociated sulphonic acid (corresponding yields of *meta*-isomer are 56% and 73%, with perhaps a small decrease from 9% to 6% ± 2% in the yields of the *para*-isomer). Partial rate factors for the $—SO_3^-$ substituent are very low (10^{-6}–10^{-7}), but greater than those for methyl phenyl sulphone ($PhSO_2Me$) studied under the same conditions[138].

The percentage of *ortho*-substitution is influenced strongly by steric effects. As steric requirements of $—SO_3H$ (or $—SO_3^-$) substituents are similar to those of a *t*-butyl group[105], adjacent $—SO_3H$ substituents are unfavourable. Also, if fuming sulphuric acid is used, the sulphonating reagent is even more bulky, e.g. $H_2S_4O_{13}$ in 104–109% sulphuric acid[140]. Sulphonation of benzenesulphonic acid in fuming sulphuric acid (101.2–115%) at 25 °C gives 97–98% *meta*-product, and the *ortho*-isomer was not observed[140,141]. There may also be other mechanistic differences between these results and those discussed above for nitrations, because from changes in isomer distributions for methylbenzenesulphonic acids, it was proposed that in fuming sulphuric acid ($\geqslant 115\%$) the species undergoing sulphonation may be $ArSO_3H_2^+$ or the sulphur trioxide complex (ArS_2O_6H)[140].

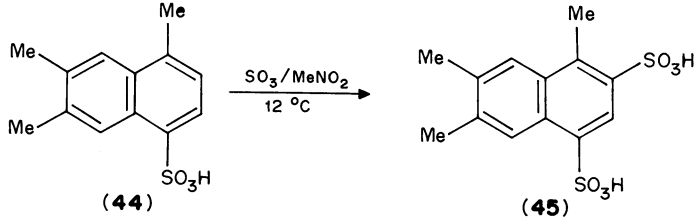


(42)



(43)

Steric effects strongly influence reactions of naphthalenesulphonic acids (**42**, **43**) and other planar arenes, for which peri-substitution (e.g. to give the 1,8-disulphonic acid product from naphthalene) has not yet been observed[142]. Even when less bulky methyl groups are present, peri-sulphonation is unfavourable; e.g. sulphonation of 1,6,7-trimethylnaphthalene with sulphur trioxide in nitromethane at 0 °C gives **44** by attack at one of the α-positions, but further reaction at 12 °C gives **45** (equation 28) rather than attack at one of the two remaining α-positions[143].

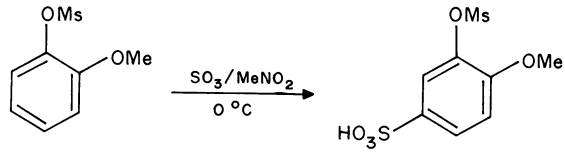


(44) (45) (28)

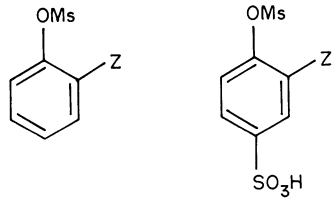
Kinetically-controlled sulphonation of **42** also shows the deactivating effects of the SO_3H (or SO_3^-) substituent because, in 98.5% sulphuric acid at 25.0 °C, the products are 58% 1,5-, 32% 1,6- and 10% 1,7-disulphonic acids[144]. Only in the case of **43** is a small amount of disulphonation of one ring observed; products are 4% 1,3-, 74% 1,6-, 18% 1,7- and 4% 2,6- + 2,7-disulphonic acids[144]. Whereas the largest partial rate factor (i.e. most reactive position) for sulphonation of benzenesulphonic acid is even lower than for nitration (*ca* 10^{-8}), much larger values are found for naphthalenesulphonic acids (0.012 for **42** and 0.13 for **43**)[144].

Patents are still appearing on further substitution reactions of naphthalene disulphonic acids by both kinetically and thermodynamically controlled processes, which have been of great commercial importance for many years. Isomer distributions for the sulphonation of other arenesulphonic acids and some alkyl derivatives have been compiled[142].

Because most of the substituent effects of sulphonic acid groups and their derivatives are deactivating in electrophilic substitutions, directing effects will often be dominated by the electronic effects of other groups present in the molecule of interest; e.g. sulphonation of mesylate **46** with sulphur trioxide in nitromethane at 0 °C gives the 5-sulphonic acid **47** (equation 29), as expected, because the methoxyl group is a powerful *para*-directing group. Under the same conditions, 2-chlorophenyl mesylate (**48**, Z = Cl) gives the 4-sulphonic acid (**49**, Z = Cl) and, surprisingly, 2-methylphenyl mesylate (**48**, Z = Me) also gives a 4-sulphonic acid (**49**, Z = Me), suggesting that the polarizability of the OSO_2Me substituent is significantly larger than that of chloro or methyl[136].

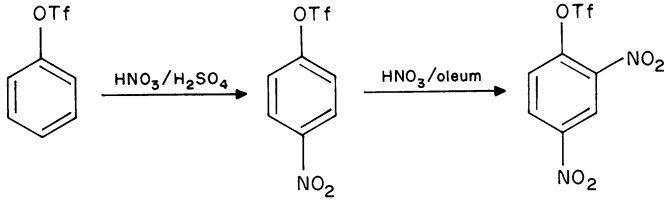


(46) (47) (29)



(48) (49)

Nitrations of phenyl mesylate (**40**)[145] and phenyl tosylate[146] were studied at the turn of this century. More recently, phenyl triflate (**50**) has been nitrated to the 4-substituted product **51**, which under vigorous conditions (concentrated nitric acid in oleum) gives **52** in 89% yield[147] (equation 30).



(30)

(50) (51) (52)

These results can be interpreted in terms of substituent constants for the quantitative evaluation of directing and activating effects (Section V).

V. SUBSTITUENT CONSTANTS

Substituent effects on C—O cleavage for esters C-OSO_2Z showed the large rate effects of the substituent Z (Section II.A.3). Hence, substituent constants for the general group —OSO_2Z need to be obtained for a wide range of Z substituents, and there are at least five similar general groups —CH_2OSO_2Z, —$NHSO_2Z$, —CH_2NHSO_2Z, —$NMeSO_2Z$ and —CH_2NMeSO_2Z. If ten different Z substituents (e.g. Z = Br, Cl, F, OH, OMe, O^-, Me, CF_3, Ph etc.) were chosen, then there would be sixty values for each substituent constant. In addition, there are two other general groups of substituents, —SO_2Y and —CH_2SO_2Y (for which Y could be any of the first six substituents listed for Z as well as others). Considering also the many different types of substituent constants,

TABLE 7. Substituent constants for ester groups containing —CH_2O units

Substituent	σ^*	σ_I	σ_I^q
$CH_2OSO_2C_6H_4Me$-*p*	1.31[a]	0.23[b]	1.28[c]
$CH_2OSO_2CF_3$	1.98[d]		
CH_2OCOMe		0.16[b]	0.88[c]

[a]From Reference 148.
[b]From Reference 149.
[c]From pK_a values of 4-substituted quinuclidinium perchlorates; data from Reference 150.
[d]Reference 56.

TABLE 8. Substituent constants for sulphonate esters and amides[a]

Substituent	σ_m	σ_p	σ_I	σ_R
OSO_2Me	0.39	0.36	0.58	
		0.33[b]	0.61[b]	−0.28[b]
OSO_2Ph	0.36	0.33	0.58	
OTs			0.59	
		0.29[b]	0.54[b]	−0.21[b]
OSO_2CF_3	0.56[c]	0.53[c]	0.70[c]	−0.20[c]
		0.47[b]	0.84[b]	−0.36[b]
$NHSO_2Me$	0.2	0.03		
	0.32[c]	0.21[c]	0.42[c]	−0.21[c]
$NMeSO_2Me$	0.29[c]	0.24[c]	0.34[c]	−0.10[c]
$N(SO_2Me)_2$	0.47[c]	0.49[c]	0.45[c]	0.04[c]
$NHSO_2Ph$	0.18[d]	0.00[d]	0.32	
$NHSO_2CF_3$	0.44[c]	0.39[c]	0.49[c]	−0.10[c]
$NMeSO_2CF_3$	0.46[c]	0.44[c]	0.48[c]	−0.04[c]
$N(SO_2CF_3)_2$	0.71[e]	0.80[c]	0.70[c]	0.10[c]
OMe	0.10	−0.12	0.3	−0.43
OAc	0.32[d]	0.23[d]	0.35[d]	−0.22[d]
$OCOCF_3$	0.56	0.46	0.65	−0.21[d]
NMeAc	0.31[c]	0.26[c]	0.36[c]	−0.10[c]
$NMeCOCF_3$	0.41[c]	0.39[c]	0.43[c]	−0.04[c]

[a]Data from Reference 149, unless stated otherwise; typical uncertainty ± 0.05 or more; similar σ_I values are quoted in Reference 151.
[b]Data from Reference 56.
[c]Data from Reference 152.
[d]Average value.
[e]Data from Reference 153.

TABLE 9. Substituent constants for acid derivatives[a] and sulphones

Substituent	σ_m	σ_p	σ_I	σ_R
SO_2NH_2	0.53[b]	0.58	0.44[c]	0.12[c]
SO_2NMe_2	0.51[b]	0.65[b]	0.42[c]	0.12[c]
SO_2NHPh	0.56	0.65		
SO_2OH	(0.55)			
SO_2OR	0.71	0.90	0.50	0.09
SO_2F	0.9[b]	1.0[b]	0.75[c]	0.26[c]
SO_2Cl	0.92	1.04	0.80[c]	0.24[c]
SO_2Me	0.64	0.73	0.6[b]	0.1[b]
SO_2Ph	0.60[b]	0.7[b]	0.52	0.1
SO_2CF_3	0.78[b]	0.92[b]	0.73	0.15[b]
$CONH_2$	0.28	0.31	0.27[b]	0.0
CO_2H	0.35[b]	0.44[b]	0.32	
CO_2R	0.35	0.44	0.32[b]	0.16

[a]Data from Reference 149 unless stated otherwise; typical uncertainty ± 0.05 or more; similar σ_I values are quoted in Reference 151.
[b]Average value.
[c]Data from Reference 154.

it is clear that there are hundreds of possible permutations of substituents and their substituent constants. From the data currently available, it is not possible to provide a survey even closely approaching the desired scope.

Limited data are available for substituents insulated by a methylene group (Table 7). A much wider range of results is available for $—OSO_2Z$, $—NHSO_2Z$ and $—NMeSO_2Z$ type substituents (Table 8) and for $—SO_2Y$ type substituents (Table 9). These two tables include selected data for corresponding carbonyl compounds, and Table 9 also includes data for selected sulphones.

The results in Table 7 and other σ_I values (Tables 8 and 9) show the greater inductive effects of sulphonate esters in comparison with carboxylate esters. Similarities between these two types of ester can be seen in the σ_R values (Table 8 and 9), which are of similar magnitude and of negative sign (consistent with *para*-substitution, Section IV). Also, substituent constants for sulphonic acids and derivatives are similar to those of sulphones (Table 9).

VI. MISCELLANEOUS TOPICS

A. Other Aspects of Sulphonate Ester Hydrolysis

Electron donation by the OTs group (negative σ_R value, Table 8) is also seen in the acid-catalysed hydrolysis of 1-hexynyl tosylate (**53**) to the acid **55**, via rate-limiting protonation of the β-carbon to give the cation **54** (equation 31). The tosylate ester **53** hydrolyses at about half the rate observed for propynyl benzoate, but reacts about three times faster than the corresponding phosphate ester. Under neutral conditions the phosphate reacts fastest, but for base-catalysed reactions the carboxylate ester again reacts fastest. All of the reactions under neutral and basic conditions are at least 10^2 faster than corresponding reactions of phenyl esters[155].

$$\underset{\textbf{(53)}}{RC{\equiv}COTs} \xrightarrow{H^+} \underset{\textbf{(54)}}{[RCH{=}\overset{+}{C}OTs]} \longrightarrow \underset{\textbf{(55)}}{RCH_2CO_2H} + TsOH \qquad (31)$$

Tosylates can be hydrolysed photolytically in a deprotection process useful for syntheses of carbohydrates and nucleic acids (Section II.C.3)[156]. In a recent reinvestigation of the reaction mechanism, it has been shown that the first step is electron transfer from a photo-excited donor to a tosylate radical anion (equation 32)[157]:

$$ArSO_2OR + \text{donor} \longrightarrow [ArSO_2OR]^{-\bullet} + [\text{donor}]^{+\bullet} \qquad (32)$$

Cleavage of the radical anion gives the sulphonyl radical (equation 33), which may react as shown in equations 34 and 35:

$$[ArSO_2OR]^{-\bullet} \longrightarrow ArSO_2^{\bullet} + RO^- \qquad (33)$$

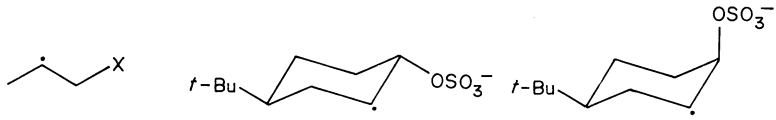
$$ArSO_2^{\bullet} + HO^- \longrightarrow [ArSO_2OH]^{-\bullet} \qquad (34)$$

$$[ArSO_2OH]^{-\bullet} + [\text{donor}]^{-\bullet} \longrightarrow ArSO_2OH + \text{donor} \qquad (35)$$

By considering the implications of this mechanism, it was possible to devise an improved procedure for syntheses in which selective hydrolysis was achieved at a more suitable wavelength ($> 300\,nm$)[158]. Solvation of the alkoxy anion formed in equation 33 may

determine the mode of cleavage, because tosylate radical anions formed in the gas phase by chemical ionization mass spectrometry undergo cleavage of the S—C bond[159].

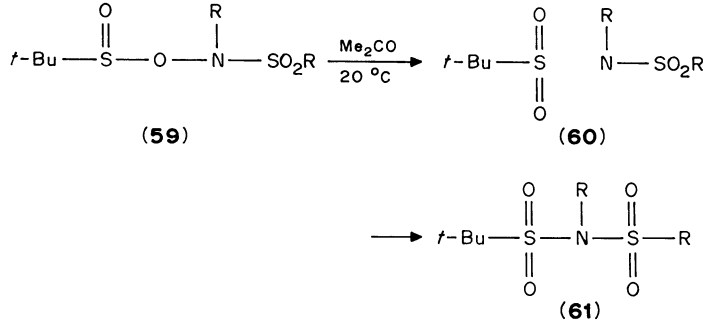
Hydrolyses of a range of β-substituted radicals (**56**, X = Cl, Br, OMs) show the reactivity order OMs > Br > Cl, but rates were surprisingly fast in comparison with conventional hydrolyses of halides and sulphonates. Some rate constants $> 10^6\ s^{-1}$ were observed, in contrast to typical hydrolyses[33] having rate constants $< 10^{-2}\ s^{-1}$. It was suggested that solvation of incipient ions may be greater for hydrolyses of the radicals **56**[160]. An attempt was made to gain further mechanistic insights from a study of the stereochemistry of the indirect hydroxylation of cyclohexenes by $SO_4^{-\bullet}$ radical anions, first giving the sulphate radical anions (**57**, **58**), which are hydrolysed before the radicals are trapped by a thiol H-donor[161]. Not surprisingly, considering just the size of $SO_4^{+\bullet}$ radical anions compared with hydroxyl radicals, the indirect process was more stereoselective than the direct attack. A preference for inversion of stereochemistry during hydrolysis ruled out formation of a symmetrically-solvated cyclohexene cation radical intermediate, and an ion-pair intermediate was proposed[161].



(**56**) (**57**) (**58**)

B. Other Radical Reactions

N-[(*t*-Butylsulphinyl)oxy] sulphonamides (**59**) rearrange with N—O cleavage via sulphonamidyl radicals **60** to give **61** in *ca* 20% yield in a radical cage recombination process, along with products formed after escape from the cage (equation 36)[162].



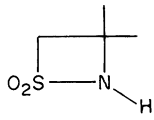
(**59**) (**60**) (**61**) (36)

C. Sultones and Sultams

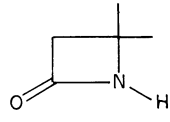
Although the reactions of cyclic sulphonic esters (sultones) and amides (sultams) are discussed elsewhere in this book (Chapter 19), directing and activating effects will be discussed briefly here. The C—O bond in sultones is activated towards nucleophilic attack, and this general area has been reviewed recently[163]. Alkaline hydrolyses of five-membered ring cyclic esters are particularly rapid in comparison with six-membered or open-chain analogues, although there is not yet general agreement on the mechanistic reasons for this[164]. S—O rather than C—O cleavage in the reaction of hydroxide ion with

four- and five-membered ring sultones has been attributed to a stereoelectronic effect; electron donation to the sulphonyl group by the ester oxygen is less when the C—S—O—C dihedral angle is reduced[165].

Comparisons have been made between hydrolyses of the sultam (**62**) and the lactam (**63**). Both were relatively stable over days in water (pH 13) at 30 °C, with the sultam decomposing at twice the rate of the lactam. However, at a pH of 2.3, the sultam (**62**) had a half-life of only 12 minutes, whereas the lactam (**63**) remained unchanged after more than 24 hours[166].

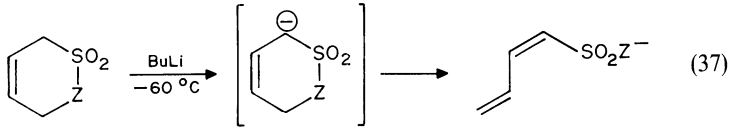


(**62**)



(**63**)

The acidity of C—H bonds next to a sulphonyl group provides a synthetically useful ring-opening reaction of both sultones and sultams. On treatment with butyl lithium, the β,γ-unsaturated δ-sultone (**64**, Z = O) and the corresponding sultam (**64**, Z = *N*-alkyl) gave the carbanion **65**, which underwent ring-opening to give butadiene derivatives **66** (equation 37)[167].



(37)

(**64**) (**65**) (**66**)

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CHAPTER **17**

Sulfenes

J. F. KING and RAJENDRA RATHORE

Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7

The chemistry of sulphonic acids, esters and their derivatives
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GLOSSARY

k_w	first order rate constant for the reaction (of a sulfonyl chloride) with water
k_{OH}	second order rate constant for the reaction (of a sulfonyl chloride) with aqueous hydroxide ion
k_B	second order rate constant for the reaction (of a sulfonyl chloride) with a base (other than hydroxide)
KIE	kinetic isotope effect
NRKR	non-reciprocal kinetic resolution (Section IV, A.1 and Ref. 44), a kinetic resolution reaction such that the kinetic resolution in, say, the reaction of (±)-A with (+)-B, differs from that in the reaction of (±)-B with (+)-A.
Lg	leaving group
Np	neopentyl, $(CH_3)_3CCH_2$
⚡	flash thermolysis (alias flash vacuum thermolysis or flash vacuum pyrolysis), a thermally induced reaction carried out in the vapour phase at temperatures of 400–500 °C or higher and residence times of the order of milliseconds (or less). (symbol: P. de Mayo, unpublished).
β_{lg}	'beta-leaving group'; in a reaction involving a leaving group (Lg), the slope of a plot of log k vs pK_{LgH} for the various leaving groups, where k is the rate constant of the reaction and pK_{LgH} is the pK_a of the conjugate acid of the leaving group.
betylate	a sulfonic ester of the general formula $ROSO_2(CH_2)_n\overset{+}{N}R'_3X^-$; where R and R′ may be alkyl or aryl groups (though R′ is most commonly methyl); n may be specified in the name, as in [2] betylate for $ROSO_2CH_2CH_2\overset{+}{N}R'_3X^-$.

I. INTRODUCTION

Sulfenes (**1**) are the inner anhydrides of sulfonic acids, derived formally by the removal of one molecule of water from one molecule of the acid. They occur chiefly as short-lived intermediates in a number of valuable synthetic reactions; it is probably fair to state that they are, surprisingly, both more frequently used and less well-known than their analogues such as sulfur trioxide or ketenes. This suggests that, although a number of aspects of sulfene chemistry have been presented in reviews[1–4], there is a place for an up-to-date source whereby chemists may become better acquainted with the chemistry of sulfenes; we hope that this chapter will fill the need for the present.

$RR'C{=}SO_2$
(1)

II. SULFENES AND ANALOGUES

The name sulfene was proposed[5] from the analogy with ketene, and is commendable for both euphony and brevity, qualities not obvious in the official names, thioaldehyde dioxide and thioketone dioxide[6].

The analogy of sulfonyl and carbonyl species is useful not only for naming the former but also as a mnemonic for keeping track of their chemical behavior, and with sulfenes and ketenes the analogy is informative. Both classes of compounds readily undergo nucleophilic addition of protonated nucleophiles (HNu) to give the corresponding acid derivatives, and both undergo noteworthy cycloaddition reactions.

It may also be helpful in understanding the chemistry of sulfenes to note their place in the following tabulation.

$R_2C{=}S$ thiones	$RN{=}S$ thionitroso compounds	$O{=}S$ sulfur monoxide (singlet)
$R_2C{=}SO$ sulfines	$RN{=}SO$ *N*-sulfinylamines	$O{=}SO$ sulfur dioxide
$R_2C{=}SO_2$ sulfenes	$RN{=}SO_2$ *N*-sulfonylamines	$O{=}SO_2$ sulfur trioxide

Looking down the first column we see that a sulfene may be regarded as the most highly oxidized form of the thiocarbonyl group, or, alternatively, as the most highly oxidized member of the series of inner anhydrides of the oxy-acids, i.e. the sulfenic, sulfinic and sulfonic acids. From this viewpoint it is not surprising that sulfene is the member of the series most likely to undergo nucleophilic attack at the sulfur atom.

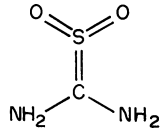
Another series of inner anhydrides, namely that of the general formula $X = SO_2$, is found in the bottom row of the table; the members are sulfenes, *N*-sulfonylamines and sulfur trioxide, the inner anhydrides of, respectively, sulfonic, sulfamic and sulfuric acids. The analogy is again helpful; one of the most conspicuous features of sulfur trioxide is its high reactivity toward water and other nucleophiles; this property is shared by sulfenes and sulfonylamines[7].

Before proceeding to the actual chemistry, mention should be made of a point of terminology. As will be shown (and would indeed be predicted from the analogy with ketenes and sulfur trioxide), sulfenes are electrophilic species reacting rapidly with nucleophilic reagents. The usual mode of reaction is attack of the nucleophile at sulfur, but there is evidence for attack at carbon in some instances. We have previously referred to attack at sulfur as 'normal' and that at carbon as 'abnormal'[8–10], while others[11,12] have used the term 'inverse' for attack at carbon. In the light of the thioketone–sulfine–sulfene analogy noted above, it would seem appropriate to adopt a common terminology, namely the self-explanatory terms 'thiophilic' and 'carbophilic' attack. The terms 'normal' and 'abnormal' have also been used for the formal reverse processes, i.e. sulfene formation by loss of a leaving group (nucleofuge) from sulfur ('normal') or carbon ('abnormal'). The term nucleofuge can take the adjectival form nucleofugal[13], which would then lead us to suggest the terms 'thiofugal' and 'carbofugal'. We recognize, however, that 'nucleofugic' also has its proponents[14], and if these should carry the day, 'thiofugic' and 'carbofugic' would become the appropriate forms.

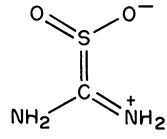
III. DETERMINATION OF THE PROPERTIES OF SULFENES

In contrast to such analogues as ketenes, sulfines and sulfur trioxide, no sulfene has been isolated and characterized at room temperature. There were a few claims in the early

literature of observing, or even isolating, a sulfene but these have been descredited (see Reference 3). 'Thiourea dioxide' can be formally regarded as a sulfene (**2**), but it is clear from its chemistry and its structure as determined by X-ray crystallography[15] that the formamidinium sulfinate structure (**3**) is the better description.

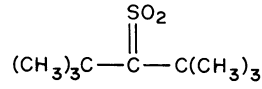


(**2**)

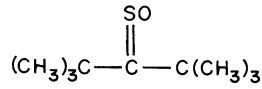


(**3**)

To date, all efforts to prepare a sulfene sufficiently stabilized or sterically protected as to be isolable at room temperature, while still showing the general properties of a sulfene, have been fruitless. Attempts to obtain di-*tert*-butylsulfene, **4**, for example, from either the corresponding sulfine[16] (**5**) or by other routes, were without success in our hands[17], and, we are led to believe, those of others as well.

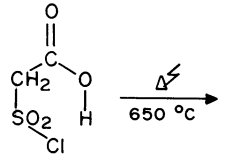


(**4**)

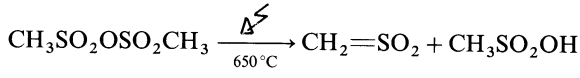


(**5**)

Greater success, however, has been achieved in experiments using low-temperature matrix isolation. Flash vacuum thermolysis[18] (with trapping at −196 °C) (equations 1 and 2) and flash photolysis[19] (also at −196 °C) (equation 3) gave products showing peaks assigned to sulfene itself ($CH_2{=}SO_2$) at 3170, 3040, 1330, 1230 and 950 cm^{-1}; the first pair of peaks was ascribed to C—H stretching and the second to S—O stretching vibrations. The following pieces of evidence serve to show that these bands are indeed due to sulfene; (a) the same bands appear from all three reactions, along with peaks appropriate to the by-products (e.g. carbon dioxide and ketene), (b) other flash thermolysis experiments, including deuterium labelling studies, are fully consistent with formation of sulfene in the gas phase under these conditions[20], and (c) warming of the flash thermolysis product (to −140 to −80 °C) gave products appropriate to the sulfene, e.g. methanesulfonyl chloride from the chlorosulfonylacetic acid thermolysate[18].



(1)



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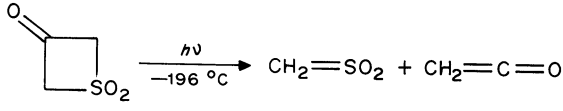


(3)

One further direct observation of a sulfene has been described[21]. The reaction of 2,5-dimethylphenylmethanesulfonyl chloride with triethylamine in aqueous tetrahydrofuran

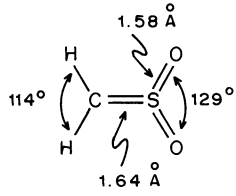
has been reported to show a transient absorption with $\lambda_{max} = 315$ nm. The signal, which shows up clearly after 50 ms but disappears in less than one second, was ascribed to the sulfene, $ArCH{=}SO_2$ (Ar = 2,5-dimethylphenyl).

Two attempts, by rather indirect methods, to estimate the π-bond energy of sulfene, have led to widely differing results. One, which was obtained by averaging separately estimated minimum and maximum values[22], gave $E_\pi(C{=}SO_2) = 35 \pm 5$ kcal mol^{-1}; this value was based on a bond dissociation energy for the S—Cl bond in sulfonyl chlorides of 58 kcal mol^{-1}, and any change in this would require exactly the same change in the estimated E_π. Benson[23] has suggested a π-bond energy of 60 ± 3 kcal mol^{-1}, i.e. a value identical within experimental uncertainty to that of the carbon–carbon double bond. In our view Benson's value seems high in the light of the observation that 2-chloroethanesulfonyl chloride reacts with tertiary amines to form ethenesulfonyl chloride[24,25]. With pyridine, for example, the reaction proceeds entirely[26] to ethenesulfonyl chloride with no sign of any product from the sulfene, $ClCH_2CH{=}SO_2$ (equation 4); this observation requires that the transition state in which there is partial C=C formation and C—Cl cleavage be distinctly lower in energy than that in which there is partial $C{=}SO_2$ formation and S—Cl cleavage. When one notes that the S—Cl bond is much weaker than

$$CH_2{=}CHSO_2Cl \longleftarrow ClCH_2CH_2SO_2Cl \longrightarrow\!\!\!\!\!\!\times\!\!\!\!\!\!\longrightarrow [ClCH_2CH{=}SO_2] \qquad (4)$$

the C—Cl bond (by ~20 kcal mol^{-1}), the above experiment would appear to require that $E_\pi(C{=}C)$ be substantially greater than $E_\pi(C{=}SO_2)$. The discrepancy in the $E_\pi(C{=}SO_2)$ values is such as to commend the CNEBI approach[27] to the skeptical reader.

Semiempirical MO calculations on sulfenes have been reported[28,29]. The computed geometry for sulfene has all of the atoms in a common plane; one result is shown in structure (**6**). The geometry with representative force constants is described as permitting



(**6**)

the IR spectrum of sulfene to be computed 'in reasonable agreement with experiment' (i.e. the values reported earlier in this section). The results with substituted sulfenes suggested that electron-donating substituents should stabilize a sulfene.

IV. METHODS OF GENERATING SULFENES

From the foregoing discussion it is evident that any discussion of the chemistry of sulfenes is in fact a description of reactions in which sulfenes are believed to be formed and then to react, without (except for the few special instances mentioned above) any direct signs of sulfene participation. The case for sulfene intermediacy is usually indirect though not necessarily lacking in rigour. In practice, we have a core of carefully studied reactions in which a number of pieces of evidence combine to prove that sulfenes are formed and then react. In addition to these, there are two classes of reactions for which sulfene intermediacy can reasonably be discussed. The first of these consists of reactions which are either straightforward extensions of known sulfene reactions for which the appropriate tests for the sulfene have not been done, or, alternatively, reactions which can be rationalized as

proceeding via the sulfene but where the supporting evidence is incomplete; these reactions are included in this account usually with a qualification of some kind, e.g. 'consistent with' or 'appears to arise from', and so on. The second class of reactions includes those for which sulfene participation would appear to account for the products but which lack either supporting evidence or a sufficiently close analogy to an established sulfene process; these are described with more caution, e.g. 'possible sulfene reactions'.

A number of methods including product analysis, isotopic labelling, kinetics and kinetic isotope effects, and stereochemical studies have been used to show the presence of sulfenes. The case for the existence of sulfenes has been summarized before[1,3] and, except for the next section (IV.A.1), which is necessarily complex, the present account will note, as briefly as possible, the evidence for each method of sulfene formation, the reasons for concluding that sulfenes are present and the extent to which non-sulfene reactions also appear with this method.

Not included in the list below, but nonetheless a reaction by which one might reasonably imagine sulfenes to be formed, is the oxidation of sulfines. In practice, however, the reaction of sulfines with such oxidizing agents as peroxyacids or singlet oxygen[30–33] leads, not to sulfenes or to any sign of their typical products, but to the corresponding carbonyl compound (or derivatives) as in equation 5. For the reaction with peroxyacids

$$R_2C{=}SO_2 \longleftarrow\!\!\times\!\!\longleftarrow R_2C{=}SO \xrightarrow{[OX]} R_2CO \qquad (5)$$

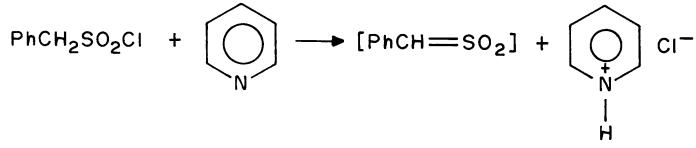
the α-sultine has been put forward as a likely intermediate[32]. Walter and Bauer[33] have raised the possibility that sulfenes could be formed as short-lived species from the oxidation of thioamide *S*-oxides[33]; the ease with which the products may be accounted for on the basis of the α-sultine, taken with the absence of typical sulfene products, forces the conclusion that either α-aminosulfenes are not produced in this transformation, or their reactions are not typical of sulfenes.

A. Base Induced Elimination from $RR'CHSO_2Lg$; Thiofugal Formation of Sulfenes

1. The evidence for and the mechanism of sulfene formation

The archetype of this reaction, and the most important source of sulfenes in practice, is the reaction of simple sulfonyl halides with a tertiary amine as in equations 6 and 7. The

$$CH_3SO_2Cl + Et_3N \longrightarrow [CH_2{=}SO_2] + Et_3\overset{+}{N}HCl^- \qquad (6)$$



(7)

evidence for sulfene formation in these reactions was derived initially from the formation of characteristic products in the presence of suitable traps. Much of this work has been reviewed in detail previously[1–3], and in this account we shall summarize the earlier studies and discuss relevant newer work.

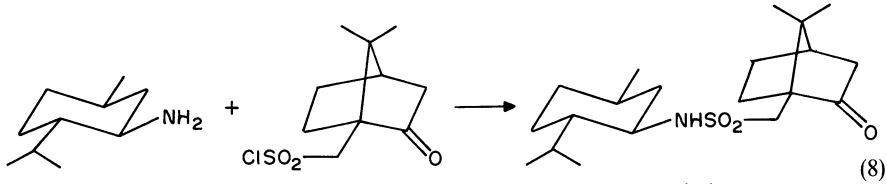
Though the earliest investigations of the groups of Wedekind[5,34] and of Staudinger[35] were clearly consistent with sulfene intermediacy, the case for sulfenes was suggestive rather than compelling and for many years sulfenes were not among the received intermediates of conventional organic chemistry. The discovery of the sulfene–enamine and related cycloadditions[36–39] altered the picture dramatically, and sulfenes came to be

regarded as likely, though not rigorously demonstrated species, with interesting synthetic potential. Soon afterwards deuterium-labelling experiments, in which the products of reactions 6 and 7 in the presence of deuterated alcohols, ROD, were found to yield the monodeuterated esters, CH_2DSO_2OR and $PhCHDSO_2OR$[40,41], provided the argument which clinched the case for sulfenes from sulfonyl chlorides. This conclusion was extended to sulfonyl bromides and methanesulfonic anhydride, which were also found to yield the monodeuterated ester on reaction with triethylamine and an alcohol in an organic medium[41].

Further insight was obtained by kinetic studies, which showed that reaction of methanesulfonyl chloride with triethylamine and 2-propanol to form isopropyl methanesulfonate was first order in sulfonyl chloride, first order in triethylamine and zero order in 2-propanol[42]. This observation requires the formulation of an intermediate which is formed in the rate-determining step and then reacts with the zero-order reagent in a relatively fast step. The kinetic observation gives strong support for the idea of the sulfene as an intermediate in these reactions.

A complication in this study was the observation of mixed second- and third-order kinetics with water or aniline as the trap (in 1,2-dimethoxyethane, DME). Deuterium labelling showed that both the second- and third-order reactions proceeded by way of the sulfene. More recent observations show that the third-order term is more pronounced in benzene (being seen with 2-propanol as the sulfene trap), and becomes less marked as the solvent polarity increases to DME and methylene chloride[43]. The original kinetic study[42] also presented a case for an E1cB-like E2 process for the reactions of phenyl methanesulfonyl chloride with tertiary amines, and provided evidence that the sulfene is not formed via the sulfonylammonium salt, $RSO_2\overset{+}{N}R_3$, i.e. by nucleophilic catalysis.

An unusual result in the form of 'non-reciprocal kinetic resolution' (NRKR) led to yet another line of evidence for the formation of a sulfene[44] as a slowly formed, rapidly consumed intermediate. Two contrasting results were found experimentally. (a) On the one hand, reaction of (±)-menthylamine (±**7**) with (+)-camphor-10-sulfonyl chloride (+**8**) (equation 8) gave a product in which one diastereomer of the sulfonamide (**9**) was



(**7**) (**8**) (**9**) (8)

about twice as abundant as the other, and the unreacted menthylamine was correspondingly enriched in one enantiomer (i.e. underwent partial kinetic resolution). (b) On the other hand, the converse reaction, i.e. that of (−)-menthylamine (−**7**) with (±)-camphor-10-sulfonyl chloride (±**8**), gave equal amounts of the two diastereomers and no sign of any resolution of **7**. What at first glance might appear to be a violation of a fundamental principle of parity may be readily explained on the basis of the sulfene mechanism. For the first case—that in which kinetic resolution is observed—the product ratio is determined in the second step, i.e. by the relative efficiencies of the (+)-amine vs the (−)-amine in trapping the '(+)-sulfene'. As it turns out trapping by the (−)-amine is about twice as fast as that by the (+)-amine leading to an excess of the diastereomer of **9** incorporating the (−)-amine, with a concomitant partial resolution of the amine. In the second case the product ratio is determined in the sulfene formation step and, as it happens, the two sulfenes are formed at about the same rate. Each of these sulfenes reacts with the (−)-

amine to give equal amounts of the two diastereomers of **9**; even though one of the sulfene trapping reactions is faster than the other, no kinetic resolution is found in the products because all of the sulfene molecules are ultimately converted to **9**. The validity of this picture was supported by rate measurements, though these are not really necessary to show 'non-reciprocal kinetic resolution'. The experiment therefore provides evidence based on kinetic considerations without actual rate measurements.

With an eye to clarifying the nature of the sulfene-forming process by observing the effect of systematic variations in structure, we turned to the kinetic study of aryl arylmethanesulfonates, $ArCH_2SO_2OAr'$, in a partly aqueous medium[45]. About the same time a related, and in many ways complementary, investigation was begun independently by Williams and coworkers[46]. The two groups concurred in concluding that the reactions took place by way of 'reversible' and "irreversible' E1cB processes, depending on the substituents in the leaving group. The combined results of these investigations provide a formidable array of evidence for the proposed mechanistic picture, not only for the intermediacy of the sulfene, but also for one of the most fully developed cases for the E1cB mechanism in organic chemistry. The chief points are as follows. (a) Trapping experiments gave characteristic sulfene products[45], and showed the reaction to be kinetically zero order in sulfene traps[46]. (b) H–D exchange of starting materials and specific base catalysis were found in the substrates reacting by the 'reversible' mechanism; those proceeding by the 'irreversible' process showed general base catalysis, a primary deuterium isotope effect and no H–D exchange in $ArCH_2SO_2OAr'$[45,46]. (c) A plot of $\log k$ vs pK_a of ArOH in the reaction of $PhCH_2SO_2OAr$ with OH^- showed a clear break around $pK_a \sim 6.5$. For the region above pK_a 6.5 the slope corresponded to $\beta_{lg} = 2.4$, a value fully appropriate to rate-determining S—O bond cleavage as in the $(ElcB)_{rev}$ process; a much smaller gradient (corresponding to $\beta_{lg} \sim 0.3$) was seen below pK_a 6.5, as expected for the $(E1cB)_{irr}$ reaction, in which the rate-determining step is carbanion formation[46]. (d) The lines obtained in a Hammett plot of (i) the rates of H–D exchange in the 'reversible E1cB substrates', and of (ii) sulfene formation from the 'irreversible E1cB substrates' were 'almost collinear', in agreement with the simple picture that the rate-determining step in the different reactions is the same[45], (e) Non-linear plots of k_{obs} vs buffer concentration ('buffer plots'), and also H–D exchange at high buffer concentration, were observed with substrates at the reversible–irreversible break point, pointing to a change in mechanism with change in buffer concentration with these substrates[45,46]. The mechanisms and the structural features associated with each are summarized in Scheme 1.

$$Ar'CH_2SO_2OAr \underset{k_{-1}[BH^+]}{\overset{k_1[B]}{\rightleftharpoons}} Ar'CH{-}SO_2OAr \xrightarrow{k_2} Ar'CH_2{=}SO_2 \longrightarrow \text{sulfene products}$$

(a) *Reversible E1cB* ($k_{-1}[BH^+] > k_2$): Ar = Ph, 3- and 4-methoxyphenyl, 3-nitrophenyl, 4-cyanophenyl, 3- and 4-chlorophenyl, 4-acetylphenyl, 4-formylphenyl.
(b) *Irreversible E1cB* ($k_2 > k_{-1}[BH^+]$): Ar = 2,4-, 2,5- and 2,6-dinitrophenyl.
(c) *Marginal* (depending on buffer concentration): Ar = 2- and 4-nitrophenyl, 2-nitro-4-chlorophenyl, 2-nitro-4-chlorophenyl.

SCHEME 1

Williams and coworkers[46] made the interesting suggestion that with the most nucleofugal groups, e.g. 2,4-dinitrophenoxide, the $(E1cB)_{irr}$ mechanism proceeded as an essentially concerted reaction via a carbanion of 'no discrete existence'. On further investigation of the reaction of the 2,4-dinitrophenyl esters they observed curvature in the plots of rate constants vs buffer concentrations[47]. Such curvature is not accounted for by the simplest E1cB-like E2 mechanism and these authors postulated that the rate-retarding effect of the general acid was achieved by protonation of the sulfene–aryloxide encounter

complex. It is evident that this system has considerable complexity and leads to difficulties associated with the great speed of some of the reactions, and admirable though the work of Williams and coworkers is, the final word on these mechanisms may not be in.

Pritzkow and coworkers[48] reported the first measurements on the rate constants for reaction of hydroxide with a series of alkanesulfonyl chlorides; they used a stopped-flow electrical conductivity method, and observed variations in rate constants which they interpreted in terms of steric hindrance to sulfene formation. Farng and Kice[49] examined the reactions of nucleophiles with series of alkyl α-disulfones and related substrates, and showed that basic nucleophiles commonly formed the sulfene, though certain highly nucleophilic but not very basic species such as azide ion proceeded by a direct displacement mechanism. They also concluded that, for a given nucleophile, direct substitution would be more likely to appear with an alkanesulfonyl chloride than with the corresponding alkyl α-disulfone. Beck and Doerffel[21], using a fast reaction method in which the reaction was followed photometrically, reported rate constants for the reaction of $ArCH_2SO_2Cl$ (where Ar = Ph and 2,5-dimethylphenyl) with both hydroxide and water (in aqueous THF) and triethylamine (in THF). As has been noted in Section III, a transient signal seen in reaction of (2,5-dimethylphenyl)methanesulfonyl chloride with triethylamine was interpreted as arising from the intermediate sulfene.

Much more recently we have had reason to make a systematic examination of the kinetics and mechanism of hydrolysis of simple alkanesulfonyl chlorides with variation in pH[50]. The pH–rate profile of alkanesulfonyl chlorides, $RR'CHSO_2Cl$ and their α-deuterated isotopomers, $RR'CDSO_2Cl$, conformed to a rate law of the form shown in equation 9. The deuterated substrates showed a sizeable primary kinetic isotope effect (KIE) for the k_{OH} and k_B terms (k_H/k_D with OH^- ranging from 4.0 with 2-propanesulfonyl chloride to 7.7 with phenylmethanesulfonyl chloride); no KIE was seen in the k_w values. The primary KIEs were in accord with those previously obtained from the product ratios following intramolecular[42] or intermolecular[51] competition experiments. Deuterium labelling was found to agree perfectly with the kinetic pattern, no deuterium exchange being observed in the simple hydrolysis region (i.e. pH range in which k_{obs} was pH-independent) and clean mono-exchange being seen when either the $k_{OH}[OH^-]$ or $k_B[R_3N]$ term predominated completely.

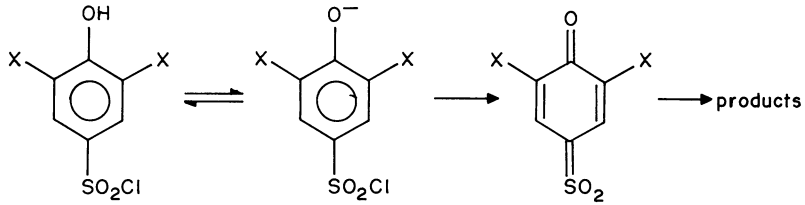
$$k_{obs} = k_W + k_{OH}[OH^-] + k_B[R_3N] \tag{9}$$

The excellent agreement between the deuterium-labelling and KIE experiments in aqueous solution is to be contrasted with what is found when the reaction is carried out in an organic medium, specifically, with triethylamine and isopropyl alcohol in CH_2Cl_2[50]. Reaction of $CH_3CD_2SO_2Cl$ gave essentially entirely the monodeuterated product, $CH_3CHDSO_2OCH(CH_3)_2$, but the rate of reaction was the same, within experimental error, as that of $CH_3CH_2SO_2Cl$, i.e. the sulfene is being formed but, in the organic medium, by a reaction without a primary kinetic isotope effect. The k_H/k_D values for the reaction of ethanesulfonyl chloride with (a) hydroxide ion in water, (b) triethylamine in water and (c) triethylamine in CH_2Cl_2 were, respectively, 5.6, 2.9 and 1.0. These results serve to (a) indicate a progressive change in the structure of the sulfene-forming transition state (presumably to become more like the products as the basicity or solvent polarity is lowered) and, at the same time, (b) to point out the necessity of using more than one method for studying these reactions; without the deuterium-labelling experiment it would have been perfectly reasonable to interpret the lack of primary kinetic isotope effect as indicating a 'non-sulfene' process.

Sulfene formation is not restricted to the simple alkanesulfonyl chlorides; rather it is the common, though not invariable, route when a compound of the general formula $RR'CHSO_2Lg$, which can reasonably eliminate HLg, is treated with a basic reagent. The nature of the base, of the leaving group, Lg, and of the alkyl portion, can all determine

whether or not a sulfene is formed. Generally, arylmethanesulfonyl derivatives yield the arylsulfene readily with a variety of bases and leaving groups. 2,4-Dinitrophenyl phenylmethanesulfonate is a serviceable source of phenylsulfene, not just for mechanistic study[45,46] but for practical synthetic purposes as well[52,53]. 2,4-Dinitrophenyl methanesulfonate, however, was inert to conditions under which the phenylmethanesulfonate reacted readily[52].

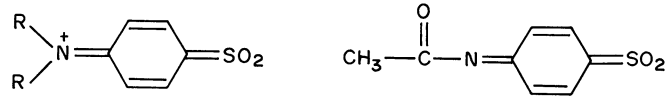
Though benzenesulfonyl chloride itself cannot form a sulfene by elimination of HCl, various substituted arenesulfonyl chlorides have this potential. The very first discussion of sulfenes in the literature[54] concerned the possibility of sulfene formation from a substituted 4-hydroxybenzenesulfonyl chloride (**10**) as in equation 10. Subsequent studies clarified the nature of the product (which was polymeric)[55,56] and of the yellow color ascribed by the early workers to the sulfoquinone intermediate; relatively recently a good kinetic case has been presented[57] for the reaction of **10** (X = Me) according to equation 10.



(10)

(**10**) X = Br, CH_3, etc.

Closely related 'sulfoquinonimine' species, e.g. **11** (R = H) and **12**, have been suggested as arising from 4-aminobenzenesulfonyl chloride and certain derivatives[58]. Related to these



(**11**) (**12**)

observations, though not strictly speaking sulfene-formation by a base-induced process, is the suggestion[59] that the deviation from the Hammett plot observed in the rate of hydrolysis of 4-(dimethylamino)benzenesulfonyl chloride could be accounted for on the basis of the intermediacy of **11** (R = CH_3). No sign, however, of the formation of a quinonoid sulfene by removal of a hydrogen from an *alkyl* group has been observed; 2,5-dimethylbenzenesulfonyl chloride in the presence of D_2O and Et_3N gave a product with no deuterium incorporation[60].

2. *Sulfene formation vs other reactions*

The preceding section dealt primarily with the evidence that demonstrated sulfenes to be intermediates in these processes and also, where the evidence warranted it, with the mechanism of the sulfene formation. A continual point of concern is whether or not the reaction is really proceeding by way of the sulfene or not. In this section we shall attempt to find what circumstances of substrate, base and (where different) nucleophile tend to lead to the elimination–addition (sulfene) reaction, and which to some other process, notably the direct displacement reaction. Sometimes, indeed, it takes only a rather small change in conditions to alter the mechanism completely. For example, it has been noted above that azide ion reacts with α-disulfones or sulfonyl chlorides by the direct displacement[49]. This is also seen in the reaction of methanesulfonyl chloride with aqueous sodium azide when the

pH is below 6; above pH 8, however, the azide is formed via the sulfene, as is shown by (a) the formation of $CH_2DSO_2N_3$ and (b) the observation that the reaction rate is zero order in azide[50]; a rather small change in pH thus leads to a complete change in mechanism. A corollary of this observation is that, in many experiments in aqueous solution in which the pH is not controlled, the reaction may very well proceed partly by one route and then, as the pH changes, by another.

It was found quite early in the study of sulfene chemistry with isotopic substitution that the results were capable of different (and contradictory) interpretation. Truce and Campbell[41] found that the reaction of triethylamine with roughly equivalent quantities of methanesulfonyl chloride and methanol-*d* gave a mixture of undeuterated and monodeuterated esters with the former commonly predominating slightly. They interpreted their observations in terms of competing elimination (sulfene) and substitution ('non-sulfene') reactions. Our view[40], on the other hand, was that essentially all of the reaction of triethylamine and the alkanesulfonyl chlorides was taking place via the sulfene route and that the undeuterated ester arose by return of the protium originally on the sulfonyl chloride and which had been introduced into the active hydrogen pool by the formation of the sulfene.

The Truce–Campbell picture of competing displacement and elimination, which has been taken up by others[1,61,62], is, in our view, incorrect. There are indeed other instances in which sulfene formation competes with direct displacement (see below), but it is our conclusion that the reaction of simple alkanesulfonyl chlorides with alcohols in the presence of triethylamine in benzene (or other aprotic organic solvents) is not one of them. Since the real picture is already complex, we feel that we had best get rid of any complications that are merely errors.

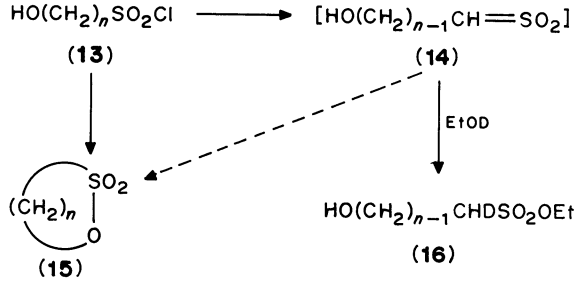
The case against the Truce–Campbell picture has been presented only in part before[63], and has two separate lines of reasoning. The first of these is to show that the undeuterated ester can arise from the sulfene, i.e. that the mere observation of undeuterated ester does not constitute a *prima facie* case for the direct displacement process. It seemed reasonable to us that the proton of the Et_3NH^+ (formed as the by-product in the reaction of CH_3SO_2Cl and Et_3N) could, in view of the known ease of such exchange processes[64,65], simply exchange with the deuteron in methanol-*d* prior to agglomerating to form a crystalline precipitate. In a simple experiment designed to test this idea, we found[63,66] that $PhCD_2SO_2Cl + CH_3SO_2Cl + CH_3OH + Et_3N$ (all in equimolar amounts in benzene) gave not only $PhCHDSO_2OCH_3$ but also $CH_2DSO_2OCH_3$ as well as $CH_3SO_2OCH_3$ (in the ratio 33:67). This experiment shows that the label can be transferred from one alkanesulfonyl group to another under these conditions, in full accord with the sulfene formation plus isotope mixing picture, and hence that the Truce–Campbell direct displacement proposal is not required. The second part of our case is that there is good reason to believe that the direct displacement cannot take place under these conditions. The key experiment is that a direct displacement intermediate, $CH_3SO_2\overset{+}{N}Et_2Me$ (as the triflate salt), was treated under reaction conditions as close as possible to those of a reaction of CH_3SO_2Cl and CH_3OD with diethylmethylamine (in benzene–acetonitrile 10:3) and the products found to be distinctly different[66]. From the sulfonylammonium salt, for example, there was some ($\sim 10\%$) $CHD_2SO_2OCH_3$, whereas from the sulfonyl chloride there was none. This indicated that any direct displacement process with CH_3SO_2Cl and $MeNEt_2$ and CH_3OD was at most a minor process under these conditions. In this and related work on the multiexchange reaction in aqueous medium[67,68] using a series of tertiary amines, the ratio of direct displacement to elimination diminished in the order Me_3N, Me_2NEt and $MeNEt_2$. The absence of observable direct displacement with CH_3SO_2Cl and CH_3OD with $MeNEt_2$ makes it highly unlikely that any significant direct displacement occurs with triethylamine.

The reaction of $CH_3SO_2\overset{+}{N}Et_2Me\ CF_3SO_3^-$ with $MeNEt_2$ and CH_3OD in benzene–

acetonitrile, noted above, also showed a substantial portion of the *undeuterated* ester, $CH_3SO_2OCH_3$, even in the presence of a large excess of CH_3OD. This would indicate that the sulfonylammonium salt is undergoing a measure of direct displacement. Further examples of what we believe are genuine cases of the displacement–elimination competition are given below.

The original experiments of Truce and Campbell[41] and in our laboratory[42] showed that sulfene formation occurred with methanesulfonyl and ethanesulfonyl chlorides, as well as phenylmethanesulfonyl and 2-propene-1-sulfonyl chlorides. It was therefore with surprise that we read the report of Panov and coworkers[61] asserting that 1-butanesulfonyl chloride reacted with triethylamine and methanol-*d* in benzene to give only the undeuterated ester, i.e. that no sulfene was formed in the reaction. These results were sufficiently at variance with our own observations with ethanesulfonyl chloride that we undertook to repeat the Soviet authors' experiment. Our results[66] showed the major product under the reported[61] reaction conditions to be, in fact, the monodeuterated ester ($CH_3CH_2CH_2CHDSO_2OCH_3$, $>90\%$, as shown by ^1H and ^2H n.m.r. and mass spectrometry). It was also shown that a series of sulfonyl chlorides including 1-pentanesulfonyl, 1-hexadecanesulfonyl and 1-docosanesulfonyl chlorides all gave the monodeuterated ester in high isotopic yield ($>95\%$) on reaction with triethylamine and methanol-*d* (in twenty-fold excess) in methylene chloride[66]. It would appear reasonable to conclude at this point that the formation of esters by the reaction of 1-alkanesulfonyl chlorides with triethylamine in organic media takes place, within experimental uncertainty, entirely by way of the elimination–addition (sulfene) route. This generalization may be extended to other alkanesulfonyl chlorides such as phenylmethanesulfonyl chloride[40] and 2-propene-1-sulfonyl chloride[41]. With secondary sulfonyl chlorides there is only one exchangeable hydrogen and the deuterium labelling experiment is a less powerful mechanistic tool; but the observation, in addition to those mentioned above, that α-deuterated ester is formed from 2-propanesulfonyl[41] and 2-octanesulfonyl[66] chlorides with triethylamine and methanol-*d*, taken with the formation of enamine adducts from 2-propanesulfonyl and cyclohexanesulfonyl chlorides[69], combine to present a good case for the sulfene route with secondary alkanesulfonyl chlorides and triethylamine.

One exception to the generality of ester formation by way of the sulfene has been found in the base-promoted conversion of the simplest ω-hydroxy-1-alkanesulfonyl chlorides (**13**) into their sultones (**15**)[70,71] as in equation 11. Formation of **15a**, **15b** and



(11)

(a) $n=2$, (b) $n=3$, (c) $n=4$, (d) $n=5$, (e) $n=6$

15c evidently proceeds by the direct displacement reaction, as is shown by the lack of α-deuteration when the reaction was done in the presence of a deuterated alcohol; the alkyl esters formed from **15a** and **15c** in these experiments were appropriately α-monodeuterated as in **16**. With the higher homologues **13d** and **13e**, both the sultones

and the ethyl esters are largely monodeuterated, indicating that both products come from the sulfenes (**14d** and **14e**)[71]. 2-Hydroxyethanesulfonyl chloride (**13a**) evidently forms some of the sulfene (**14a**) on reaction with tertiary amines in aqueous or organic media. Its reaction with water or hydroxide, however, proceeds chiefly by way of the sultone (**15a**) along with a minor direct displacement pathway, but no sign whatever of the sulfene, even at high pH[70].

Evidence for sulfene formation has been obtained for sulfonyl chlorides in addition to the limited array already discussed. We note, in particular, chloromethanesulfonyl chloride[72], phenylethanesulfonyl chloride[40], benzoylmethanesulfonyl chloride[73], ethoxycarbonylmethanesulfonyl chloride[74], cyanomethanesulfonyl chloride[75], methanedisulfonyl chloride[76], 2-propene-1-sulfonyl chloride[77,78], 2-propyne-1-sulfonyl chloride[79], (trimethylsilyl)methanesulfonyl chloride[80], (dichlorophosphinyl)methanesulfonyl chloride[81] and fluoromethanesulfonyl chloride[11].

Most of the examples given until now in this section have used triethylamine as the tertiary amine. The use of other bases, including other tertiary amines, can lead to quite different results. It was shown in the early deuteration studies[40] that the simple reaction of phenylmethanesulfonyl-d_2 chloride with methanol in the absence of added base proceeds without deuterium loss; the reaction is presumably a direct displacement like the simple alcoholysis of arenesulfonyl chlorides[82–85]. This accords well with the observations on hydrolysis, as mentioned in the previous section, in which the k_W term was associated with a simple direct displacement[50]. Mechanistic variation is possible even in solvolyses, as is shown by the difference between methanesulfonyl and chloromethanesulfonyl chloride, on the one hand, and dichloromethanesulfonyl chloride, on the other[86]. The first two, as might be expected, undergo deuterolysis without incorporation of deuterium, whereas the product from the dichlorosulfonyl chloride is the deuterated sulfonic acid. Recovered dichloromethanesulfonyl chloride is also partly deuterated; this, taken with the observations that (a) the hydrolysis of Cl_2CHSO_2Cl was retarded by acid and (b) the relative rates of hydrolysis of these compounds followed the sequence $Cl_2CHSO_2Cl \gg CH_3SO_2Cl > ClCH_2SO_2Cl$, led to the suggestion of a reversible ElcB mechanism (equation 12)[86].

$$Cl_2CHSO_2Cl \overset{H_2O}{\rightleftharpoons} Cl_2\bar{C}SO_2Cl \xrightarrow{slow} Cl_2C{=}SO_2 \xrightarrow{H_2O} Cl_2CHSO_3H \qquad (12)$$

Changes in mechanism with change in substitution were also observed[87] in a series of sulfonyl chlorides of the general structure $X{-}CH_2CH_2SO_2Cl$. The sulfonyl chloride was treated with pyridine and neopentyl alcohol (NpOH) in CD_3NO_2. With X = PhS, $PhSO_2$, or AcO, the reaction proceeded by way of the sulfene $XCH_2CH{=}SO_2$, with the product being either $XCH_2CH_2SO_2ONp$ or $CH_2{=}CHSO_2ONp$, depending on the nucleofugality of X. With X = Cl or $ClSO_2$, the first reaction was not sulfene formation, but rather elimination of HX to form ethenesulfonyl chloride, $CH_2{=}CHSO_2Cl$, which then gave its characteristic product mixture (see Section IV.B.2). With ethanesulfonyl chloride (X = H), however, slightly more than half of the reaction (as judged by deuterium substitution) went by way of the sulfene and almost as much by a direct displacement (i.e. a general base or nucleophilic catalysis) process. Recall that, as noted above, triethylamine, in contrast to pyridine, reacts with ethanesulfonyl chloride and isopropyl alcohol in CH_2Cl_2 *entirely* by the sulfene route[50].

A further variation in mechanism is found with methanesulfonyl chloride and *p*-toluidine. The reaction with triethylamine goes via the sulfene, but with pyridine by a direct displacement[88], perhaps involving general base catalysis. The key variable in this case would appear to be the basicity of the amine; with *N*-ethylmorpholine (pK_a 7.7) the sulfene route predominated (< 87%) but with *N*-methylimidazole (pK_a 6.95) it was the minor pathway (~20%). Phenylmethanesulfonyl chloride, it may be noted, reacts by the sulfene pathway with either pyridine or triethylamine and *p*-toluidine[88].

Change in reaction pathway may also be seen with change in the size of the base. Methanesulfonyl chloride in D_2O with trimethylamine, quinuclidine or 1,4-diaza[2.2.2]bicyclooctane (DABCO)[67,68] gives $CD_3SO_3^-$ as the major product. Though much of the H–D multiexchange apparently arises from differences in the subsequent reaction of the sulfene, it would appear that in the reactions of methanesulfonic anhydride and methanesulfonyl chloride with aqueous trimethylamine nucleophilic attack at sulfur with formation of the sulfonylammonium salt, $MeSO_2N^+Me_3$, contributes to, respectively, 87% and 44% of the reaction[63]. With aqueous triethylamine, however, the product from either the anhydride or the sulfonyl chloride is almost entirely $CH_2DSO_3^-$, formed presumably from the sulfene. The direct nucleophilic attack of the amine at sulfur is also reduced by increasing the size of the alkyl group of the sulfonyl chloride; multiexchange with ethanesulfonyl chloride and DABCO–D_2O is relatively minor[67].

The reaction of alkanesulfonyl chlorides in aqueous medium with aryloxide anions is evidently a sulfene reaction[50,51], but in non-polar media there is reason to believe that non-sulfene processes, e.g. a general base-assisted displacement, may well be important[61,62,66]. A series of papers by investigators in the Ukraine reports observation of mixed second- and third-order kinetics with the third-order term assigned to such a general base-catalyzed process[89]. The mechanistic picture drawn by these authors may well be correct, but our confidence would be enhanced if they were more careful in noting and resolving differences between their experimental results and those already reported in the literature. In the case of the reaction of equimolar amounts of CH_3SO_2Cl, CH_3OD and triethylamine in benzene, for example, the authors' ^1H n.m.r. data[62] correspond to essentially pure $CH_2DSO_2OCH_3$. This experiment had already been reported by Truce and Campbell[41] to yield a mixture of 48% $CH_2DSO_2OCH_3$ and 52% $CH_3SO_2OCH_3$, and was, of course, one of the key experiments that led these authors to suggest the intervention of a direct displacement by triethylamine, as already discussed in this section. In our hands[66] repetition of this experiment have results in full agreement with those of Truce and Campbell. In addition, in the light of an earlier report on a third-order sulfene formation[42], it would appear to us that the case for general base-catalyzed substitution would be more convincing if the kinetic argument were bolstered by deuterium exchange studies. It should perhaps be noted that special care is needed for these experiments since aryl methanesulfonates exchange hydrogens very readily, e.g. in a separatory funnel with aqueous hydroxide concentrations appropriate for extraction of unreacted phenols[50].

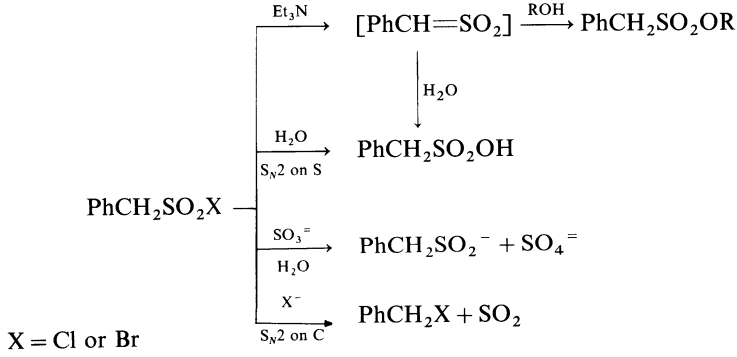
Almost all of the competing 'non-sulfene' reactions noted to this point are those in which a nucleophile attacks the sulfonyl sulfur rather than the α-hydrogen. Another place for nucleophiles to attack a sulfonyl chloride or bromide is at the halogen, with reduction of the substrate to the sulfinate anion; this feature is associated with 'soft' nucleophiles[90]. Aqueous sodium sulfite, for example, is commonly used as a reagent for preparing the sodium sulfinate; this reaction predominates completely even with phenylmethanesulfonyl chloride, which rapidly forms the sulfene at pH 8, i.e. that of the sodium sulfite solution. Reaction of phenylmethanesulfonyl chloride with triethylamine and triphenylphosphine gave[52] a mediocre (32%) yield of benzyltriphenylphosphonium chloride (the sulfene product, see Section V.A.4.a), plus a substantial yield of triphenylphosphine oxide formed by competing redox reactions. Use of 2,4-dinitrophenyl phenylmethanesulfonate gave the phosphonium salt in 77% yield.

Organometallic reagents commonly reduce sulfonyl chlorides to sulfinates and it was therefore not surprising to find that the reaction of phenylmethanesulfonyl chloride with butyllithium[91] or phenyllithium[92] yielded mainly lithium phenylmethanesulfinate. Use of the sulfonyl fluoride, however, gave principally **17**, plus small amounts of trisulfone and higher oligomers[92], which can be regarded as arising from the sulfene; formation of a small amount of the sulfene adduct in the presence of ketene *O,O*-diethyl acetal points to the formation of at least some sulfene in this reaction[92].

$PhCH_2SO_2CHSO_2R$ $R = CH_2CH_2CH_2CH_3$ or Ph
|
Ph
(17)

Sulfonyl fluorides have not been much used as sources of sulfenes, presumably because of their low reactivity relative to, say, sulfonyl chlorides. Phenylmethanesulfonyl fluoride does not react with triethylamine under mild conditions, but does react with *p*-toluidine in methanol at 45 °C after a few days; the deuterium exchange pattern was consistent with sulfene formation by an $(E1cB)_{rev}$ mechanism[93]. The mechanism of the reaction of phenylmethanesulfonyl fluoride evidently changes with conditions, since Williams and coworkers had observed that its reaction with aqueous hydroxide showed rate-controlling proton transfer, as in either an E2 or $(E1cB)_{irr}$ process[46]. Sulfonyl fluorides have been proposed as sulfene sources from such fluorinated sulfonyl fluorides as 1,2,2,2-tetrafluoroethanesulfonyl fluoride by Knunyants and Sokol'skii and coworkers[94].

One further form of competition with sulfene formation is the substitution of the 'SO_2Lg' group, particularly the halosulfonyl function, by the nucleophile. This is perhaps best illustrated by the reaction of bromide ion with phenylmethanesulfonyl bromide in an S_N2-on-carbon process to give benzyl bromide and sulfur dioxide[95]. This, and the other competing modes of reaction of phenylmethanesulfonyl bromide and chloride summarized in Scheme 2, serve to emphasize that sulfene formation is by no means the



SCHEME 2

only reaction mode open to a nucleophile and the generalized sulfonyl substrate, $RR'CHSO_2Lg$. Closely related to the above halide-catalyzed desulfonylation reaction is the unimolecular decomposition of sulfonyl derivatives as in equation 13. This is found whenever the R group in RSO_2Lg is so constituted that the carbocation, R^+, is relatively stable. The hydrolysis of 2-methyl-2-propanesulfonyl chloride to give *tert*-butyl alcohol, HCl and HSO_3^- is an example[50]. In most cases this S_N1 decomposition of sulfonyl derivatives 'competes' only in the sense that the sulfonyl derivative is lost before one has the opportunity to react it with the reagent under study. The original work of Wedekind and Schenk[5] in 1911 began with an attempted synthesis of diphenylsulfene, which failed because they were unable to prepare the planned precursor, diphenylmethanesulfonyl chloride. This sulfonyl chloride has yet to be reported, with most attempts yielding benzhydryl chloride[96]. We found 2-chloro-4-nitrophenyl diphenylmethanesulfonate to be a serviceable source of diphenylsulfene; the 4-nitrophenyl ester was unreactive to our base, while the 2,4-dinitrophenyl ester rapidly underwent desulfonylation to diphenylmethyl

TABLE 1. Sulfene formation from $RR'CHSO_2Lg$

Lg	Typical reagent	Evidence and remarks	References
Cl	R_3N, $RR'NH$, RNH_2, RO^-, ArO^-	See discussion in Section IV.A.1; competing reactions; (a) direct displacement, especially with the less basic nucleophiles, (b) reduction to $RR'CHSO_2^-$ with soft nucleophiles	40–44
Br	Et_3N (etc.)	Similar to Cl	41
F	BuLi, PhLi, OH^-,	Reaction slow with weak bases, less subject to reduction to $RR'CHSO_2^-$	46, 91, 92, 93
RSO_2O	Et_3N (etc.)	D-labelling; apparently greater tendency for direct displacement	41, 63
RSO_2	R_3N, OH^-	D-labelling; smaller tendency for direct displacement	49
ArO	Et_3N, OH^-	Kinetics and labelling (Section IV.A.1); poor leaving groups[a] → $(E1cB)_{rev}$, better leaving groups[b] → $(E1cB)_{irr}$	45–47, 52, 53
	OH^-	^{18}O and D labelling	97
R_3N^+	R_3N	Enamine adduct formation; multiexchange of hydrogen seen; direct displacement may compete	63, 68

[a]E.g. phenoxide (see Scheme 1).
[b]E.g. 2,4-dinitrophenoxide (see Scheme 1).

2,4-dinitrophenyl ether, presumably as in equation 13[96].

$$RSO_2Lg \longrightarrow R^+ + SO_2 + Lg^- \longrightarrow RLg + SO_2 \qquad (13)$$
$$Lg = Cl, OAr, \text{ etc.} \qquad \xrightarrow{R'OH} ROR'$$

At this point we summarize in Table 1 those reactions which are believed to yield a sulfene by base-induced elimination from compounds of the general structure $RR'CHSO_2Lg$.

B. Sulfenes from $RR'CXSO_2Lg$; Thiofugal Sulfene Formation

1. *Desilylative elimination*

Block and Aslam[98] have reported sulfene formation as in reaction 14. It proceeds readily at room temperature in two hours, and has certain advantages in comparison with the reaction of methanesulfonyl chloride with triethylamine. These include formation of the sulfene adduct with cyclopentadiene, bromomethanesulfonyl bromide with bromine,

$$Me_3SiCH_2SO_2Cl + F^- \xrightarrow{CH_3CN} [CH_2{=}SO_2] + Me_3SiF \qquad (14)$$

and a product derived from an initially formed sulfene adduct with 2,6-diphenylbenzoisofuran. None of these products is formed in the presence of triethylamine, either because the sulfene–triethylamine adduct is formed (and reacts further) faster than the sulfene–diene adduct (see Section V.B), or, as in the case of the bromine reaction, the halogen reacts with the amine and no sulfene is formed at all. The fluorodesilylation route would thus appear to provide sulfene under mild conditions in the presence of species with relatively low reactivity toward sulfene, and hence to provide favorable conditions for looking at reactions with reagents of comparatively low reactivity to sulfenes (or high reactivity toward amines). The reaction has been extended to include (trimethylsilyl)-methanesulfonic anhydride, 1-(trimethylsilyl)propanesulfonic anhydride and 1-(trimethylsilyl)cyclopropanesulfonyl chloride[99].

The initial report of the synthesis of (trimethylsilyl)methanesulfonyl chloride[100] described its ready hydrolysis to hexamethyldisiloxane and methanesulfonic acid, the reaction being complete, for example, after ten minutes in 5% aqueous sodium hydroxide at room temperature. The intermediacy of sulfene seems likely, for the alkaline cleavage at least.

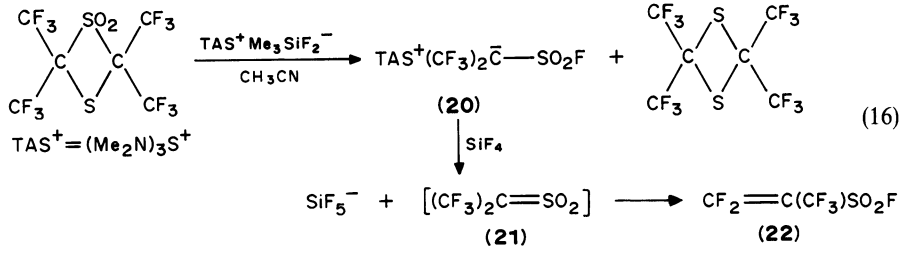
2. *Vinylogous nucleophilic attack on 1-alkenesulfonyl halides*

Reaction of tertiary amines with ethenesulfonyl chloride has been shown[101] to proceed via the ammoniomethylsulfene as in equation 15. Trapping of the sulfene with an alcohol generally yields both the ethenesulfonic ester (**18**) and the [2]betylate (**19**); with water, ethenesulfonic acid and the betaine, $R_3\overset{+}{N}CH_2CH_2SO_3^-$, are formed. For synthetic purposes the formation of the ester mixture does not generally create problems since **19** is readily converted to **18** by shaking with aqueous carbonate, and **18** is converted to **19** by a simple two-step sequence. The 'betylates' (**19**) show useful properties as alkylating agents, largely because of their ability to participate in various phase transfer processes[102]. As has been noted in Section IV.A.2, 2-chloroethanesulfonyl chloride and 1,2-ethanedisulfonyl chloride both yield ethenesulfonyl chloride on reaction with tertiary amines; under most conditions the reaction carries on to yield the above mixture of ethenesulfonic and 2-ammonioethanesulfonic acid or their derivatives[87].

$$R_3N + CH_2{=}CHSO_2Cl \longrightarrow [R_3\overset{+}{N}CH_2CH{=}SO_2] \xrightarrow{R'OH} \underset{\textbf{(18)}}{CH_2{=}CHSO_2OR'}$$
$$\Big\downarrow R'OH \qquad (15)$$
$$\underset{\textbf{(19)}}{R_3\overset{+}{N}CH_2CH_2SO_2OR'}$$

3. *From the anion of 1,1,1,3,3,3-hexafluoro-2-propanesulfonyl fluoride with BF_3 or SiF_4*

The title anion (**20**) is prepared and converted to bis(trifluorethyl)sulfene (**21**) by the ingenious procedure[103] shown in equation 16. With 'moderately electron-rich' terminal

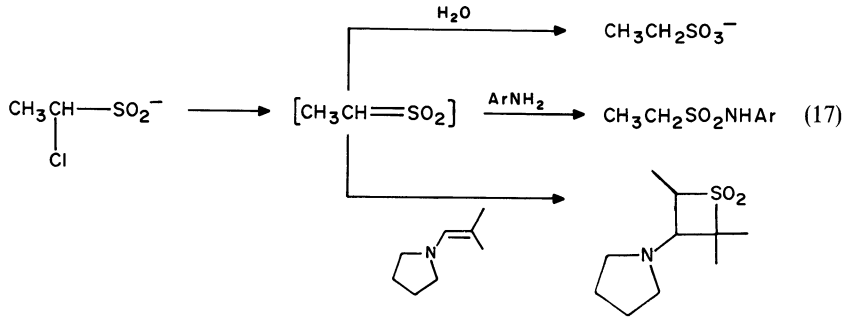


(16)

olefins such as methyl vinyl ether or phenyl vinyl sulfide, [2 + 2] cycloadducts, and with dienes either [2 + 2] or [2 + 4] cycloadducts, were obtained. With most sulfenes as commonly produced 'very electron-rich' olefins, such as enamines and ketene acetals, are usually required to yield cycloadducts, but whether the higher reactivity observed with **21** under these conditions reflects an intrinsically higher reactivity of **21**, or the absence of rapid side-reactions consuming the sulfene, has not been determined.

C. Carbofugal Formation of Sulfenes from $RR'C(Lg)SO_2^-$

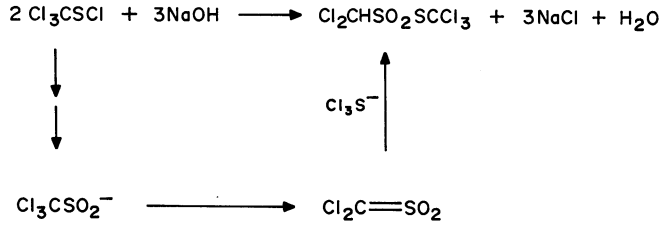
The possibility of nucleophilic attack on the carbon atom of a sulfene (carbophilic attack) as opposed to the more usual bond formation at the *sulfur* atom (thiophilic attack) (see Sections I and V.A.3) prompted the investigation of sulfene *formation* by loss of the leaving group from the carbon (carbofugal formation). Evidence for such reaction was found with 1-chloroethanesulfinate anion which, (a) when warmed in the presence of water, gave ethanesulfonate anion, (b) with *p*-toluidine yielded the sulfonamide and (c) with an enamine, the corresponding enamine adduct[104] (equation 17). The reaction, which appears to be a simple elimination of halide from the α-halosulfinate anion, has been observed with chloromethanesulfinate and the corresponding bromosulfinates[63,104] and is probably general.



(17)

Not long after the appearance of our original report on carbofugal formation of sulfenes, Dykman[105] rationalized the overall transformation shown on the first line in equation 18 by including the reaction in the second line. The closely related sulfene formation, $Cl_2CHSO_2^- \longrightarrow [ClCH{=}SO_2]$, was subsequently suggested by Šilhánek and Zbirovský[106].

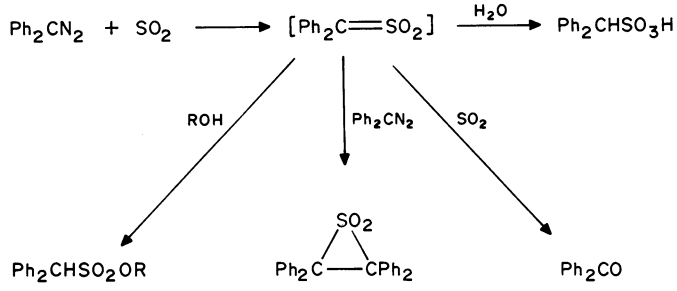
Because the starting material in this mode of generating sulfenes is a sulfinate (which is reactive toward sulfenes), its synthetic application is obviously limited to use in the presence of sulfene traps more reactive than the sulfinate.



(18)

D. Diazoalkanes and Sulfur Dioxide; the Staudinger–Pfenninger Reaction

In 1916 Staudinger and Pfenninger[107], prompted by the ketene-sulfene analogy, reported that diphenyldiazomethane and sulfur dioxide gave products appropriate to the intermediate formation of diphenylsulfene as in equation 19. Sulfene formation in this way

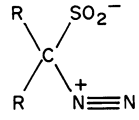


(19)

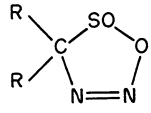
is fairly general but has not been very much used. The formation of ethylene sulfones (thiirane 1,1-dioxides) is notable as one of the few routes to these species; these undergo, amongst other reactions, desulfonylation with formation of the double bond, thereby providing a serviceable route to alkenes[108]. In this reaction both of the starting materials are capable of reacting with the sulfene and it is therefore not the method of choice for generating sulfenes to react with weak sulfene traps. The presence of catalytic reagents can be critical; we found that the reaction of phenyldiazomethane and sulfur dioxide in 2-propanol gave only *trans*-stilbene and *cis*-1,2-diphenylethylene sulfone, but in the presence of a tertiary amine like pyridine, isopropyl phenylmethanesulfonate was formed in high yield[88]. Another complication was observed in the reaction of diazomethane and sulfur dioxide. These reagents react in the absence of other materials to form ethylene sulfone[109], presumably via the sulfene, but do not yield alkyl methanesulfonate in the presence of an alcohol. The product that is observed instead is the methyl alkyl sulfite which probably arises as shown in equation 20. The first step is analogous to the presumed hydration of SO_2 to form sulfurous acid, the second reaction is simply methylation of the acid by diazomethane. The key feature here may be the reactivity of diazomethane as an alkylating agent, relative to other diazoalkanes.

$$ROH + SO_2 \rightleftharpoons ROSO_2H \xrightarrow{CH_2N_2} RO{-}SO{-}OCH_3 \qquad (20)$$

The mechanism by which the sulfene is formed is not known, though the intermediacy of either **23** or **24** (or both) seems reasonable. Sulfene formation from **23** would be a carbofugal process like that from an α-haloalkanesulfinate anion already discussed in Section IV.C.



(23)

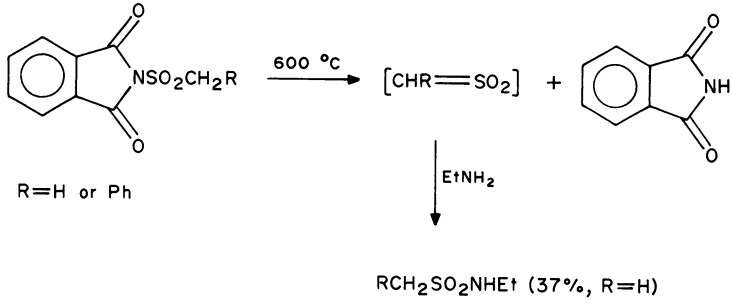


(24)

E. Thermal Generation of Sulfenes

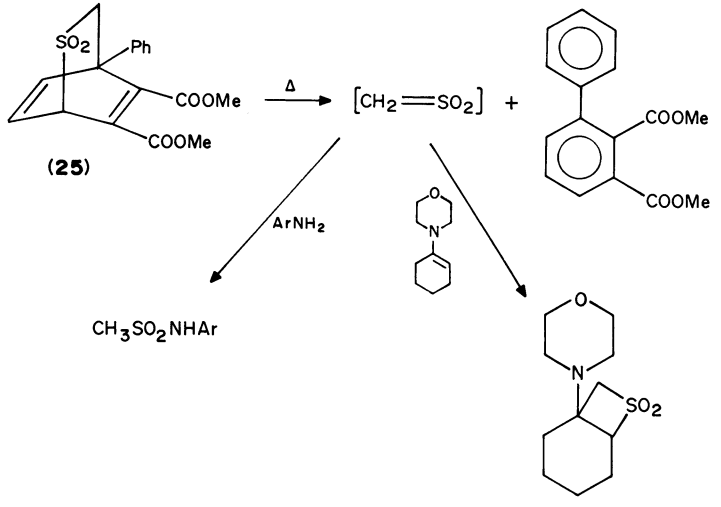
1. Thermal elimination reactions

Generation of sulfene by flash vacuum thermolysis of chlorosulfonylacetic acid and methanesulfonic anhydride has already been noted (see Section III). Similar treatment of *N*-alkylphthalimides leads to products expected from the intermediate sulfene[110] as in equation 21.



(21)

A reverse Diels–Alder extrusion of sulfene from **25** with aromatization of the cyclohexadiene system (equation 22) proceeded readily[111] in the liquid phase above

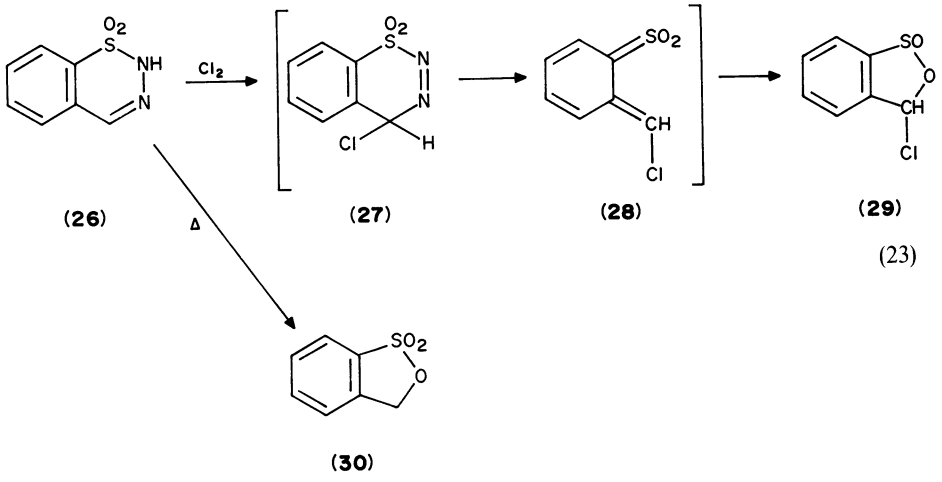


(22)

200 °C, but, unfortunately, **25** was not sufficiently volatile for flash vacuum thermolysis. With only small changes in the substrate structure a competing desulfonylation-rearrangement[112] to form a seven-membered ring structure has also been observed under the reaction conditions[113,114].

In contrast to the above thermal elimination processes, in which there is good reason to invoke sulfene formation, the chlorination of **26** is perhaps more appropriately labelled a

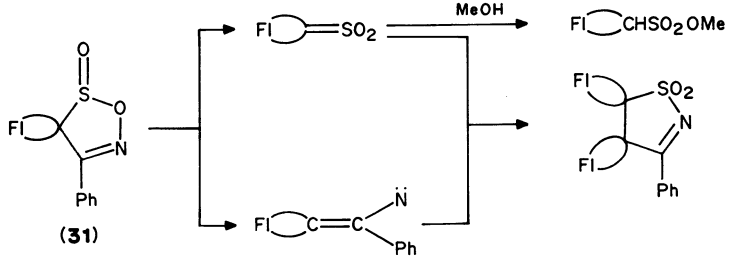
'possible sulfene reaction'. This reaction can be rationalized as proceeding via thermal extrusion of nitrogen from **27** to give **28**, which cyclizes to **29**[115] as in equation 23. Thermolysis of **26** yields **30**, perhaps analogously[115].



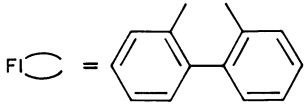
(26) (27) (28) (29) (30)

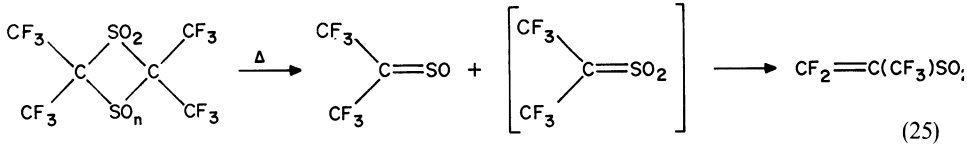
(23)

Heating of **31** has been suggested[116] to proceed by the interesting reactions summarized in equation 24.



(31) (24)





(32) (33) (21) (22)

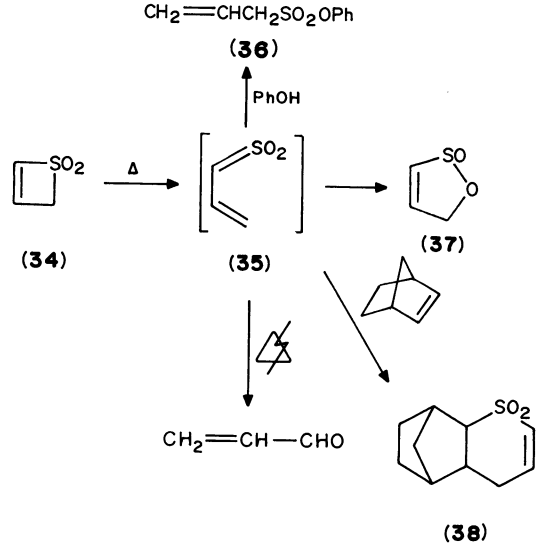
(25)

Gas phase thermolysis of the sulfone–sulfoxide (**32**, $n = 1$) yield[117] sulfine **33** and sulfonyl fluoride **22** (equation 25); the latter was presumably formed from the sulfene (**21**) (cf. Section IV.B.3). The corresponding bis-sulfone (**32**, $n = 2$) gave some **22** and hexafluoroacetone[117], also probably from the sulfene (**21**) by thermal desulfinylation (Section V.C).

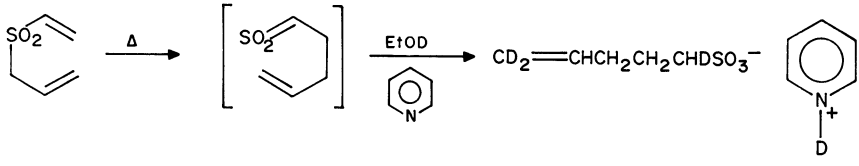
2. *Thermal rearrangements*

Electrocyclic ring opening of thiete 1,1-dioxide (**34**), in both the vapor and liquid phases, readily yields vinylsulfene (**35**) which, as is indicated in equation 26, is either trapped to form a characteristic product (e.g. **36**), cyclizes to the sultine **37**, or, in the gas phase at high temperature, desulfinylates to acrolein[118] (Section V.C.). Vinylsulfene (**35**) produced from **34** also reacts with [2.2.1]bicycloheptene to form the [2 + 4] cycloadduct (**38**)[119].

Thermal [3,3] rearrangement of allyl vinyl sulfones, the 'sulfo-Cope' rearrangement (equation 27), proceeds readily in the liquid phase above 165 °C, and has the potentially useful synthetic feature of generating a new carbon–carbon bond[120].



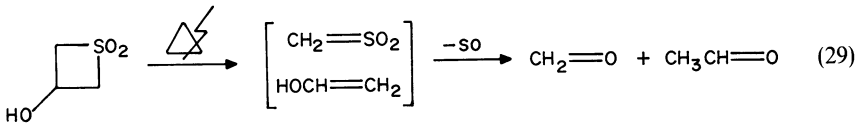
(26)



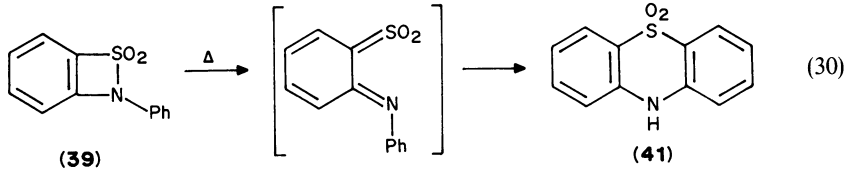
(27)

$$CH_2{=}CHSO_2Cl \xrightarrow{\Delta} [Cl{-}CH_2CH{=}SO_2] \xrightarrow{-SO} ClCH_2CHO \qquad (28)$$

Other thermal rearrangements probably leading to sulfenes include (a) formation of chloroacetaldehyde from ethenesulfonyl chloride[120] as in equation 28, (b) generation of formaldehyde and acetaldehyde from 3-thietanol 1,1-dioxide[118] shown in equation 29, and (c) rearrangement[121] of *N*-phenylbenzothiazete 1,1-dioxide (**39**) to **41**, probably via **40** (equation 30).



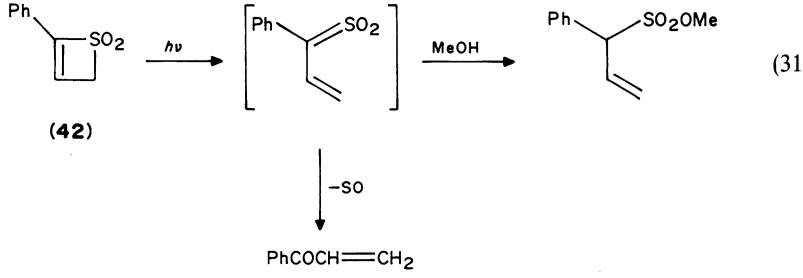
(29)



(30)

F. Photochemical Generation of Sulfenes

Mention has already been made in Section III of the photochemical formation of sulfene from thietanone 1,1-dioxide[19], presumably by a [2 + 2] cycloreversion. Langendries and DeSchryver have also observed photochemical electrocyclic ring opening of thiete 1,1-dioxides, e.g. **42**, forming either the products of desulfinylation or sulfene trapping[122], as in equation 31.

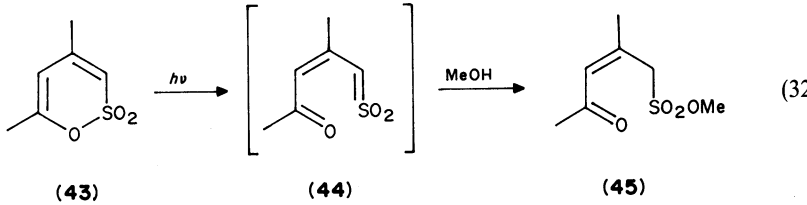


(31)

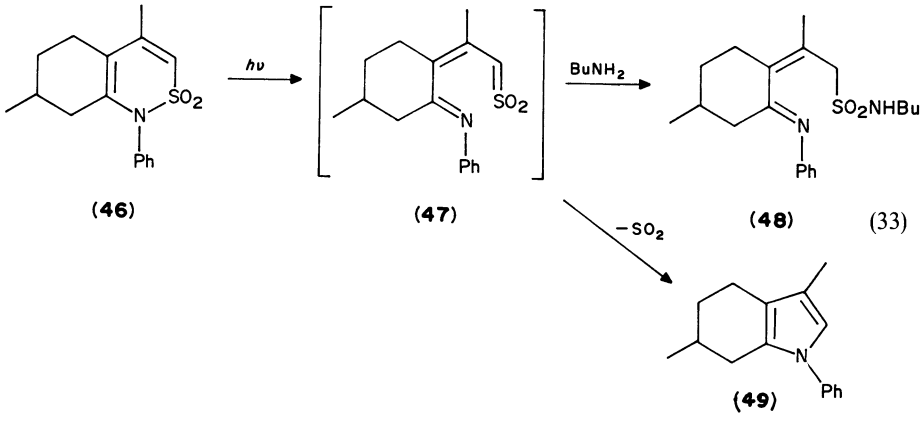
Photochemical cyclohexadienic cycloreversion was observed originally with sultones[123–125] and is illustrated by equation 32; it has been extended to sultams[8] (equation 33) and sulfones[126,127] (equation 34).

One well-known photochemical reaction which could, in principle, yield sulfenes is the Norrish type II cleavage of appropriate β-keto sulfones; the specific examples investigated gave no sign of sulfene formation[128].

From the ketene–sulfene analogy α-diazosulfones might be expected to undergo a thermal or photochemical analogue of the Wolff rearrangement to form sulfenes. Evidence



(32)



for the photochemical 'sulfo-Wolff' rearrangement (equation 35) has been obtained[129], but the yields were disappointing.

$$ArSO_2CHN_2 \xrightarrow{h\nu} [ArCH{=}SO_2] \xrightarrow{MeOH} ArCH_2SO_2OMe \quad (10\%) \qquad (35)$$

V. REACTIONS OF SULFENES

The reactions of sulfenes are many and various and their presentation requires that they be sorted out into categories which, hopefully, help to show a measure of order in this abundance. We have chosen three main groups: nucleophilic additions, cycloadditions, and thermal and photochemical processes. This arrangement is somewhat arbitrary, since the reactions are not all well-understood and, of those that are, not all fit perfectly into the chosen scheme. It is our view that this ordering, however imperfect, does serve the purpose of providing the reader with both an overview of sulfene chemistry and a means of gaining access to a specific piece of information.

One class of reaction evidently missing from this list is the reaction of sulfenes with electrophiles. Sulfene itself is strongly electrophilic and this class may be expected to be small. One class of reaction formally involving a sulfene and an electrophile is the cycloaddition with chloral and related carbonyl compounds. Evidence has been obtained for the importance of tertiary amines in this process and, as is discussed in Section V.B.5, it is unlikely that it is a simple reaction of a sulfene with an electrophile. The reaction of (trimethylsilyl)methanesulfonyl chloride with cesium fluoride in the presence of bromine has been formulated as proceeding via $CH_2{=}SO_2 \longrightarrow BrCH_2SO_2^+$, and the possibility of a carbanionic intermediate such as $\bar{C}H_2SO_2X$ dismissed because a reaction with methyl iodide instead of bromine showed no sign of any $CH_3CH_2SO_2X$[98]. The failure to observe any of the methyl iodide trapping product could arise, however, because another species, e.g. sulfene itself, is a more efficient trapping agent, and the possibility of a carbanion

process has not, in our view, been completely excluded: we mention it here as the most likely example of a possible sulfene–electrophile combination.

A. Nucleophilic Addition Reactions

1. Thiophilic addition with protonation: sulfonylation of alcohols, amines and related compounds

The everyday job of sulfenes is to make sulfonic esters, and an array of other sulfonyl compounds. The reaction may be summed up by equation 36:

$$RR'C{=}SO_2 + HNu \longrightarrow RR'CHSO_2Nu \qquad (36)$$

where HNu = H_2O, ROH, RNH_2[130], RR'NH[130], RSH[131,132], RSO_2NH_2[50], $(RCO)_2NH$[133], $(RCO)_2CHR$[91], RCOOH[91] and RR'C=NOH[91,134–136], PhNHOH[137] and R may be alkyl, aryl or other groups.

A number of examples of sulfene trapping by water, alcohols or amines have already been given in the earlier part of this chapter, e.g. in Scheme 2, **35** → **36**, **44** → **45**, **51** → **52**, or the formation of **9** and **48**.

Virtually all of the vast number of methanesulfonate, or 'mesylate', esters prepared to facilitate elimination or substitution of a hydroxyl function have been prepared from sulfene; the standard procedure using methanesulfonyl chloride and triethylamine in dichloromethane has been described by Crossland and Servis[138]. To be sure, sulfene intermediacy is not required for alkanesulfonate ester formation; the reaction, as has been noted (in Section IV.A.2), will proceed without base promotion via the direct displacement route, but it is usually sufficiently sluggish, however, that the further reaction of the ester with the alcohol competes with ester formation[139]. This makes the procedure a poor one for most practical purposes, although we recently encountered an instance, namely the preparation of neopentyl 2-chloroethanesulfonate[87], in which the direct reaction of the alcohol and sulfonyl chloride without base was the method of choice; this arose because (a) the product is stable and (b) 2-chloroethanesulfonyl chloride does not yield the corresponding sulfene with tertiary amines (Section IV.A.2).

As was noted earlier (Section IV.D) sulfene trapping is subject to base catalysis[88]. The same paper also noted that product ratios varied with the structure of the base (equation 37). In this example the stilbene is formed via reaction of the sulfene with phenyldiazomethane, the reaction which is observed in the absence of any other sulfene traps.

$$PhCHN_2 + SO_2 + ROH + ArNH_2 \longrightarrow PhCH_2SO_2OR + PhCH_2SO_2NHAr + PhCH{=}CHPh$$

no base	0	:	0	:	100
Et_3N	10	:	85	:	~3
Me_2NCH_2CN	41	:	8	:	51

(where R = isopropyl and Ar = *p*-tolyl)

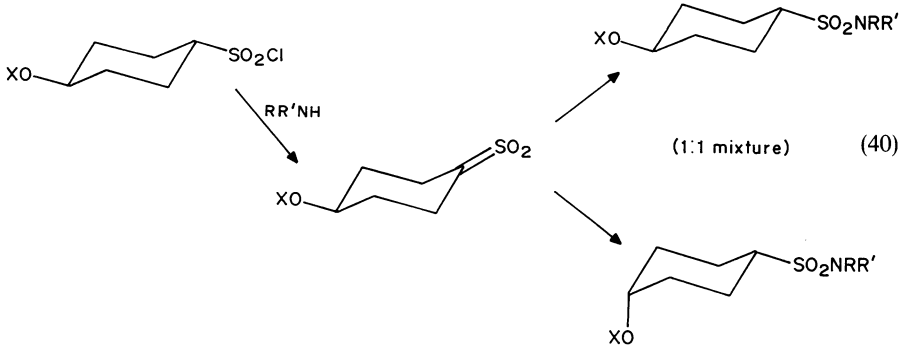
The detailed mechanism of sulfene trapping with alcohols and amines and the like is not fully understood, but equations 38 and 39 seem reasonable for sulfene and its simplest derivatives in organic media[26]. The first step (equation 38) is regarded as a general base catalyzed reaction, thereby avoiding formation of the highly acidic SO_2Z^+H system (Z = OR or NHR). The second step (equation 39) is believed to involve only the BH^+ counterion with no participation of any BH^+ from the main body of the solution[26]. Note that the ion pair as initially formed will have the BH^+ group in the vicinity of the Z component and not in the 'preferred' setup for protonation of α-sulfonyl carbanions

(i.e. near the carbanion and *anti* to the C—Z bond; see Reference 140 and the sources cited); the second step would therefore not occur instantly and other reactions, such as reversal of step 1 or loss of β-substituents[26] when $R' = XCH_2$, may occur.

$$RR'C{=}SO_2 + ZH + B \rightleftharpoons RR'\bar{C}{-}SO_2Z\ BH^+ \quad (38)$$

$$RR'\bar{C}{-}SO_2Z\ \overset{+}{B}H \longrightarrow RR'CH{-}SO_2Z + B \quad (39)$$

The prediction of the experimental outcome in potentially complex systems depends not only on the fate of the sulfene once it is formed, but, as has been discussed extensively in Section IV.A.2, whether the reaction proceeds by way of the sulfene or by another pathway. In many practical cases the precise route to the desired product is of no consequence, but sometimes it does matter, e.g. if there is any concern about (a) selectivity with different functional groups (as in the next paragraph), or (b) stereochemistry or H–D exchange α to the sulfonyl group. Cram and coworkers[141] observed that 2-octanesulfonyl-2-*d* chloride gave fully deuterated *N*-methyl 2-octanesulfonanilide-2-*d* on reaction with *N*-methylaniline (presumably by direct displacement), but partly exchanged *N*,*N*-dimethyl 2-octanesulfonamide with *N*,*N*-dimethylamine (presumably, at least in part, from the sulfene). In contrast, however, the reaction of camphor-10-sulfonyl-10-d_2 chloride (**8**) with menthylamine (**7**) proceeded with mostly (92%) monoexchange[44], and hence the kinetic resolution in the reaction **7** + **8** → **9** (Section IV.A.1, equation 8) arises in the reaction of **8** with the sulfene and not in any direct displacement. Restriction to just one mechanistic pathway, however, does not ensure a single product, as may be seen from the recent results[142] summarized in equation 40. Low stereoselectivity in the trapping of cyclohexylidene sulfenes had been noted earlier[42,143].



(40)

X = Ts or Ac

RR'NH = CH_3NH_2 or piperidine

Stoodley and Whiting[144] have reported *O*-mesylation of a bicyclic heterocyclic alcohol with mesyl chloride and triethylamine in dichloromethane (presumably via the sulfene) and *N*-mesylation of the same substrate with mesyl chloride in pyridine; whether the latter product arises via direct displacement or some other route does not appear to have been determined. These and other results in this paper show the sensitivity of the sulfonylation reactions to the precise conditions, a feature that could lead to opportunity in one situation and difficulty in another.

General base promotion, though the likely pathway for the reactions in organic media discussed above, is not the only conceivable mechanism for addition of HZ. Specific base

catalysis, i.e. addition of the conjugate base of HZ, followed by protonation (equation 41), certainly can occur. This is seen, for example, in the reaction of sulfene in water. Product ratio studies concur with the following scheme[50].

$$RR'C{=}SO_2 + Z^- \rightleftharpoons RR'\bar{C}{-}SO_2Z \xrightarrow{BH^+} RR'CHSO_2Z \qquad (41)$$

(where BH^+ may be HZ)

$$[CH_2{=}SO_2] + H_2O \xrightarrow{k_{WT}} CH_3SO_2OH \qquad (42)$$

$$[CH_2{=}SO_2] + OH^- \xrightarrow{k_{HT}} CH_3SO_3^- \qquad (43)$$

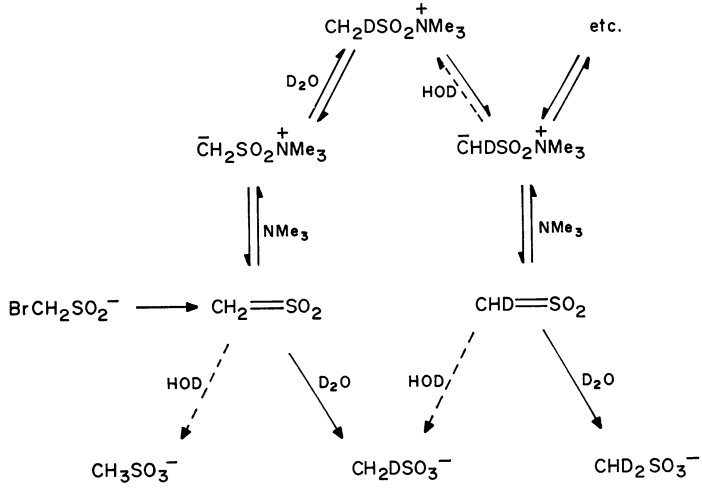
For sulfene itself $k_{HT}/k_{WT} = 160$ (at 25 °C), i.e. the two reactions shown by equations 42 and 43 have the same rate at pH 11.8, with the hydroxide reaction (via equation 41) dominant above this, and water trapping (via equations 38 and 39 with $B = ZH = H_2O$) below.

The reaction of aryloxide (ArO^-) and sulfonamide (RSO_2NR) anions with sulfene at pH values well above the pK_a values of the conjugate acids[50] may be presumed to follow a similar addition–protonation mechanism.

The H–D multiexchange reaction, or at least that portion of it which arises from initial formation of the sulfene, provides another example[63,67]. Perhaps the clearest illustration is found when the sulfene is formed from bromomethanesulfinate anion[63] (equation 44). This can be rationalized by the reactions shown in Scheme 3.

$$BrCH_2SO_2^- \longrightarrow CH_2{=}SO_2 \xrightarrow[D_2O]{Me_3N}$$

$$\underset{8\%}{CH_3SO_3^-} + \underset{79\%}{CH_2DSO_3^-} + \underset{2\%}{CHD_2SO_3^-} + \underset{11\%}{CD_3SO_3^-} \qquad (44)$$



SCHEME 3

The sulfonylammonium ions, e.g. $CH_2DSO_2NMe_3^+$, were not directly observed in this reaction mixture, their presence having been inferred from the multiexchange experiments and the different results obtained with other, e.g. bulkier, tertiary amines. Separate synthesis of $CH_3SO_2NMe_3^+ FSO_3^-$ and related species and a study of their reactions provided evidence[68] for Scheme 3.

The nucleophilic addition–protonation mechanism is not confined to aqueous media. Reaction of phenylmethanesulfonyl-d_2 chloride and triethylamine in the presence of triethylammonium fluoride gave $PhCHDSO_2F$[132]. Experiments with $Et_3NH^+Cl^-$ and a mixture of the fluoride and chloride salts suggested that Cl^- was also capable of trapping the sulfene, but that the fluoride was more reactive toward sulfene by a factor of 4.6.

Sulfene trapping competition experiments have been carried out with a series of aromatic amines[132]. In each case phenylsulfene was formed from phenylmethanesulfonyl chloride with triethylamine in the presence of an equimolar mixture of *p*-toluidine and another aniline derivative. The product ratio ('X-anilide': *p*-toluidide) varied from 1.12 for *p*-anisidine to 0.12 for *m*-nitroaniline, and gave a good fit to a Hammett plot with $\sigma = -1.04$; this accords with a transition state possessing a partial positive charge in the aromatic amine.

It was shown quite a number of years ago[131] that diphenyldiazomethane, sulfur dioxide and thiols give the diphenylmethanesulfonyl thiolesters, Ph_2CHSO_2SR, presumably by way of diphenylsulfene. One minor side-reaction in the formation of Ph_2CHSO_2SPh led to Ph_2CHSPh, probably by direct alkylation of thiophenol by the diazoalkane. Thiolester formation has also been found with phenylmethanesulfonyl chloride, triethylamine and phenylmethanethiol, but yields are limited by the tendency of the thiolester to react with the thiol under the reaction conditions to form the disulfide and sulfinate anion[132]. Deuterium labelling results were consistent with sulfene intermediacy, and in a competition experiment with 2-propanol and phenylmethanethiol the ester predominated over the products from reaction of phenylsulfene with the thiol[132], a not unexpected result in the context of (a) the observations on F^- vs Cl^- noted earlier in this section, and of (b) HSAB theory assuming one may view a sulfene as a 'hard' electrophile.

Among the other active hydrogen species trapping sulfenes are phthalimide[133], sulfonamides[50,132], carboxylic acids[91] and β-diketones[91]. The reactions of phthalimide and sulfonamides lead simply to the *N*-sulfonyl derivatives; in the latter case this may appear as a side-reaction of the product in the preparation of sulfonamides[132]. In D_2O at pH 10 reaction of CH_3SO_2NPh with methanesulfonyl chloride gave $CH_3SO_2NPh(SO_2CH_2D)$, as expected of a sulfene process[50]. The initial product of the reaction of carboxylic acids with sulfenes would be the mixed sulfonic carboxylic anhydrides; these are powerful acylating agents which, in the absence of other nucleophiles, are expected to react with the carboxylic acids to give the carboxylic anhydrides. It has been noted that phenylmethanesulfonyl chloride and triethylamine with (a) benzoic acid gave benzoic anhydride and benzoyl chloride, and with (b) 3-nitrobenzoic acid the anhydride in 63% yield[91].

In principle, β-diketones may react at the enolic hydroxyl or the α-carbon; in practice, in two examples studied both modes of reaction were seen[91]. Dimedone with phenylmethanesulfonyl chloride and triethylamine yielded the sulfonic ester of the enol, while dibenzoylmethane gave quantitative conversion to the sulfone, $(PhCO)_2CHSO_2CH_2Ph$[91].

Oximes are readily sulfonylated by sulfenes to yield the *O*-sulfonyl oximes (**53**)[91,134–136] (equation 45). Aldoxime sulfonates (**53**, R′ = H) are easily converted to the nitriles, $RC{\equiv}N$[134], while the benzophenone derivative (**53**, R,R′ = Ph) undergoes the Beckmann rearrangement to benzanilide[91]. Attempts to observe cycloaddition of sulfenes and nitrile oxides led to α-chloroaldoxime sulfonic esters (**53**, R = Cl)[134–136,145]. It is not known if the

product arose by reaction of the sulfene (a) with the nitrile oxide followed by uptake of Cl^- or (b) with chloroaldoxime presumed to be present in the mixture.

$$RR'C{=}NOH + R''CH_2SO_2Cl + Et_3N \longrightarrow \underset{\textbf{(53)}}{RR'C{=}NOSO_2CH_2R''} \qquad (45)$$

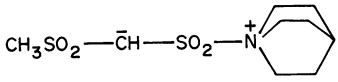
2. Thiophilic addition without immediate protonation: addition, cyclization, polymerization

The simple thiophilic addition of a nucleophile to a sulfene without further reaction (equation 46) is a rare process because **54**, the species which results from this reaction, is normally highly reactive, capable, among other things, of reacting further with another sulfene molecule. A possible instance of this reaction may be occurring in the conversion of Opitz' 'triethylamine–sulfene adduct' (**55**)[146] to the trimethylamine analogue (**57**)[147], a reaction which, in the light of the other reactions of **55**, may well be proceeding via mesylsulfene (**56**) as shown in equation 47. The trimethylamine 'adduct' (**57**) is a crystalline solid, stable in the presence of atmospheric moisture, which readily supplies the sulfene (**56**) for reaction with other reagents including water, amines, enamines and enol ethers[147]. The triethylamine 'adduct' (**55**) is hygroscopic and at room temperature is gradually converted into a variety of products including $CH_3SO_2CH_2SO_2NEt_2$, $CH_3SO_2CH_2SO_2CH_2SO_2CH_3$ and $CH_3SO_2CHClSO_2CH_2SO_2CH_3$[148].

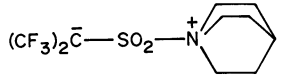
$$RR'C{=}SO_2 + Nu \rightleftharpoons \underset{\textbf{(54)}}{RR'\bar{C}{-}SO_2Nu^+} \qquad (46)$$

$$\underset{\textbf{(55)}}{CH_3SO_2\bar{C}HSO_2\overset{+}{N}Et_3} \underset{NEt_3}{\overset{-NEt_3}{\rightleftharpoons}} \underset{\textbf{(56)}}{CH_3SO_2CH{=}SO_2} \underset{-NMe_3}{\overset{NMe_3}{\rightleftharpoons}} \underset{\textbf{(57)}}{CH_3SO_2\bar{C}HSO_2\overset{+}{N}Me_3} \qquad (47)$$

A number of these zwitterionic trialkylamine–sulfene 'adducts' have recently been characterized by Sundermeyer and coworkers[149], who have obtained structures by X-ray analysis for some of these materials, e.g. **58** and **59**. These observations provide not only rigorous proof of the structures of these zwitterionic 'adducts', but also interesting information on the nature of their chemical bonding. The carbanionic carbon is nearly planar and the X—$\bar{C}$—S—N dihedral angle is roughly 90°. Analogous X-ray structures on α-lithiosulfones ('sulfonyl carbanions')[140] show the X—C—S—C dihedral angle to be in the range 80 ± 10°. Similarly the heteroatomic analogues, sulfonamides and sulfonic esters, have been found[150] to display a strong preference for having the respective C—N—S—C and C—O—S—C dihedral angles around 75°. Sundermeyer and coworkers[149] report C—S bond lengths for the C—SO_2 bonds in the range 1.62–1.66 Å and S—N bond lengths of 1.87–1.91 Å. These authors point out that the short C—S bond is closer to that in an isolated thiocarbonyl group (1.66 Å) than that in a sulfone (~1.80 Å)[151], and prefer to write the structures in the form $RRC{=}SO_2 \longleftarrow NR'_3$. Similar short C—S bond lengths (e.g. 1.64 and 1.61 Å) have been reported for α-lithiosulfones[140], clearly pointing to considerable double-bond character in all $\bar{C}$—SO_2 compounds; indeed, by the same reasoning it is clear that this holds for compounds of the general formula $\ddot{X}$—SO_2 where $\ddot{X}$ = N or O, as well as C^-. We prefer to use conventional bonding notation in representing the sulfene–amine 'adducts' (e.g. as in **58** and **59**), and also for sulfonyl



(58)



(59)

carbanions, sulfonamides and sulfonic esters, but the sizeable double-bond character in these species should be kept clearly in mind.

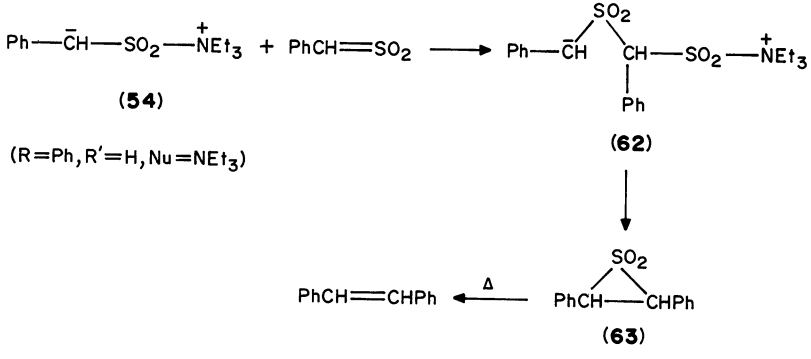
A notable chemical feature reported by Sundermeyer in this work is the *carbophilic* addition to fluorosulfene to give the sulfino-betaine (**60**)[11] as in equation 48. This is evidently a particularly simple illustration of carbophilic (alias 'abnormal' or 'inverse') addition to a sulfene, which is discussed more fully in Section V.A.3. This reaction is to be contrasted with that observed by the same authors with the chlorinated[152] analogue and related species[149], which presumably proceeds by 'normal' thiophilic addition to form the unstable primary adduct (**54**, R = H, R′ = Cl, Nu = NMe_3), which on reaction with another sulfene molecule followed by a proton shift gives the more usual dimeric 'adduct' **61** (equation 49). The reasons why **60** rather than **54** is produced from fluorosulfene may be complex, but the observation is consistent with the usual deactivating effect of α-fluoro (and α-alkoxy) substituents in carbanion formation (at sp^2 hybridized carbons)[153].

$$FCH_2SO_2Cl + Me_3N \longrightarrow [FCH{=}SO_2] \xrightarrow{Me_3N} \underset{\textbf{(60)}}{Me_3\overset{+}{N}FCHSO_2^-} \qquad (48)$$

$$ClCH_2SO_2Cl + Me_3N \longrightarrow [ClCH{=}SO_2] \xrightarrow{Me_3N} \underset{\textbf{(61)}}{ClCH_2SO_2C(Cl)SO_2\overset{+}{N}Me_3} \qquad (49)$$

As noted above, **54** is evidently a highly reactive species which, from various lines of evidence, is very probably implicated in a number of reactions in which the initial step was the formation of the sulfene. Mention has already been made of the further transformations of **55**. Rather similar oligomeric products had been reported earlier by Fusco and coworkers[154] in the reactions of some secondary sulfonyl chlorides with triethylamine; it is attractive to postulate the intermediacy of **54** (probably with Nu = NEt_3).

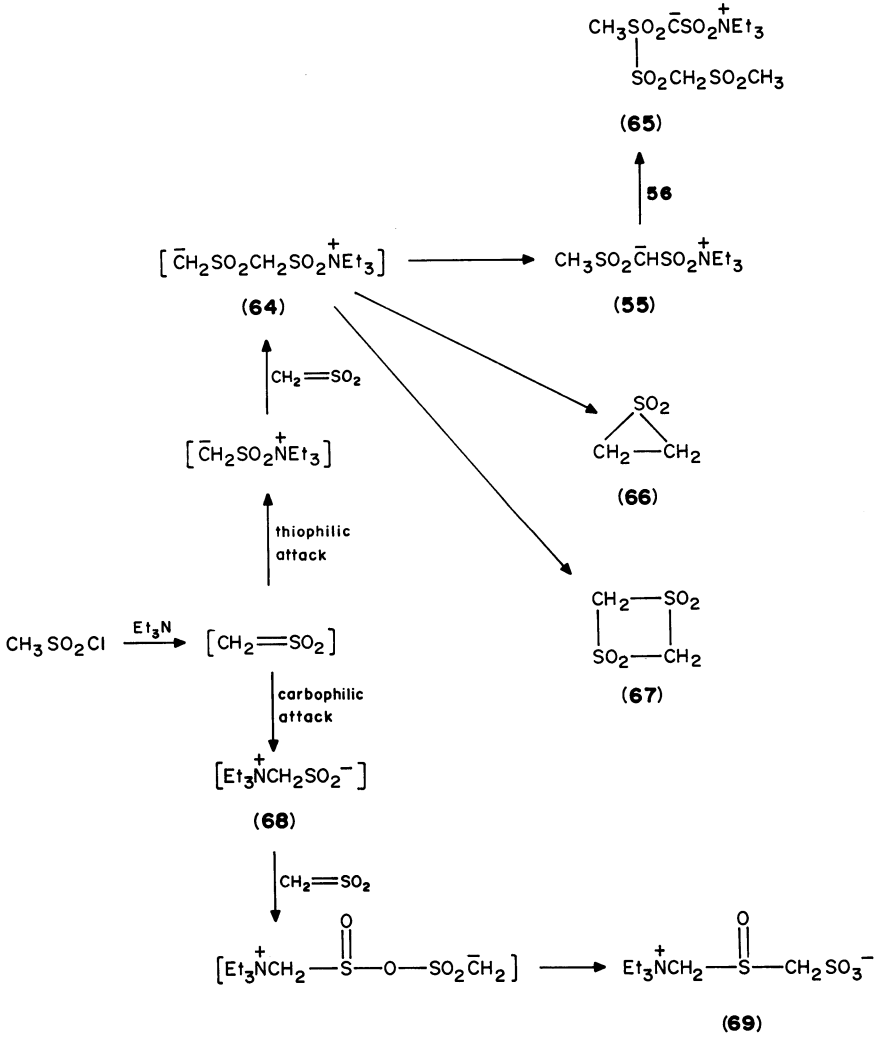
One of the earliest known sulfene reactions is the formation of stilbene from phenylmethanesulfonyl chloride and triethylamine[5]. Subsequent reinvestigation of this reaction showed the product to contain not only *trans*-stilbene but also *cis*-2,3-diphenylthiirane 1,1-dioxide (*cis*-**63**) as well as the thiobenzoyl chloride *S*-oxides which are discussed in the next section; the proportions of the components vary with change in solvent polarity[40,155]. A more likely mechanism[156] than the phenylcarbene dimerization originally suggested by Wedekind and Schenk[5] is given by equation 50. By this scheme *trans*-stilbene arises from *trans*-**63**, which is known to be desulfonylated to *trans*-stilbene under very mild conditions[157]. In conformity with this mechanism, in which the yield of the product clearly must depend on the ease of formation of **54** relative to other processes, it was found that the yield of stilbene products dropped from 70% to 21% to 2% (and the yield of the thiobenzoyl chloride *S*-oxides rose accordingly), as the base was changed from trimethylamine to triethylamine to tributylamine[156].



(50)

The formation of thiirane 1,1-dioxides has been extended to the reactions of 3-phenyl-2-propene-1-sulfonyl and those of other arylmethanesulfonyl chlorides[158], and recently to primary alkanesulfonyl chlorides[159]. 1-Octanesulfonyl chloride with triethylamine in acetonitrile at −40 °C, for example, gave an 88% yield of a 76:24 mixture of the *trans*- and *cis*-2,3-diheptylthiirane 1,1-dioxides; this material on thermolysis at 80–100 °C produced a 75:25 mixture of the (*E*)- and (*Z*)-8-hexadecenes (in 76% yield). Methanesulfonyl chloride (in ether at 0 °C) gave a 64% yield of thiirane 1,2-dioxide (ethylene sulfone, **66**)[159], hitherto only available from reactions with diazomethane[109] (see Section IV.D and below).

The methanesulfonyl chloride reaction is interesting because of the remarkable variety

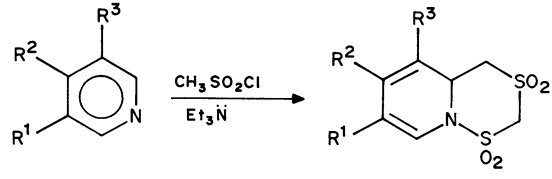


SCHEME 4

of products that are produced with tertiary amines in inert solvents. The formation of Opitz' triethylamine and trimethylamine 'adducts' (**55** and **57**) (in acetonitrile at −40 °C) has been noted above. Grossert and Bharadwaj[160] presented evidence for the slow formation of a tetrameric zwitterionic 'adduct' (**65**) under these conditions. With slightly different reaction conditions (trimethylamine in THF at −20 °C), 1,3-dithietane 1,1,3,3-dioxide ('sulfene dimer', 'disulfene', **67**) is generated in 18% yield[161]. The 'sulfene dimer' (**67**) is formally the product of a [2 + 2] cycloaddition but, as has been pointed out by Block and Aslam[98], who noted that $Me_3SiCH_2SO_2Cl$ with CsF in the absence of sulfene traps gave no sign of **67**, cyclization of the dimeric zwitterion (e.g. **64**) is a more likely route than the direct cycloaddition. This picture accords well with observations on at least some of the other formal cycloadditions, e.g. those involving a sulfene and a carbon–oxygen double bond (see Section V.B.5), and the dimerization of α-ketosulfenes (equations 82 and 125, below).

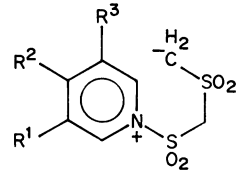
To add further complexity to the scene, Hanefeld and Spangenberg[162] have described the formation of an interesting compound formulated as the betaine **69** (12% yield from methanesulfonyl chloride and triethylamine in THF at 0 °C); both *N*-methyl- and *N*-ethylmorpholine, but neither tributylamine nor diisopropylethylamine, gave analogous products. Scheme 4 provides a summary with some possible mechanisms. Obviously the initially formed dimeric zwitterion (**64**) is a key intermediate in this picture and it would appear that variations in the yields of **55**, **66** and **67** are determined by subtle, perhaps conformational, factors not well-understood at present. The betaine **69**, however, would appear to arise, not from the more usual thiophilic attack, but from carbophilic attack; this topic is taken up in greater detail in the next section.

The reaction of sulfene with certain pyridines has been found by Grossert[163,164] to form the unusual heterocyclic system **70**, perhaps by simple cyclization of **71**, the pyridine analogue of **64** (equation 51). 2,6-Dimethoxypyridine, in which direct bonding to the nitrogen may be inhibited by the methoxy groups, undergoes what is postulated to be electrophilic attack by sulfene or its dimer to form, ultimately, the 3-substituted product **72**[164].



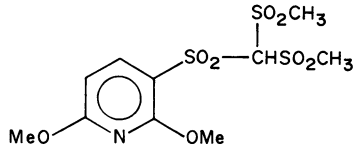
(51)

(70)



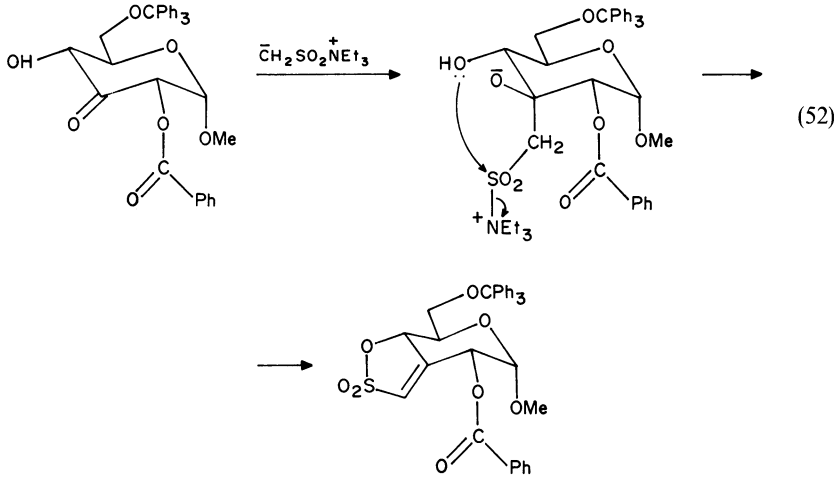
(71)

(a) $R^1, R^2, R^3 = H$
(b) $R^1, R^3 = CH_3, R^2 = H$
(c) $R^1, R^3 = H, R^2 = CH_3$



(72)

Yunker and Fraser-Reid[165] have reported formation of an unsaturated sultone from an α-keto alcohol, suggesting the mechanism shown in equation 52.

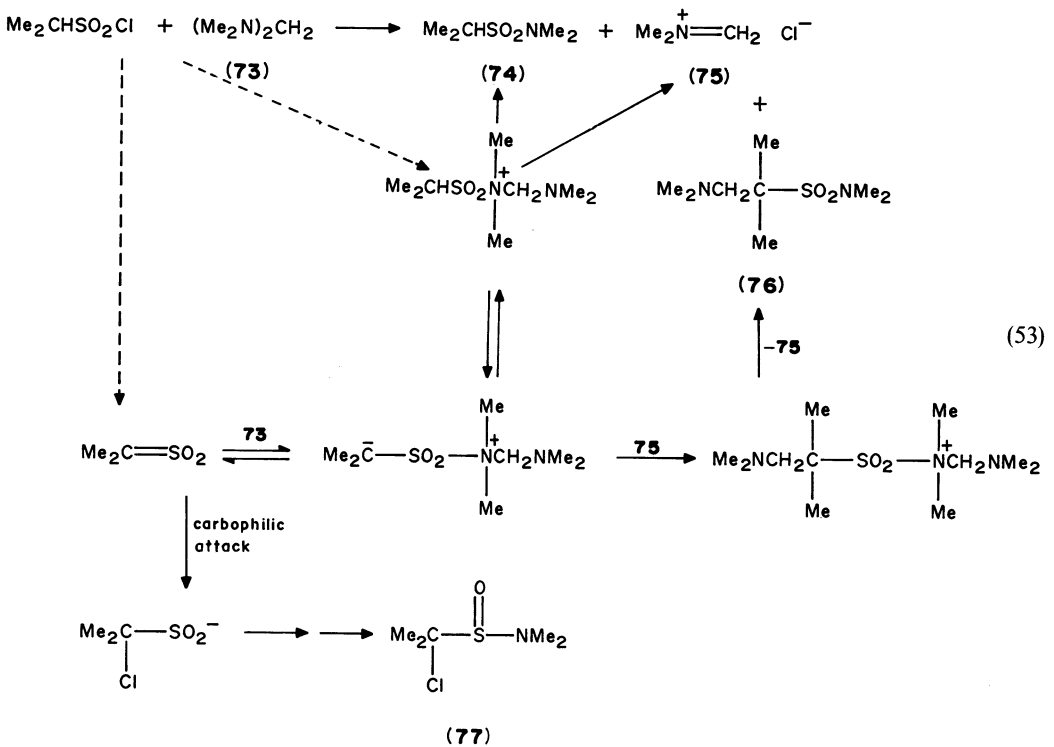


Böhme and Pindur[166] have reported an interesting set of reactions of alkanesulfonyl chlorides with bis-dimethylaminomethane. They appear to involve the sulfene, perhaps with thiophilic addition to form the sulfene–aminal 'adduct', plus a small amount of carbophilic addition, to account for the products (**74**, **75**, **76** and **77**) from 2-propanesulfonyl chloride; alternative routes to two of the intermediates are shown with dotted arrows in equation 53.

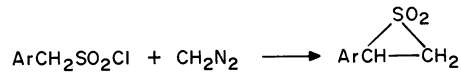
A more usual route to thiirane 1,1-dioxides than that given above is the reaction of diazoalkanes with sulfur dioxide, appropriately called the Staudinger–Pfenninger reaction (see Section IV.D)[107,108]. The synthesis evidently has two stages, (i) reaction of the diazoalkane and the sulfur dioxide to form the sulfene, and (ii) trapping of the sulfene to form the thiirane 1,1-dioxide (**78**). Confirmation of the second stage was provided by Opitz and Fischer[37,167] who found that generation of a sulfene from a sulfonyl chloride (and triethylamine) in the presence of a diazoalkane also gave the thiirane 1,1-dioxide; this procedure[167–169], which is illustrated by equation 54, permits the synthesis of unsymmetrical thiirane 1,1-dioxides and their corresponding alkenes.

The principal alternative process in the reaction of sulfenes and diazoalkanes is the formation of the 1,3,4-thiadiazine compound (**79**); other products may be produced by the further reaction of **78** or **79** (e.g. the alkene or azine by their respective desulfonylations). It has been suggested[109] that the initial reaction is to form the zwitterionic intermediate (**80**), which may then proceed to **78**. In a relatively recent study[170], which also provides a useful summary of earlier work, it is proposed that a direct [3 + 2] cycloaddition of the diazoalkane to the sulfene gives **79** while the alternative reaction to form **80** leads to **78** (equation 55), and that the different reactions derive from the existence of two low-lying sulfene MOs of different symmetries[29].

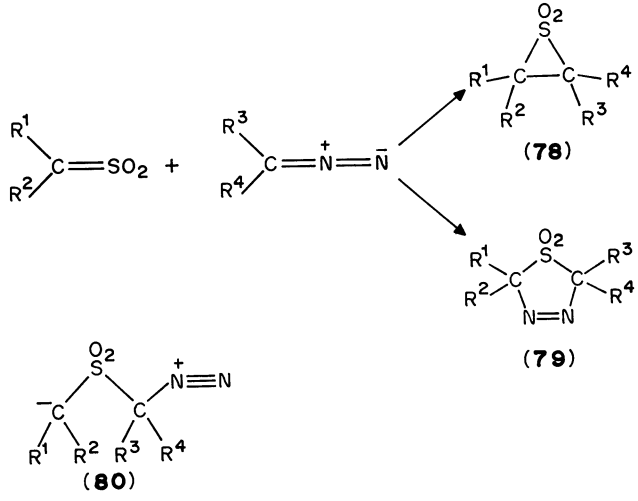
Thiirane 1,1-dioxides are also implicated in reactions of certain phosphorus and sulfur ylides with sulfenes. In the simplest cases, as in equation 56, the chief reaction was sulfonylation[171,172]. But with ylides lacking a hydrogen on the original ylide carbon, a more complex reaction occurred giving the thiirane 1,1-dioxide **81** and a rearranged sulfene addition product **82** (equation 57). Acyl-stabilized sulfonium ylides also give an array of products, some derivable from thiirane 1,1-dioxides[173,174]. The initial step in


Me2CHSO2Cl + (Me2N)2CH2
Me2CHSO2NMe2 + Me2N+=CH2 Cl−
(73)
(74)
(75)
Me2CHSO2NCH2NMe2
Me2NCH2C—SO2NMe2
Me
(76)
−75
Me2C=SO2
73
Me2C−—SO2—NCH2NMe2
75
Me2NCH2C—SO2—NCH2NMe2
carbophilic attack
Me2C—SO2−
Cl
Me2C—S—NMe2
O
(77)

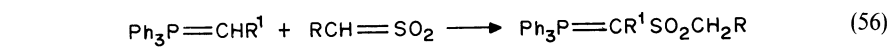
(53)



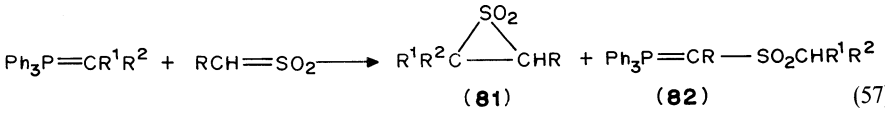
(54)



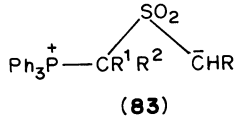
(55)



(56)



(57)



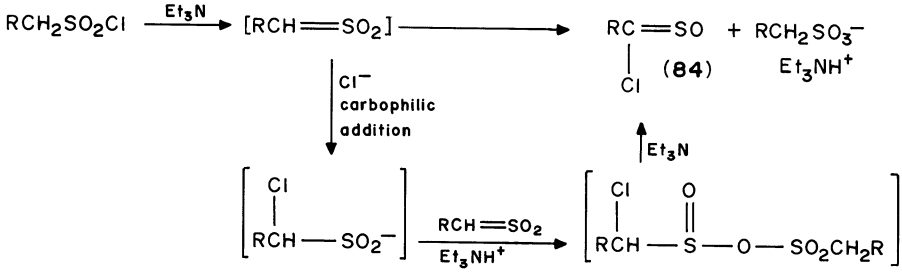
(83)

these reactions would appear to be the thiophilic addition of the ylide to the sulfene to form the zwitterion, e.g. **83**, which may (a) transfer a hydrogen to give the simple acylation product, (b) cyclize to thiirane 1,1-dioxide, (c) rearrange by attack of the carbanion on the phosphorus, or (d) react by yet another pathway. The reaction of sulfenes with aryliminotriphenylphosphoranes, the nitrogen analogues of the triphenylphosphoranes (ylides), has also been investigated[175]. The products, though complex, are readily accounted for on the basis of the initial thiophilic addition. The reaction of an iodylide has been described; the product (15% yield) is evidently derived from sulfonation with subsequent displacement of iodobenzene[176].

3. Carbophilic addition and subsequent reactions

The basic idea that a nucleophile might attack a sulfene at the carbon rather than the sulfur atom was introduced some time ago[8,155,177] to account for some of the earliest observations in sulfene chemistry[5,34]. The case for carbophilic addition is now sufficiently strong that it must be included in any prudent discussion of possible reactions of sulfenes.

The formation of thioacyl chloride *S*-oxides (chlorosulfines, **84**), first reported by Wedekind and coworkers[5,34], was the reaction that prompted the suggestion of this mode of addition in the first place. The proposed mechanism is shown in Scheme. 5.



SCHEME 5

Intramolecular carbophilic addition was also put forward to account for the formation of the pyrrole **49** on irradiation of sultam **46** (see Section IV.F); attack of the nitrogen atom on carbon to form the sulfinate zwitterion, followed by loss of sulfur dioxide, readily leads to **49**[8].

At this point we were able to demonstrate the carbofugal generation of sulfenes from α-halosulfinate anions (Section IV.C), and hence that the transition state for this reaction must be experimentally accessible. From the principle of microscopic reversibility the reverse reaction, i.e. the carbophilic addition of a halide ion to a sulfene, must go through the same transition state, and would therefore be expected to be readily observable experimentally as well. Shortly after this Dykman[105] postulated carbofugal formation of dichlorosulfene from trichloromethanesulfinate anion (equation 58). Subsequently Kempe and Norin[178] suggested the reverse process to explain the production of trichloromethanesulfinate anion from dichloromethanesulfonyl chloride and triethylamine. This in turn was followed not long after by observations by Šilhanék and Zbirovský consistent with the formation of chlorosulfene from dichloromethanesulfinate anion[107] (equation 59). Much more recently further evidence was added to the trichloromethanesulfinate–dichlorosulfene picture by Hanefeld and coworkers[179], who isolated (a) a characteric sulfene–indanetrione product from reaction of dichloromethanesulfonyl chloride with triethylamine and indanetrione, and (b) triethylammonium trichloromethanesulfinate when indanetrione was omitted.

$$Cl_3CSO_2^- \rightleftharpoons Cl_2C{=}SO_2 + Cl^- \qquad (58)$$

$$Cl_2CHSO_2^- \longrightarrow ClCH{=}SO_2 + Cl^- \qquad (59)$$

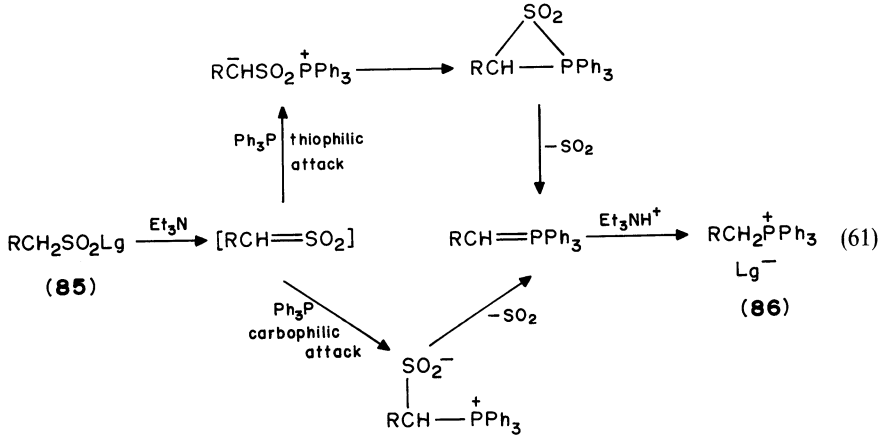
In the meantime Rheude and Sundermeyer[11] reported what may be the least ambiguous example of carbophilic addition, the formation of the ammoniosulfinate zwitterion **60**, mentioned earlier, and shown in equation 60. Further evidence for the 'carbophilic adduct' structures has recently been obtained from X-ray crystallography[180]. The net result of these considerations is that there is a strong case for carbophilic addition to sulfenes and hence for the amphiphilic character of sulfenes. The factors that promote carbophilic addition are not well-understood but a few points may be noted here. (a) HSAB

considerations suggest the possibility that 'soft' nucleophiles might be more inclined to attack at carbon than 'hard'. (b) Snyder's semiempirical MO calculations show a change in charge distribution with substituents, with electron-donating substituents leading to a net partial positive charge on carbon and a lowered positive charge on the sulfur atom[28]; such an effect could be altering the charge densities in fluorosulfene relative to sulfene or chlorosulfene. (c) As has been mentioned in the previous section, the stabilities of the carbanions formed by thiophilic attack, i.e. $RR'\bar{C}SO_2Nu$, should be considered, and where R and R′ clearly destabilize the carbanion, carbophilic addition could become important. Finally it should be explicitly noted that product ratios in these reactions are not necessarily a direct function of the ratios of thiophilic to carbophilic attack. Where one of these reactions simply regenerates the starting material, for example, then the slower mode of addition may still be the pathway to the observed reaction product.

$$FCH_2SO_2Cl \xrightarrow{Me_3N} [FCH{=}SO_2] \xrightarrow{Me_3N} \underset{\textbf{(60)}}{Me_3\overset{+}{N}CHFSO_2^-} \qquad (60)$$

4. Nucleophilic reactions of uncertain mechanism

a. Phosphinative desulfonylation. Triphenylphosphine and triethylamine react with 2,4-dinitrophenyl phenylmethanesulfonate (**85a**) to give the phosphonium salt (**86a**) in 87% yield[52]. In the absence of triethylamine no **86a** is formed, pointing to the intermediacy of the sulfene. It is easy to formulate two reasonable reaction mechanisms (equation 61), but harder to choose between them. With phenylmethanesulfonyl chloride (**85b**) a lower yield (32%) of the phosphonium ion was obtained; reduction of the chlorosulfonyl group with triphenylphosphine[181] evidently competed with sulfene formation. Methanesulfonyl chloride gave no sign of the phosphonium salt, though methanesulfonic anhydride gave a 41% yield of **86c**. Tributylphosphine and triethylamine and **85a** yielded no indication of any phosphonium ion.



(61)

(**a**) R = Ph, Lg = 2,4-dinitrophenoxide

(**b**) R = Ph, Lg = Cl

(**c**) R = H, Lg = OSO_2CH_3

b. Desulfinylation with sulfur dioxide. It was noted in the original paper of Staudinger and Pfenninger announcing the reaction of diphenyldiazomethane and sulfur dioxide[107] (Sections IV.D and V.A.2) that excess sulfur dioxide gave benzophenone, and it was postulated that diphenylsulfene and sulfur dioxide gave a four-membered heterocycle which decomposed to the ketone and S_2O_3. Tokura and coworkers[182] also encountered carbonyl compounds with various diazoalkanes, including benzaldehyde in the reaction with phenyldiazomethane. Brophy and collaborators[183] have prepared some substituted pivalophenones by this route and suggested a five-membered heterocyclic intermediate. In a study in our laboratory[96] it was found that phenylsulfene [from $(PhCH_2SO_2)_2O$ and 2,6-lutidine] gave benzaldehyde, and that a diphenylsulfene source gave benzophenone (equation 62). These findings support the notion that the sulfene is really an intermediate in this reaction. Sulfur dioxide, however, is evidently not a very efficient sulfene trap, and other reactions commonly predominate. The reaction would also appear to be of rather limited generality, with all of the known examples involving a sulfene with at least one aryl substituent. Experiments with ^{18}O-labelled sulfur dioxide showed that about two-thirds of the oxygen atoms of the benzophenone come from the sulfur dioxide, whereas the previously suggested mechanisms predict that all of the oxygen in benzophenone must come from the SO_2; a number of possible mechanisms were presented but no decision among them was made[96].

$$Ph_2CHSO_2OAr \xrightarrow{\text{2,6-lutidine}} [Ph_2C{=}SO_2] \xrightarrow{SO_2} Ph_2C{=}O \qquad (62)$$

Ar = 2-chloro-4-nitrophenyl

c. Sulfene insertion into a metal–hydrogen bond. Insertion of sulfene into metal–hydrogen bonds in compounds of chromium, molybdenum and tungsten has been reported by Lorenz[184], and in one example was supported by a deuterium labelling experiment (equation 63).

$$CpW(CO)_3D + CH_3SO_2Cl + Et_3N \longrightarrow CpW(CO)_3(SO_2CH_2D) + Et_3NH^+ \qquad (63)$$

B. Cycloaddition Reactions

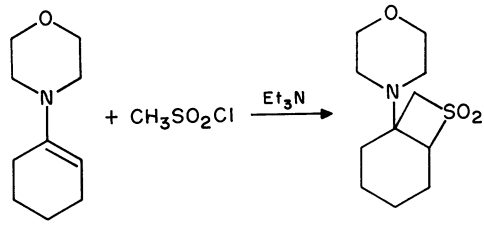
The revival of interest in the chemistry of sulfenes that took place in the early 1960s was much stimulated by the discovery of a number of cycloaddition processes leading to four-membered ring sulfones, and other, often unfamiliar, ring systems. If the formation of mesylates and the like, as detailed in Section V.A., belongs to the workaday world of sulfenes, then the cycloadditions surely represent their night life or holidays, with a striking array of the unusual and entertaining. In ordering these reactions for presentation, we have simply sorted them out according to substrate, with the sequence following a tendency toward lower nucleophilicity as the list progresses.

1. Enamines and ynamines

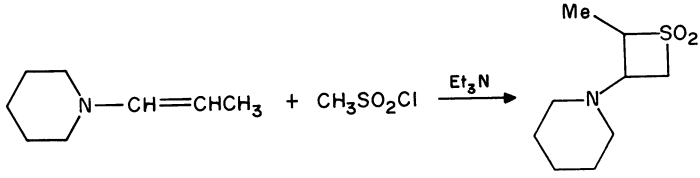
The reaction of methanesulfonyl chloride with cyclohexanone enamine in the presence of a proton acceptor produced a four-membered cyclic aminosulfone (equation 64). Stork and Borowitz[36] suggested sulfene formation as the first step of this reaction.

At the same time Opitz and Adolph[37] also reported that *N*-(1-propenyl)piperidine was not *C*-sulfonylated by methanesulfonyl chloride and triethylamine in cold ether, but was converted into 2-methyl-3-piperidinothietane 1,1-dioxide (in 88% yield) (equation 65).

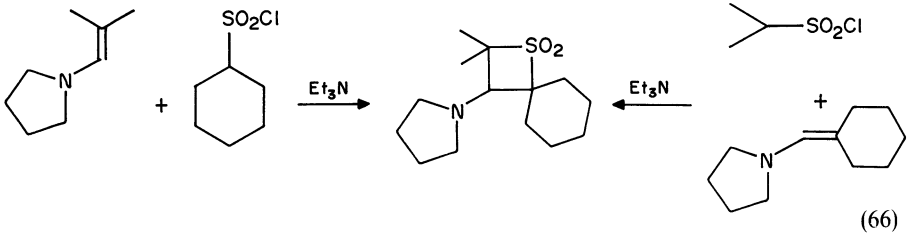
Methanesulfonyl chloride and methanesulfonic anhydride and other alkanesulfonyl chlorides react with enamines of aldehydes and ketones in the same manner with no



(64)



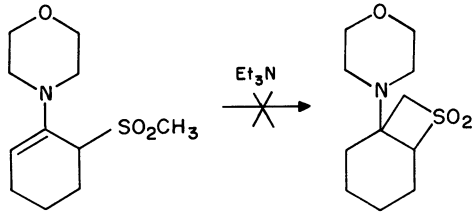
(65)



(66)

obvious restrictions regarding solvent and temperature[1]. Secondary alkanesulfonyl chlorides reacted smoothly in CH_3CN at $-40\,°C$ with various enamines to give [2 + 2] cycloadducts[1]. An elegant experiment of Opitz and Rieth[69] demonstrated that the same product was formed from *N*-(2-methyl-1-propenyl)pyrrolidine and cyclohexanesulfonyl chloride and from *N*-(cyclohexylidenemethyl)pyrrolidine and 2-propanesulfonyl chloride as shown in equation 66. A tabulation of a large number of cycloaddition reactions of enamines and sulfenes has been provided by Müller and Hamer[185].

Stork and Borowitz[36] were able to rule out an alternative mechanism, in which an initially formed mesylated enamine underwent cyclization, by preparing the mesylated species (**87**) and showing that it did not yield the cycloadduct (equation 67). Borowitz[36] also demonstrated that only electron-rich olefins (such as enamines, ketene dialkyl acetals, etc.) give [2 + 2] cycloadducts when the sulfene is generated from alkenesulfonyl chlorides and triethylamine, and no cycloadduct was formed in the presence of cyclohexene, ethoxyacetylene or anthracene.

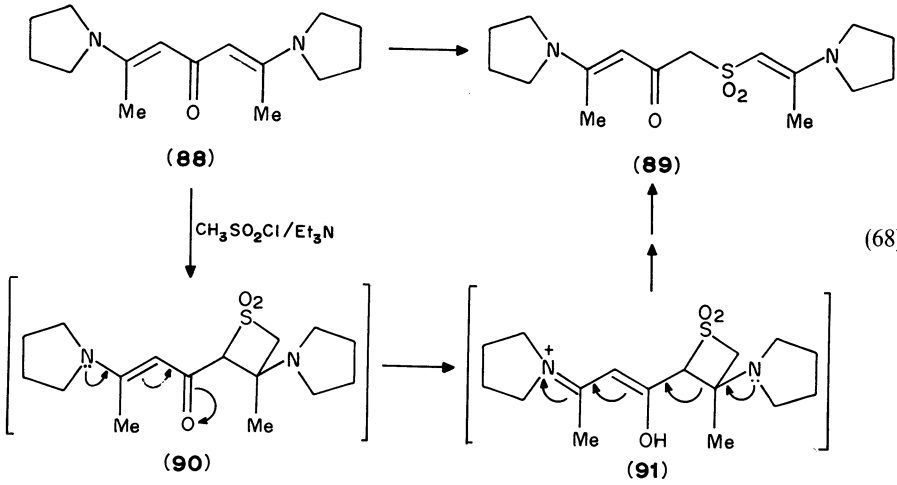


(67)

(**87**)

Wells and Abbott[186] carried out a systematic study of the addition of sulfene generated from methanesulfonyl chloride and triethylamine to various enamines in ether and acetonitrile. They found that both cyclic and acyclic products were produced in these solvents.

In an interesting experiment, it was demonstrated by Stephen and Marcus[187] that sulfenes prefer to add to electron-rich olefins in a [2 + 2] manner even when other pathways are available. In a dienaminoketone (**88**) there are two alternative ways in which a sulfene can react (a) to form a [4 + 2] adduct with the enaminoketone or (b) to give the usual [2 + 2] adduct with the enamine double bond. In fact the sulfene insertion product (**89**) was formed, presumably by the rearrangement of the [2 + 2] cycloadducts **90** and **91** as shown in equation 68.

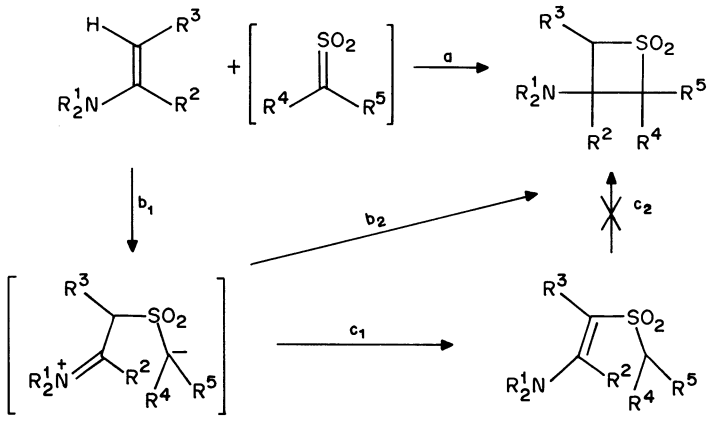


(68)

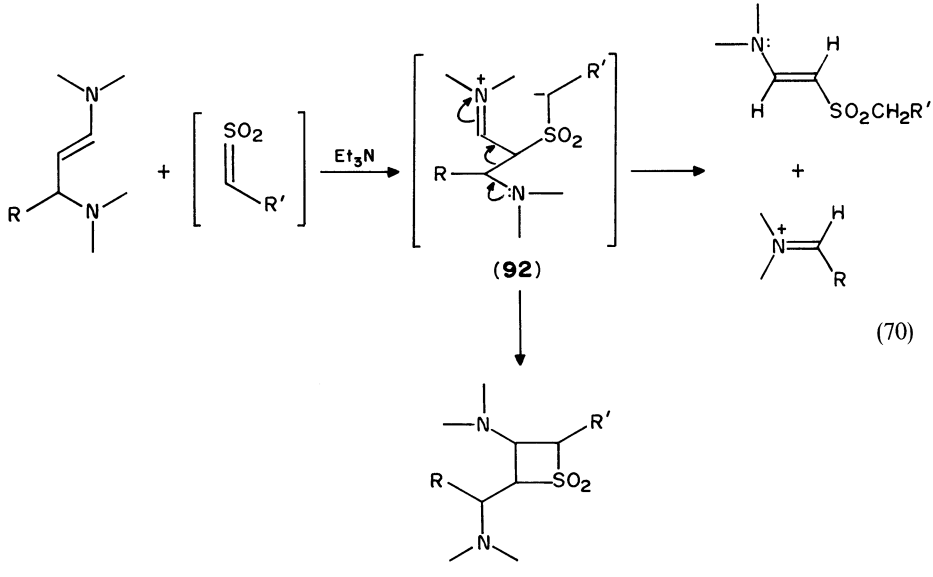
An important question about the mechanism of the cycloaddition of sulfene and enamines is whether the reaction is stepwise or concerted (equation 69)[1]. Paquette and Rosen[188] have carried out an elegant set of experiments to show that in the particular examples chosen, at least, sulfenes react with enamines in a stepwise process (path b) to form the [2 + 2] cycloadduct. This is in accord with the Woodward–Hoffmann rules in which a concerted [$\pi 2s + \pi 2s$] cycloaddition is forbidden[189]. The reaction of sulfene and phenylsulfene with *N,N,N,N*-tetramethylpropene-1,3-diamine, *N,N,N,N*-tetramethyl-1-butene-1,3-diamine and 1,3-bis(dimethylamino)- 3-phenyl-1-propene gave a wide variety of products. The presence of *trans*-2-dimethylamino-1-phenylmethylsulfonylethylene as a common product from the reaction of the various diamines and phenylsulfene (equation 70) points to the involvement of a zwitterionic intermediate such as **92**.

Opitz[1] has pointed out that if the sulfene–enamine reaction is concerted it should be stereospecific, and if it is stepwise then stereospecificity would be observed only if the intermediate is very short-lived. The reaction of sulfene with *trans*-*N*-(1-propenyl)-morpholine gave one product but the *cis*-enamine gave both stereoisomers. No definite conclusion can be drawn from these results, however, as *cis–trans* isomerization of enamines prior to sulfene addition cannot be ruled out[1].

Paquette[72] has described experiments designed to assess the stereoselectivity of the sulfene–enamine reaction. He found that sulfenes reacted stereoselectively with bicyclic enamines giving a single product, where the sulfene attacks the bicyclic enamine from *exo* side in most of the cases. Stephen and Marcus[190] further supported this result when they

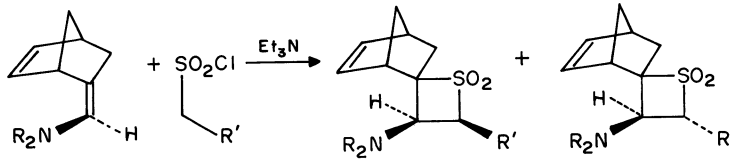


(69)



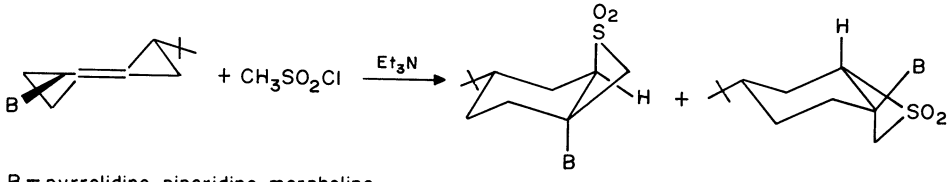
(70)

obtained only a single cycloadduct in each reaction of the sulfene with various enamines derived from norbornanone (equation 71), though an attempt to determine the stereochemistry of the adduct was inconclusive.



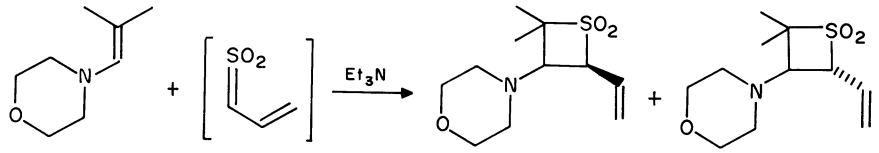
(71)

A recent report by Valentin and coworkers[191] has shown that the reaction of methanesulfonyl chloride with 4-*tert*-butylcyclohexanone enamines in the presence of the triethylamine gave a 1:1 mixture of two diastereomers (equation 72), indicating a complete lack of stereoselectivity.



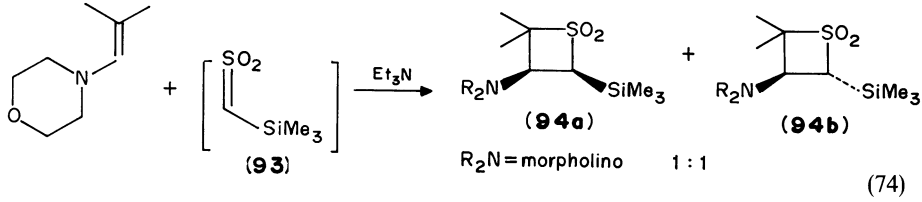
(72)

Drozd and coworkers[78] have also shown that addition of vinylsulfene with enamines as in equation 73 is not stereoselective.



(73)

Shipov and collaborators[80] have recently found that (trimethylsilyl)sulfene (**93**) generated from (trimethylsilyl)methanesulfonyl chloride and triethylamine reacts with an isobutyraldehyde enamine to give a mixture of *cis* and *trans* cycloadducts **94a** and **94b** (equation 74).

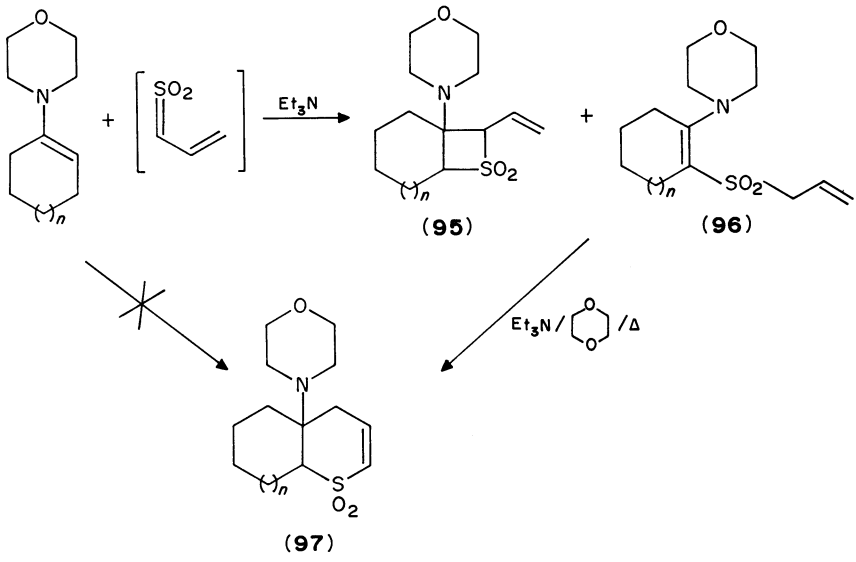


(74)

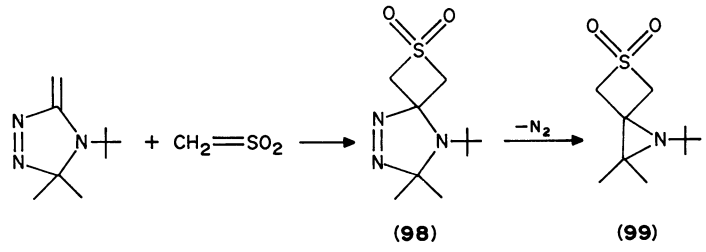
Vinylsulfene (CH_2=CH—CH=SO_2), produced *in situ* from 2-propene-1-sulfonyl chloride by treatment of triethylamine, afforded[77] both [2 + 2] cycloadducts **95** and acyclic sulfones **96** with various enamines (equation 75). No [4 + 2] adducts **97** were isolated initially in any reaction, though they are formed by refluxing **95** and **96** in triethylamine and dioxane[77].

Triazoline, which is formally an α-azoenamine, has been shown by Schwan and Warkentin to react with sulfene to produce the expected [2 + 2] cycloadduct **98** along with spiroaziridine **99** (equation 76)[192].

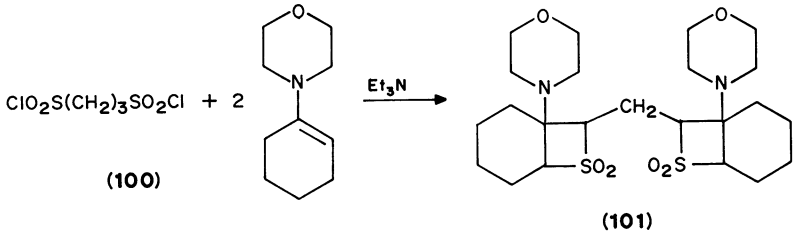
Disulfonyl chlorides and their reactions with enamines have also been investigated[76,193]. The reaction of 1,3-propanedisulfonyl chloride (**100**) with triethylamine in the presence of 1-morpholino-1-cyclohexene gave the double cycloadduct **101** (equation 77) which can be separated into *meso* and *dl* forms by recrystallization[194].



(75)

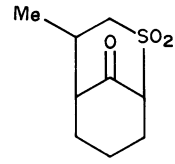


(76)



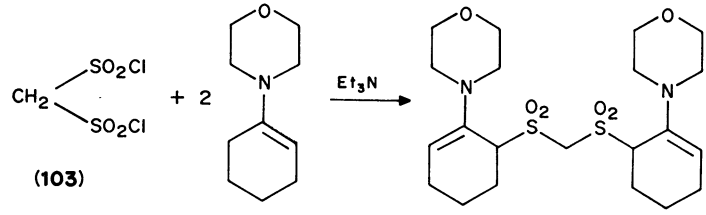
(77)

Similar reaction of 1,2-propanedisulfonyl chloride, however, did not yield a double adduct but gave a low yield (6%) of a product formulated[193] as a ketosulfone **102**. In the light of the known ease with which 1,2-ethanedisulfonyl chloride is converted to ethenesulfonyl chloride by tertiary amines[26], it would seem likely that the reaction may well involve 1-propenesulfonyl chloride and that further experiments are needed for a better understanding of the mechanism of this reaction.



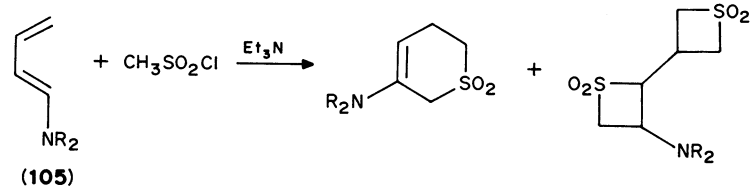
(102)

Reaction of methanedisulfonyl chloride (**103**) with enamines in the presence of triethylamine gave an acyclic product **104** (equation 78)[76]. The formation of **104** is to be contrasted with the double four-membered ring cycloadduct obtained in the reaction of **103** with ketene diethyl acetal (see Section V.B.2).

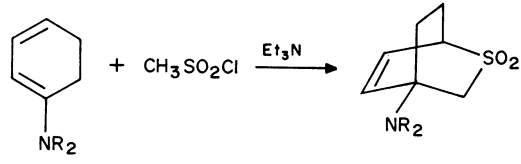


(103) (104) (78)

Dienamines show interesting behavior towards sulfene. With the acyclic dienamine **105**, [4 + 2] cycloaddition was found to compete with the usual [2 + 2] cycloaddition (equation 79)[194,195] whereas the cyclic dienamine **106**, in which the cisoid structure is fixed, gave only the [4 + 2] cycloadduct (equation 80)[196]. Addition of sulfene to 1-dimethylamino-1,3-cyclooctadiene (**107**) has been shown to give a mixture of products (**108**, **109**, **110** and products derived from further reaction of **110**), depending upon reaction conditions (equation 81)[197].

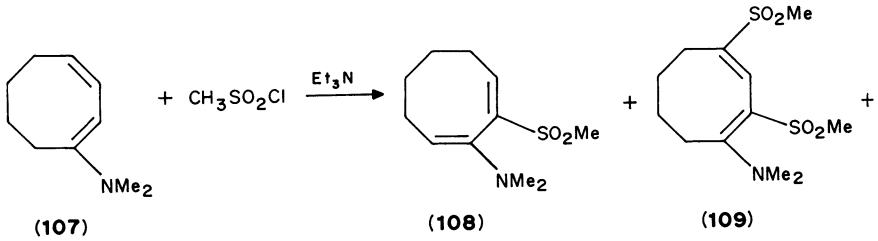


(105) (79)

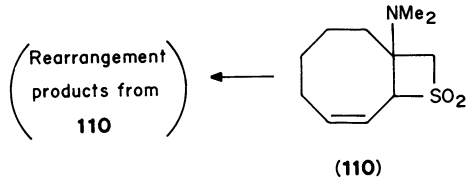


(106) (80)

The reaction of benzoylmethanesulfonyl chloride with enamines evidently depends on the enamine structure; 2-methyl-1-pyrrolidinyl-1-propene in the presence of triethylamine gave, in addition to the six-membered ring dimer[154], a [2 + 2] cycloadduct of benzoylsul-

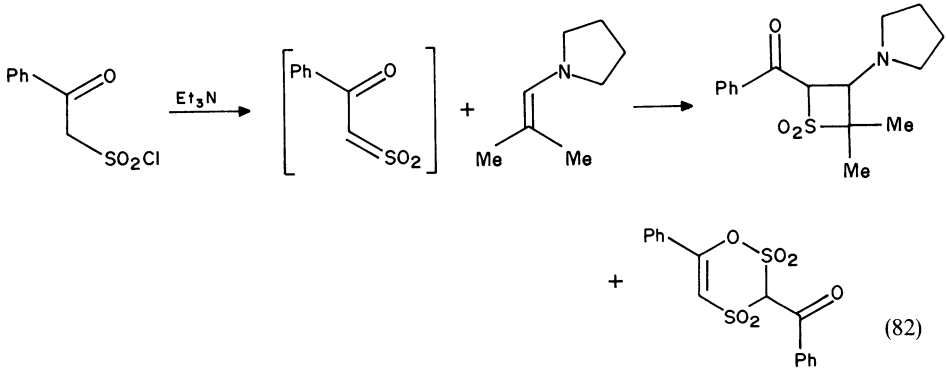


(107) (108) (109)

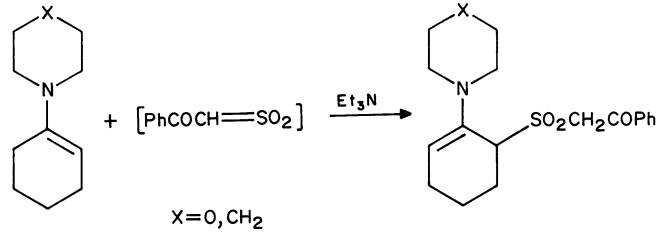


(110)

(81)

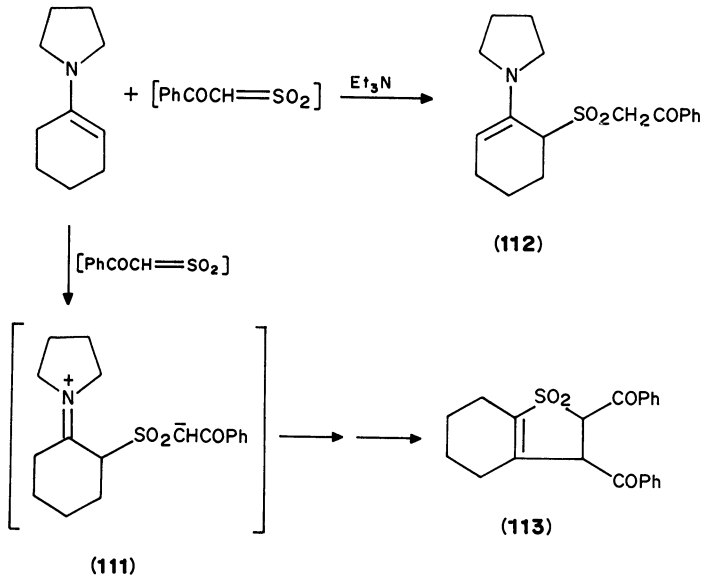


(82)



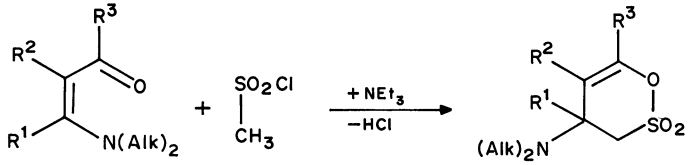
(83)

fene and the enamine[198] (equation 82). However, the enamines derived from cyclohexanone gave only acyclic sulfones (equation 83)[73]. A similar reaction of benzoylsulfene with 1-(1-pyrrolidinyl)-cyclohexene gave the acyclic product (**112**) and in addition, a second product given the structure **113**, and formulated as arising by further addition of benzoylsulfene to the zwitterionic intermediate **111** followed by elimination of both sulfur dioxide and pyrrolidine (equation 84)[73].



(84)

Sulfenes act as dienophiles toward ketoenamines giving [4 + 2] cycloadducts (equation 85); the yields are good when $R^1 = H$ and very low when $R^1 = Me$[199].



(85)

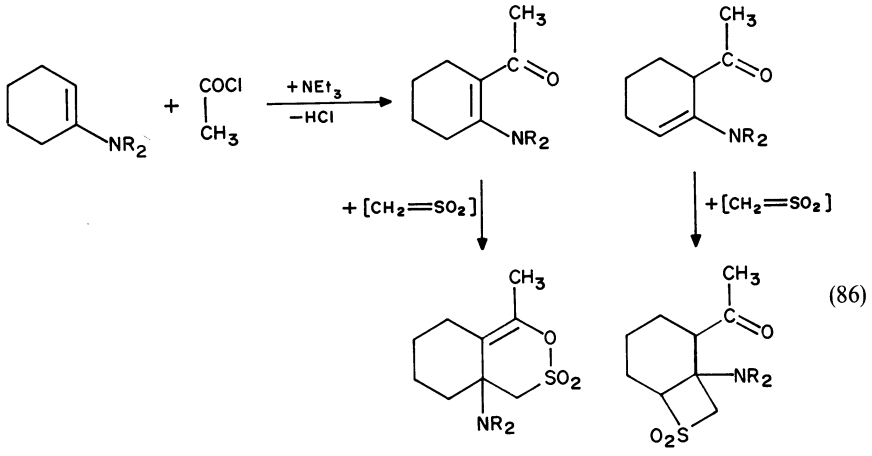
$N(Alk)_2$		
piperidino	$R^1 = H$, $R^2 = CH_3$, $R^3 = CH_3$	80%
pyrrolidino	$R^1 = H$, $R^2 = H$, $R^3 = CH(CH_3)_2$	75%
dimethylamino	$R^1 = H$, $R^2 = H$, $R^3 = Ph$	80%
dimethylamino	$R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$	7%

The ability of sulfenes to add in [4 + 2] fashion with conjugated ketoenamines and [2 + 2] fashion with enamines (and unconjugated ketoenamines) was used by Opitz and coworkers as evidence that acylation of cyclohexenylamines gives a mixture of conjugated and unconjugated ketoenamines (equation 86)[199].

Schenone and coworkers[200] have published a series of papers showing the generality of the sulfene–ketoenamine cycloaddition reaction (equations 87–90).

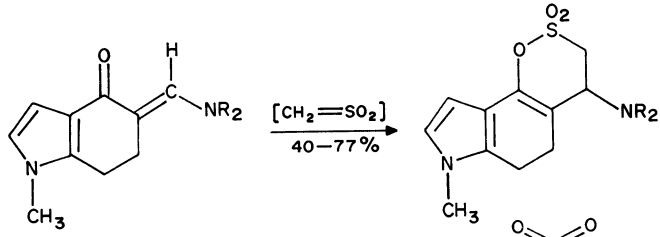
Thionoenamines have also given [4 + 2] cycloadducts with sulfene[201] (equation 91).

Several groups[202–204] reported almost simultaneously that sulfenes, generated from sulfonyl chlorides and triethylamine, also react with the acetylenic analogue of enamines (i.e. ynamines or alkynylamines) to give a mixture of the dialkylaminothiete 1,1-dioxides (equation 92). Block and Aslam[98] reported that sulfene generated from



NR_2 =		
Pyrrolidino	32%	8%
Piperidino	9%	57%
Morpholino	5%	66%

(86)



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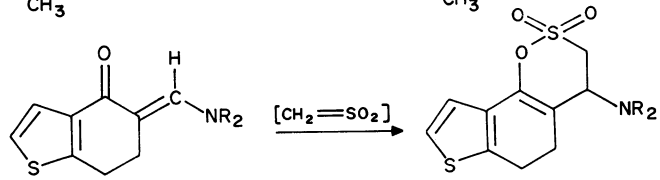
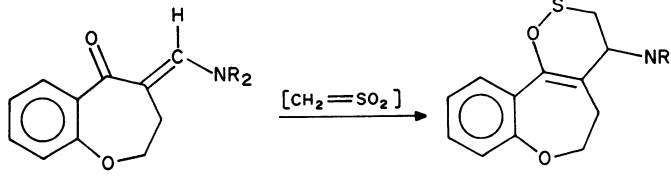
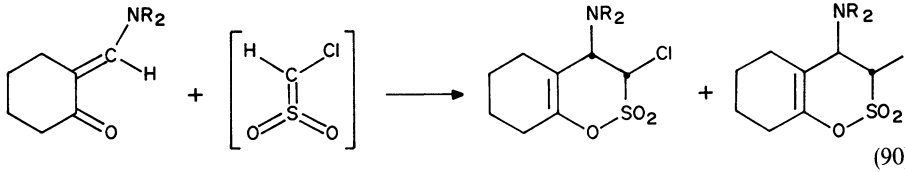


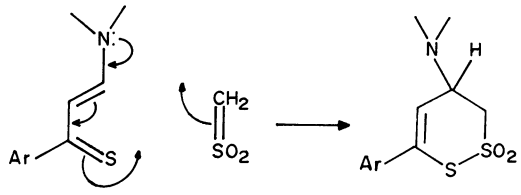
(88)



(89)

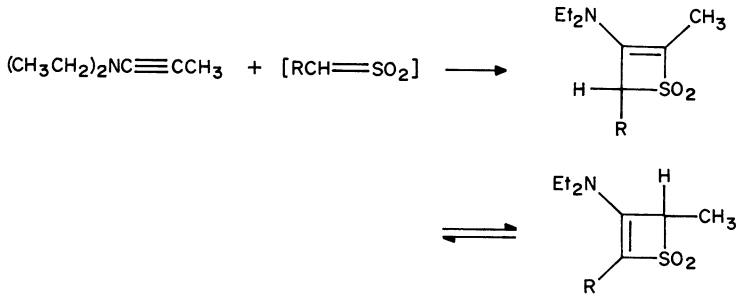


(90)



(91)

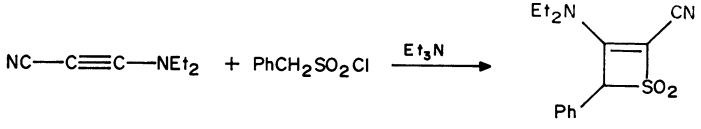
Ar = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$



(92)

(trimethylsilyl)methanesulfonyl chloride and cesium fluoride also reacts with ynamines to afford the [2 + 2] cycloadduct in good yield.

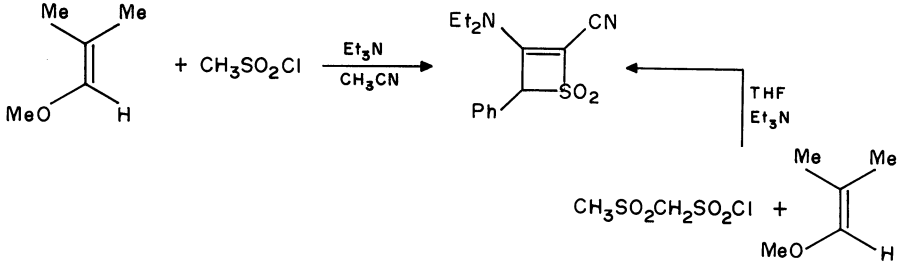
A similar reaction of a cyanoynamine with phenylsulfene also gave the four-membered cyclic sulfone (equation 93)[205]. Formation of the four-membered sulfones from cycloaddition of ynamines–sulfenes is again proposed to occur through a zwitterionic intermediate[205].



(93)

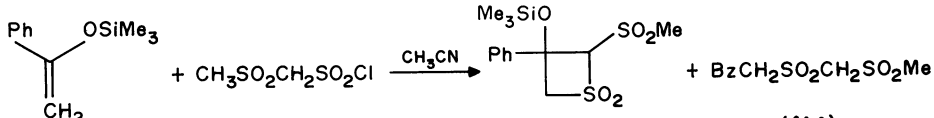
2. *Vinyl ethers, ketene acetals and aminals*

Vinyl ethers react with mesylsulfene (equation 94)[39,147], though there are apparently no reports of their reaction with sulfene and its simplest analogues[39].



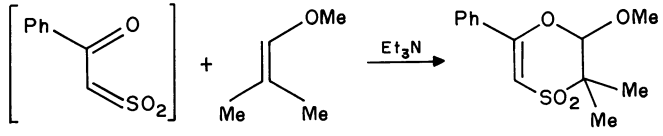
(94)

Siloxyalkenes, synthetic equivalents of enols, also did not give any product with sulfene but on reaction with the more reactive mesylsulfene gave a mixture of *cis* and *trans* [2 + 2] cycloadducts and an acyclic product **114** (equation 95)[206].



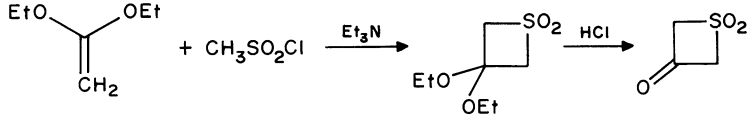
(114) (95)

This suggests that vinyl ethers require strongly electrophilic sulfenes to react. Benzoylsulfene, for example, reacts with an enol ether to give a [4 + 2] cycloadduct (equation 96); one may recall that a [2 + 2] adduct is usual with enamines[198] (equation 82).



(96)

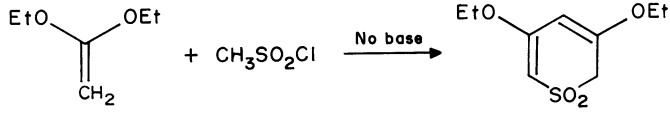
Ketene diethyl acetals, which are more nucleophilic than vinyl ethers, add to a wide array of sulfenes to produce [2 + 2] cycloadducts[36,39,207]. The reaction of methanesulfonyl chloride with ketene diethyl acetal gave 3,3-diethoxythietane 1,1-dioxide, which can be hydrolyzed to 3-oxothietane 1,1-dioxide by concentrated hydrochloric acid (equation 97)[207]. The reaction of methanesulfonyl chloride with two equivalents of ketene



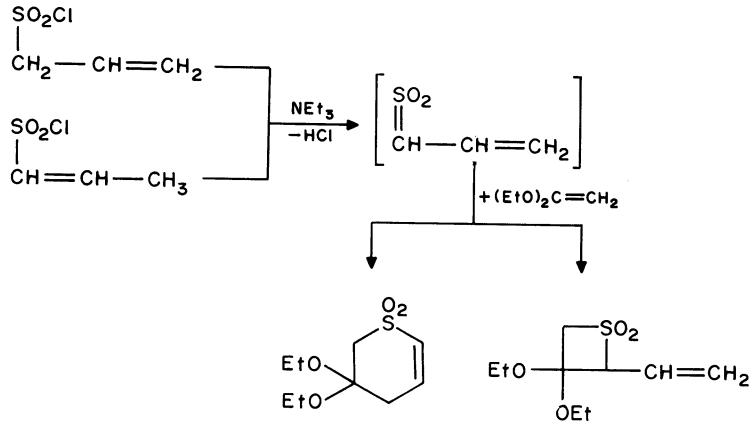
(97)

diethyl acetal in the absence of triethylamine yielded a different product (**115**) (equation 98)[207]. Truce and Norell[207] have demonstrated the intermediacy of sulfenes in the above reactions, as both 1- and 2-propenesulfonyl chlorides gave approximately the same ratio of 1,2- and 1,4-cycloadducts with ketene diethyl acetal (equation 99).

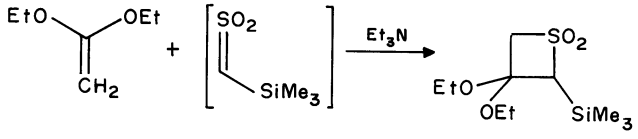
Shipov and coworkers[80] recently reported that (trimethylsilyl)methanesulfonyl chloride in the presence of triethylamine reacts with ketene diethyl acetal to produce a [2 + 2] cycloadduct in 95% yield (equation 100).



(115) (98)



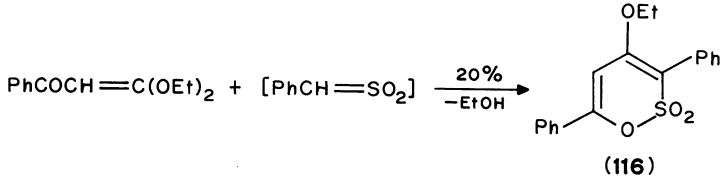
(99)



(100)

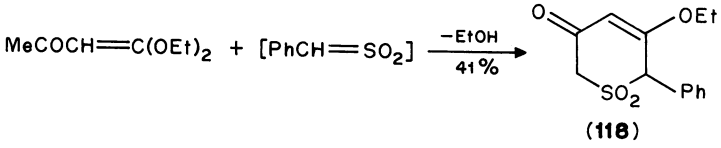
Benzoylketene diethyl acetal[207] has been found to undergo [4 + 2] cycloaddition with phenylsulfene to give a δ-sultone (**116**) (equation 101), whereas acetyl ketene diethyl acetal gave **118**, perhaps via **117** (equation 102)[207].

Analogous thioacylketene thioacetals have been reported to give a [4 + 2] adduct with sulfene (equation 103) under similar reaction conditions[209].



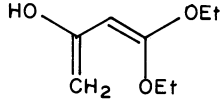
(101)

(116)

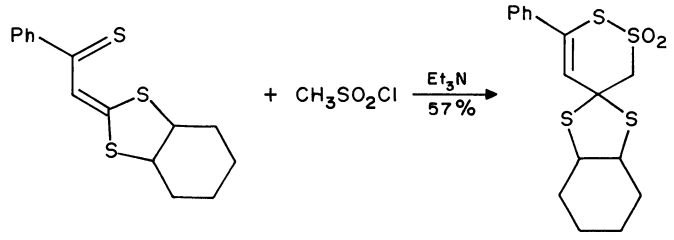


(102)

(118)

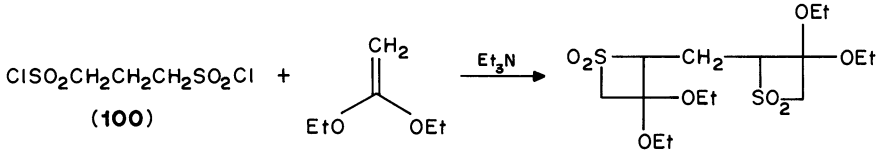


(117)



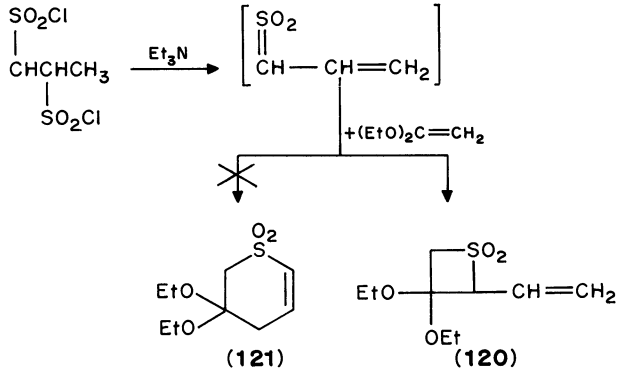
(103)

Reaction of 1,3-propanedisulfonyl chloride (**100**) with two equivalents of ketene diethyl acetal gave the double cycloadduct **119** (equation 104); like the corresponding enamine



(104)

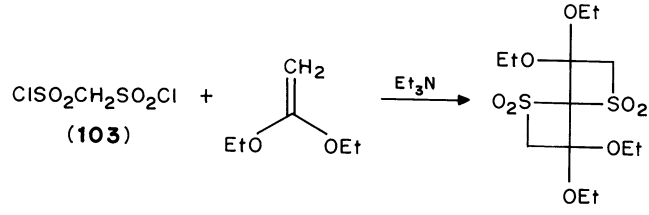
adduct (**101**, equation 77), it is a separable mixture of *dl* and *meso* forms[193]. The same reaction of 1,2-propanedisulfonyl chloride with ketene diethyl acetal gave a low yield of a product **120** (equation 105) which would seem to be derived from the cycloaddition of



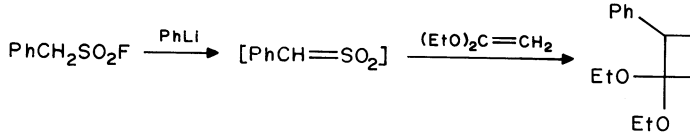
(105)

vinylsulfene[193], the expected intermediate if the disulfonyl chloride reacted with triethylamine[26]; failure to observe any sign of the [4 + 2] cycloadduct (**121**) may be due to the poor yield or to an entirely different mechanism[207]: Methanedisulfonyl chloride (**103**) with ketene diethyl acetal (equation 2) in the presence of triethylamine gave a double cycloadduct **122** in 45% yield (equation 106) which is described as arising from the disulfene (SO_2=C=SO_2), but which can easily be accounted for by other mechanisms[76].

As has been noted already in Section IV.A.2, Tokura and coworkers[92] used benzenesulfonyl fluoride and phenyllithium to generate phenylsulfene, which reacted with ketene diethyl acetal to give a [2 + 2] cycloadduct (equation 107).

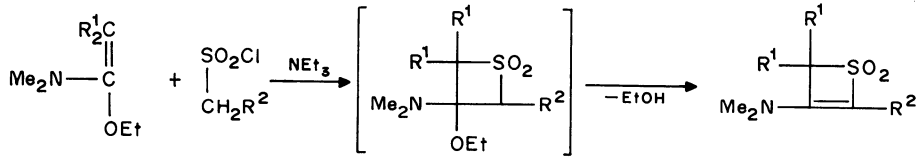


(106)



(107)

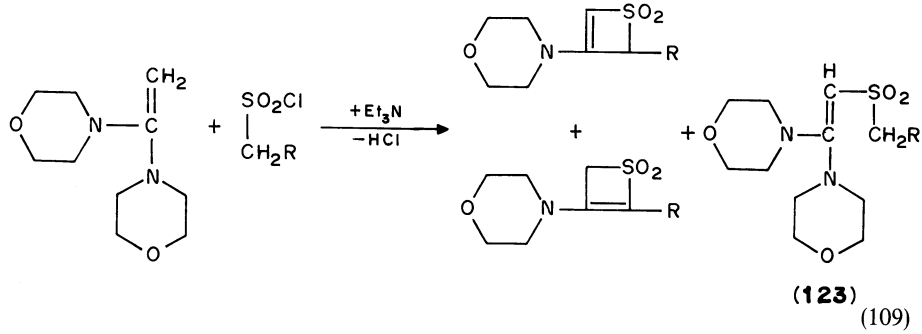
The reaction of ketene *O,N*-acetals with sulfenes resulted in a [2 + 2] cycloadduct, which produced the 3-dialkylaminothietene 1,1-dioxide by spontaneous elimination of alcohol (equation 108)[210].



R^1, R^2 = H, H; Me, Pr; Me, H.

(108)

Similarly, the reaction of ketene *N,N*-acetals with sulfenes may lead to a [2 + 2] cycloadduct (which eliminates dialkylamine) or to an open-chain sulfone **123** (equation 109). In most of these reactions both types of products are formed, but in varying



(123)

(109)

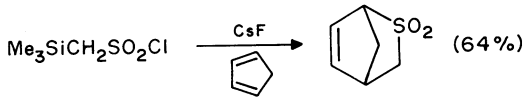
amounts depending upon the polarity of the solvent and the alkyl group of the sulfonyl chloride; highly polar solvents and the higher alkyl groups favor the formation of acyclic

products, while methanesulfonyl chloride and low polarity solvent tend to give cyclic products[210,211].

The mechanism of the above reactions is believed to be similar to that of other nucleophilic olefins; the sulfene adds to ketene *O,N*- or *N,N*-acetals to produce a zwitterionic intermediate, which either cyclizes to give a four-membered sulfone or abstracts a proton to give the acyclic sulfone[1].

3. *Alkenes and dienes*

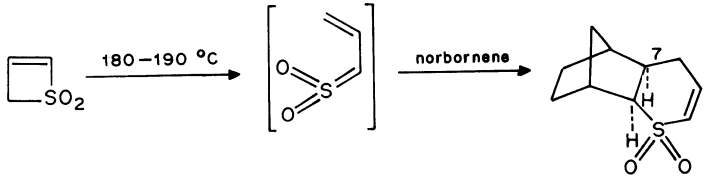
Sulfenes generated from alkanesulfonyl chlorides and tertiary amines have not been observed to react with simple olefins or dienes[1,36], but Block and Aslam[98] reported that sulfene from (trimethylsilyl)methanesulfonyl chloride with cesium fluoride reacted with dienes to afford [4 + 2] cycloadducts (equation 110). Slightly greater yields of the



(110)

cycloadducts were obtained when (trimethylsilyl)methanesulfonic anhydride was used instead of (trimethylsilyl)methanesulfonyl chloride[99].

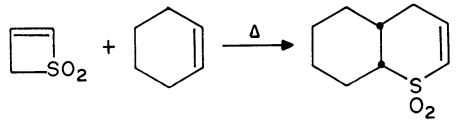
Dittmer and coworkers[119] generated vinylsulfenes by thermolysis of thiete 1,1-dioxides which, in the presence of norbornenes, gave the Diels–Alder-type cycloadducts **124** in good yield (equation 111) (see also Section IV.E.2). Thermolysis of thiete 1,1-dioxide in



(111)

(124)

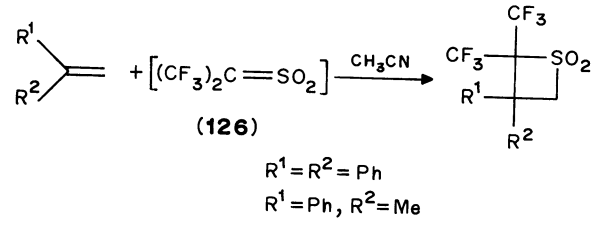
cyclohexene for 5 days gave mainly tar and a very low yield (0.6%) of the cycloadduct **125** (equation 112)[119].



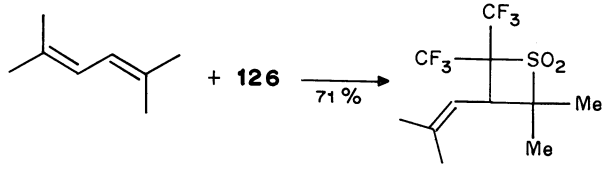
(112)

(125)

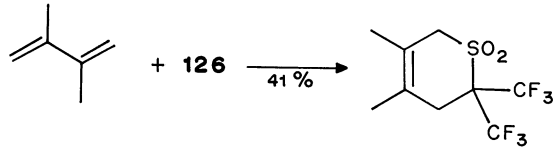
As has been noted already in Section IV.B.3, Smart and Middleton[103] generated bis(trifluoromethyl)sulfene (**126**) in solution by treating $[(Me_2N)_3S^+\ C(CF_3)_2SO_2F$ with silicon tetrafluoride or boron trifluoride. This sulfene adds to various dienes and olefins to give [4 + 2] and [2 + 2] adducts in moderate to good yields (equations 113–117).



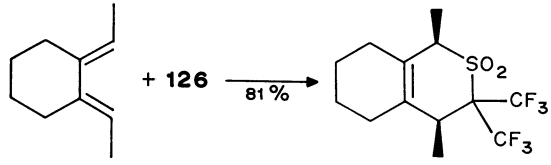
(113)



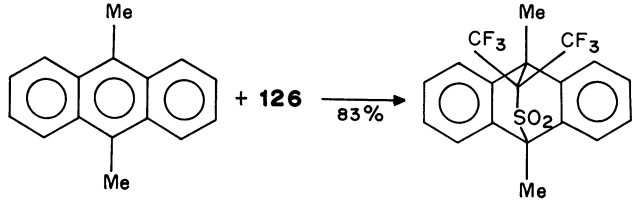
(114)



(115)



(116)

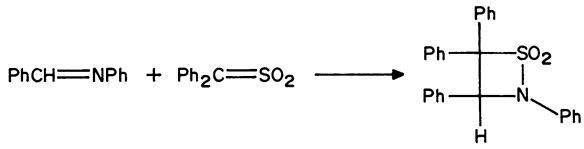


(117)

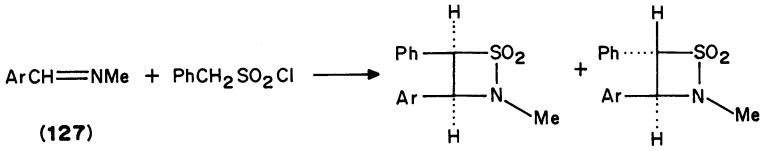
4. Carbon–nitrogen double bonds

The first cycloaddition of sulfene to the C=N bond was reported by Staudinger and Pfenninger[107], who showed that the reaction of diphenylsulfene, generated from diphenyldiazomethane and sulfur dioxide, gave a four-membered cyclic compound with benzylideneaniline (equation 118).

Hiraoka and Kobayashi[212] have reported that phenylsulfene adds to various Schiff bases (**127**) to give a mixture of *cis*- and *trans*-1,2-thiazetidine 1,1-dioxides with the *cis* isomer predominating (equation 119). The preferential formation of the *cis* isomer in this reaction (equation 119) suggested to these authors that the reaction is a concerted



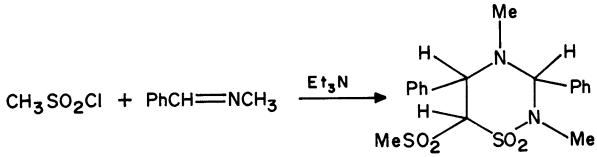
(118)



(119)

Ar = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$

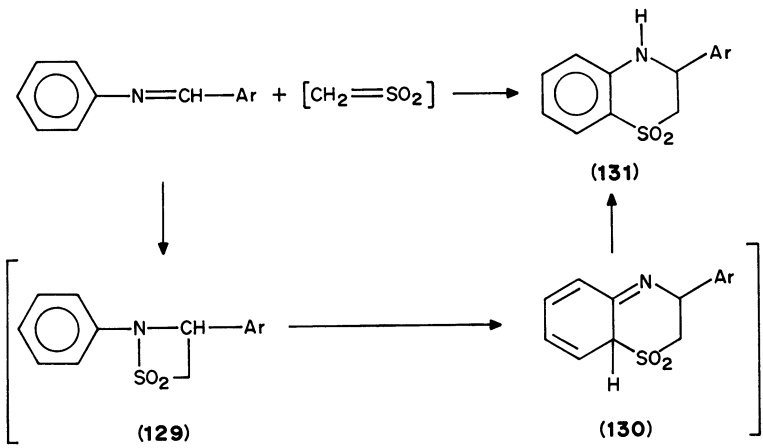
[π2s + π2a] cycloaddition[189]. The best yields of these 1,2-thiazetidine 1,1-dioxides were obtained with two equivalents of **127** to one equivalent of phenylmethanesulfonyl chloride without other base[212]. These authors[212] also reported that alkylsulfenes did not give any identifiable products with *p*-substituted benzylidenemethylamines, but in the case of sulfene itself the reaction gave sultam **128** in 28% yield (equation 120).



(128)

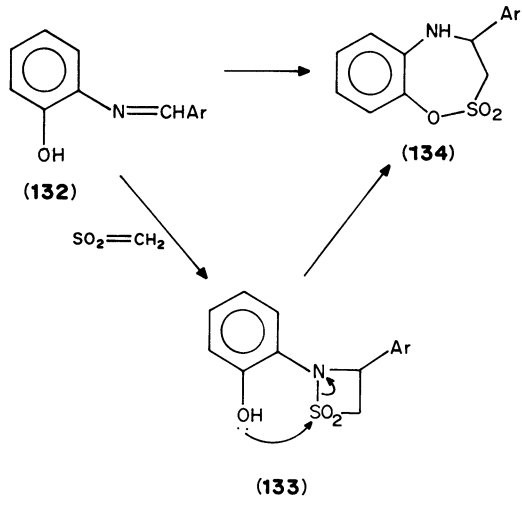
(120)

Rai and coworkers[213] have claimed that reaction of sulfene, generated from methanesulfonyl chloride and triethylamine, with benzylideneanilines afforded 1,4-benzothiazine 1,1-dioxides (**131**) in good yields (equation 120), and suggested that **131** resulted from rearrangement of an initial [2 + 2] cycloadduct **129** (equation 121).



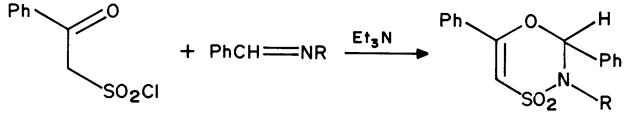
(121)

Recently, Rai and Kaur[214] have reported that reaction of sulfene with *N*-benzylidene-2-hydroxyanilines (**132**) gave **134**, suggesting that it arose by rearrangement of the initial [2 + 2] cycloadduct **133** (equation 122).



(122)

Tsuge and Iwanami[73] reported that benzoylsulfene adds to C=N bonds of benzylideneamines to give [4 + 2] and [2 + 2] cycloadducts, depending on the reaction conditions. When triethylamine was used to generate sulfenes only [4 + 2] cycloadducts were obtained (equation 123), and in the absence of triethylamine both [4 + 2] and [2 + 2] cycloadducts were formed (equation 124). When the substituents in the anils



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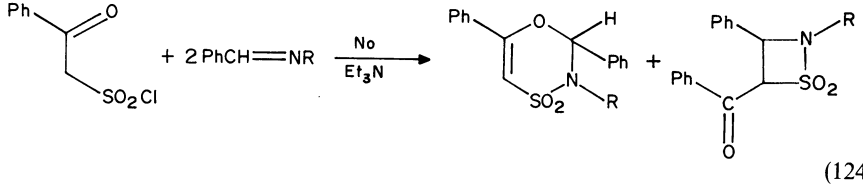
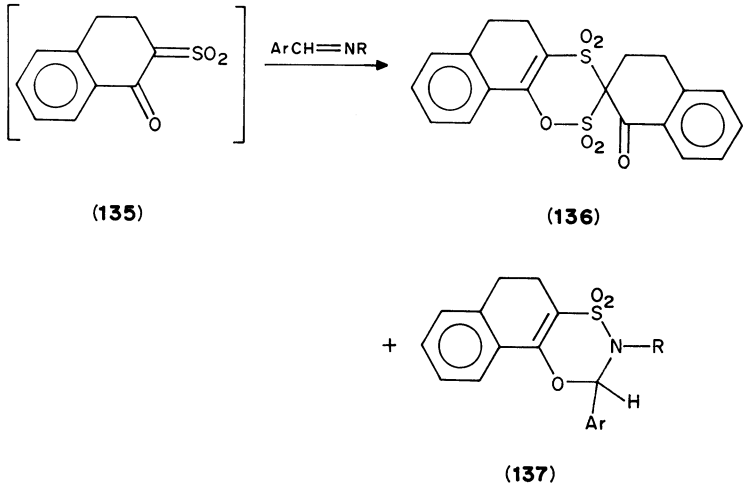


(124)

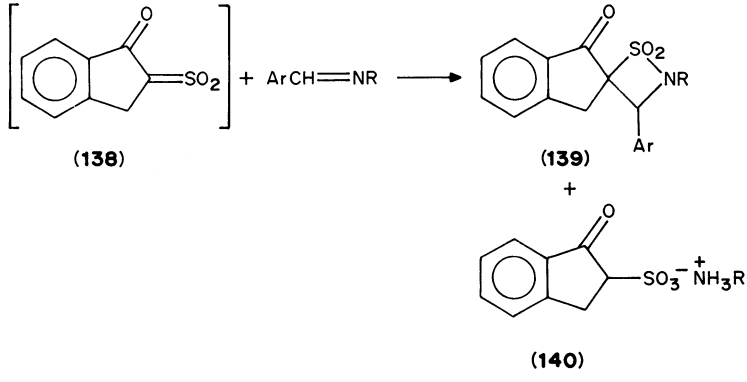
were aromatic, e.g. phenyl and *p*-tolyl, the reactions required a long time and gave only the [2 + 2] cycloadducts in the presence of triethylamine; this was attributed to instability of [4 + 2] aromatic cycloadducts compare to the corresponding *N*-alkyl compounds[73].

The cyclic α-tetralone sulfene (**135**) with benzylideneanilines in the presence of triethylamine afforded only the dimer **136**, however benzylidenealkylamines gave [4 + 2] cycloadducts **137** (equation 125)[73]. The chemical behavior of the α-indanone sulfene (**138**),

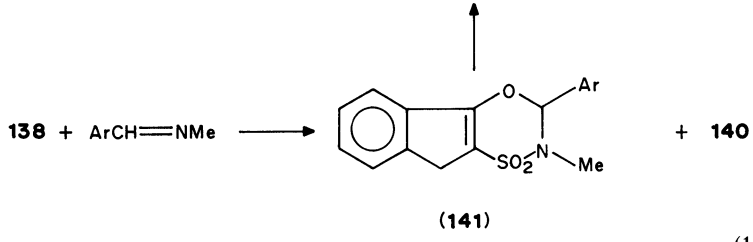


(125)

generated from 2-chlorosulfonyl-1-indanone and triethylamine, was different from that of **135**. The reaction of **138** with benzylideneanilines in the presence of triethylamine gave only the [2 + 2] cycloadduct (**139**) and no dimer (equation 126)[73]. The reaction of most benzylidenealkylamines, however, gave both [2 + 2] cycloadducts (**139**) and the ammonium sulfonate salts (**140**). In the case of benzylidenemethylamine a [4 + 2] cycloadduct **141** was obtained along with **140** (equation 127). Since the [4 + 2] cycloadduct

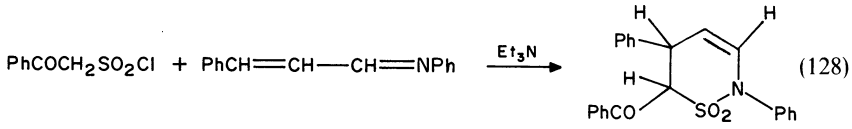


(126)



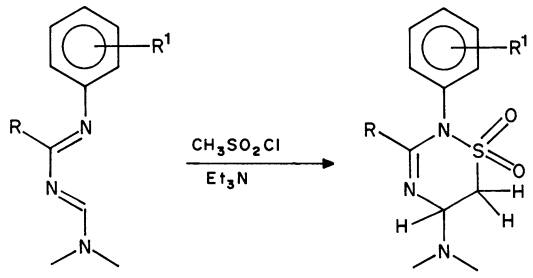
(127)

(**141**) can be easily hydrolyzed to **140** under mild conditions, the α-ketosulfonate salts (**140**) in the other reactions may arise from the corresponding [4 + 2] cycloadducts (**141**)[73]. The reaction of benzoylsulfene with cinnamylideneamines in the presence of triethylamine produced [4 + 2] cycloadducts in 26–43% yields (equation 128)[73].



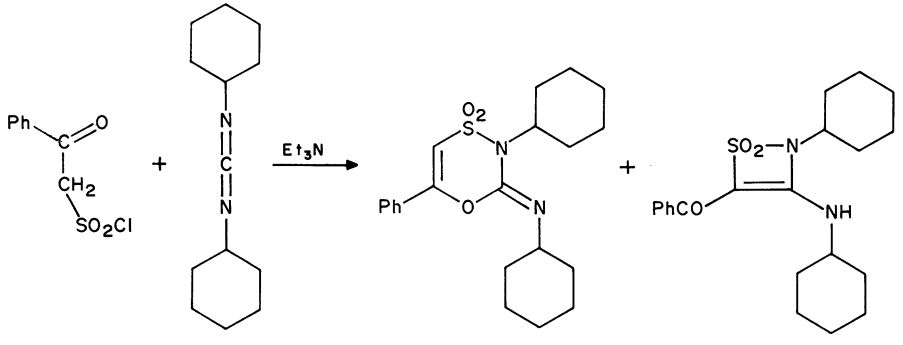
(128)

Mazumdar and collaborators[215] recently reported that 1,3-diazabutadienes with sulfenes in the presence of triethylamine gave good yields of [4 + 2] cycloadducts (equation 129).



(129)

Reaction of dicyclohexylcarbodiimides with benzoylsulfene in the presence of triethylamine has been reported[216] to result in the formation of [4 + 2] and [2 + 2] cycloadducts (equation 130). A similar reaction with diphenylcarbodiimide[216] gave the [4 + 2]

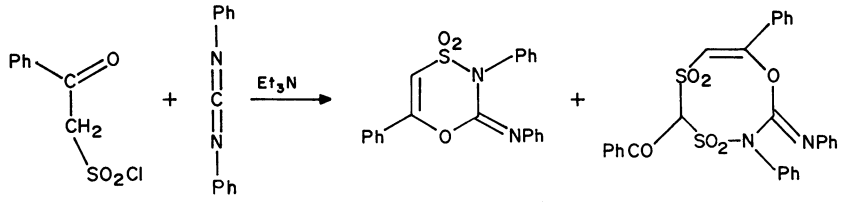


(130)

cycloadduct and **142**, a 2:1 adduct of benzoylsulfene and carbodiimide (equation 131).

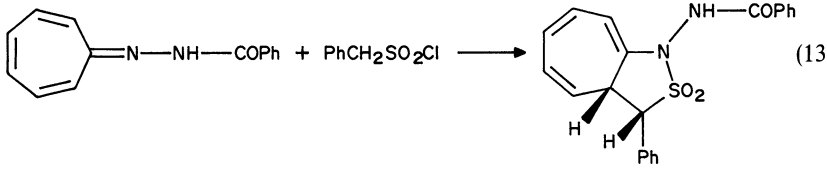
The reaction of tropone hydrazone with phenylsulfene in the presence of triethylamine gave a [8 + 2] cycloadduct (equation 132) in 48% yield[217].

Truce and Shepherd[218] have reported that various sulfenes react with azaheptafulvene in a stereoselective manner to produce the corresponding γ-sultams (equation 133).

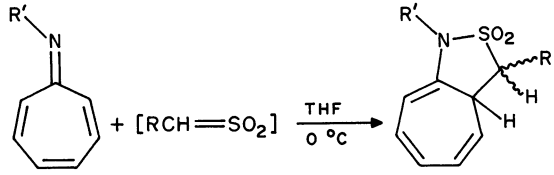


(142)

(131)



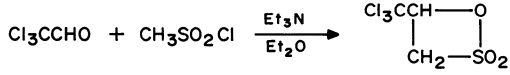
(132)



(133)

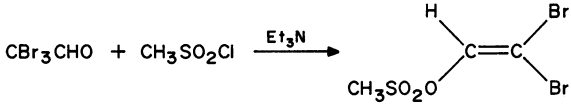
5. Carbon–oxygen double bonds

The reaction of chloral with sulfene generated from methanesulfonyl chloride and triethylamine has been found to give β-sultone (equation 134)[219,220]. It was observed[156] that



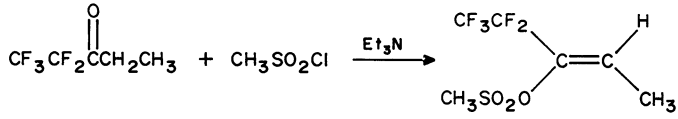
(134)

the yield of the sultone from ethanesulfonyl chloride and chloral varied from 54% with trimethylamine and 50% with DABCO to 10% with triethylamine and 0% with tributylamine (under one set of conditions), and it was concluded that this observation precludes a simple sulfene–chloral cycloaddition mechanism and points to a zwitterionic intermediate derived from the amine and either the sulfene or chloral. Formation of β-sultones has been found to be general with many perhalogenated carbonyl compounds[221], an exception being bromal, which gave 2,2-dibromovinyl methanesulfonate[222] (equation 135).



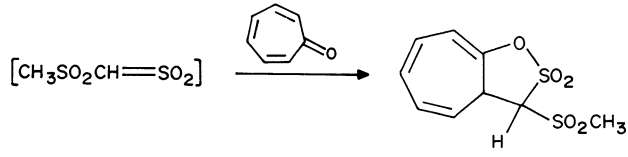
(135)

Unlike their fully halogenated analogues, halogenated ketones and aldehydes containing one or more α-hydrogens gave the vinyl mesylate esters (equation 136) under similar reaction conditions[227,223].

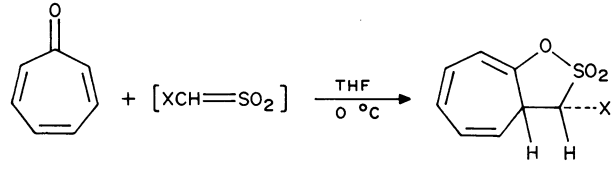


(136)

Ciabattoni and Cabell[224] reported that the reaction of mesylsulfene (from mesylmesyl chloride or a threefold excess of mesyl chloride) with tropone in the presence of triethylamine gave a tropone–mesylsulfene adduct (equation 137). Later, Truce and Lin[225] found that a number of substituted sulfenes also add to tropone (equation 138) in a highly stereoselective fashion to form the corresponding γ-sultones.



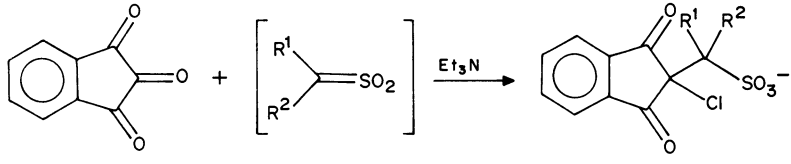
(137)



(138)

X=Ph, p-ClC_6H_4, p-$NO_2C_6H_4$, PhCO, CN, CH_2=CH

Hanefeld and coworkers[179] have recently noted that the reaction of sulfenes generated *in situ* from sulfonyl chlorides and tertiary amines, with vicinal tricarbonyl compounds such as indan-1,2,3-trione, alloxane, diethyl mesoxalate and 1-methyl-1,2,3,4-tetrahydroquinoline-2,3,4-trione, afford products derived mainly from ring opening of β-sultones (equation 139).

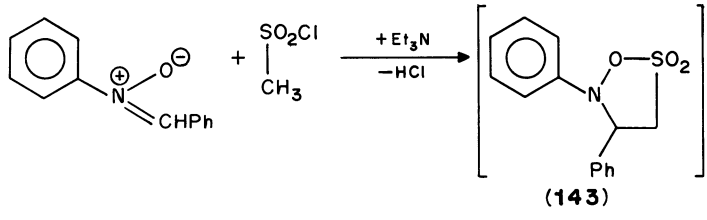


(139)

The formation of six-membered cyclic dimers of α-ketosulfenes has been mentioned above (equations 82 and 125)[73,154].

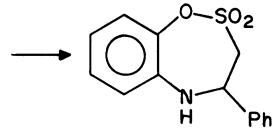
6. 1,3-Dipoles

Truce and coworkers[137,226] reported that sulfenes act as dipolarophiles towards *C,N*-diphenylnitrone to produce 1:1 adducts **144**, which are believed to arise from rearrangement of the initial [3 + 2] cycloadducts (e.g. **143**, **144**), (equation 140); this proposal was



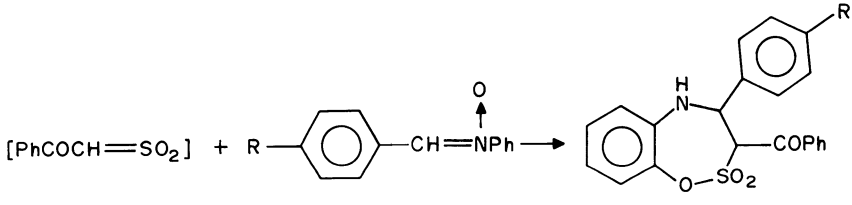
(143)

(140)

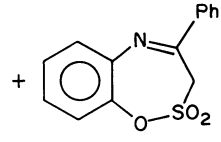


(144)

supported by ^{18}O-labelling studies. The reaction is general and a number of substituted azasultones have been synthesized by this method[136,137,226]. Benzoylsulfene and two cyclic α-ketosulfenes **135** and **138** also reacted with diarylnitrones to produce the rearranged adducts (**145**), accompanied by a by-product **146**, which apparently arose from **145** by the elimination of ArCHO (equation 141)[73].



(145)

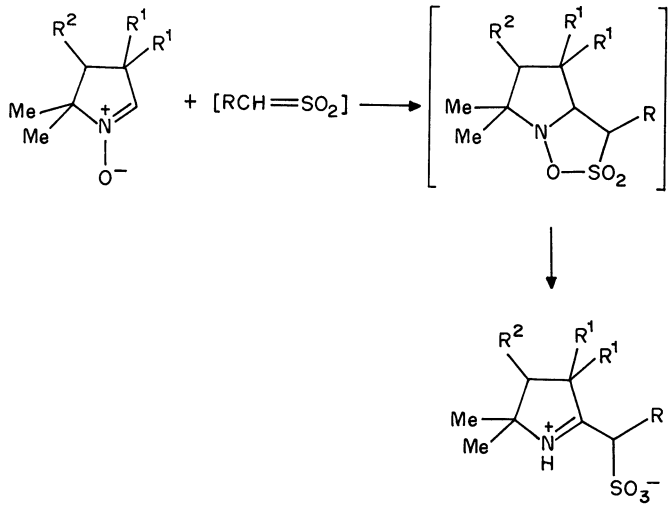


(146)

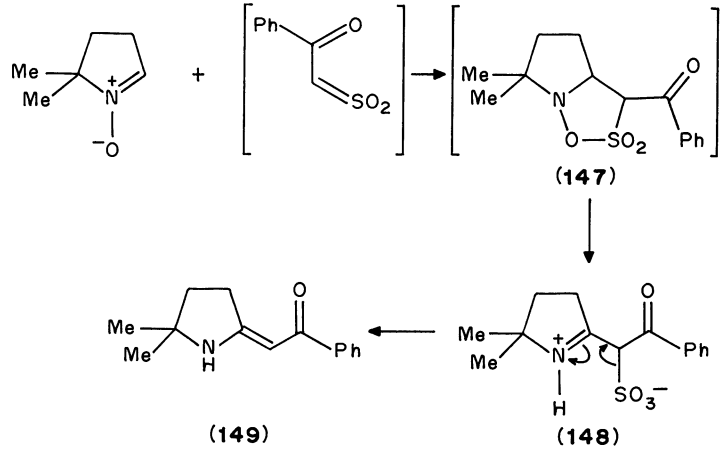
(141)

The reaction of sulfenes with cyclic nitrones such as 1-pyrroline 1-oxide, in the presence of triethylamine, gave good yields (50–70%) of β-iminosulfonic acids which can easily be reduced to taurine derivatives (equation 142)[227].

Benzoylsulfene and cyclic nitrones gave β-aminoenones and β-iminosulfonic acids (e.g. **149** and **148**) (equation 143), with the relative yields depending upon the nature of solvents used[73]. Similar products were obtained with the two cyclic α-ketosulfenes **135** and **138**. The authors suggested that the initial products of these reactions were [3 + 2] cycloadducts (**147**), which rearranged to give **148** and **149**[73].

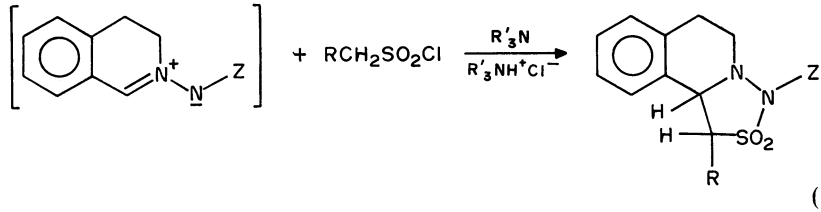


(142)



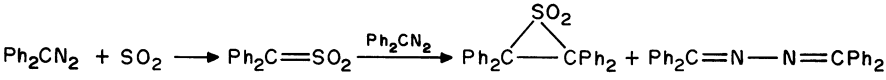
(143)

Highly reactive dipoles, such as azomethine imines, react with sulfenes in the presence of triethylamine to produce the [3 + 2] cycloadducts in good yields (equation 144); the reaction is evidently general[228].



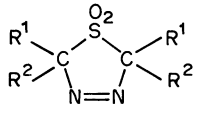
(144)

Staudinger and Pfenninger[35] first noted that diphenylsulfene, generated from diphenyldiazomethane and SO_2, reacted with another molecule of diphenyldiazomethane to produce not only the three-membered ring sulfone as already discussed (see equation 19), but also a small amount of the ketazine **150** (equation 145). Subsequent investigations,

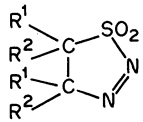


(150) (145)

especially with disubstituted diazomethanes, have led to the isolation of 1,3,4-thiadiazines **151**, presumably formed by a 1,3-dipolar addition of the diazomethane and the sulfene; these thiadiazines are readily converted thermally or photochemically to the azine and, at rather high temperatures, to the corresponding alkenes, usually in rather mediocre yields[109,170,183,230,231]. Staudinger and Pfenninger's original suggestion of an isomeric thiadiazine (**152**) as a precursor to the other products has not been supported by more recent studies, and Quast and Kees[170] have proposed that the different products arise from two quite different pathways involving low-lying unoccupied MOs of different symmetry (see equation 55, Section V.A.2).



(151)

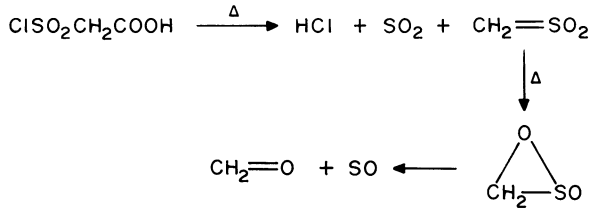


(152)

C. Thermal and Photochemical Desulfinylation, Cyclization and Desulfonylation

It has been noted already (Sections III and IV.E.1) that flash vacuum thermolysis of chlorosulfonylacetic acid at 640 °C gave sulfene, identified by trapping experiments and direct observation of its infrared spectrum (equation 1)[18,19]. When the reaction was carried out similarly except that the temperature was 940 °C, the major product was formaldehyde (in 50–75% yield, isolated as dimethoxymethane by trapping with methanol)[20]. It would appear that conversion of a sulfene to the analogous aldehyde or ketone with the loss of the elements of sulfur monoxide is a general high-temperature reaction of sulfenes; under conditions of flash thermolysis, where residence times are believed to be of the order of a few milliseconds, this 'desulfinylation' reaction sets in around 700–800 °C. Examples quoted earlier are the formation of chloroacetaldehyde on thermolysis of ethenesulfonyl chloride (equation 28)[120], of acetaldehyde and formaldehyde from 3-thietanol 1,1-dioxide (equation 29)[118], and hexafluoroacetone[117] from **32** (see Sections IV.E.2 and IV.E.1, respectively). Flash thermolysis of 'sulfene dimer' (**67**) at 900 °C gave formaldehyde as well as ethylene and sulfur dioxide; **67** was recovered unchanged below 700 °C[232].

These results are consistently accounted for by a thermal desulfinylation[118] via an α-sultine, as in equation 146. The fate of the sulfur monoxide fragment is not clear, but a red material appears on the surface of the trap and this is converted on warming to room temperature to a yellow, insoluble, presumably polymeric, material. This observation is



(146)

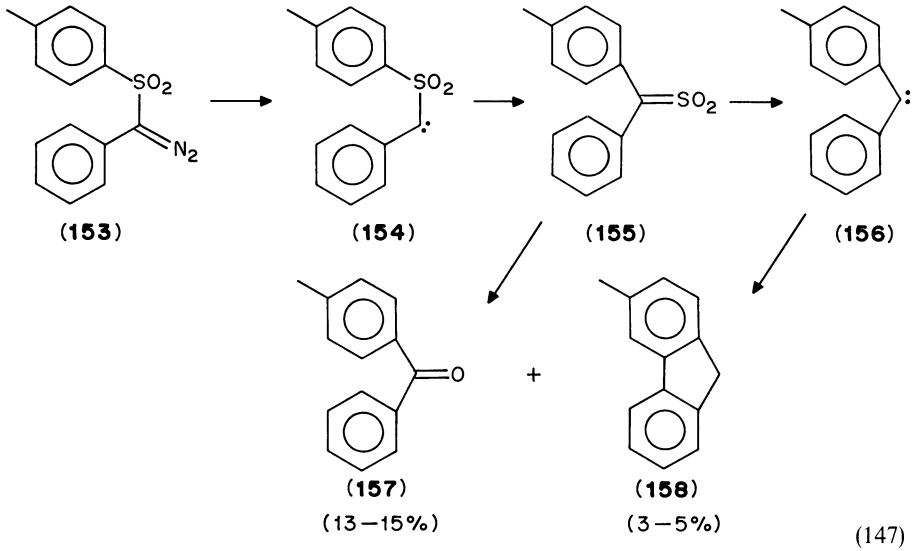
compatible with disproportionation of sulfur monoxide to disulfur monoxide and conversion of this to poly(sulfur oxide)[233].

Langendries and DeSchryver[122] reported the photochemical conversion of thiete 1,1-dioxide into analogous α,β-unsaturated carbonyl compounds, presumably by desulfinylation of the sulfene; evidence for the formation of the vinyl sulfene was obtained from a trapping experiment (equation 31, Section IV.F)[122].

Hiraoka has suggested that the α-sultine may be formed from sulfene and then be converted into carbonyl sulfide under photolytic, electron transfer or thermolytic conditions[234]; the evidence that sulfene is formed and that the carbonyl sulfide arises from sulfene in these reactions, however, is not strong.

As has been mentioned elsewhere (Sections IV.E.2 and V. C) *thermal* rearrangement of thiete 1,1-dioxide also leads to the vinylsulfene[118]. In the absence of sulfene traps the product is the unsaturated sultine (e.g. **37**); flash thermolysis of thiete 1,1-dioxide above 800 °C yields acrolein (equation 26, Section IV.E.2)[118]. The sulfur dioxide adducts of benzobenzvalene, which can be regarded as homologues of thiete 1,1-dioxide (**34**) and (**37**), evidently thermolyze to 1-indenylsulfene, which desulfinates to 1-indenecarboxaldehyde or undergoes 1,3-dipolar addition of methyl acrylate to form another sultine[235]. Photochemical generation of sulfene by a cyclohexadienic ring opening (Section IV.F) by Hall and Smith[127] also led to sultines, both five- and seven-membered.

Thermal loss of sulfur dioxide, i.e. desulfonylation to form a carbene and sulfur dioxide, was originally put forward by Wedekind and Schenk in 1911 to explain the formation of stilbene in the reaction of phenylmethanesulfonyl chloride with triethylamine[5]. As we have already recounted, another mechanism is much more likely for that transformation, but



(147)

Sarver, Jones and van Leusen[236] have provided an interesting example in which it would appear that a small amount of the postulated thermal desulfonylation has taken place. Under conditions of flash thermolysis the α-diazosulfone **153** was converted into *p*-tolyl phenyl ketone and 2-methylfluorene (equation 147). The conversion **153** ⟶ **154** ⟶ **155** is the sulfo-Wolff rearrangement, a process which has been induced photochemically[129] (Section IV.F). The ketone **157** may be readily formulated as arising from desulfinylation of the sulfene (**155**), while the 2-methylfluorene (**158**) is a characteristic product of the rearrangement of *p*-tolyl phenyl carbene[237], so much so that the formation of **158** provides a good circumstantial case for the formation of the carbene (**156**), though in very low yield.

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CHAPTER **18**

Biological activity of sulfonic acid derivatives

ASHER KALIR

Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

and

HENRY H. KALIR

Department of Neurology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

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I. INTRODUCTION

Sulfonic acids and their numerous derivatives are important constituents of living organisms. It suffices to mention 2-aminoethanesulfonic acid (taurine, TA) **18** and related compounds—cysteic acid **27**, guanidoethanesulfonic acid (guanidotaurine, GES) **33**, 2-hydroxyethanesulfonic acid (isethionic acid) **29**, 3-aminopropanesulfonic acid (homotaurine, HTA) **34** ($n = 3$) and others. These acids, and particularly TA, possess physiological properties essential for the normal action and well-being of diverse species and naturally they were, and are, intensively studied. The results have been published in numerous articles, reviews and books[1–5]. Many other substituted derivatives of alkanesulfonic acids have been found to exert a wide range of pharmacological activity, e.g. amsacrine **5** (antineoplastic)[21–31], dipyrone, **17** ($R = -CH_2SO_3H$)(analgetic)) etc.

The best known and most extensively investigated group of aromatic sulfonic acids consists of 4-aminobenzenesulfonamide and its numerous congeners. They are active medicinal agents, useful in treatment of a variety of infections, hypertension, diabetes etc.[6,7]

II. ALIPHATIC SULFONIC ACIDS

The simplest compound in this series is methanesulfonic acid (**1**, (X and R = H) R = H). This is a very strong acid and its esters are powerful alkylating agents.

XCH_2SO_2OR (**1**) $\qquad$ $CH_3SO_2CH_2SO_2OCH_2CH_2X$ (**2**)

The esters (**1**, X = H, R = Me or Et) are carcinogenic[8] and mutagenic[9–11]. The effect of the mutagenicity of the ethyl ester was compared with that of γ-radiation[12,13]). Both compounds show synergism of mutant frequencies in the mouse lymphoma mutagenicity assay[14]. Eder and Kutt published recently[15] the results of testing the reaction of 22 methanesulfonates with model nucleophiles, in order to predict the mutagenic effect on S. typhimuria TA100. In general, the secondary esters exerted high S_N1 reactivities, as measured by trifluoroacetic acid solvolysis and H_2O hydrolysis, and distinct mutagenic activities. The primary compounds (with the exception of the methyl ester) showed low S_N1 reactivity and low mutagenic potential.

2-Chloroethyl halomethanesulfonates (**1**, X = Cl, Br or I; R = $ClCH_2CH_2$—) showed activity in inhibiting proliferation of L1210 leukemia cells in culture and against P388 leukemia. The most active compound was **1**, X = Cl[16,17].

Several related ethyl methylsulfonylmethanesulfonates (**2**, X = H, F, Cl and Br) were evaluated for their ability to induce sister chromatid exchanges in L1210 cells[18].

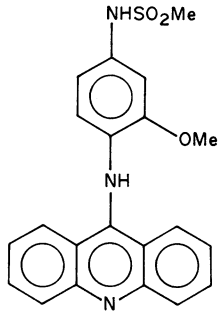
The chloro derivative **2**, X = Cl was the most active and was selected for clinical trials. The diester of 1,4-butanediol (busulfan) **3** is an alkylating agent, specific for the granulocyte series and used in therapy of chronic myeloid leukemia[19].

$(—CH_2CH_2OSO_2CH_3)_2$ (**3**) $\qquad$ $CH_3SO_2NHN(CH_3)O_2SCH_3$ (**4**)

The search for better alkylating agents is being pursued, e.g. the recently prepared 1,2-bis(methylsulfonyl)-1-methylhydrazine **4** was found to be highly active against several Trypanosoma species in mice[20].

III. METHANESULFONAMIDES

Substituted methanesulfonamides have been long known as useful drugs. A compound that recently attracted considerable attention is amsacrine **5**, 4′-(9-acridinylamino)-



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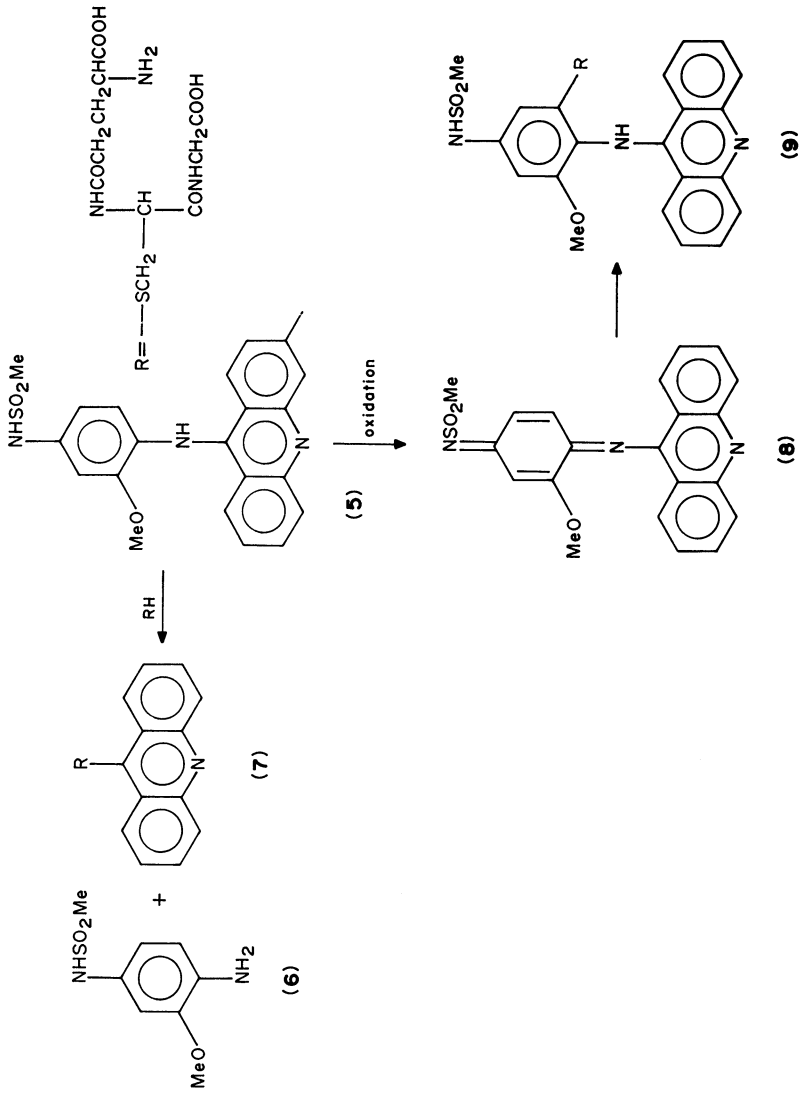
methanesulfone-*m*-anisidide, AMSA. This agent and its numerous analogs were prepared and evaluated by Cain, Baguley, Denny and coworkers[21–31].

A. Biological Activity

AMSA has been found to act against lymphoblastic leukemia in adults. Byrd found activity against Rauscher leukemia virus and Vaccinia virus in tissue culture[32]. Legha and coworkers concluded that **5** showed significant activity in the treatment of patients with refractory acute leukemia[33]. Wadler and collaborators published a short review on the pharmacokinetics and clinical pharmacology of AMSA. They included the partially positive results of clinical trials, particularly in combination with other drugs (cytosine–arabinoside) in patients with relapsed acute lymphocytic and nonlymphocytic leukemia[34]. Pavkov and colleagues investigated thoroughly and reported extensively the toxicity of AMSA and single and multiple treatment regiments in beagle dogs. It produces various lesions at lethal doses. The LD_{50} in CDF_1 mice were 810 (male) and 729 mg m^{-2} (female)[35]. Byrd reported for 5-HCl LD_{50} i.p. mice, 60 mg kg^{-1}[32]. Incidentally, it has been reported that AMSA is a strong, competitive inhibitor of aldehyde oxidase[36].

B. Mode of Action

AMSA intercalates between base pairs in DNA and distorts the double helix. It reacts with topoisomerase II (an enzyme that can unlink two intertwined DNA circles via its strand-passing activity)[36]. **5** was inactive as a possible inducer of DNA-repair replication in cultured human cells[37]. Pullman published recently a review on the molecular mechanisms of specificity of AMSA–drug interactions[38]. Quantitative structure activity relationships (QSAR) were derived between the antileukemic activity against leukemia L1210 and physicochemical properties of 509 of tumor-active anilinoacridines, including AMSA and congeners[39]. Schneider and collaborators proposed that an additional labile protein factor is required for the cytotoxicity of the AMSA complex with DNA topoisomerase II and DNA[40]. Crawford and coworkers advanced a possibility that anticancer agents, including AMSA, are involved in generation of toxic oxy radicals which destroy neoplastic cells[41].



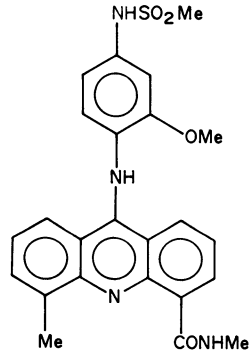
SCHEME 1. Metabolism of amsacrine[42–46]

C. Disposition and Metabolism

The metabolism of AMSA in mice was studied by Cysyk's group using a ^{14}C-labeled compound at C-9 position. The identified metabolites were 4-amino-3-methoxymethanesulfonanilide **6** and the corresponding thioether of acridine **7**, probably a product of a nonenzymatic, nucleophilic attack on the 9-carbon atom by endogenous thiols like glutathione GSH (see Scheme 1). Thioethers of low molecular weight thiols were eliminated in urine and bile; 50% of injected dose was excreted in 2h[42]. A metabolite that contained a GSH conjugate linked to the 5-position of the aniline ring in **9** has been found in the bile of rats[43]. It is probably formed by addition of GSH to the cytotoxic *N*-methanesulfonyl-*N'*-(9-acridinyl)-3'-methoxy-2',5'-cyclohexadiene-1',4'-diimine **8**, that is obtained from AMSA under the influence of liver monooxygenase[44,45]. Przybylski studied and identified these and some other minor metabolites by HPLC and FD mass spectrometry[46].

D. CI-921

Among the impressive number of compounds prepared and investigated by Baguley, Denny and coworkers in order to establish the steric requirements for DNA binding and biological activity, they found that *N*,5-dimethyl-9-[(2-methoxy-4-methylsulfonylamino)phenylamino]-4-acridinecarboxamide (CI-921, **10**) was mutagenic



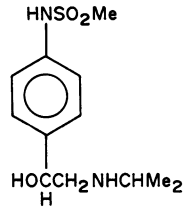
(10)

to Salmonella typhimurium and caused extensive chromosomal aberrations in a Chinese hamster test culture[28]. It was considerably more active than AMSA against P388 leukemia, Lewis lung carcinoma and LC-12 lung tumor[27,31]. It was noted that **10** had exceptionally high oral activity[24].

E. Other Agents

Other agents of physiological interest are the substituted methanesulfoanilide, sotalol (**11**)—a nonselective β-adrenergic receptor blocker with antiarrhythmic activity[47,48], and soterenol, another methanesulfonanilide (**12**)—a bronchodilator[49].

A series of sulfonamidobenzoquinolizines, **13**, was prepared by Ward, Lattimer and coworkers[50–52]. These agents are powerful and selective α-adrenoceptor antagonists. Introduction of a second sulfonyl group [**13**, R = —$(CH_2)_2NHSO_2R'$; R' = Me or Et] reduced antagonist potency at α-adrenoceptors but increased their antagonist activity for



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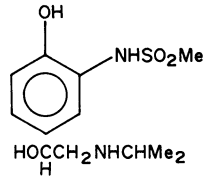

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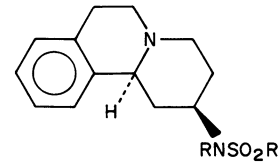
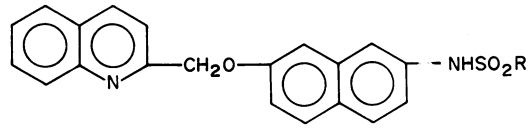


(13)

α_2-adrenoceptors. *N*-(Arylmethoxy)phenyl or -naphthylsulfonamides, e.g. **14**, have been found as orally active leukotriene D_4 antagonists. The most potent derivative was **14**, R = CF_3[53].



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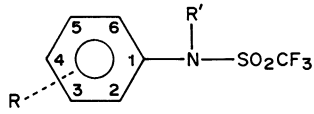
F. *N*-Phenyltrifluoromethanesulfonamides (15)

These are potent herbicides[54,55]. Among about 180 prepared analogs (R = 4-Me, R' = H), the compound has been found to be very active and was introduced commercially under the names of Destun or Perfluidone. This compound stimulates to some extent some hepatic drug metabolizing enzymes. The above effect varies with different animal species[56,57]. Related compounds (**15**, R = 3-PhCO–, R' = –COOEt) possess antipyretic and antiinflammatory activity[58].



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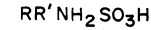

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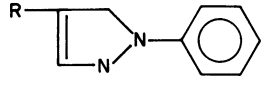
G. Aminomethanesulfonic Acid

The parent compound, **16** (R,R' = H), has a limited physiological activity, especially when compared to its nearest homolog—taurine. It exerts some inhibitory effects, e.g. on the growth of the cyanobacterium Synechococcus 6301[59], and on the photorespiration in rice[60]. A series of N-substituted derivatives of **16** was tested for antimitotic properties in vitro. The most active agent was **16** (R = 3-ClC_6H_4–, R' = NO_2)[61]. One of the well-known derivatives of **16** is dipyrone (**17**, R = $-CH_2SO_3H$)[62], which is the methanesulfonyl derivatives of aminopyrine (**17**, R = H). Although it has been a very popular



(17)

analgetic or antipyretic[63], now it is used for veterinarian rather than for human treatment because of its side effects, e.g. agranulocytosis. The metabolism of **17** and methods for the determination of the metabolites in serum, urine and saliva by TLC[64,65] and HPLC[66] have been published.

IV. 2-AMINOETHANESULFONIC ACID AND DERIVATIVES

The parent compound taurine **18** (TA) was reported for the first time by Tiedemann and Gmelin in 1827[67]. TA melts at 320 °C (dec.), pk_a −0.3, pk_b −9.06[68].

A. Biosynthesis and Metabolism (Scheme 2)

The formation of TA from its precursors was discussed by Eldjarn and coworkers[69] and later by Jacobsen and Smith[1].

(a) L-Cysteinesulfinic acid (3-sulfino-L-alanine, CSA) **20** is formed from cysteine (Cys) **19** by the action of Cys dioxygenase[1,70,71], and is decarboxylated to hypotaurine (HT) **21** by CSA decarboxylase[72–74]. HT, the main precursor of TA, has been obtained by several other pathways listed below.

(b) Conversion of Cys to pantetheine, hydrolysis to cysteamine **22**[75] and its oxidation to HT[76] by the action of cysteamine dioxygenase[77]: It has been found that in most animal tissues TA is produced preferentially from Cys bound to phosphopantothenate rather than from the free amino acid (through CSA) when both forms are present at equal concentrations[78]. Liver homogenate converted 50% of **22** to HT and TA during four hours of incubation[79].

(c) An additional biosynthetic possibility is the oxidation of cystine **23** to cystine disulfoxide **24** (or the isomeric thiolsulfonate[80]), decarboxylation to the corresponding cystamine derivative **25** and conversion to HT and TA[1,81]. This transformation has been observed after introvenous injection of cystamine into mice rats[82].

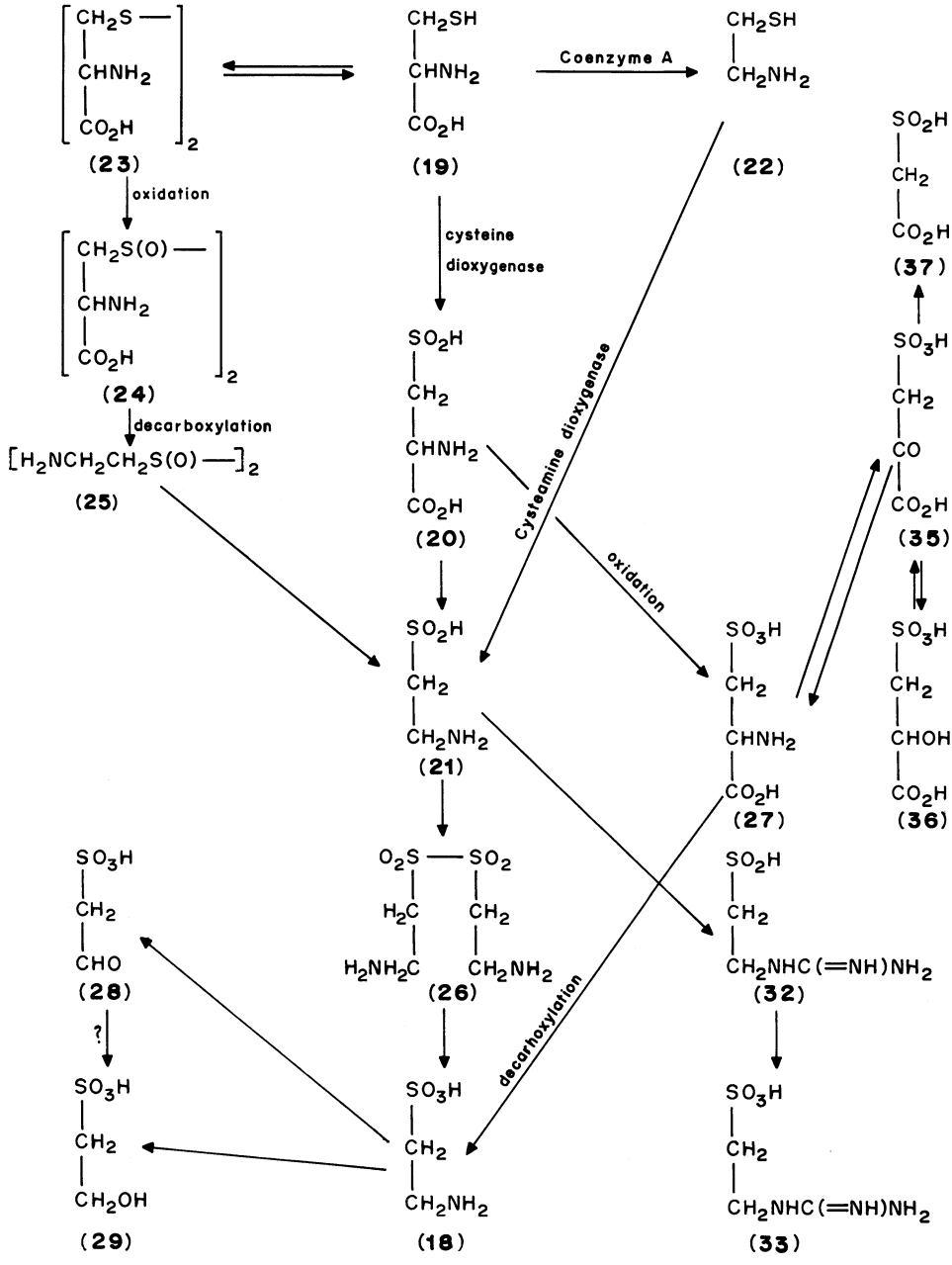
HT is oxidized to TA, probably with the help of HT oxidase[70]. Recently Fellman presented evidence that HT is first oxidized by a hydroxyl radical to bis-aminoethyl-α-disulfone **26**. The hydroxyl radical is generated by a liver microsomal NADPH oxidase. **26** has been prepared from HT in the presence of chemically or enzymatically generated radicals and was characterized by NMR and mass spectrometry. It has been found in male sexual tissue which contains HT and TA in respectively high concentrations[83]. A relatively minor pathway consists of oxidation of CSA to cysteic acid (cysteinesulfonic acid, CA **27**) and its decarboxylation to TA under the influence of CSA decarboxylase[70].

TA is converted to sulfoacetaldehyde **28** by the action of TA dehydrogenase[84], and to isethionic acid **29** by certain bacteria[85]. Bacteria isolated from sewage mud are able to grow on TA as a sole carbon and nitrogen source. They convert TA to **28** with consequent liberation of sulfite and production of acetate[86].

The transport and metabolism of TA in the brain was reviewed by Kontro[87]. TA is excreted in urine and bile. The rate of excretion depends on the availability of TA[88]. In order to establish the adaptation of the transport of TA in the renal proximal tubule to the level changes, the problem was studied by employing isolated renal brush border membrane vesicles[89].

B. Physiological Activity

The physiological activity of TA and its involvement in biological functions of living organisms is so diversified that it is very hard to describe it in detail within the scope of this review. Wright and coworkers[90], Huxtable[91] and Chesney[92] recently summarized these functions that encompass almost all bodily systems.



SCHEME 2. Biosyntheses and transformations of taurine and congeners[1,69–86,148,150]

Nervous System. TA is present in relatively high concentrations in the central nervous system (CNS) and brain[1,91]. The concentration decreases after birth[93,94] and the possible factors involved in perinatal decline have been investigated using primary culture of cortical neurons[95]. They suggest that it may result from the decreased Cys uptake along with the development of neurons. In mice brain the maximum concentration level of TA was reached at one week of age[96]. The uptake of TA and comparison with other neuroactive amino acids has been studied extensively. A model for the binding and release of TA in the rat hypothalamus has been proposed[97]. TA displaced the low and high affinity of γ-aminobutyric acid (GABA) binding in rat brain membranes through possible interaction with GABA recognition site[98], and facilitated efflux of GABA and TA from mouse cerebral cortex slices[99]. The possible role of TA as an inhibitory transmitter or a CNS modulator and the existence of a separate taurinergic system have been suggested[100–102]. In mice and rats the intracerebroventricular administration of TA decreased the release of dopamine into the synaptic cleft, and increased the synthesis by striatal neurons and its level in limbic forebrain. The effects were greater than those elicited by GABA[103]. TA acts as an antiepileptic against experimental seizures in various animals[104]. Its utility in humans has been discussed[105,106].

Inotropic effects. The concentration of TA in muscles, and particularly in heart, is high ($30\,mM\,kg^{-1}$)[92]. Inotropy is positive at low, and negative at high, calcium concentrations[107]. TA exerts antiarrhythmic action[108] and it has been found to prevent myocardial damage induced by isoproterenol or by adriamycin[109]. Drug-induced depletion of TA potentiates myocardial ischemic injury[110].

Muscular activity of TA was briefly summed up by Iwata and colleagues[111]. They suggest that there are two regulatory systems of TA transport in skeletal muscles after their stimulation.

Reproductive system. The presence of TA (and HT) improves the quality of fertilization of bovine follicular oocytes in vitro[112] and this may be related to their ability to sustain sperm mobility and fertility[113]. However, TA is less effective than HT in maintaining hamster sperm mobility in vitro[114]. TA concentration in sperm (also of HT and GABA) decreases after castration and is restored by administration of testosterone propionate[115]. TA and HT are present in mammalian oviductal fluids, and their high concentration (0.5–2 mM) might protect sperm against the harmful effect of high K^+ concentration[116]. Let us add that TA is an osmotically active cell and organ component[91,117]. This may be important for osmotic adaptation of cells like spermatozoa.

Nutritional importance. TA deficient diet or addition of TA uptake blockers, e.g. guanidoethanesulfonic acid **33**, affects the visual system and causes retinal degeneration and growth depression in cats and monkeys[118–122]. The TA content in breast milk is considerably higher than that found in cow milk or several infant formulas[123]. Electroretinograms of children fed parenterally for a long period of time were abnormal and became normal after addition of TA[124].

Additional effects of taurine. TA induces hypothermia in mammals[100,125,126]. It is a hypoglycemic agent and acts as an insulin agonist[127]. TA has been found to prevent toxic symptoms in rats after KCN injection[107]. TA is the most abundant amino acid in lymphocytes and has a protective effect against cell damage produced by a model of lipid peroxidase[128], as a protector of hamster lung epithelium from acute NO-induced alterations and perhaps from other oxidant gases[129], and against ionizing radiation (weak)[130]. TA could induce nonspecifically antibody production in cultured DOA/2 mouse spleen cells[131]. Antitaurine antibodies can be used to demonstrate the presence of TA in various organs and tissues[95,132].

C. N-Substituted 2-Aminoethanesulfonic Acids

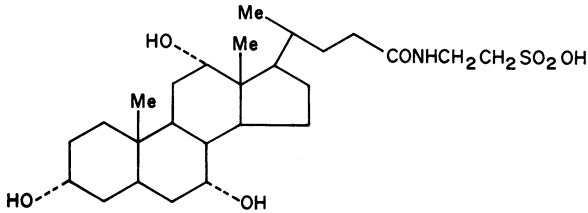
$$RHNCH_2CH_2SO_3H$$

(30)

The *N*-methyl derivative (**30**, R = Me) prevented toxic symptoms in rats given KCN, but the effect was weaker than with TA[107]. TA dipeptides such as L-glutamyl [R = $HOOC(CH_2)_2CH(NH_2)CO$—] are endogenous substances in the brain[133,134]. Their effect on the inhibition of binding, uptake and efflux of labeled glutamate, kainate, GABA and TA in brain synaptosomal preparations was investigated[135]. The results showed that they affect these functions to some extent but the question about their involvement in neurotransmission has not been resolved. L-glutamyl-TA has been bound to slow down the metamorphosis in frogs[136].

D. Bile Acid Conjugates with Taurine

Taurocholic acid **31** is a component of bile and plays an important role in digestion of fats. It is abundant in bile of carnivorous animals like cat, dog and rat, while herbivorous



(31)

animals, like rabbit, produce glycocholate—a conjugate of cholic acid with glycine. TA-conjugated bile acids prevent hypercholesteremia and decrease lithogenicity[106,119]. It has been established that TA-conjugation of bile acids protects human cells in culture[137].

E. 2-Guanidoethanesulfonic Acid (GES)

This acid or taurocyanamine **33**, mp 228–230 °C, was prepared by guanidylation of TA with isomethylthiourea $NH{=}C(NH_2)SMe$ or by oxidation of 2-guanidoethanesulfinic acid **32**[138,139] (see Scheme 2). 91% of GES was excreted in urine unchanged during 24 h after administration to mice; no TA, CA **27** or ISE **29** were detected[140]. Wild type strain of Pseudomonas contains in enzyme that liberates urea from GES and utilizes it as nitrogen source[141]. GES is an inhibitor of TA uptake and causes TA deficiency as stated above. Pretreatment with 1% drinking solution of GES led to significant brain-cell dehydration in cats[142]. Intravetricular administration of GES and homologs produced hypothermia in mice[143].

V. HOMOLOGS OF TAURINE AND DERIVATIVES

The most important of these compounds is 3-aminopropanesulfonic acid or homotaurine (**34**, *n* = 3, HTA), mp 290–292 °C[144].

$$H_2N(CH_2)_nSO_3H$$

(34)

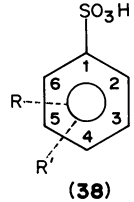
HTA is structurally related to GABA. It inhibits strongly tritium-labeled GABA binding to synaptic membranes[136] and mimics some of its actions like contractions of

guinea pig duodenum[145] or depressant effects on chicken[146]. Like TA it increased the synthesis of dopamine in brain[103] but did not maintain sperm mobility in vitro[114]. HTA was a strong inhibitor of TA uptake by cardiac sarcolemmal membranes[107]. It is more efficient than TA in producing hypothermia[100]. Several of its homologs were also checked and found even more active (**34**, $n = 4$ or 5)[143].

Isethionic acid (ISA) or 2-hydroxyethanesulfonic acid **29** (Scheme 2) is found in mammalian tissues in minute quantities. It has been found in a relatively high concentration (0.2 mmol g^{-1}) in squid axoplasm[147]. Isethionic acid is probably obtained from TA by dehydrogenation through the intermediate sulfoacetaldehyde **28**. The appropriate enzyme—TA dehydrogenase—is produced by enteric bacteria[84,85,148]. It is found in minute quantities in mammalian tissues[105]. Its physiological role is unclear, but it is of interest that it stimulates TA uptake in cardiac preparations[107].

L-Cysteic acid or 3-sulfo-L-alanine **27** (CA), mp 264–266 °C[149], is one of precursors of TA in organisms. CA is the product of microbial metabolism and is probably obtained from L-cysteinesulfinic acid **20**[70,83,148]. It is present in plasma, urine and tissues in concentrations comparable to those of CSA[150]. Apart from decarboxylation to TA (Scheme 2) CA undergoes deamination to β-sulfopyruvic acid **35**, which in turn could be reduced to β-sulfolactic acid **36**. These three acids are reversibly interconverted to vivo. β-Sulfopyruvic acid could be decarboxylated to sulfoacetic acid **37**[150]. The study of binding of CA to crude synaptic membranes from rat cerebral cortex showed two different systems: one of the systems is Na^+ dependent, the other is not. Injection of CA into rat brain produced EEG seizures[151]. The content of CA in primary cultured neurons, obtained from fetus and neonate, decreased during the first seven days after the inoculation of cells. The uptake of cysteine by these cells was competitively inhibited by CA[95]. The inotropic effect of CA on isolated guinea-pig ventricular strips in low-calcium medium was studied and compared with that of TA and an additional structural analog, orthanilic acid (**38**, R = 2-NH_2). The effect was positive, although the mechanisms of action for **27** and **38** could be different[152].

The homolog of CA—homocysteinesulfonic acid, **39**, is of interest as a glutamate and aspartate analog. It has been prepared by oxidation of homocystine with bromine, mp 261–263 °C[153]. It is a potent central excitatory compound[154], and elicited excitation in cerebellar Purkinje neurons. This action was compared with that of NMDA[155]. **39** has



(38)

$HO_3S(CH_2)_2CH(NH_2)COOH$

(39)

been found to be present endogenously in rat brain extracts[156]. Its role as a putative neurotransmitter has been suggested[157]. The neurotoxicity of both stereoisomeric forms was studied in dissociated cell cultures, prepared from fetal mouse neurocortex. The L isomer was more active with ED_{50} of approximately 40 μM[158].

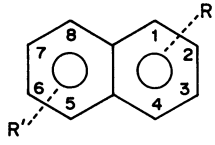
VI. AROMATIC SULFONIC ACIDS AND THEIR DERIVATIVES

A. Acids

Benzene and naphthalenesulfonates are found in various industrial sewages. The sulfonates could be metabolized to phenolic substances by enzymes isolated from sewage

bacterias. Thus unsubstituted benzene sulfonic acid (**38**, R, R′ = H) could be converted to catechol with the liberation of sulfite SO_3^{2-}[86]. Substituted acids (**38**, R = 3-NO_2, 3-NH_2 or 4-NH_2) may serve as the sole source of carbon and energy in aerobic, carbon-limited cultures of bacteria (nonidentified) taken from an industrial sewage plant. The sulfur from the sulfonate group was recovered quantitatively as SO_4^{2-} at the end of the growth[159].

Naphthalenesulfonic acids (**40**, R = 1- or 2-SO_3H; R′ = 6-SO_3H) could be utilized as a



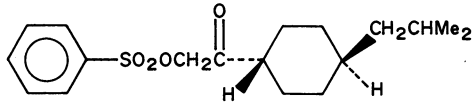
(40)

growth substrate by a Moraxella strain from industrial sewage. Regioselective 1,2-dioxygenation resulted in desulfonation and catabolism to 5-sulfosalicylic acid (3-carboxy-4-hydroxybenzenesulfonic acid, **38**, R = 3-COOH, R′ = 4-OH), which also could serve as a carbon source. Cells grown in the presence of sulfosalicylic acid exhibited high gentisate 1,2-dioxygenase ability[160]. Other sulfonic acids (**40**, R = 1- or 2-SO_3H, R′ = H; R = 1-SO_3H, R′ = 3- or 5-NH_2) were converted to the corresponding hydroxy derivatives by the action of Pseudomonas and Arthrobacter species. Experiments with O^{18} showed that the OH group was derived from molecular oxygen[161].

Substituted acids [e.g. **40**, R = 1-PhNH—, R′ = 8-SO_3H; R = 2-(4′-MeC_6H_4NH—), R′ = 6-SO_3H; R = 1-$NH(CH_2)_2NHCOCH_2I$, R′ = 5-SO_3H] have been used as fluorescence probes of biological structures and it was suggested that they will allow study of processes occurring in biological macromolecules during a few milliseconds[162]. The above-mentioned sulfosalicylic acid is a clinical test reagent, used mainly for detection of protein in urine[163]. Bromsulfalein or disodium 3,3′-(tetrabromophthalidylidene)bis-[6-hydroxybenzenesulfonate] is used for determination of the functional capacity of liver[164]. Sulfanilic acid (4-aminobenzenesulfonic acid, **38**, R = 4-NH_2), in addition to its industrial uses, is an analytical and antibacterial agent[165].

Several substituted benzenesulfonates have been reported to possess pharmacological properties. Doxium (2,5-dihydroxybenzenesulfonate or dobesylate, **38**, R = 2-OH, R′ = 5-OH), is a vasotropic agent, that increased the contractile force in normally working and tetrodoxin-arrested preparations of dog cardiac Purkinje fibers and the adjacent ventricular tissue[166,167].

2-(*trans*-4-Isobutylcyclohexyl)-2-oxoethyl benzenesulfonate **41** was developed as a lipase inhibitor and hypolipidemic agent[168]. It is metabolized in the body to the free

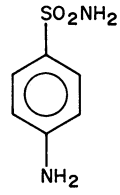


(41)

benzenesulfonic acid[169]. Studies of the binding of 4-substituted benzenesulfonic acids (and sulfonamides) established two binding sites on dihydrofolate reductase[170].

B. Aromatic Sulfonamides

Since their discovery in 1935[171,172] sulfonamides or derivatives of 4-aminobenzenesulfonamide (sulfanilamide) **42** are used extensively in the treatment and prevention of



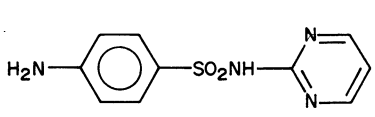
(42)

bacterial infections. Thousands of these agents were prepared[173], and many were introduced into human and veterinarian medicine. It suffices to mention that the last (11th) edition of the Merck Index lists more than fifty sulfonamides used in medical and veterinarian practice[174].

In addition to their antibacterial activity, it has been found that they also act as diuretics, antihypertensives, hypoglycemics and even antipsychotics. Their clinical use is described in well known medical and pharmacological books[6,7].

1. Antibacterial agents

Sulfonamides are active against gram-positive and gram-negative bacteria. They are bacteriostatic and exert their action by inhibiting the utilization of 4-aminobenzoic acid, necessary for the synthesis of folic acid (pteroylglutamic acid)[173,175]. Substitution at the sulfonamide nitrogen yielded derivatives with different properties. These are sparingly soluble in water (compared to sulfanilamide, 7.5 g l^{-1} at 25 °C[176]) and mixtures of several sulfonamides are often used in order to achieve higher dosage. The best known active derivatives are sulfadiazine (4-amino-*N*-2-pyrimidinylbenzenesulfonamide) **43**[177], sulfamethoxazole [4-amino-*N*-(5-methyl-3-isoxazoyl)benzenesulfonamide, **44**][178], sulfisoxazole [4-amino-*N*-(3,4-dimethyl-5-isoxazoyl)benzenesulfonamide, **45**][164] and sulfasalazine **46** (2-hydroxy-5-{{4-[2-pyridinylamino)sulfonyl]phenyl}azo} benzoic acid)[179,180].



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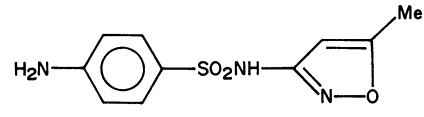

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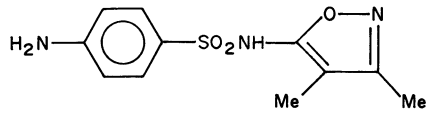
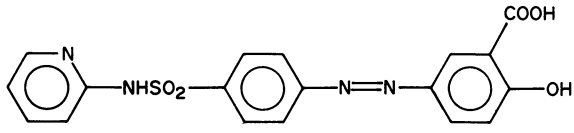


(45)

The activity and use of sulfonamides has been potentiated by addition of synergists that also inhibit bacterial enzymatic synthesis. The best known is trimethoprim {5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine} **47**[181,182] that binds dihydrofolic acid reductase. **43** and **47** are listed as antimalarial drugs[183].



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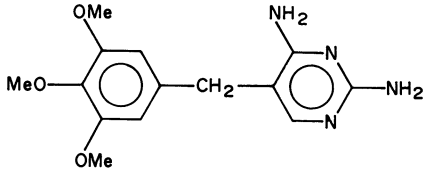
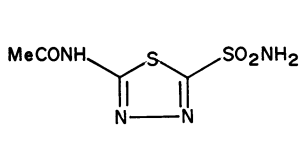


(47)

During the prolonged use of sulfonamides it has been found that microorganisms developed resistance as a result of mutations that led to increased ability to inactivate the drugs, and particularly to increased synthesis of 4-aminobenzoic acid, essential for their growth. The clinical uses, indications and contraindications are discussed in two recent chapters[173,175].

2. *Diuretic agents*

It has been found that some sulfonamides act as carbonic anhydrase (an enzyme that catalyzes the reaction between CO_2 and water with the formation of H^+ and HCO_3^-). The first compound prepared was acetazolamide (2-acetamido-1,3,4-thiadiazole-5-sulfonamide) **48**, which increases the urine volume after administration[184,185]. Other agents like hydrochlorothiazide (6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiazine-7-sulfonamide-1,1-dioxide) **49** were developed later and are more effective. They inhibit



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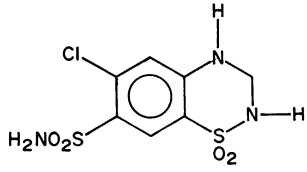

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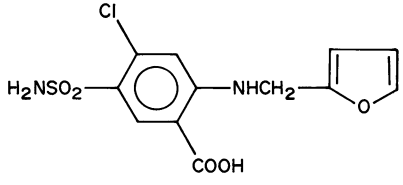
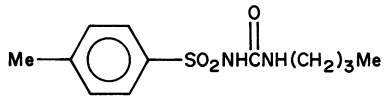


(50)

reabsorption of sodium chloride in addition to the inhibition of carbonic anhydrase[186]. Substituted 3-carboxybenzenesulfonamides also inhibit reabsorption of sodium chloride in the loop of Henle and have a powerful diuretic effect. The best known drug in this series is furosemide (4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid) **50**[184,185]. Recently, the preparation of a substituted thiophenesulfonamide has been described. It acts in vitro as a potent carbonic anhydrase II inhibitor[187].

3. *Sulfonylureas*

These compounds structurally related to sulfonamides are oral hypoglycemic drugs and used for treatment of non-insulin-dependent diabetes. The best known derivatives are tolbutamide [(1-*n*-butyl-3-*p*-tolylsulfonyl)urea, **51**] and the more potent glyburide {*N*-}4-[*β*-(2-methoxy-5-chlorobenzamido)ethyl]benzosulfonyl}-*N'*-cyclohexylurea, **52**[188,189].



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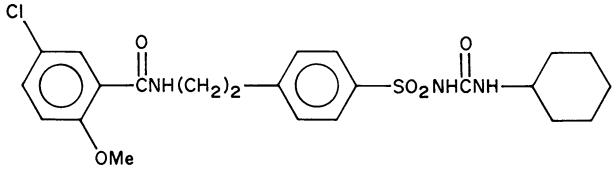
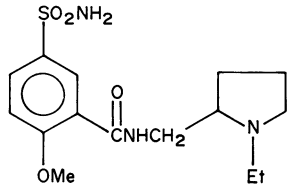


(52)

4. *Other pharmacologically active sulfonamides*

Sulfadiazine **43** is listed as an antimalarial[183] and sulpiride (**53**) as an antipsychotic[190].

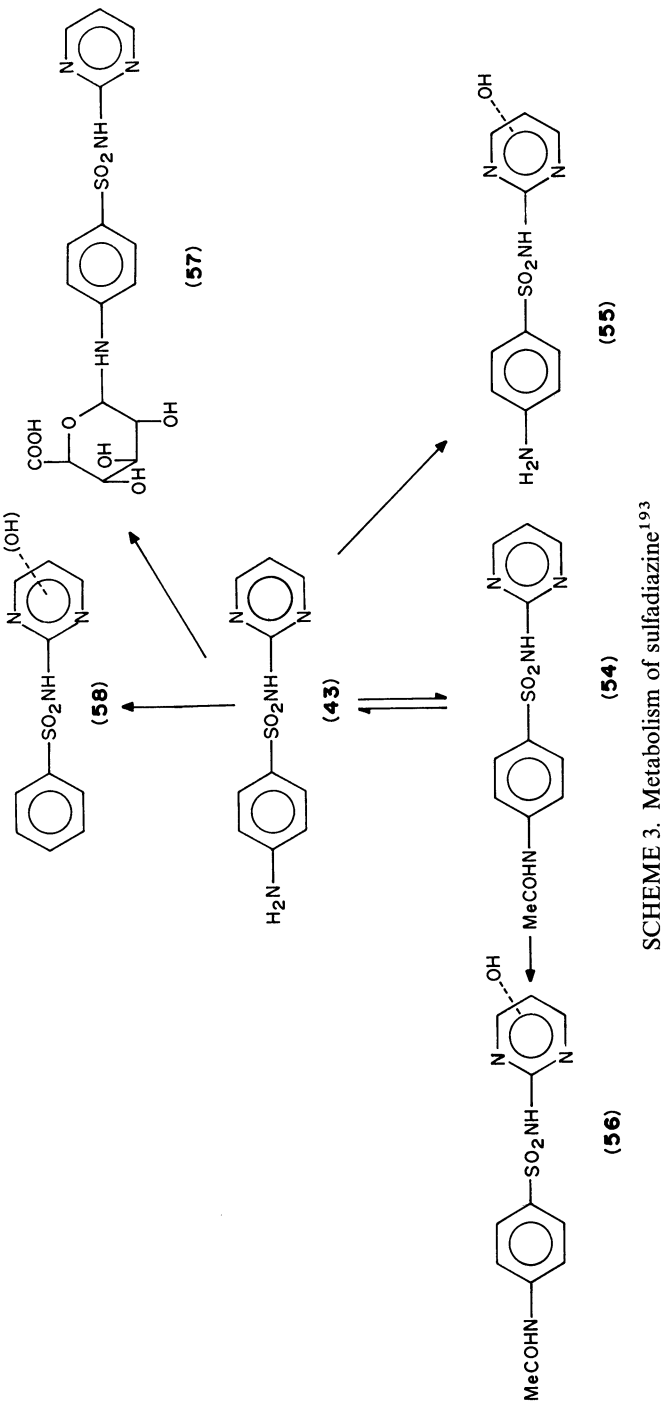


(53)

C. Metabolism of Sulfonamides

The importance of sulfonamides in treating various diseases brought about an extensive investigation of their fate in the body. In recent years these efforts were summarized in two issues of *Antibiotics and Chemotherapy*. They deal with the metabolism[191] and pharmacokinetics[192] of these compounds.

Possible metabolic transformations are given for sulfadiazine **43** in Scheme 3[193]. They include N_4-acetylation to **54**, hydroxylation of the heterocyclic pyrimidine ring at the 4- or 5-position to yield **55**, depending on the species investigated, combination of



SCHEME 3. Metabolism of sulfadiazine[193]

both reactions to give **56**, glucuronidation to **57** and deamination to **58** (with possible hydroxylation of the pyrimidine ring).

Other sulfamides, depending on their structures, could be hydroxylated at the aromatic ring, O-dealkylated in cases of ethers, e.g. **53**, N_4-hydroxylated with subsequent glucuronidation, glycolated at N_4 to ($HOCH_2COHN\text{-}C_6H_4SO_2N=$), reported, e.g., for sulfamethoxazole **44**. The metabolic pathways and rates of disposition are dependent on the structure of the drug and species involved. The products of transformation have been identified and determined by synthetic and physicochemical methods, such as colorimetry, TLC, HPLC, NMR and mass spectrometry[191–193].

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CHAPTER **19**

Sultones and sultams

A. J. BUGLASS

Anglia Higher Education College, Cambridge, UK

and

J. G. TILLETT

University of Essex, Colchester, UK

The chemistry of sulphonic acids, esters and their derivatives
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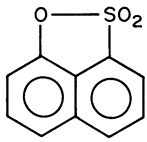
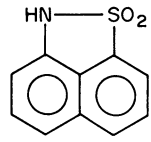
I. INTRODUCTION

Sultones are heterocyclic compounds containing the —O—SO_2— group and are internal esters of the corresponding hydroxysulphonic acids. The term 'sultone' was introduced by Erdmann to describe one of the simplest aromatic sultones—1,8-naphthosultone (**1**)[1]. As


(**1**)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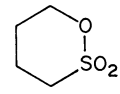
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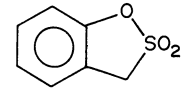

(**4**)

internal esters, sultones are the sulphur analogues of lactones. The term 'sultam' was similarly introduced for the corresponding sulphur analogue of lactams—cyclic derivatives of aminosulphonic acids, e.g. 1,8-naphthosultam (**2**)[2,3]. Various systems of nomenclature are in use in *Chemical Abstracts* and in the literature[4–6]. The aliphatic sultone **3** can be named as 4-hydroxy-1-butanesulphonic acid sultone, butane δ-sultone or, more precisely, butane-1,4-sultone in which the numbers correspond to carbon atoms bearing sulphur and oxygen, respectively; the latter system can easily be extended to unsaturated systems.

Bicyclic systems in which the sultone ring is fused to an aromatic ring have been named from the aromatic system as are aromatic sultones. Thus **1** and **4** are commonly termed 1-hydroxynaphthalene-8-sulphonic acid sultone and *o*-hydroxy-α-toluenesulphonic acid sultone, respectively.

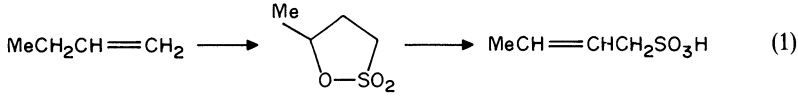
In recent years there has been a slow shift to the use of systematic IUPAC nomenclature for heterocycles in which the compounds **1** and **4** are termed naphth [1,8-*cd*]-1,2-oxathiole-2,2-dioxide and 3*H*-1,2-benzoxathiole-2,2-dioxide, respectively. In this chapter we have preferred to use where possible the simplest system.

II. SYNTHESIS OF SULTONES

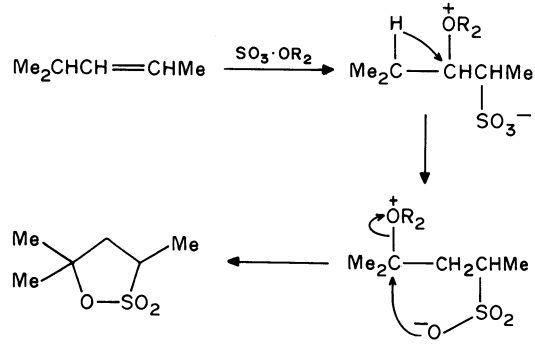
A. Saturated Aliphatic Sultones

1. Formation via concurrent C—O and S—C bond formation

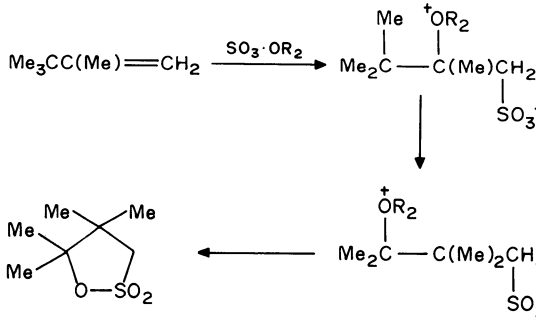
Sulphonation of alkenes has provided much of the impetus for the preparation and study of the sultones since β- and γ-sultones in particular have been found to be precursors in this route to alkenesulphonic acids. Equation 1 shows the formation of 5-methyl-1,2-oxathiolane-2,2-dioxide (butane-1,3-sultone) (**5**) and but-2-enesulphonic acid via the sulphonation of but-1-ene, although it will be seen later that the major product depends to a large degree on experimental conditions. Preparation of sultones via alkene sulphonation has been extensively covered in a recent review by Roberts and Williams[7] and in earlier reviews by Breslow and Skolnik[8] and Mustafa[9]. There is no doubt that a major reason for the considerable activity in this field is due to the potential of sultones as surfactants[10] or as precursors of surfactants[11] or anti-static agents[12].


(**5**) (1)

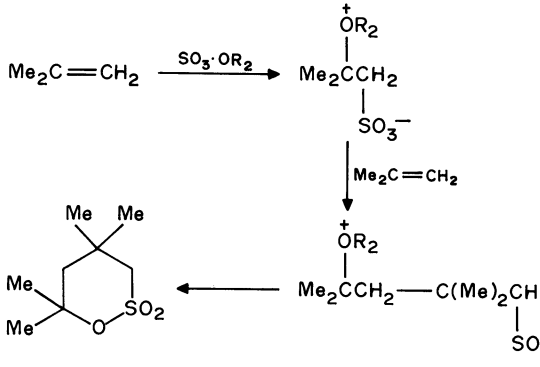
Investigations into the mechanism of alkene sulphonation and formation of sultones were pioneered by Bordwell and his coworkers in the 1940s and 1950s[13–24]. Using a sulphur trioxide–dioxane complex as the sulphonating agent, Bordwell's group were able to prepare a large number of γ- and δ-sultones. The initial formation of a dioxane-complexed β-carbenium sulphonate (or 'β-zwitterion') and its subsequent rearrangement or dimerization to yield typical sultones is shown[21] in equations 2–4. The driving force for the rearrangements and dimerizations observed can be interpreted as being the resultant formation of more stable carbocation centres. In this way secondary carbenium ions are converted to tertiary carbenium ions via 1,2-hydride shifts (equation 2). Similarly tertiary



(2)



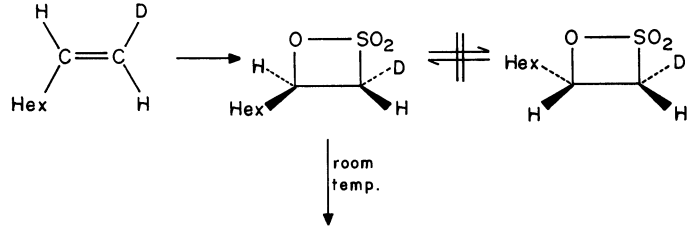
(3)



(4)

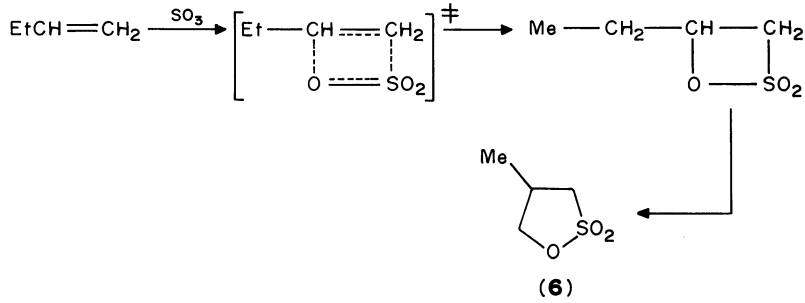
carbenium ions are converted to tertiary ions where the new cationic site is more remote from the highly electron-withdrawing and powerfully destabilizing sulphonate group. This occurs via a 1,2-methide shift as shown in equation 3. Dimerization achieves the same goal where 1,2-methide shifts are not feasible (equation 4).

Although alkene sulphonation is an established route to γ- and δ-sultones, there have been a few cases where β-sultones have been isolated[16]. Although the β-sultones are generally unstable and require special conditions for longevity (especially low temperatures), fluorinated β-sultones are relatively stable and are commonly prepared by the alkene sulphonation route (see Section II.D). The isolation of β-sultones and their detection in alkene sulphonation mixtures by NMR[25–27] has led several workers to question the mechanisms proposed by earlier investigators—particularly the involvement of the initial 'β-zwitterion' (see equations 2–4). These observations, along with the fact that there is a small reactivity spectrum for related alkenes towards sulphonation reagents, has led both Roberts'[25,28] and Cerfontain's groups[26,27] to propose that formation of β-sultones occurs via thermally allowed concerted (π^2s + π^2s) cyclo-addition mechanism for the first step of alkene sulphonation (equation 5). The observed stereoselective formation



(5)

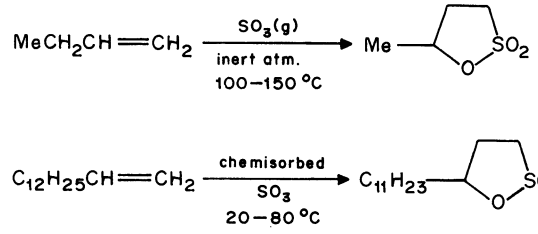
of β-sultones provides particularly strong evidence for this mechanism. Internal alkenes seem to behave in a similar manner to terminal alkenes, except that in the former case, the β-sultones are rather more stable. In the light of these recent findings, the formation of a typical γ-sultone, such as **6**, can be written as proceeding via an initial β-sultone, as shown in equation 6.



(6)

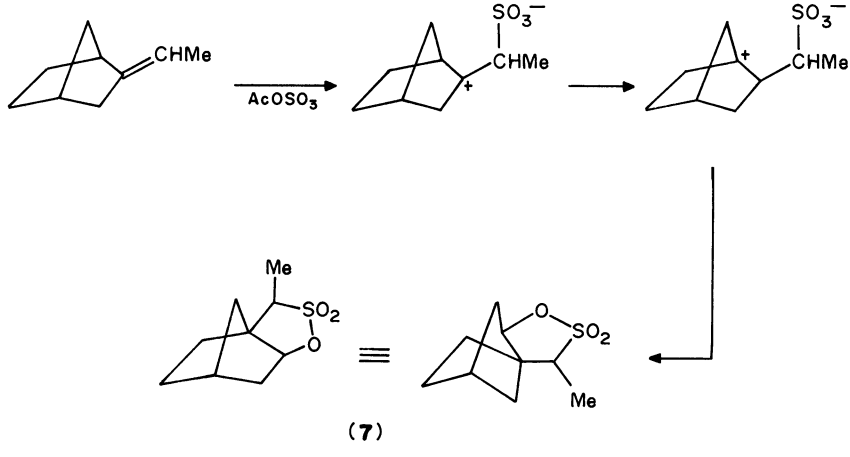
(6)

A variety of sulphonation agents has been used in the preparation of sultones from alkenes. These include liquid-phase sulphur trioxide, Lewis base-complexed sulphur trioxide such as SO_3-dioxane[29] and SO_3-pyridine[25], gaseous sulphur trioxide[30] and chemisorbed sulphur trioxide[31]. Examples are shown in equation 7. More recently the reagent acetyl sulphate has been used in the sulphonation of ethylidenenorbornane to produce the γ-sultone **7**[32]. The reaction pathway proposed for the formation of **7**

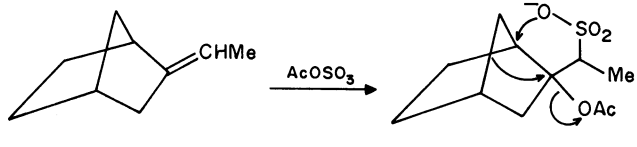


(7)

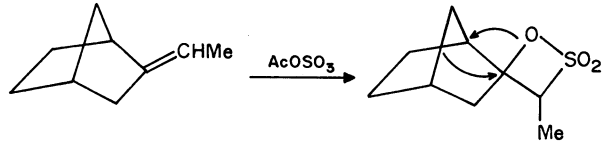
(equation 8) seems unlikely in view of the strained carbenium ion involved. Roberts and Williams[7] have suggested a more concerted mechanism involving acetylsulphonation of the double bond alleviating the need for the involvement of a strained carbenium ion (equation 9). Alternatively formation of **7** may occur via initial β-sultone formation (equation 10), although there is at present no evidence for participation of β-sultones in acetylsulphonations.



(8)



(9)



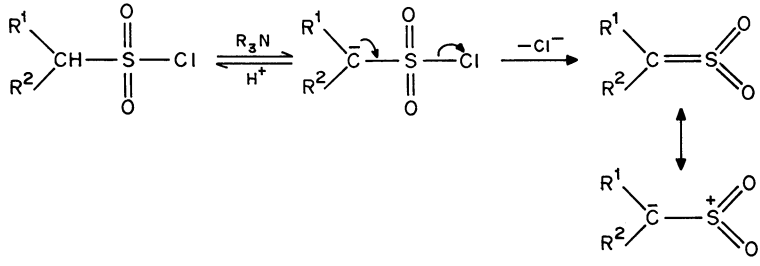
(10)

The yields of γ- and δ-sultones obtained from the sulphonation of alkenes depend largely on the nature of the sulphonation reagent and reaction temperature. The sulphur trioxide–Lewis base complexes effect less charring than uncomplexed sulphur trioxide, but the lower reactivity of the former tends to lead to lower yields of sultones under the

same conditions used with the latter reagent. However, the recent work of Robbins and Broaddus[33] shows that uncomplexed sulphur trioxide at low temperatures (−78 °C) and with low concentrations of reactants can lead to high yields of γ-sultones.

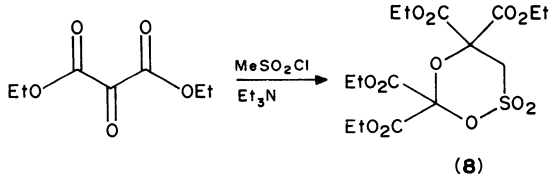
2. *Formation via concurrent C—C and S—O bond formation*

Sulphenes, generated *in situ* from alkanesulphonyl halides and tertiary amines (equation 11), were the subject of much attention during the 1960s[34], mainly concerning their addition to C=C bonds. Surprisingly, the addition of these ylids to carbonyl bonds



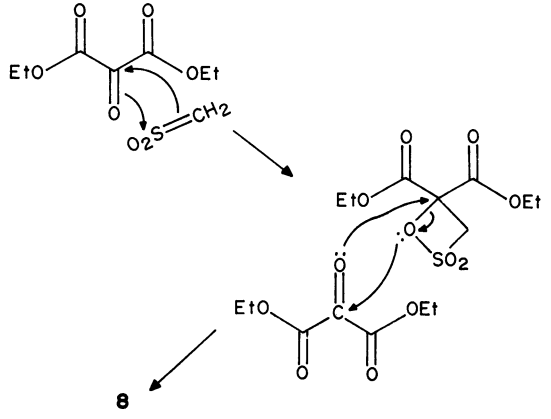
(11)

to form (initially, at least) β-sultones has received relatively little attention until the recent reports of Hanefeld and co-workers[35–37]—but see also Sections II.B.2 and II.D.2. A possible reason for this is that, apart from polyhalogenated derivatives (Section II.D), the initial β-sultones are rapidly transformed to other products, including δ-sultones. This aspect is typified by the work of Hanefeld's group, as illustrated by addition of sulphenes to various tricarbonyl compounds such as diethyl mesoxalate to give the δ-sultone **8** (equation 12).[35] A possible mechanism for the formation of **8** is shown in equation 13.



(8)

(12)

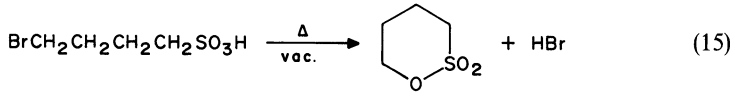


(13)

3. Cyclization via C—O bond formation

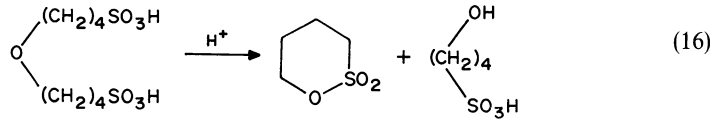
a. Thermal cyclization of functionalized sulphonic acids and their salts or derivatives. Some of the earliest routes to γ- and δ-sultones involve thermal cyclization of halogeno or hydroxyalkanesulphonic acids[38–40] as illustrated by equations 14 and 15.

(14)

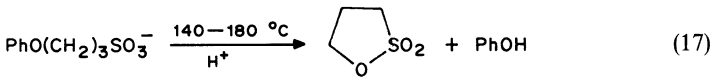


(15)

These reactions, essentially thermal cycloeliminations, provide reasonably facile syntheses of simple aliphatic sultones and were once the subject of much activity in the patent literature[7]. Although at least one seven-membered sultone has been prepared by this method[41], γ- and δ-sultones are formed most easily. Similar syntheses have been achieved by heating aryloxyalkanesulphonic acids[42] or bis (butane-4-sulphonic acid) ether in the presence of acid (equation 16)[43]. More recently the thermal cyclization of potassium 3-phenoxypropanesulphonate has afforded the γ-sultone **9** in good yield (equation 17)[44].



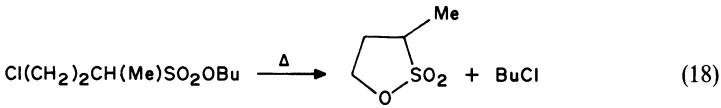
(16)



(17)

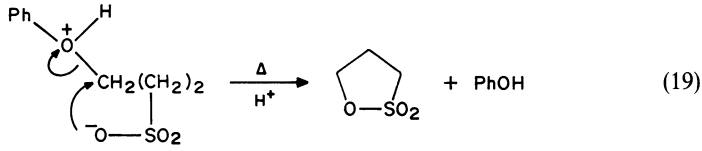
(9)

Similarly 3-methyl-1,2-oxathiole-2,2-dioxide[45] and some δ-sultones have been prepared by heating halogenoalkanesulphonate esters (equation 18). All of these variations most probably rely on the ability of reasonably conformationally-flexible molecules to undergo internal displacements of the kind shown in equation 19, although there has been very



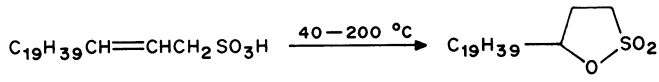
(18)

(10)



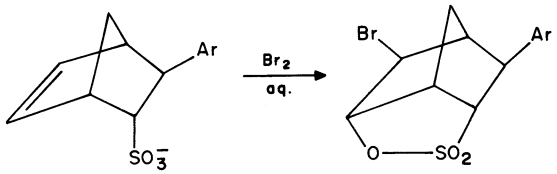
(19)

little mechanistic interpretation of these reactions in the literature There are several examples in the literature of ring closure via C—O bond formation being effected by internal cycloaddition reactions (equation 20)[46].



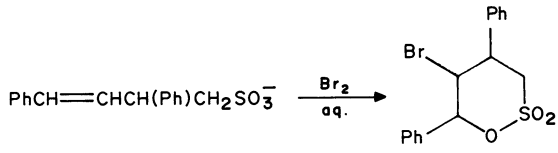
(20)

b. Reactions of alkenesulphonate salts with dihalogens ('halosultonation'). Monohalogenated γ- and δ-sultones have been prepared by the bromination or chlorination of the salts of 2- and 3-alkenesulphonic acids (equations 21 and 22)[47,48].



(21)

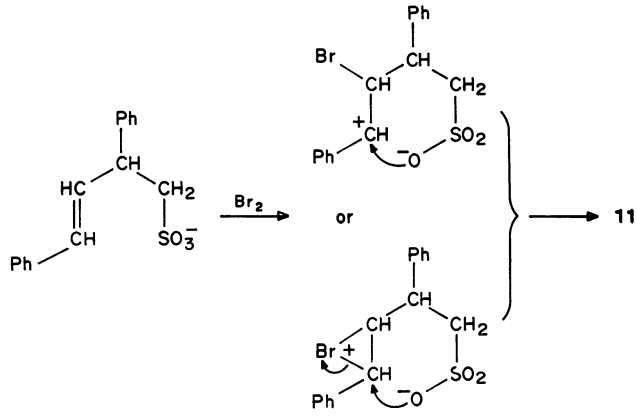
endo—trans isomer



(22)

(11)

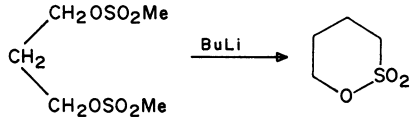
These 'halosultonation' reactions generally proceed smoothly at ambient temperature and although there is little mechanistic discussion in the literature, it seems likely that cyclization proceeds via nucleophilic attack of the sulphonate group on either an open[23] or bridged[14] carbenium ion intermediate. Equation 23 illustrates such a mechanism for the formation of 5-bromo-4,6-diphenyl-1,2-oxathiin-2,2-dioxide (**11**).



(23)

4. Cyclization via C—C bond formation

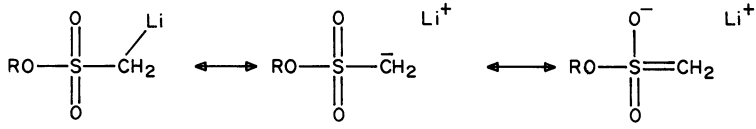
Metallation of alkanesulphonate esters of alcohols which have been functionalized at the 2- or 3-positions leads to γ- and δ-sultones often in good yield. In this way δ-sultone **12** was prepared from propane-1,3-dimethylsulphonate (equation 24) by Durst and Tin[49].



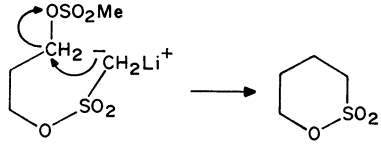
(24)

(12)

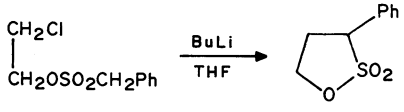
This method relies on the considerable acidity of the α-methyl hydrogen atoms and on the formation of resonance-stabilized carbanions of the type:



If there is a good leaving group at the 2- or 3-position, then ring closure, via C—C bond formation, is afforded by internal nucleophilic displacement of the kind shown in equation 25. The best leaving groups appear to be sulphonates, but halogens can also be displaced as shown by the formation of the γ-sultone **13** in equation 26. In accord with the mechanism already discussed, dimethyl sulphonate esters of unsymmetrical diols such as



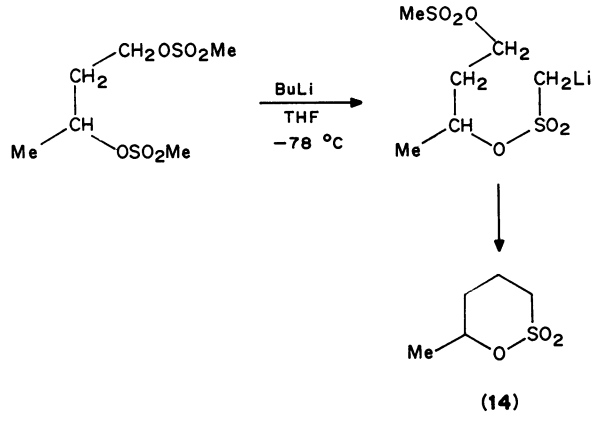
(25)



(26)

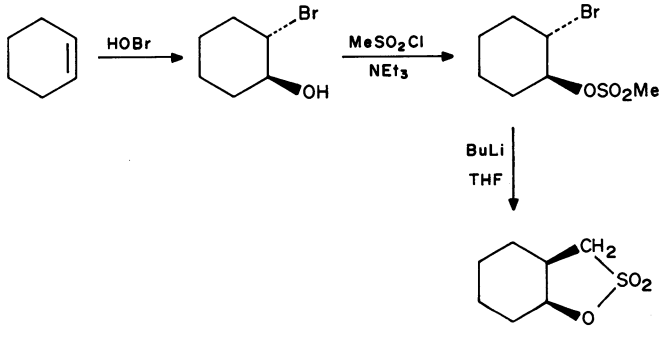
(13)

1,3-butanediol have been cyclized with preferential displacement at the primary carbon atom to give 6-methyl-1,2-oxathiin 2,2-dioxide (**14**) (equation 27)[49]. This method is especially useful in that the starting materials (1,2-diols or 1,2-halohydrins) are often readily available in stereochemically pure forms. This means that sultones with at least partially defined stereochemistries can be synthesized (equation 28)[49]. In a similar manner, a number of carbohydrate-derived sultones have been prepared by Fraser-Reid and his coworkers[50]. Their syntheses involved the deprotonation of mixed sugar disulphonate derivatives, using ethynyllithium or the dianion of ethyl acetoacetate; an example is shown in equation 29.

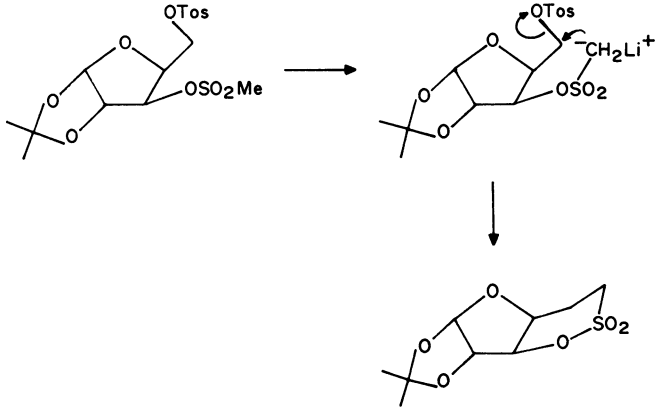

CH2OSO2Me
CH2
CH
Me
OSO2Me
BuLi
THF
−78 °C
MeSO2O
CH2
CH2
CH2Li
CH
Me
O
SO2
Me
O
SO2

(27)

(14)


HOBr
Br
OH
MeSO2Cl
NEt3
Br
OSO2Me
BuLi
THF
CH2
SO2
O

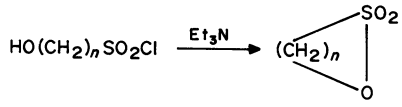
(28)


OTos
O
O
O
OSO2Me
OTos
O
CH2Li+
O
O
OSO2
O
O
SO2
O

(29)

5. Cyclization via S—O bond formation

There are relatively few examples of the syntheses of aliphatic sultones by this mode of cyclization. It relies on internal nucleophilic attack of oxygen at sulphonyl sulphur which has a good leaving group (e.g. a sulphonyl halide group). A recently reported case involves the cyclization of ω-hydroxy-1-alkanesulphonyl chlorides (equation 30)[51]. This method



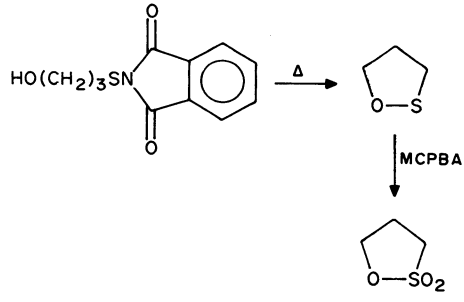
(30)

$n = 5,6$

provides a ready synthesis of the less usual seven- and eight-membered sultones. Six-membered sultone rings (δ-sultones) can also be prepared by this method ($n = 4$), the cyclization being much faster in solvent water than in non-polar solvents.

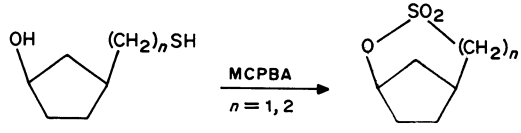
6. Oxidation of lower oxidation state sulphur compounds

Pyrolysis of *N*-(3-hydroxypropylthio)phthalimide leads to 1,2-oxathiole which can be oxidized to the corresponding δ-sultone (**15**) (equation 31)[52]. A second example is provided by the work of Pilichowski and Lhomme who prepared bridged bicyclic γ- and δ-sultones from thiomethyl and thioethylcyclopentanols respectively (equation 32)[53]. Coates and Ho[54] also prepared the spiro bicyclo δ-sultone (**16**) by a similar method (equation 33).

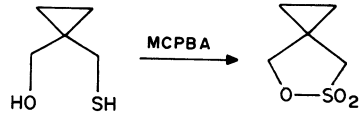


(31)

(**15**)



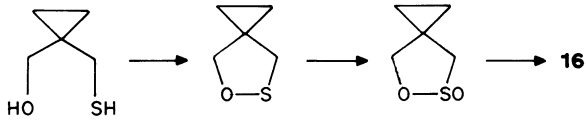
(32)



(33)

(**16**)

It has been proposed[54] that oxidative cyclizations such as these occur via the formation of the cyclic sulphinate esters (sultines) with subsequent oxidation to the corresponding sultone as shown in equation 34 for the formation of **16**.

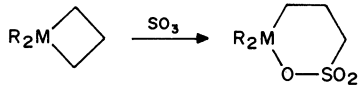


(34)

7. Bond insertion reactions of sulphur trioxide

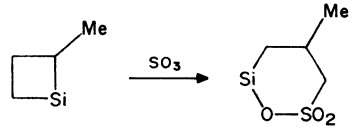
Sulphur trioxide is well known for its ability to insert into various bonds as is evident in the formation of cyclic pyrosulphates ('carbyl sulphate') from β-sultones[26]—see Section II.A.1. The mechanism of this and other insertion reactions is uncertain[26].

Dubac, Mazerolles and co-workers published several papers in the late 1960s and early 1970s describing the insertion of SO_3 into Si—C and Ge—C bonds of sila- and germacyclobutanes[55–57] to give δ-sila- and germasultones (equations 35–37). However, alkoxylated and dialkylaminated sila- and germacyclobutanes gave O—C and N—C insertion products respectively on reaction with SO_3. Similarly 1-methyl-1-phenylsilacyclobutane gave mainly 1-methyl-1-silacyclobutyl benzenesulphonate rather than the corresponding sultone (equation 38)

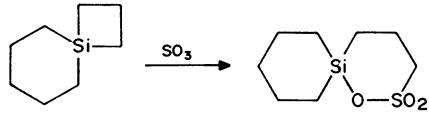


(35)

M=Si,Ge; R=alkyl



(36)



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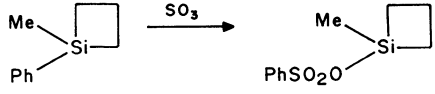


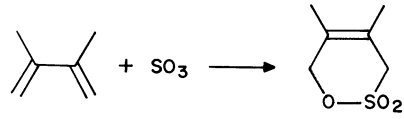
(38)

B. Unsaturated Aliphatic Sultones

1. Formation via concurrent C—O and S—C bond formation

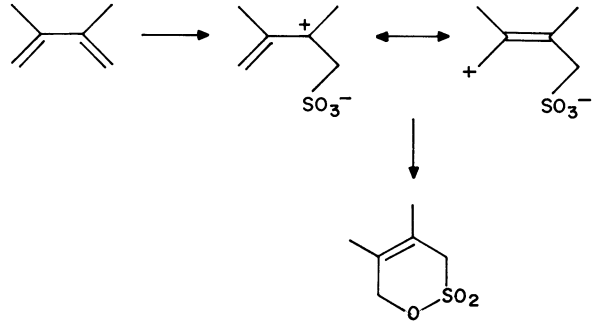
a. 1,3-Alkadiene sulphonation. Conjugated dienes can be sulphonated by sulphur trioxide reagents to give β-unsaturated δ-sultones[58,59] as illustrated by equation 39 for the

synthesis of the sultone **17**. Yields are highly variable, and appear to depend not only on reagent type and temperature (see Section II.A.1) but also on the presence of +I substituents on the alkadiene, especially at the 2- and 3-positions. There seems to be some uncertainty as to whether these reactions proceed via a Diels–Alder-type 1,4-cycloaddition route or via a route involving 1,2-addition followed by rearrangement/cyclization[60]. Certainly sulphur dioxide is known to undergo Diels–Alder-type stereoselective disrotatory additions to alkadienes[61], whilst Hamer[60] suggests an ionic mechanism (equation 40) for sulphur trioxide additions. Two other possible mechanisms are outlined in equation 41. Route 1 is a Diels–Alder 6-centre cycloaddition, whereas route 2 involves a 4-centre cycloaddition to form a β-sultone which subsequently rearranges.



(39)

(17)



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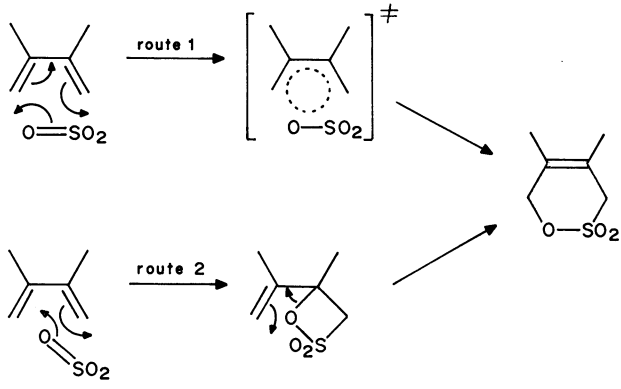
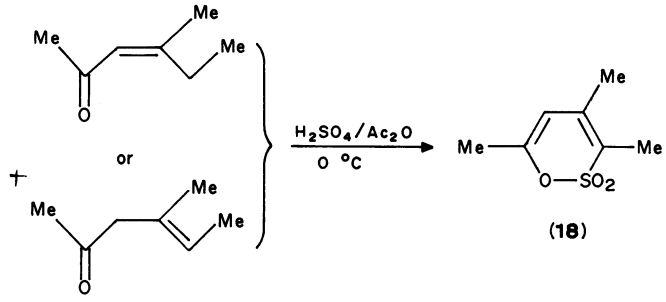


(41)

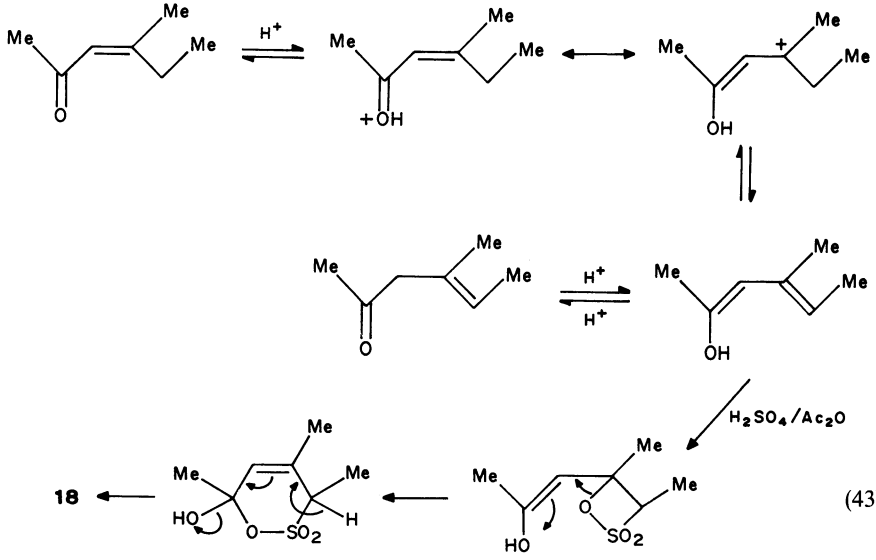
b. Sulphonation of α,β- or β,γ-*unsaturated carbonyl compounds.* Sulphonation of either α,β- or β,γ-unsaturated ketones provides a route to otherwise rather inaccessible diunsaturated sultones, such as **18** shown in equation 42[5,62]. Although the reaction

pathway seems uncertain, a possible mechanism via β-sultone formation and enolization is shown in equation 43 for the formation of **18**. Much more recently, Paull and Cheng[63] have synthesized the sultone **19** using a similar method (equation 44).

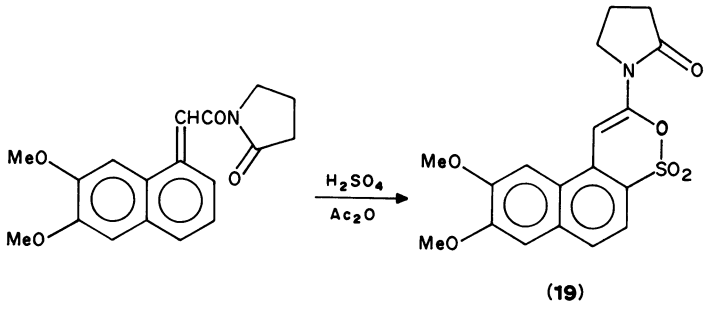


(18)

(42)



(43)

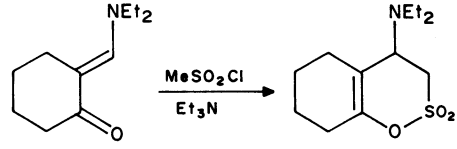


(19)

(44)

2. Formation via concurrent S—C and C—C bond formation

Addition of *in situ*-generated sulphenes (see Section I.A.2) to α,β-unsaturated carbonyl compounds to give γ-unsaturated δ-sultones is described in an early paper by Gandini and coworkers (equation 45)[64]. Their study compares the behaviour of sulphenes towards α,β-unsaturated carbonyl compounds to that of ketenes and, by analogy, two possible mechanisms for the formation of δ-sultones via β-sultones are outlined in equation 46.



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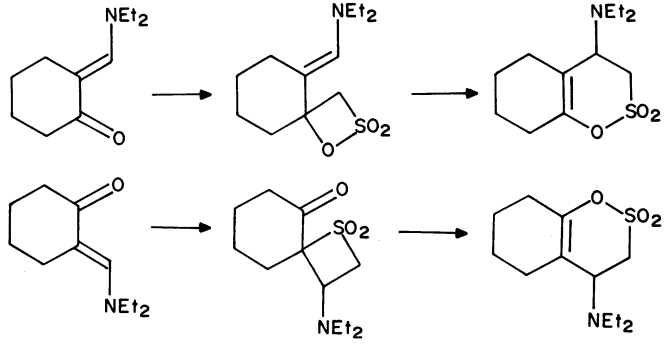
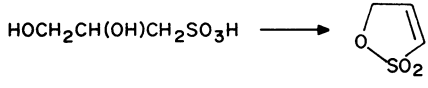


(46)

3. Synthesis involving cyclization via C—O bond formation

The synthesis of unsaturated γ-sultones by thermal cyclization is much less well documented than the corresponding method for saturated γ-sultones. However, there are reports of some preparations in the literature[66] and these are summarized in equations 47 and 48.



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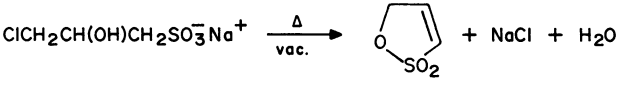
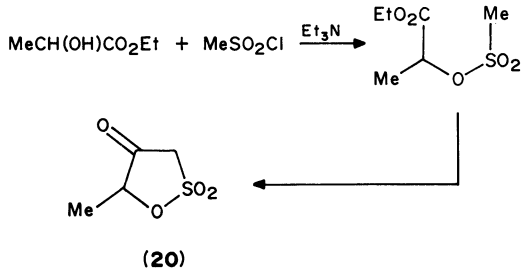


(48)

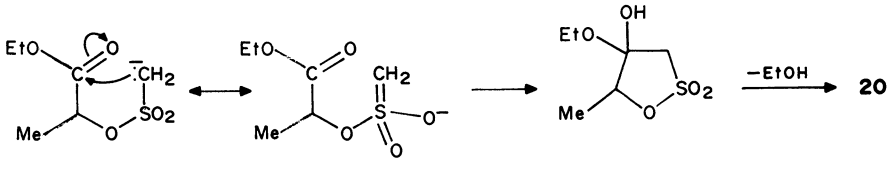
4. Cyclization via C—C bond formation

The synthetically useful β-keto γ-sultones can be prepared by the cycloelimination reactions of (α-carboxyethyl)alkyl alkanesulphonates[66], which in turn can be synthesized by reacting alkanesulphonyl chlorides with ethyl α-hydroxyalkyl carboxylates, as illustrated for the synthesis of 5-methyl-1,2-oxathiolan-4-one-2,2-dioxide (**20**) in equation 49. The ring-closure step involves the generation of a carbanion which is resonance-stabilized by the adjacent sulphonyl group (equation 50).



(20)

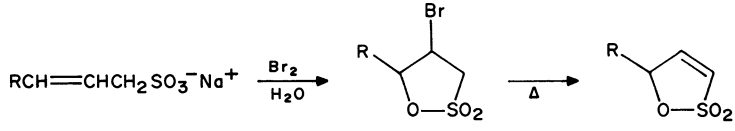
(49)



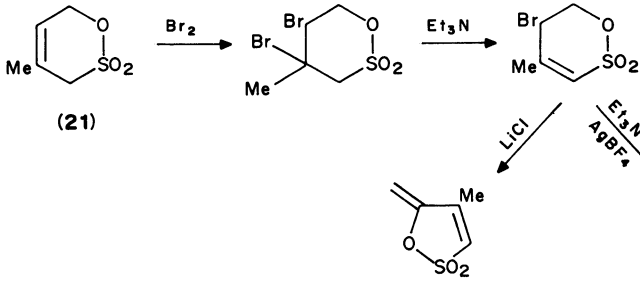
(50)

5. Elimination reactions of saturated sultones

There are several reports in the literature of the synthesis of α-unsaturated γ-sultones via the dehydrohalogenation of saturated halogenated γ-sultones[19,59,67,68]. This general mode of synthesis is illustrated in equation 51. The sodium 2-alkenesulphonate was prepared from acrolein by earlier workers[67,68], but more recently Roberts and his coworkers reported a much simplified synthesis via the sulphonation of 1-alkenes[10]. There is also a report[59] of the preparation of α-unsaturated δ-sultones, α,γ-unsaturated δ-sultones and di-unsaturated γ-sultones from the β-unsaturated δ-sultone **21** (equation 52).



(51)



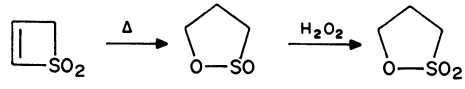
(21)

(52)

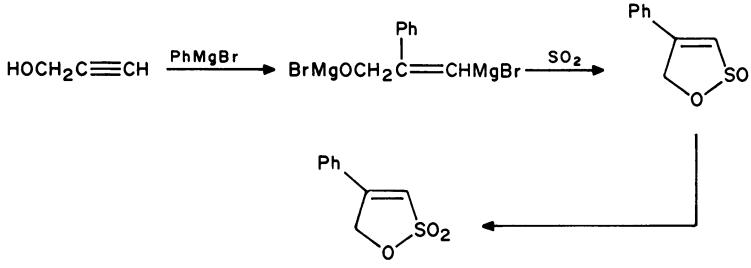
6. Oxidation of lower oxidation state sulphur compounds

Sultines (cyclic sulphinate esters) can be readily oxidized to sultones by hydrogen peroxide or potassium peroxysulphate. The first example of such a synthesis was reported by King and De Mayo and their associates[69] who prepared 1,2-oxathiole-2,2-dioxide (**22**)

from thiete dioxide (equation 53). More recently, sultones have been prepared by sulphur dioxide insertion into δ-functional vinylic Grignard reagents[70], as illustrated in equation 54 for the synthesis of 4-phenyl-1,2-oxathiole 2,2-dioxide (**23**).



(**22**) (53)

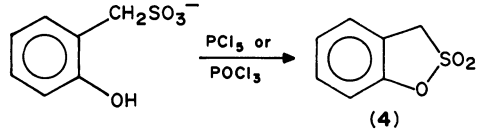


(**23**) (54)

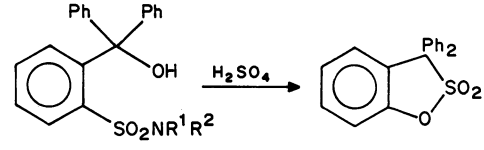
C. Aromatic Sultones

1. Cyclization via S—O bond formation

The synthesis of aromatic sultones (particularly δ-sultones) from the cycloelimination reactions of aromatic hydroxy sulphonic acid derivatives has been reported[71–74]. Examples given in equation 55 show the synthesis of the γ-benzosultones 3*H*-1,2-benzoxathiol-2,2-dioxide **4** and the 3,3-diphenyl derivative **24** where the sulphonyl group is attached to the benzene ring via oxygen. The β-keto δ-benzosultone **25** has also been prepared by this method starting from 1-bromo-(2-hydroxyphenyl)ethanone (equation 56)[75]. Naphthosultones such as naphth [1,8-*cd*]-1,2-oxathiole 2,2-dioxide (**1**) can also be prepared this way, starting from 1-naphthol-8-sulphonic acid or its salts or derivatives and reagents such as fuming sulphuric acid, PCl_5, $POCl_3$, chlorosulphuric acid, chlorine, etc., as outlined in equation 57[76–78]. This method depends on ring closure caused by nucleophilic attack of hydroxyl at the sulphonyl sulphur which usually has a good leaving group such as halogen, amine or aryloxy. The hydroxyl group is usually

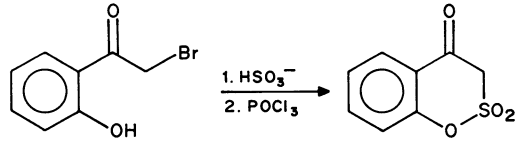


(**4**)



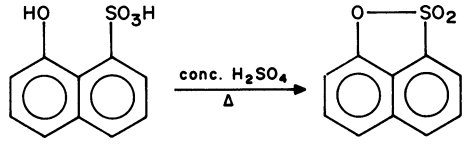
(**24**) (55)

aromatic whereas the sulphonate group is normally aliphatic (for a notable exception, see equation 55). Equation 58 illustrates these mechanistic aspects for the synthesis of **4**.

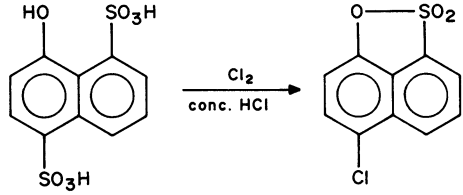


(56)

(25)



(1)



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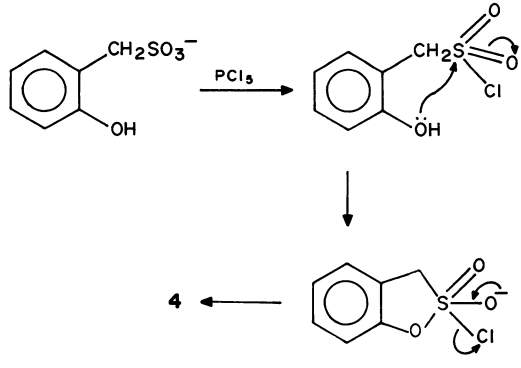
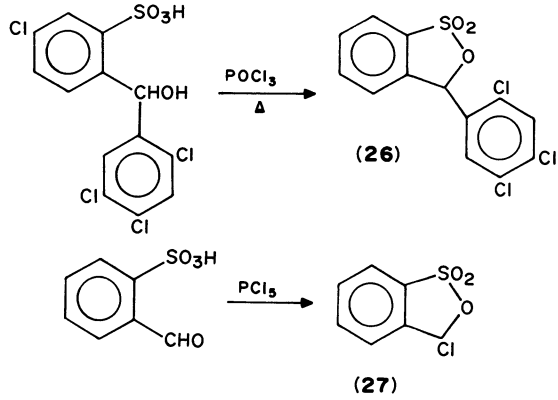


(58)

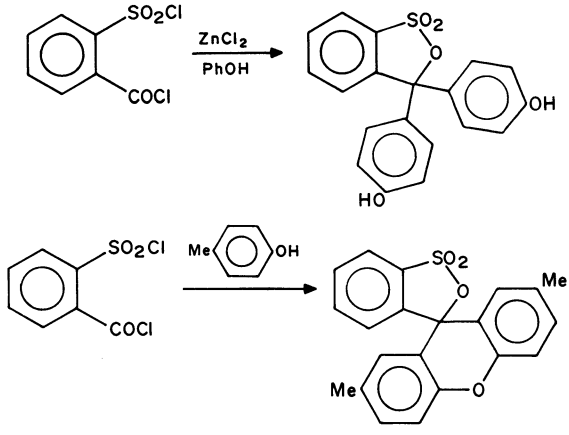
2. Cyclization via C—O bond formation

a. From o-sulphobenzoic acid derivatives. These reactions are not very well documented from a mechanistic standpoint, but probably proceed via attack of a nucleophilic oxygen of the sulphonate group on an electrophilic carbon atom, such as carbonyl or a halogenated carbon atom. The sulphonate moiety is invariably attached to an aromatic carbon atom and this method provides a useful route to 3*H*-2,1-benzoxathiole-1,1-dioxides such as **26** and **27** shown in equation 59[79,80].



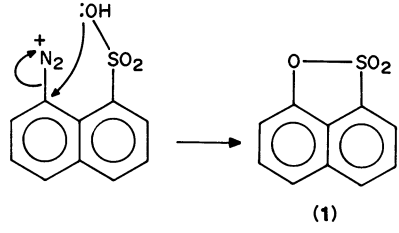
(59)

This method has been extensively exploited for the synthesis of a large group of 3*H*-2,1-benzoxathiole 1,1-dioxide derivatives known as sulphonephthaleins, many of which, such as phenol red, *p*-cresol red and bromothymol blue are well known acid–base indicators. There is excellent coverage of this subject in Breslow and Skolnik's monograph[8] and equation 60 merely serves to illustrate two representative syntheses[81,82]. The sulphonephthaleins can also be prepared from 3*H*-2,1-benzoxathiole-1-dioxide derivatives with reactive substituents (such as dichloro or carbonyl) at the 3-position (see Section III.D.3).



(60)

b. From diazotized aminosulphonic acids and their derivatives. Diazotized solutions of 8-aminonaphthalene-1-sulphonic acid when heated with water, alcohols, dilute acids or

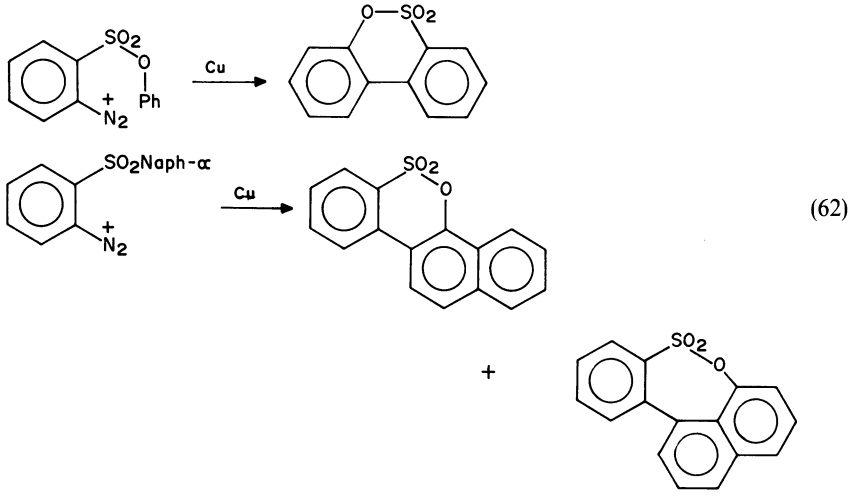


(61)

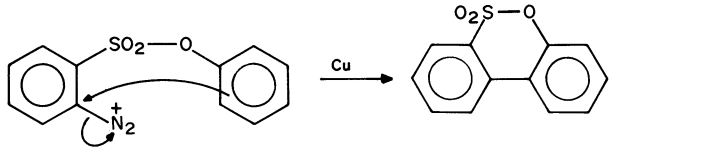
powdered copper give the naphthosultone **1**[83]. This reaction probably proceeds via an internal displacement of nitrogen as outlined in equation 61. Similar reactions have been reported for diazotized aminosulphonate esters[72], although in these cases C—C bond formation is the cause of sultone formation (See Section II.C.3a.)

3. *Cyclization via C—C bond formation*

a. From diazotized aminosulphonic acid esters. The diazotization of aromatic esters of aminosulphonic acids and subsequent reaction with powdered copper provides a very useful route to six- and seven-membered aromatic sultones in particular, as illustrated in equation 62[72,73]. These reactions presumably occur by internal electrophilic attack by an activated *ortho* carbon atom of the ester aromatic group on the diazonium ion-carrying carbon atom of the other aromatic group (equation 63).



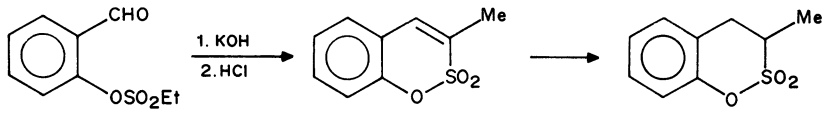
(62)



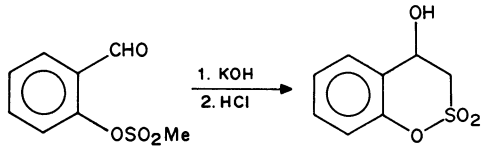
(63)

b. From alkane sulphonylsalicyl aldehydes. A variety of aromatic δ-sultones can be prepared by internal carbanion condensation with an aldehyde group. This method is especially useful for the synthesis of benz-1,2-oxathiin-2,2-dioxide derivatives[71,84] shown in equation 64. The carbanion would be resonance-stabilized by the neighbouring sulphonyl group, but it seems unclear why, under the same conditions, the ethanesulphonyl derivative gives sultone **28** via condensation, whereas the methanesulphonyl derivative gives sultone **29** via addition.

c. From aryl esters of ethenesulphonic acid. Suitably activated aryl esters of ethenesulphonic acid are capable of thermal isomerizations and give varying yields of δ-sultones of the type 3*H*-benzo-1,2-oxathiin 2,2-dioxide[71]. These esters are prepared from the



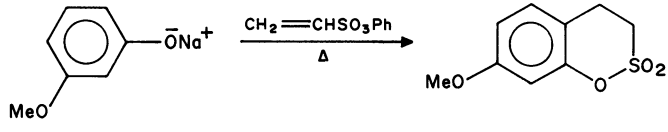
(28)



(64)

(29)

corresponding phenol and phenyl ethenesulphonate and are isomerised *in situ*, as shown by equation 65 for the synthesis of sultone **30**. The cyclizations presumably occur via an internal Friedel–Crafts-type alkylation at the most highly activated carbon atom (equation 66).



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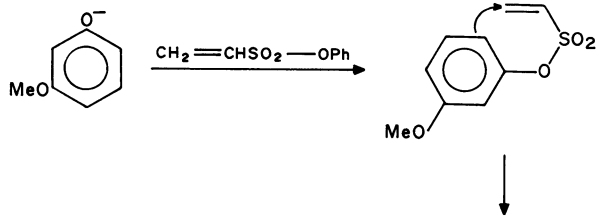


(66)

30

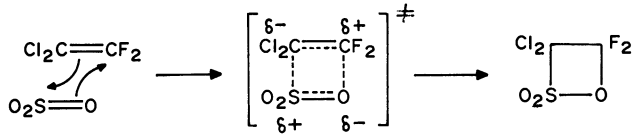
D. Polyhalogenated Sultones

There has been much interest in polyhalogenated β-sultones, particularly in polyfluorinated derivatives. Sokolskii and coworkers were especially prominent in this field in the 1960s and later. This group also published an excellent review on this subject in 1972[85]. Consequently we shall concentrate our efforts on reporting subsequent investigations on this group of compounds. Much of the interest[86–88] has stemmed from the fact that fluorinated β-sultones are precursors to sulphonyl fluorides which are important in the preparation of ion-exchange resins, surface active agents and fluorinated sulphonic acids—some of the strongest known protic acids.

1. Sulphotrioxidation of perfluoroalkenes

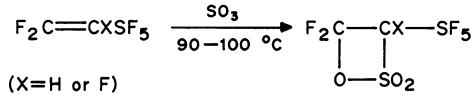
Easily the most common method of preparation is the sulphotrioxidation of halogenated alkenes. These reactions may proceed via $[\pi^2s + \pi^2s]$ addition with synchronous

S—C and C—O bond formation (equation 67). This is consistent with the observation that the β-sultone isomer formed in preference is the one with oxygen bonded to the carbon which is best able to stabilize electron deficiency in the transition state.



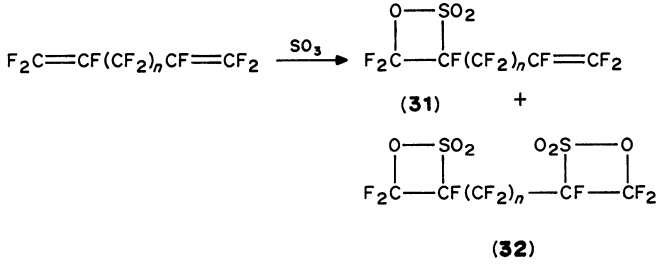
(67)

Of particular interest are the recent syntheses of pentafluorosulphur substituted β-sultones by Gard and coworkers (equation 68)[89,90].

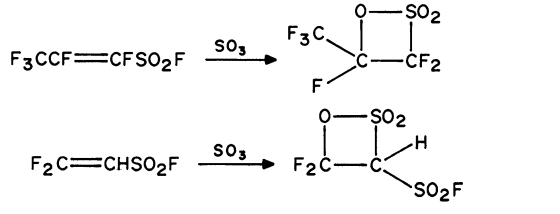


(68)

The prolific output of Sokolskii's group in the USSR includes a range of studies on the sulphotrioxidation of many unsaturated molecules, including the perfluoroalkadienes[91] as shown in equation 69. The disultone **32** is formed along with the monosultone **31** when $n = 2$ or 4, but when $n = 1$ only **31** is produced. Similarly, sulphotrioxidation of fluorinated vinyl sulphonyl fluorides performed by Sokolskii's group produced some interesting products[92,93] (equation 70). On the other hand, sulphotrioxidation of hexafluorodialkyl (or diaryl) ketenals fails to give β-sultone products (equation 71)[94,95] and sulphotrioxidation of 1,1,3,3-tetrafluoropropadiene with excess SO_3 gives the perfluoro-β-pyrosultone **33** (equation 71)[96].



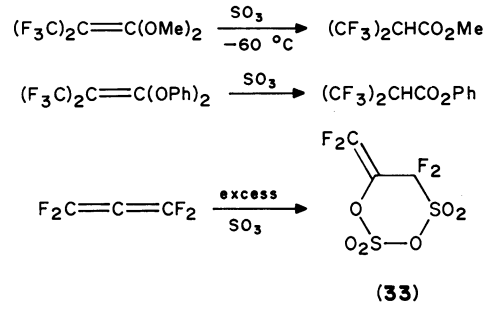
(69)



(70)

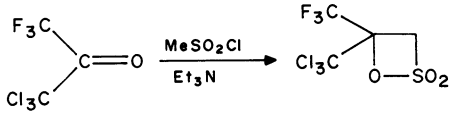
2. From alkanesulphonyl chlorides and halogenated carbonyl compounds

This much less exploited route to fluorinated and halogenated β-sultones involves the base-catalysed reaction of alkanesulphonyl chlorides with polyhalogenated aldehydes and ketones[97,98]. The method is particularly useful in the preparation of β-sultones without halogen atoms at the α-carbon atom (equation 72).



(71)

(33)

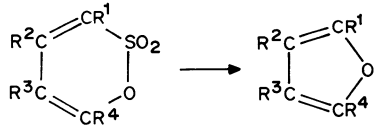


(72)

III. REACTIONS OF SULTONES

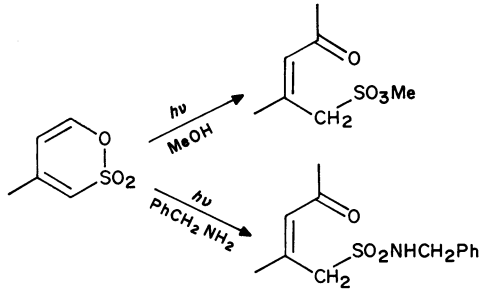
A. Thermal and Photochemical Decomposition

The pyrolysis of δ-sultones with two double bonds forms a general synthetic route to substituted furans (equation 73)[99]. De Mayo and his coworkers have shown that photolysis of unsaturated sultones in the presence of nucleophiles[100,101] produces the corresponding ketosulphonic acid derivatives (equation 74). A general mechanism was

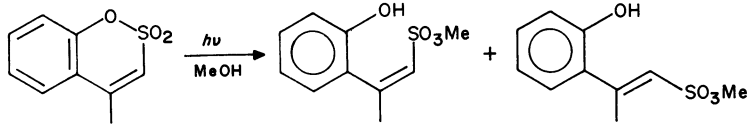


(73)

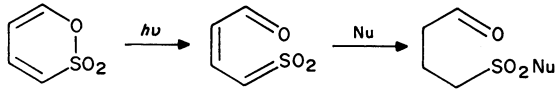
(E.g. $R^1 = R^3 = Me$; $R^2 = R^4 = H$; 54%
$R^1 = Bu$, $R^3 = Me$, $R^2 = R^4 = H$; 65%)



(74)

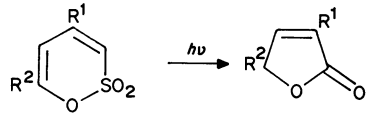


proposed involving bond rearrangement to form a sulphene intermediate which then undergoes nucleophilic attack at sulphur (equation 75). Subsequent experiments showed that sulphene intermediates would have an extremely short lifetime[102]. It has been reported that photolysis of unsaturated sultones in the absence of nucleophiles gives the corresponding unsaturated lactones (equation 76)[103]. A reaction sequence involving both dicarbonyl and ketene intermediates was proposed (Scheme 1)[103]. Sequential photolysis of these sultones (in the presence of benzophenone) leads to the formation of dimers. In a more recent study, Itokawa and his coworkers have shown that photolysis of sultones carried out in ice cold solution leads only to the formation of corresponding furan (equation 77)[104]. These products can be rationalized on the basis of a sulphene intermediate since sulphones are known to be easily decomposed to sulphur dioxide and carbene[105]. De Mayo and his group had also earlier reported elimination of sulphur dioxide during photolysis of unsaturated δ-sultones in a hot diglyme solution[102]. Clearly, whether photolysis of unsaturated sultones produces a furan or not must depend critically on the experimental conditions employed.



(75)

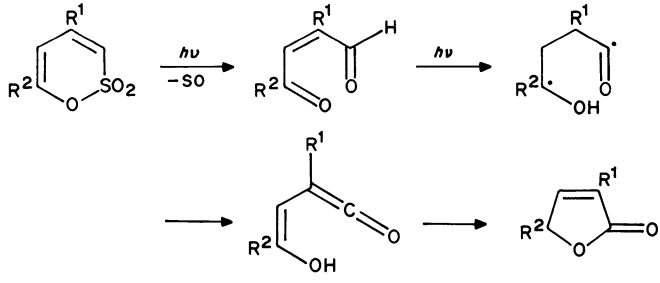
Nu=MeO, $PhCH_2$, NH_2



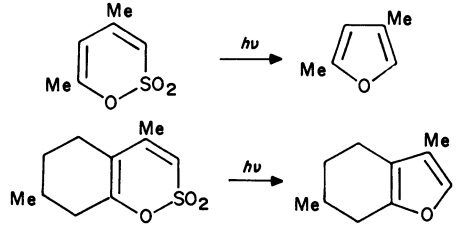
(76)

$R^1=R^2=Me$; 65%

$R^1=Me, R^2=Ph$; H 53%



SCHEME 1

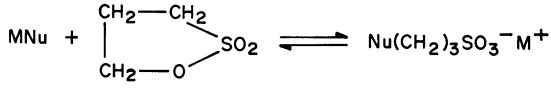


(77)

B. Nucleophilic Reactions

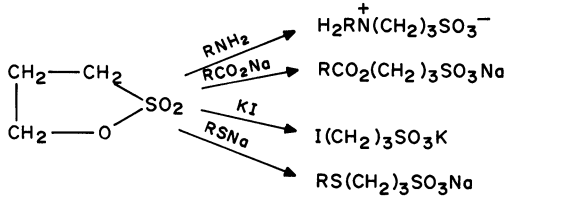
1. Introduction

Both γ- and δ-sultones are very reactive to nucleophilic attack at carbon and consequently behave as sulphoalkylating agents (Scheme 2). Such reactions have been reviewed by Hoerger[106], Fischer[107] and Roberts and Williams[7]. When the reagent is water or an alcohol (M = H, Nu = OH or OR) an equilibrium mixture is obtained. Such equilibria have been studied for the reaction of propane sultone with water and with methanol[107]. In the presence of a large volume of water hydrolysis proceeds to completion.

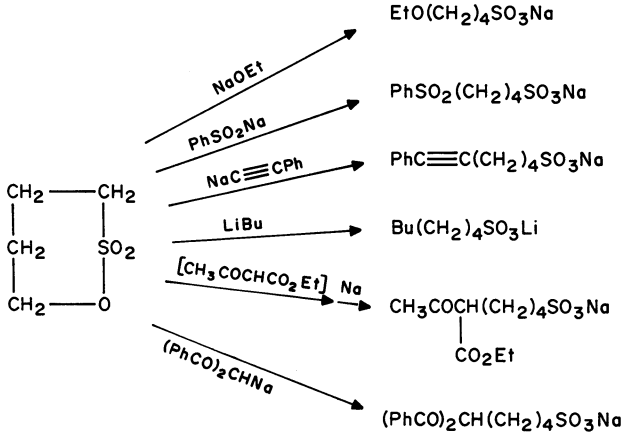


SCHEME 2

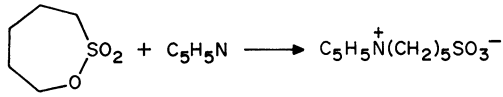
Helberger and his coworkers showed that both γ- and δ-sultones react with a wide range of nucleophiles including alcohols, amines and salts of organic acids (equation 78)[39,43,108,109]. Helberger's early work was substantiated and extended by Truce and Hoerger who showed[110] that the reactions of butane sultone with sodium ethoxide, sodium benzenesulphinate, phenylethynylsodium, butyllithium and dibenzoylmethyl sodium all follow the reaction pathway shown in Scheme 2 for propane sultone (equation 79). Although the reactions of ε-sultones have not been extensively studied, their reaction with pyridine follows the general pattern outlined above for δ- and γ-sultones (equation 80)[111]. The four-membered β-sultones react very readily with nucleophiles according to Scheme 2 to form the corresponding β-substituted sulphonic acids (equation 81).



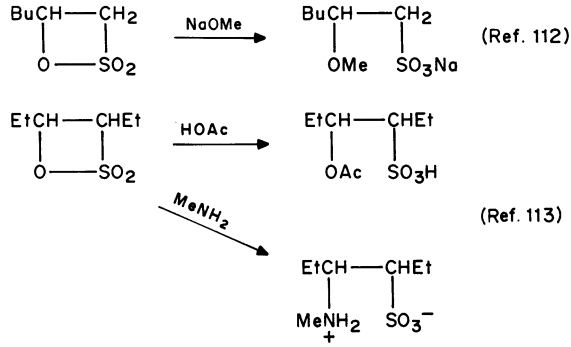
(78)



(79)

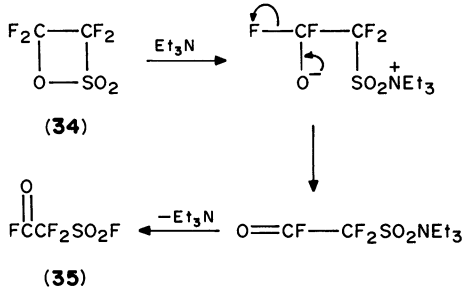


(80)

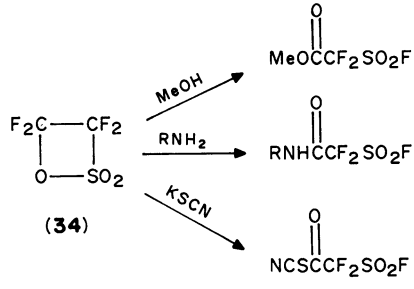


(81)

Although fluorinated β-sultones also react readily with nucleophiles[85], because of the reactive nature of the carbon–halogen bonds of the intermediates formed, rearrangement products are invariably obtained. Thus treatment of β-tetrafluoroethane sultone **34** with a catalytic amount of triethylamine leads to almost quantitative rearrangement to a sulphonic–carboxylic halide **35** (equation 82)[86]. England also showed that the sultone **34** reacts with typical nucleophiles such as alcohols, amines and potassium thiocyanate to form derivatives of fluorosulphonyldifluoroacetic acid (equation 83)[86]. It was assumed that initial rearrangement of **34** to **35** is brought about according to the mechanism shown in equation 82 and that nucleophilic attack then occurs at the acid fluoro group of **35** which is

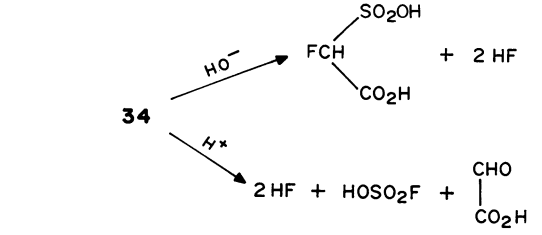


(82)

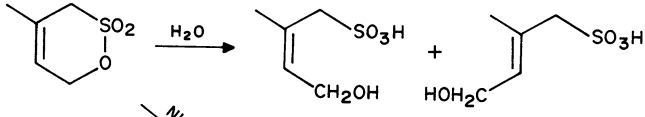


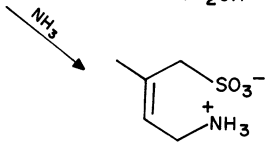
(83)

more reactive than the sulphonyl fluoride group. The hydrolysis products of fluorinated β-sultones depend on the pH of the solution used (equation 84)[85]. A few reactions of unsaturated alicyclic sultones have been reported. The six-membered β-unsaturated-δ-sultones react with a variety of nucleophiles as sulphoalkenylating agents[114]. Reaction with water or alcohols results in double-bond isomerization whereas with amines the stereochemistry is retained (equation 85). Treatment with strong bases involves 1,4-elimination to form a 1,3-dienesulphonate (equation 86)[115]. The hydrolysis of the 3,4-dimethyl analogue of **36** proceeds more than two hundred times faster than that of butane sultone presumably due to assistance from the double bond[116]. The aziridinium betaine formed from the reaction of butylamine with the unsaturated γ-sultone **37** is considered to be formed via Michael addition to the double bond (equation 87)[117]. Hydrolysis of the cyclopropylpropanesultone **38** in acetone-d_6-D_2O produces a mixture of two sulphonic acids (equation 88)[54]. The kinetic acceleration observed and attributed to cyclopropyl group participation in the hydrolysis of **38** is much less than that anticipated from the relative rates of solvolysis of cyclopropylcarbinyl and ethyl tosylates[118] (1550:1) because the cyclopropyl group in **38** is apparently skewed out of the optimum geometry for concerted participation with the leaving sulphonate group. Formation of the mixture of sulphonic acid products is considered to occur via a bicyclobutenium ion intermediate (equation 89). We referred earlier to the observation that elimination may accompany substitution under hydrolysis conditions and is indicative of C—O bond fission. Nilsson found that the % elimination increases on going from a primary to secondary and tertiary sultones (equation 90)[119]. In the hydrolysis of the tetramethyl sultone **39**, the major product is an unsaturated sulphonic acid (equation 91). The hydrolysis of sultone **40** involves a phenyl migration (equation 92)[21]. Whilst elimination from long-chain 1,4-sultones tends to give 3-alkenylsulphonates (equation 93)[120], elimination from long-chain 1,3-sultone hydrolysis gave only 3% of the Δ^2-isomer (equation 94)[121].

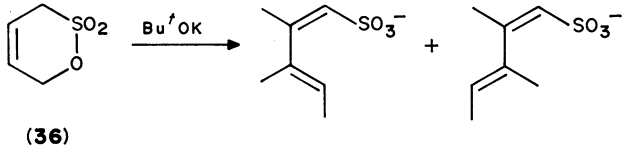


(84)



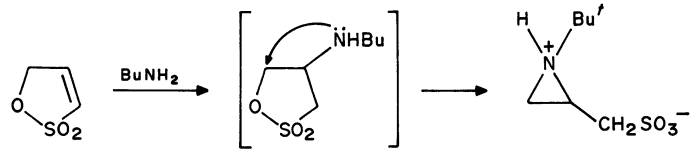


(85)

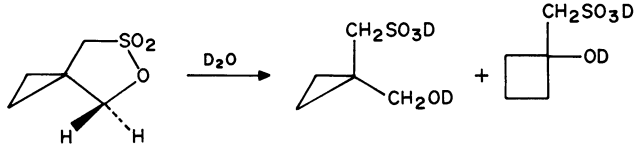


(86)

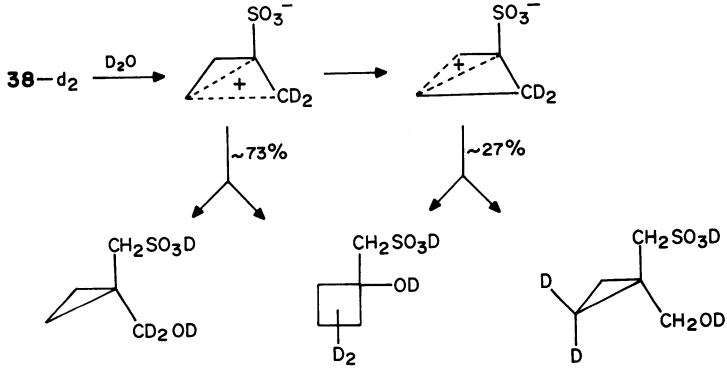
(36)



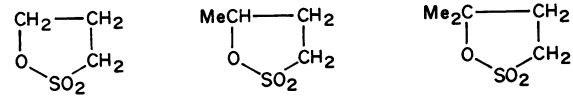
(37) (87)



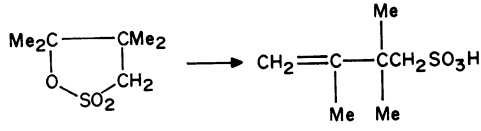
(38) (88)



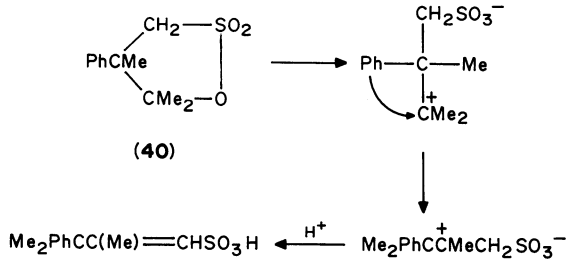
(89)



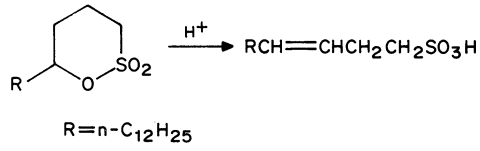
% Elimination: 0 1 15 (90)



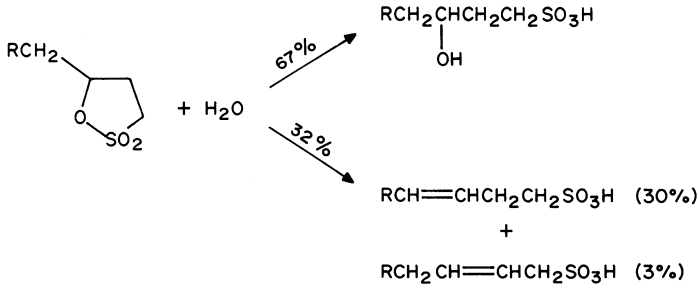
(39) (91)



(92)

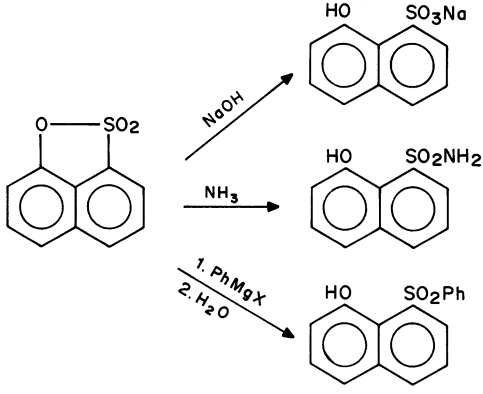


(93)



(94)

In contrast to the behaviour of aliphatic sultones, the reaction of nucleophiles with aromatic sultones involves nucleophilic attack at sulphur with sulphur–oxygen bond fission. Treatment with alkali has long been known to produce the corresponding hydroxyarenesulphonic acid[1,122]. Other typical examples include ring opening with ammonia and Grignard reagents[73,123] and are shown in equation 95 for 1,8-naphthalene sultone.

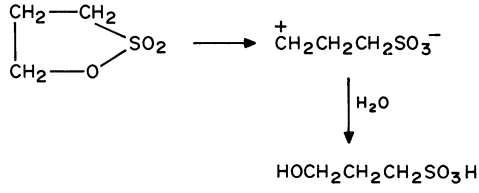


(95)

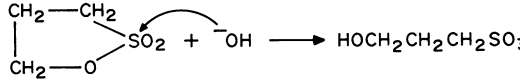
2. Oxygen nucleophiles

a. Hydrolysis of aliphatic sultones. Early studies both by Nilsson[119] and by Bordwell and his group[21] showed that the hydrolyses of substituted propane sultones occur predominantly by a unimolecular mechanism and that under hydrolysis conditions both substitution leading to hydroxyalkanesulphonate formation and elimination leading to alkenesulphonates can occur. Nagayama and his group confirmed this general pattern of behaviour for the hydrolysis of long-chain aliphatic sultones[120,124]. They also showed that δ-sultones behave in a similar way to γ-sultones.

The rate of hydrolysis of propane sultone in aqueous solution is essentially independent of pH over the pH range 4–9, consistent with a B_{AL}-E1 mechanism (equation 96). At higher pH values, however, in aqueous aprotic solvents the rate of hydrolysis increases and is attributable to an increasing contribution to the overall rate from concurrent bimolecular attack at sulphur (equation 97). Oxygen-18 tracer experiments confirmed that at pH > 12, the hydrolysis of propane sultone proceeds with 14% sulphur–oxygen bond fission. The relative rates of hydrolysis at pH > 7 in 65% aqueous acetone of five-membered: six-membered: open-chain sulphonates (propane sultone, butane-1,4-sultone and of ethyl ethanesulphonate) were found to be 37:1:7[126]. The enthalpies of activation of all three compounds were very similar and the difference in rates were attributed to differences in entropies of activation (−17.1, −24.0 and −17.9 e.u., respectively). These data, however, are composite values. It is not possible to compare the kinetic acceleration for attack at sulphur in aliphatic sultones because both the six-membered sultone and the open-chain sulphonate hydrolyse exclusively with carbon–oxygen bond fission, within the limits of experimental detection.



(96)



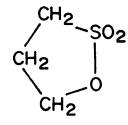
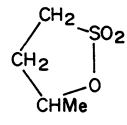
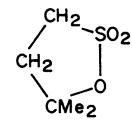
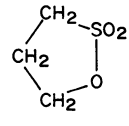
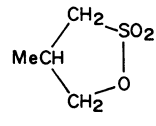
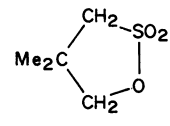
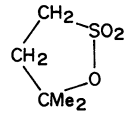
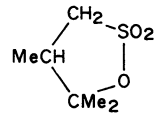
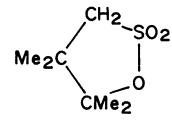
(97)

The observed reactivity sequence for aliphatic sulphonates closely resembles that for the corresponding aliphatic sulphates ethylene sulphate, trimethylene sulphate and dimethyl sulphate (12:1:6)[127] for which S—O bond fission (14%) was again only observed for the hydrolysis of a five-membered cyclic sulphate. The heats of hydrolysis have, however, been measured for aliphatic sulphate esters and the existence of considerable ring strain in the five-membered system is indicated by the fact that the heat of hydrolysis of ethylene sulphate exceeds that of dimethyl sulphate by 5–6 kcal mol^{-1}[127].

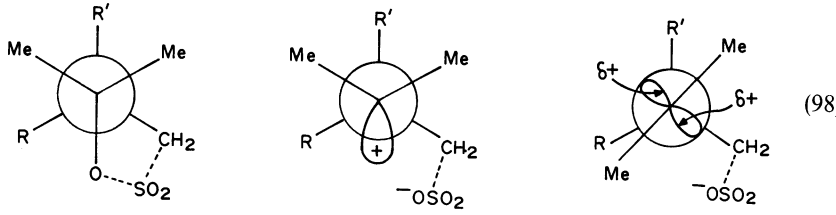
The effect of substituents on the hydrolyses of aliphatic sultones was investigated in more detail by Nilsson[119] and subsequently by Bordwell and his coworkers[21] and is shown in Table 1. The introduction of two α-methyl substituents into the γ-propane sultone ring produces an overall increase in the rate of approximately 10^3 times on going from a primary to a tertiary sultone. This is considerably less than would be anticipated from the observed increase in the rates of hydrolysis of the corresponding alkyl bromides (about 10^5–10^6)[128].

The introduction of β-methyl substituents both on primary and tertiary sultones greatly

TABLE 1. Substituent effects on hydrolysis of aliphatic sultones

			
k_{rel}(40 °C)[21]	1.0	1.3	2.6×10^3
			
k_{rel}(40 °C)[119]	300	60	1.0
			
k_{rel}(40 °C)[21,119]	1.0	0.065	0.0058
E_a (kcal mol^{-1})	20.4	19.2	20.3
$\Delta S^{\ddagger}$ (e.u.)	+2.3	−7.3	−8.5

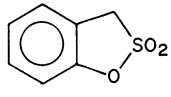
retards the rates of hydrolysis whereas data for the corresponding open-chain sulphonates would have predicted an increase in the rate. As can be seen in Table 1, the observed rate reductions seem to be associated with a decrease in the entropy of activation. Bordwell suggested that for open-chain compounds the ions of the ion-pair formed on initial cleavage of the C—O bond separate linearly. In a cyclic system this is accomplished by rotation around the C_α—C_β bonds of the ring atoms to allow separation of the sulphonate and carbenium ion centres. In tertiary sultones, however, because of the steric effect of the α-methyl groups on the sulphonate groups, rotation around both C_α—C_β and C_β—C_γ bond is necessary (equation 98). The reaction rate will clearly be sensitive to substituents which restrict such rotation and this is consistent with the values of $\Delta S^{\neq}$ shown in Table 1.



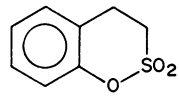
(98)

b. Hydrolysis of aromatic sultones. (i) Introduction. Kaiser and his group were the first to show that the alkaline hydrolysis of the five-membered aromatic sultones, *o*-hydroxy-α-

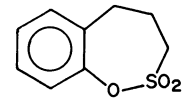
toluenesulphonic acid sultone **4** and 1-naphthol-8-sulphonic acid sultone **1** proceed some 10^5–10^6 times faster than that of the corresponding open-chain analogue, phenyl α-toluenesulphonate **43**[129,130]. Similar large rate accelerations for the hydrolysis of five-membered cyclic esters relative to both the analogous six-membered cyclic and open-chain esters have been observed for cyclic phosphates[131], phosphonates[132] and sulphates[133]. As for these other systems, Kaiser assumed that ring strain was the main driving force for the rapid hydrolysis of the five-membered sultones.



(4)



(41)



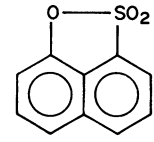
(42)

$PhCH_2SO_2OPh$

(43)

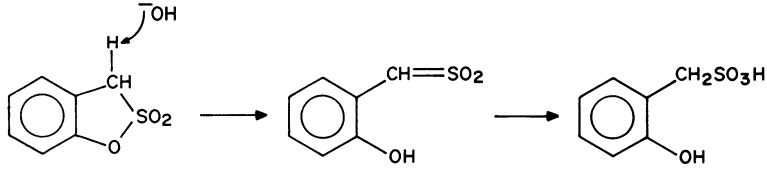
$PhSO_2OPh$

(44)

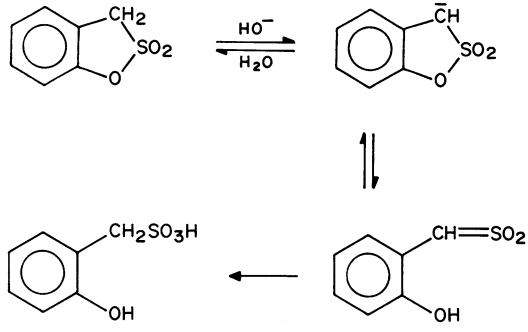


(1)

It is unlikely that alkaline hydrolysis of aromatic sulphonates would involve nucleophilic attack at the aromatic carbon atom[134]. Using oxygen-18 tracer techniques, Bunton and Frei showed that alkaline hydrolysis of phenyl α-toluenesulphonate proceeds entirely with sulphur–oxygen bond fission[135] confirming that alkaline hydrolysis proceeds via nucleophilic attack of hydroxide ion at sulphur. For many sultones and for phenyl α-toluenesulphonate, however, other mechanisms not involving direct attack at sulphur are, in principle, possible. Two such mechanisms involving the formation of carbanions and/or sulphenes as intermediates are shown for the hydrolysis of **4** in equations 99 and 100.



(99)



(100)

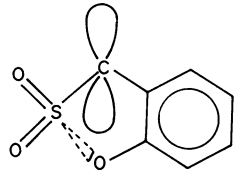
From a study of the hydrolysis of sultone **4** in D_2O–OD^- solution, Kaiser and his coworkers showed that carbanion formation occurs rapidly and reversibly from the sultone in basic solution[136]. They were able to eliminate the concerted mechanism (equation 99) as a major reaction pathway and concluded that a carbanion–sulphene mechanism (equation 100) does not provide an important pathway for the hydrolysis of five-membered sultones.

Williams and his coworkers have shown that the hydrolysis and aminolysis of aryl toluene-α-sulphonates proceed via a stepwise elimination–addition (E1cB) mechanism (equation 101)[137–139].

$$\begin{gathered} PhCH_2SO_2OAr + B \rightleftharpoons PhC\bar{H}SO_2OAr + BH^+ \\ PhC\bar{H}SO_2OAr \longrightarrow PhCH{=}SO_2 + ArO^- \\ PhCH{=}SO_2 + H_2O + B \longrightarrow PhCH_2SO_3^- + BH^+ \end{gathered} \tag{101}$$

Similar evidence for the formation of a sulphene intermediate from aryl arylmethanesulphate via an E1cB mechanism has also been reported by King and Beatson[140]. Williams proposed that the E1cB mechanism for the hydrolysis of five-membered cyclic sulphonate esters is sterically suppressed[137,138]. Molecular orbital calculations suggest that the planar configuration of the sulphene $CH_2{=}SO_2$ is more stable by some 35 kcal mol^{-1} than the corresponding perpendicular form in which the OSO plane is perpendicular to the H_2CS plane. The transition state for the elimination of the phenoxide ion from an acyclic sulphonyl carbanion would therefore be expected to resemble the planar form of the sulphene.

On the other hand, for the five-membered sultone, although the benzylic proton is labile and the phenoxide ion is a good leaving group, the E1cB mechanism is suppressed because the transition state **45** for this reaction would lead to the high-energy perpendicular sulphene. It seems reasonable to conclude therefore that the difference in reactivity of sultones and phenyl benzenesulphonate, which does not possess a potential carbanion centre, reflect differences in rate of attack at sulphonyl sulphur in cyclic and acyclic esters.

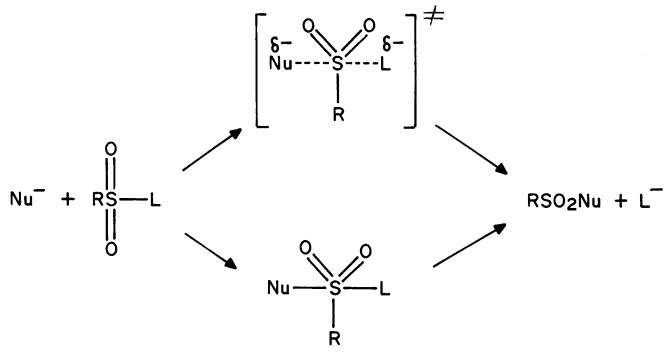


(45)

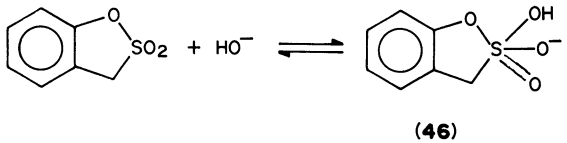
(*ii*) *Mechanism of nucleophilic substitution.* There has been considerable speculation as to whether nucleophilic attack at sulphonyl sulphur proceeds via a concerted S_N2(S)-type mechanism or in a stepwise fashion via formation of a pentacovalent intermediate (equation 102).

Attempts to detect reversible formation of an intermediate **46** with oxygen-18 tracer experiments were unsuccessful; no significant enrichment of the original ester could be observed (equation 103)[141].

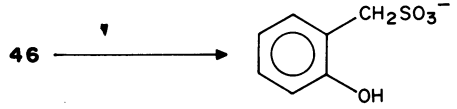
Kaiser and Kezdy have pointed out that the failure to observe oxygen exchange in the hydrolysis of sultones can be understood if the preference rules which apply to the pseudorotation of intermediates in phosphate ester hydrolysis can be applied to pentacoordinate sulphur intermediates[142]. Since on this basis negatively charged groups would be expected to occupy equatorial positions, equilibration of oxygen atoms in a



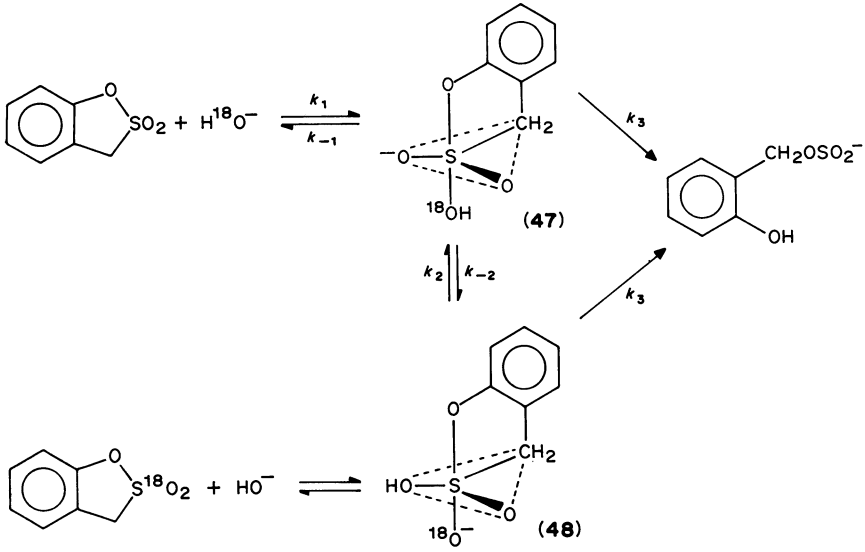
$RSO_2Nu + L^-$ (102)



(46) (103)

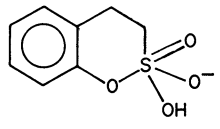


trigonal bipyramidal intermediate via a simple proton transfer as in **47** → **48**, which would place an O group in an apical position, would be very slow compared to the breakdown of the intermediate in either the forward or reverse directions, i.e. k_1 and $k_2 \gg k_3$ (Scheme 3). Other potentially alternative routes to oxygen exchange involve high-energy structures and can be excluded by the preference rules.

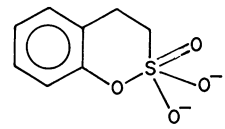


SCHEME 3

A study of the rates of alkaline hydrolysis of a series of 5-substituted 2-hydroxytoluene-α-sulphonic acid sultones showed them to be moderately sensitive to substituent effects ($\rho = +1.23$) but does not provide a method of distinguishing between a concerted mechanism and one involving a covalent intermediate[143]. The rates of hydrolysis and methanolysis of sultone **41** in strongly basic media have been correlated with H_- and H_M respectively and lead to the conclusion that an addition–elimination mechanism would involve a monoionic intermediate **49** rather than the dianionic species **50**[144].

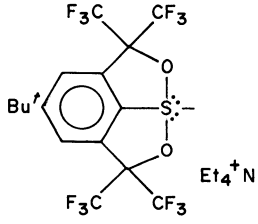


(49)

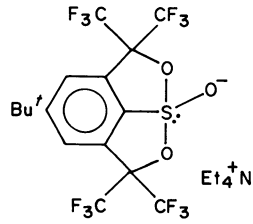


(50)

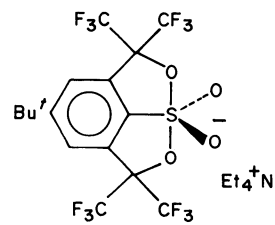
Martin and his coworkers have observed a large number of sulphuranes of the type shown in **51**–**53**[145–148]. It is particularly interesting to note that the (10-S-5) sulphurandioxide salt **53**, in which ten electrons are involved in bonding five ligands to the central sulphur atom for which a crystal structure determination has been made, is the first example of an observable analogue to the postulated intermediate in the addition–elimination mechanism for the alkaline hydrolysis of a five-membered sultone[147].



(51)

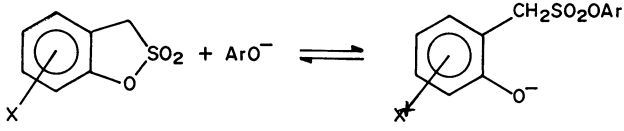


(52)

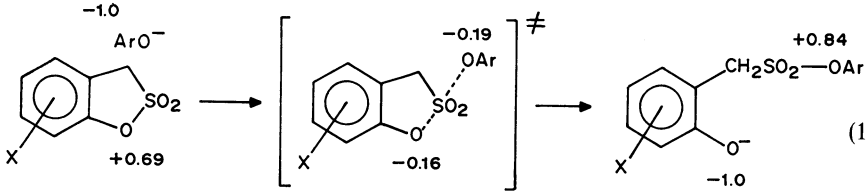


(53)

In an attempt to obtain more information about the relative importance of bond breaking and bond making for reactions of sultones with nucleophiles, Williams and his coworkers measured the rates of reaction of phenoxide ion with a series of substituted 2-hydroxyphenylmethanesulphonic acid sultones together with the corresponding equilibrium constants (equation 104)[149]. From the Brönsted β_L and β_{Nu} values the authors



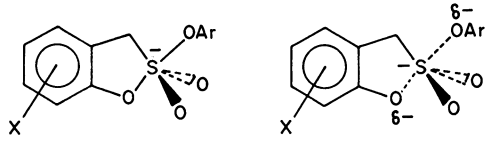
(104)



(105)

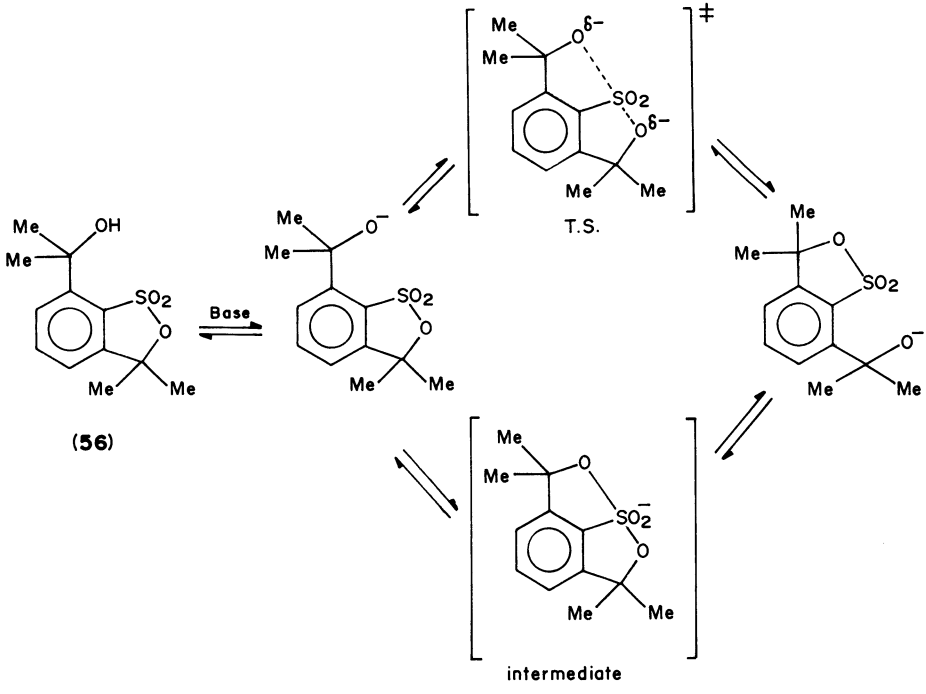
deduced that the change in effective charge on the leaving sultone oxygen (−0.85) is almost identical to the change in effective charge on the attacking phenoxide ion, consistent with a symmetric transition state and a concerted mechanism (equation 105).

Kice has suggested, however[150], that as in several other systems, the total effective charge need not be conserved, and alternatives to a symmetric transition state could be consistent with Williams' findings. Kice argued that in a structure close to that of the pentacoordinate intermediate **54**, when the electron-withdrawing capacity of the sulphur atom is greatly reduced by the negative charge, the effective charge on the sultone oxygen could be −0.16 although the extent of bond breaking was negligible. A transition state **55** almost identical to **54** would be in accord with Williams' findings if conservation of charge is not required.



(54) **(55)**

X-ray structure determinations show that the sulphuranes **51**–**53** all have abnormally long apical S—O bond lengths (1.900, 1.965; 1.969, 1.969; 1.912, 1.932 Å) supporting Kice's contention that the lowest energy structure of intermediates like **54** could have appreciable partial negative charges on entering and leaving oxygens. Kice proposes therefore that as general rule substitutions at sulphonyl sulphur are stepwise and proceed via intermediates.



(56)

SCHEME 4

Ab initio molecular orbital calculations for the intramolecular carboxyl-catalysed hydrolysis of a number of *ortho*-substituted sulphonamides also support a mechanism involving the formation of a pentacordinate intermediate[151]. Engberts and his coworkers have recently shown that the reaction of sultone **56** with Et_4NOH in CD_3OD as solvent at room temperature produces either a pentavalent sulphur species or is consistent with a dynamic equilibrium, rapid on the ^1H and ^{13}CNMR time scale between two identical sultones (Scheme 4)[152]. It seems that for a pentavalent species to be isolable (as in the case of **53**), stabilisation of apical substituents by the introduction of electronegative groups like CF_3 is essential.

(iii) Kinetic acceleration in sultones. Kaiser was one of the first to suggest that, by analogy with the situation in organophosphorous compounds, ring strain is the main driving force for the rapid hydrolysis of cyclic sulphate and sulphonate esters[134]. Thus ring strain in the five-membered ring is reduced, without the necessity for ring opening, in a transition state which has a naturally small OSO bond angle.

In recent years the importance of entropy contributions to the increased rates of reaction of five-membered cyclic esters has been recognised. Thus the high reactivity of the oxaphospholan ring has been shown to arise from a combination of both enthalpy and entropy strain[153]. On the other hand, entropy strain is the main cause of kinetic acceleration in the alkaline hydrolysis of cyclic sulphite and sulphinate esters[154,155].

The determination of the Arrhenius parameters for the alkaline hydrolysis of a series of sulphonate esters (Table 2) shows that the reactivity difference in sulphonates arises from a combination of entropy and enthalpy effects, although the latter is likely to be the dominant factor[156]. The different mechanism of hydrolysis (E1cB) of phenyl toluene-α-sulphonate **43** shows up clearly in the anomalous value of $\Delta S^{\neq}$.

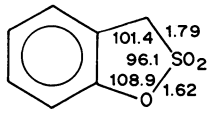
(iv) Ring strain in sultones. The origin of ring strain in five-membered cyclic esters has been the subject of much speculation. Three main possibilities have been considered: (a) angle strain[157], (b) strain-induced changes in the 2p-3d π-character of the endocyclic oxygen–heteroatom bonds[158,159] and (c) 1,3-non-bonding interactions between oxygen atoms[127].

X-ray structure analysis has confirmed the presence of considerable strain in the five-membered sultone **4** (by comparison with its six-membered analogue) which has a much smaller internal OSO bond angle of 96.1° and COS bond angle of 108.9° (compared with 101.4° and 116.5°, respectively)[160]. Thus in **4**, a relatively small perturbation of the ring angle at sulphur is required to reach a transition state geometry favourable to reaction at sulphur in the five-membered ring. Similar large angle strain has been observed in the corresponding five-membered cyclic sulphates[161]. X-ray studies of *o*-phenylene sulphate have shown that the five-membered ring is distorted into a non-planar envelope[161]. Boer and Flynn suggested that 1,3-non-bonding interaction between the lone-pairs of the ring

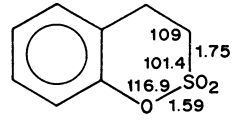
TABLE 2. Arrhenius parameters for the alkaline hydrolysis of sulphonate esters[a]

Sulphonate	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\#}$ (e.u.)
4	10.8	−14.6
41	16.0	−17.3
42	17.7	−21.5
43	23.4	+0.69
44	17.3	−17.0

[a]Data from Reference 156.



(4)



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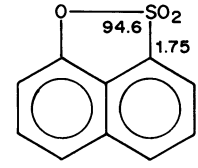


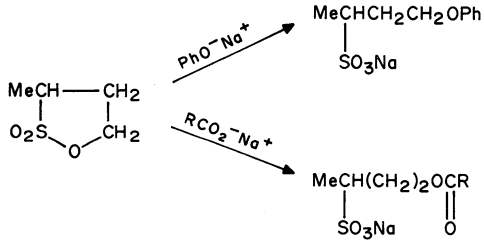
(1)

oxygen and the endocyclic oxygen could be another source of ring strain and that such interactions would be minimised in the non-planar conformation.

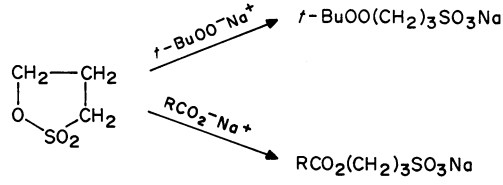
Both Wakselman's and Kaiser's groups have shown that angle strain in the sultone **4** is less than that in the corresponding naphthosultone **1** in spite of the slightly greater reactivity of the former ($k_1/k_2 \sim 1.5$)[129,130,162]. The authors have suggested that in **1** a specific conjugative interaction between the two rings (as evidenced by the shorter C—S bond length) offsets the effect of angle strain.

It seems likely, therefore, that although the major cause of enthalpy strain observed in the alkaline hydrolysis of sultones arises from angle strain, other factors such as 1,3-lone-pair–lone-pair interactions and possibly conjugative effects also contribute to destabilisation of the five-membered ring.

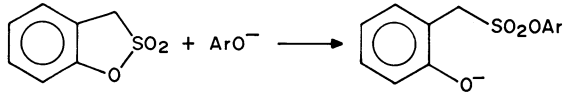
(c) Other oxygen nucleophiles. The reaction of sultones with alcohols were discussed in the previous section. Aliphatic sultones have also been shown to react readily with the sodium salts of alcohols and phenols[108,163] hydroperoxides[163], carboxylic[39] and carbonic acids (equation 106)[108].



(106)

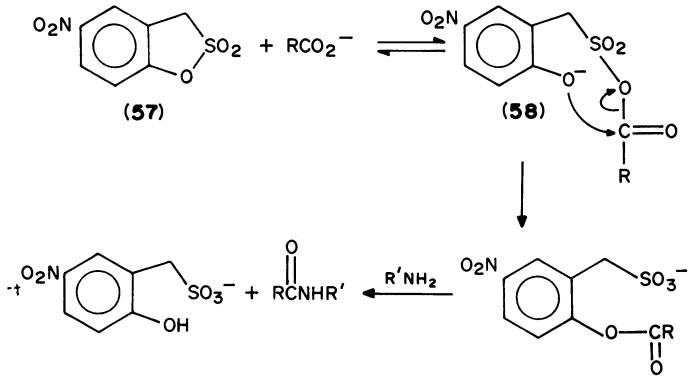


For aromatic sultones attack of oxygen nucleophiles occurs at sulphur, e.g. with phenolate ions (equations 107)[134]. Wakselman and Acher have shown that aromatic



(107)

sultones can be used as selective acylating agents in peptide synthesis[164]. Nucleophilic attack of a carboxylate salt on the nitrobenzosultone **57** leads to formation of the activated ester **58** which rapidly acylates any amine present (equation 108).



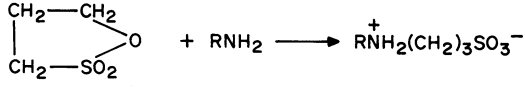
(108)

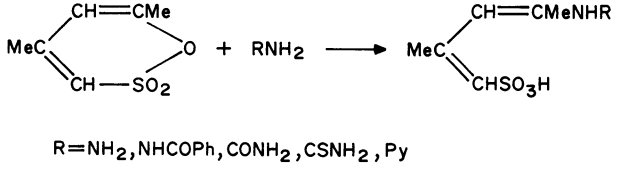
The 6-nitro- and 6,8-dinitronaphthosultones provide a superior coupling reagent[165]. Their rates of alkaline hydrolysis are lower than that of **57** and they provide a more rigid mixed anhydride than **58** which leads to more efficient intramolecular acyl transfer.

3. *Nitrogen nucleophiles*

A wide range of amines and their derivatives have been shown to react with both saturated and unsaturated aliphatic sultones to produce the corresponding aminosulphonic acids (equation 109)[166]. Amines and their derivatives react rapidly with fluorinated β-sultones to form rearrangement products (equation 110)[86].

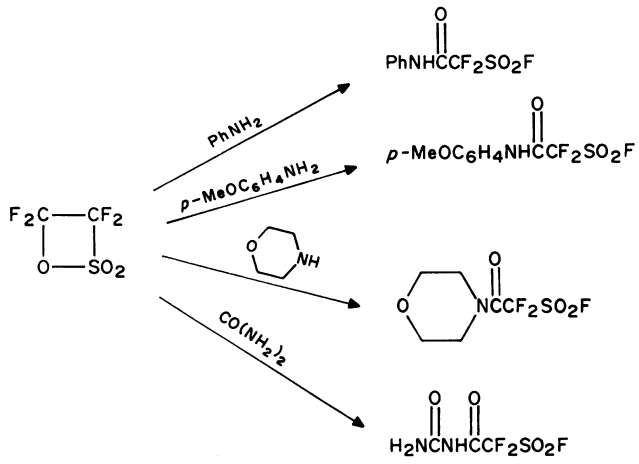
On heating, the betaines formed from the reaction of propane sultone with tertiary amines have been found to undergo polymerisation (equation 111)[167,168]. Propane sultone reacts with substituted hydrazides to form sulphonic acids (equation 112)[169]. On the other hand, unsaturated δ-sultones react with hydrazides either on fusion or in a non-polar solvent to form sultams as the major product (equation 113)[169,170]. In alcohols, either the corresponding sulphonic acids or hydrazine derivatives are obtained (equation 114). The unsaturated tricyclic δ-sultone **59** reacts with hydrazine to form the ethylpyrazole **60** (equation 115)[171]. Aliphatic sultones react almost quantitatively with potassium phthalimide[108], and with the sodium derivative of amides (equation 116)[163].





(109)

R=NH_2, NHCOPh, $CONH_2$, $CSNH_2$, Py



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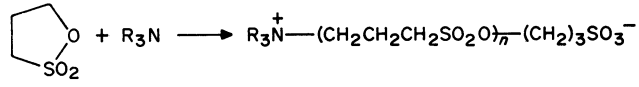
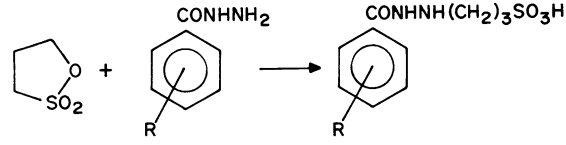
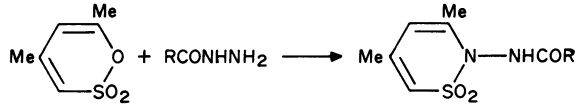


(111)



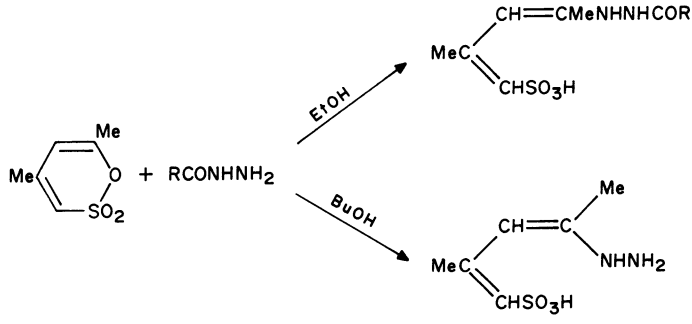
(112)

R=H, *p*-NO_2, *p*-Cl, *o*-Me, *m*-Me, *p*-Me

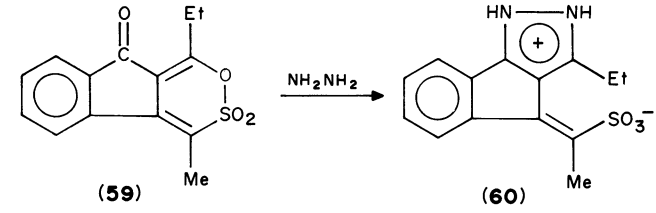


(113)

R= *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, *p*-ClC_6H_4



(114)



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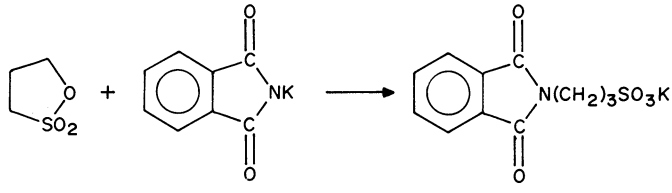

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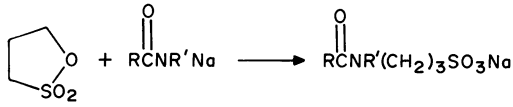
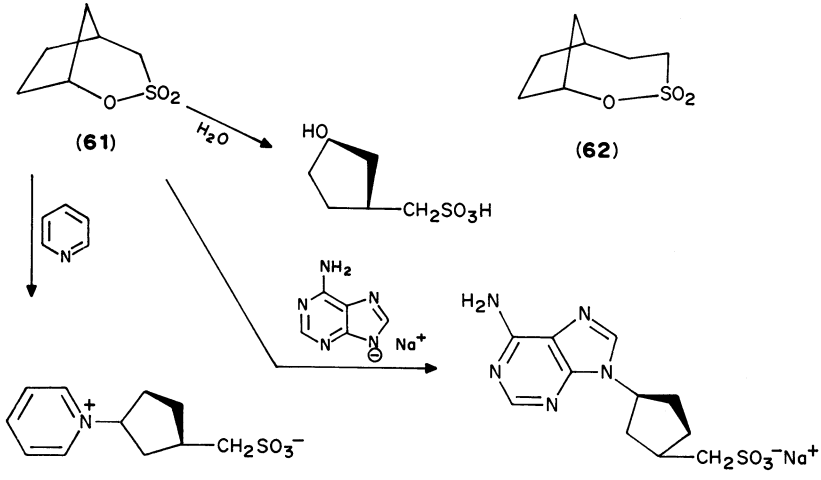


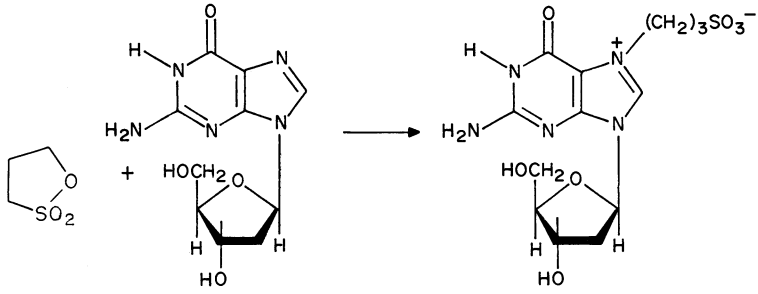
The rate of hydrolysis of the bicyclic δ-sultone **61**[53,172] proceeds some 10 times faster than that of the analogous ε-sultone **62** and some 800 times faster than that of butane sultone as determined by Bordwell and coworkers[16,21] reflecting the ability of sulphonate to act as a leaving group from the bridgehead of a bicyclic system. The sultone **61** also reacts readily with pyridine and the sodium derivative of adenine (Scheme 5).

Both propane sultone and butane sultone have been shown to be mutagenic[174] with the former being about forty times more active—consistent with its greater reactivity towards nucleophilic attack as deduced from the rates of hydrolysis[16,21]. Goldschmidt and his



SCHEME 5

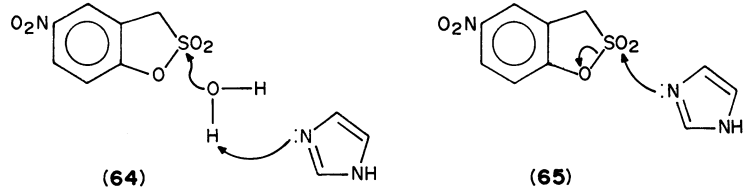
coworkers have shown[175] that propane sultone reacts irreversibly with DNA from various sources and reacts with guanosine **63** in DMSO to form the N-7 alkyl nucleoside (equation 117).



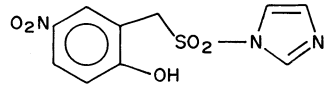
(117)

(63)

Kaiser and his coworkers showed that the hydrolysis of the five-membered 2-hydroxy-5-nitro-α-toluenesulphonic acid sultone is catalysed by bases like imidazole and *N*-methylamidazole[176]. The magnitude of the solvent isotope effect $k_H/k_D = 4.2$ and 3.5, respectively, suggested that the reaction occurs via general base catalysis (**64**) rather than nucleophilic catalysis (**65**). The authors pointed out, however, that a sulphonimidazoyl

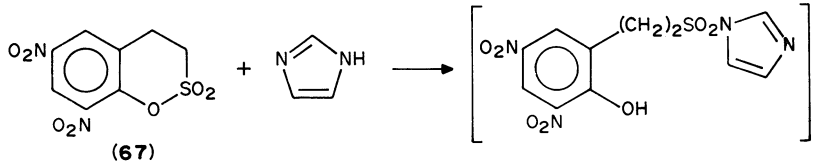


(64) **(65)**



(66)

intermediate **66** formed by nucleophilic attack at sulphur could recyclise to reactants much more rapidly than its rate of decomposition to products and hence would not be detected. Both mechanisms could therefore, in principle, proceed side by side but only the general base catalysis contributes significantly to the observed rate of hydrolysis. Such a view is substantiated by the observation that the kinetics of the reversible reaction of imidazole with β-(2-hydroxy-3,5-dinitrophenyl) ethanesulphonic acid sultone **67** can be conveniently studied because the rate of cyclisation of a sulphonyl species resulting from a six-membered ring is much lower that that of the corresponding five-membered system (equation 118)[177].

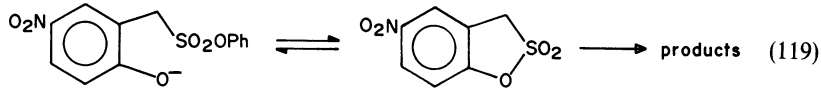


(118)

(67)

Williams and his coworkers studied the hydrolyses of a large number of nitrogen nucleophiles of different structural types and observed both general base-catalysed and nucleophilic pathways[178]. The differing behaviour showed up clearly on the Brönsted plot, primary amines ($\beta = 0.66$) following a nucleophilic catalysis pathway whilst a general base line included imidazole, *N*-methylimidazole, pyridine and 4-picoline.

The hydrolysis of phenyl 2-hydroxy-5-nitrophenylmethanesulphonate was shown to involve hydroxyl group participation leading to sultone formation (equation 119)[179].

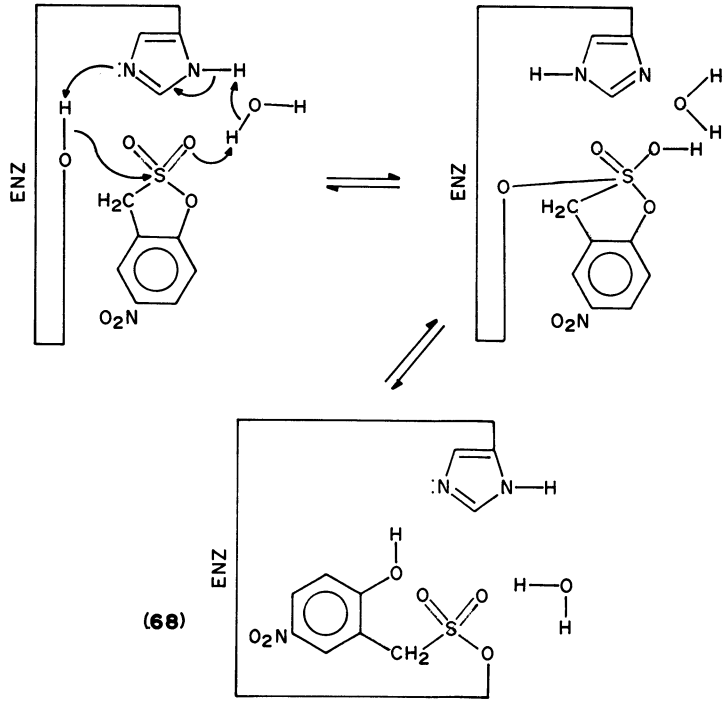


(119)

Results for the ring closure of the sulphonate substantiate Kaiser's suggestion that for catalysis of the hydrolysis of sultones by tertiary amines, the rate of re-cyclization of any sulphonyl intermediate formed would be very rapid and the nucleophilic mechanisms for such amines would have very little effect on the observed rate[176].

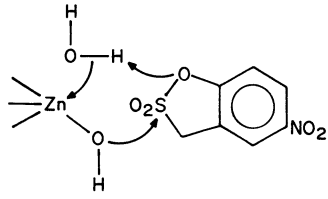
The sultone **63** also reacts rapidly and reversibly with the serine residue at position 195 at the active site of the proteolytic enzyme α-chymotrypsin to produce an inactive sulphonyl enzyme **68**.

A mechanism was suggested involving the formation of a pentacovalent intermediate whose formation and decomposition are both assisted by general acid–general base catalysis by the imidazole ring of histidine (Scheme 6)[180,181]. In a similar way, the sultone



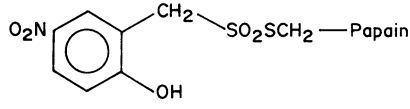
SCHEME 6

63 is hydrolyzed extremely rapidly by the zinc-containing metalloenzyme carbonic anhydrase[182]. A cyclic mechanism involving a zinc-bound hydroxide ion as the active species (**69**) has been proposed[134]. Yet another enzyme which has been reported to react



(**69**)

with **63** is the sulphydryl proteinase, papain, which reacts via a thiolsulphonate–enzyme intermediate **70**[183]. At pH 5.2, recyclization of **70** to generate the starting material via

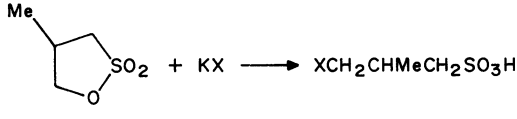


(**70**)

intramolecular nucleophilic attack of the hydroxyl group at sulphonyl sulphur can compete effectively with hydrolysis in spite of the fact that thiosulphonates normally only undergo reaction at sulphenyl sulphur. Sulphonylation and desulphonylation reactions with papain have also been studied in a more favourable system involving the corresponding 3,5-dinitrosultone[184].

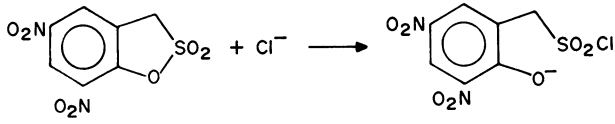
4. Other nucleophiles

The potassium halides all react with aliphatic δ-sultones to form the corresponding sulphonic acids, although the reaction with fluoride has to be carried out under more vigorous conditions (equation 120)[108]. Ciuffarin and his coworkers demonstrated that the dinitrosultone **71** reacts with tetrabutylammonium chloride in acetonitrile or nitrobenzene to form the corresponding sulphonyl chloride (equation 121)[185]. The reaction



(120)

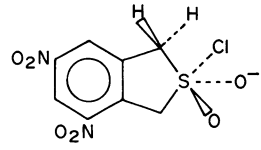
X=F, Cl, Br, I



(121)

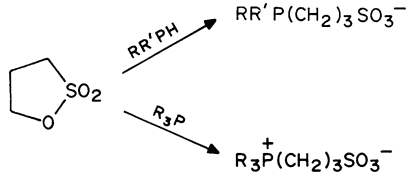
(**71**)

proceeds via the formation of an intermediate complex which can be detected by NMR and for which the authors have suggested the trigonal bipyramid **72** with chloride situated



(72)

in an apical position as a possible structure. Haas has shown that phosphines react with propane sultone according to equation 122[186,187]. Phosphite esters, on the other hand, react according to equation 123[188,189]. Breslow and Skolnik[8] have suggested that this



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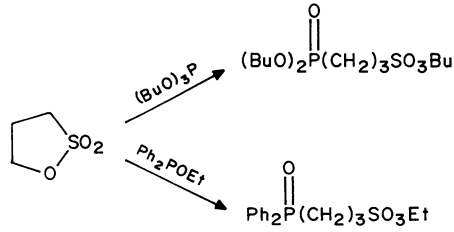


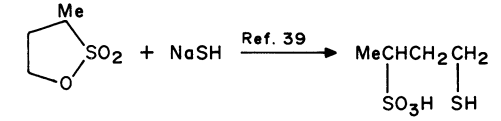
(123)

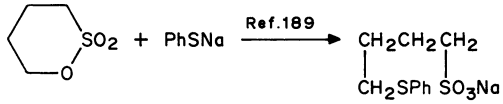
reaction occurs via a Michaelis–Arbuzov reaction involving rearrangement of an initially formed phosphonium sulphonate betaine. The reactions of aliphatic sultones with some typical sulphur nucleophiles including thiol derivatives, thiourea, thioamides and xanthates are shown in equation 124.

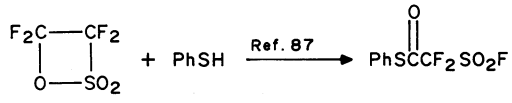
It should be noted that whilst the benzosultone behaves like a typical aromatic sultone with nucleophilic attack occurring at sulphur, the sultone **73** (3*H*-2,1-benzoxathiole 1,1-dioxide) behaves like an aliphatic sultone with reaction occurring at the alicyclic carbon atom and so acts as an alkylating agent towards nucleophiles (equation 125)[108].

Truce and Hoerger showed that carbon–carbon alkylation occurs in good yield when δ-sultones react with carbanions including malonic esters and related compounds (equation 126)[110]. Similar reactions have been shown to occur with δ-sultones[163].

Willems[111] showed that ethylmagnesium bromide reacts with butane sultone according to equation 127. In a more detailed study, Truce and Hoeger[110] found that butane sultone reacts with phenylmagnesium bromide to form the magnesium salts of both 4-phenyl-1-butanesulphonate and 4-bromo-1-butanesulphonate (equation 128). This is analogous to the behaviour of Grignard reagents with alkane sulphonate esters when both hydrocarbons and alkyl halides are formed (equation 129)[190–192]. Although a side-reaction in the reaction of Grignard[193,184] reagents with alkylsulphonates is sulphone formation, no such formation could be detected in the reaction of phenylmagnesium bromide with







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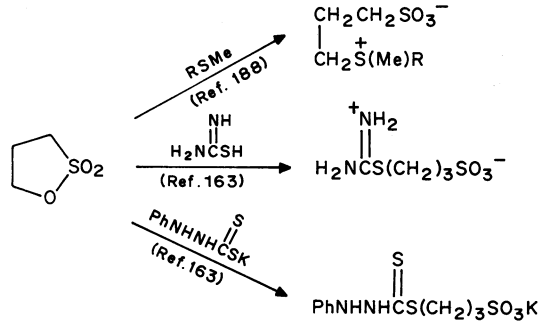

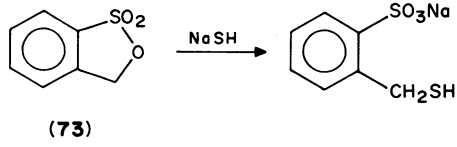

(73)

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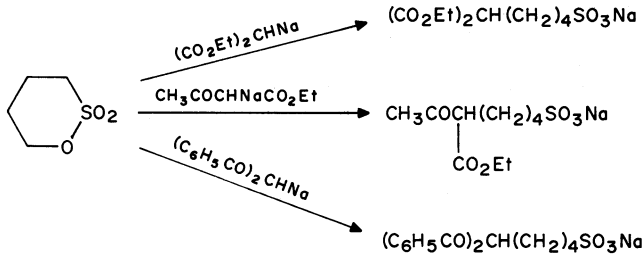

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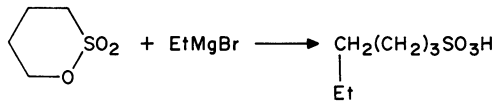

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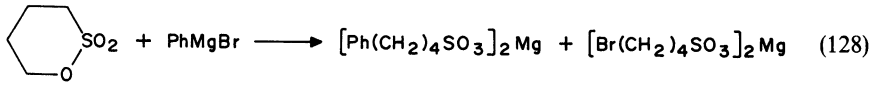
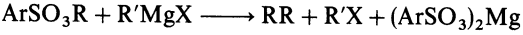
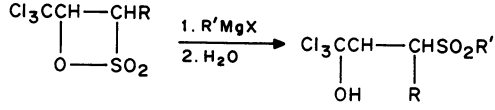


(128)

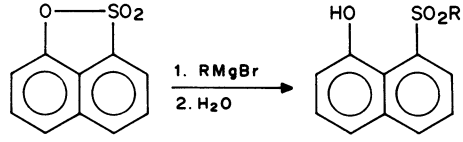


(129)



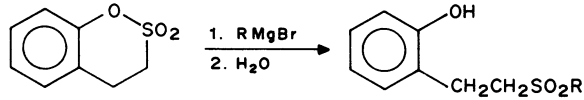
(130)

butane sultone[112]. The alkylation of β-sultones with Grignard reagents has similarly been observed (equation 130)[195]. In marked contrast to the reactions of aliphatic sultones, Mustafa and his coworkers have shown that aromatic sultones like naphthosultone and its derivatives react with phenylmagnesium bromide or α-naphthylmagnesium bromide to form sulphones as the major products (equation 131)[196–199]. Truce and Hoerger observed similar sulphonylation with aromatic δ-sultones (equation 132)[110].



(131)

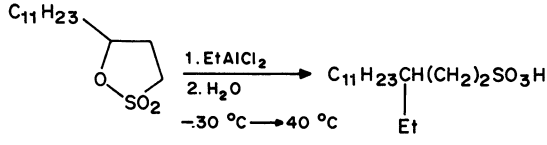
R=Ph, α-C10H7



(132)

C. Organometallic Reagents

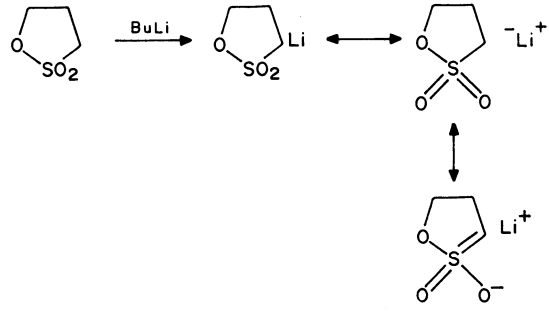
Reactions of sultones with Grignard reagents have been discussed in Section III.B.4, hence this section is concerned with all other reactions with organometallic reagents, particularly metallation reactions. At temperatures above 0 °C, organometallic reagents appear to react with γ- and δ-sultones to give, almost invariably, sulphonic acids. Thus ethylaluminium dichloride reacts with 5-undecanyl-1,2-oxathiolane 2,2-dioxide **74** to give the corresponding sulphonic acid (equation 133)[200]. Durst and du Manoir[201] have shown that lithiation at the α-position of γ- and δ-sultones results if these are treated with n-butyllithium at low temperatures. The α-hydrogen atoms of the sultone ring are the most acidic and their ionization leads to the most stable organolithium compounds



(74)

(133)

(equation 134). These are typically strongly nucleophilic, reacting with carbonyl compounds as shown in equation 135. In a later paper, Durst[202] showed that lithiation at the α-carbon atom of δ-sultones occurs preferentially at the equatorial position (equation 136). Preference for equatorial lithiation is so strong that when (*Z*)-3-methyl-5-*t*-butyl-1,2-oxathiin-2,2 dioxide (**75**) is treated with n-butyllithium and with a typical electrophile such as H^+ from water, the final product arises from equatorial lithiation, presumably via isomerization of the initially formed axial organolithium compound (equation 137). Since **75** is conformationally rigid, isomerization must occur via inversion at the carbanion-like centre at position 3 (the α-carbon atom). In a similar manner, the conformationally rigid sultone **76** gives **77** on treatment with butyllithium followed by quenching with water (equation 138).



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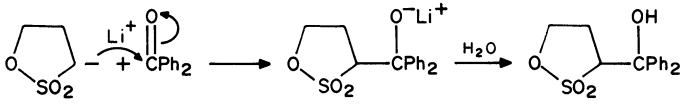
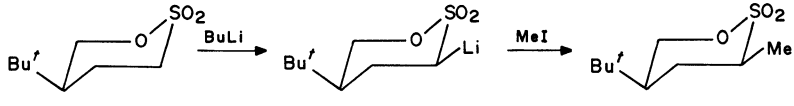
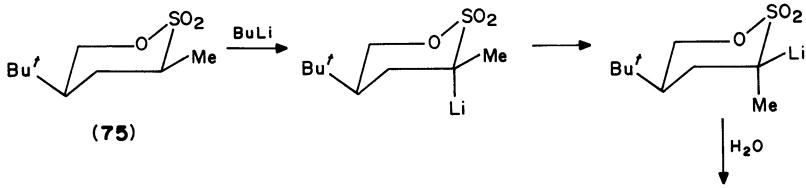
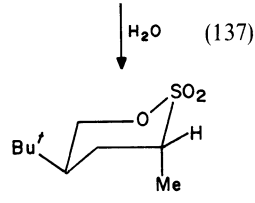


(135)

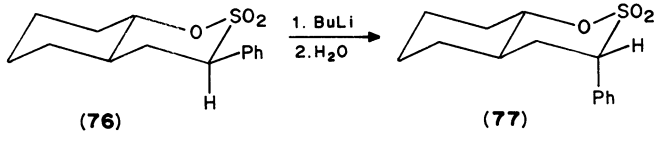


(136)





(137)

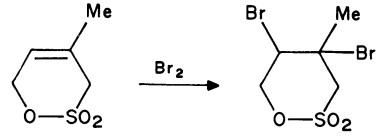


(138)

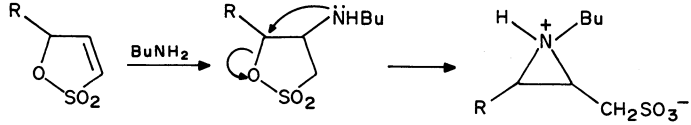
D. Addition, Elimination and Substitution

1. Addition reactions

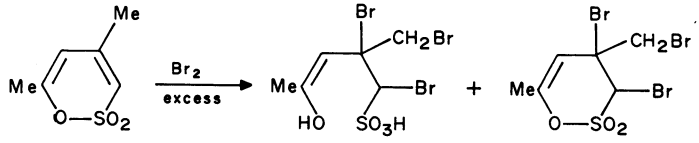
Unsaturated aliphatic sultones exhibit diversity of behaviour towards typical addition reagents. The β-unsaturated δ-sultone **78** on the one hand gives uncomplicated addition products with bromine (equation 139)[203], whereas the α-unsaturated γ-sultone **79** produces an interesting aziridinium betaine on addition of 1-butylamine (equation 140)[119]. In contrast α,γ-di-unsaturated δ-sultones do not normally undergo addition reactions at all easily; instead bromination, for example, generally leads to substitution products, either electrophilic or free-radical, depending on conditions, in keeping with their claimed aromatic character[204] (see Section II.D). However, bromination of sultones such as 4,6-dimethyl-1,2-oxathiin-2,2-dioxide (**80**) in the presence of a large excess of bromine (e.g. a three- or four-fold excess) leads not only to addition products, but also to ring opening (equation 141)[204].



(78) (139)



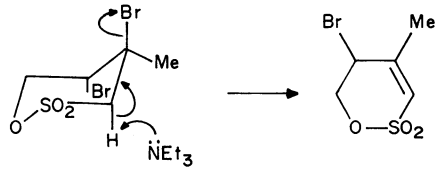
(79) (140)



(80) (141)

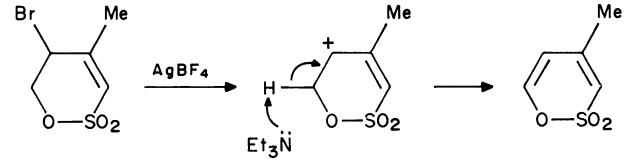
2. Elimination reactions

Halogenated saturated and α-unsaturated δ-sultones **81** and **82** undergo normal 1,2-elimination reactions in the presence of bases such as amines (equation 142)[7]. On the other hand, the sultone **82** undergoes an interesting elimination with ring contraction (equation 143) in the presence of lithium chloride[203], for which reaction Roberts and Williams suggest[7] the mechanism illustrated in equation 144. An alternative mechanism suggested by the authors is shown in equation 145. In DMF medium, the chloride ion will have enhanced nucleophilicity and lithium salts are likely to exist mainly as partially solvated ion pairs. The proposed mechanism attempts to highlight these aspects.

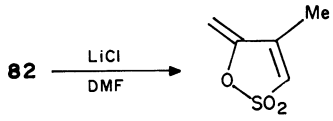


(81)

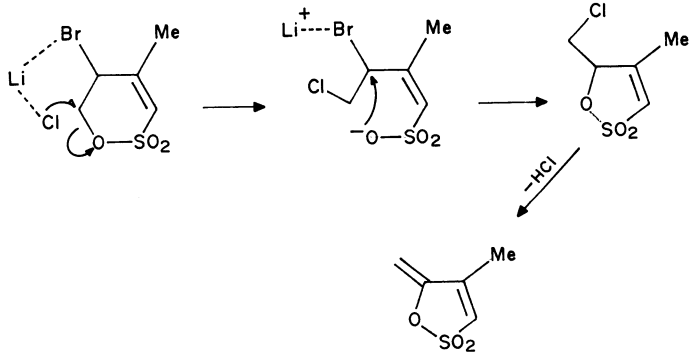
(142)



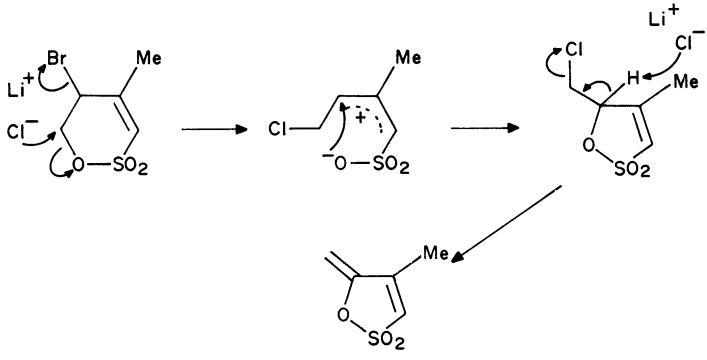
(82) (83)



(143)



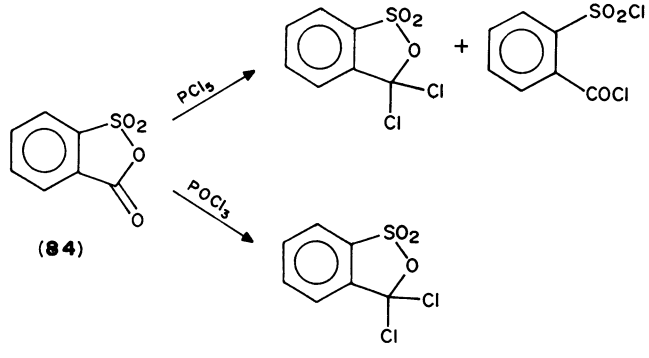
(144)



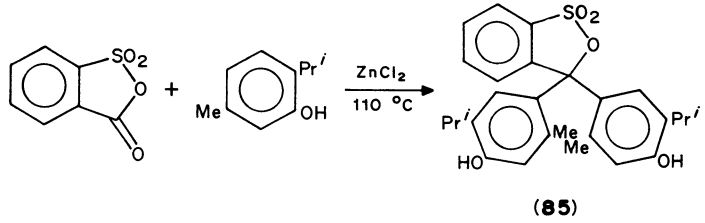
(145)

3. Reactions of keto sultones

Both β- and γ-keto γ-sultones have been the subject of much investigation and many interesting reactions have been discovered, some of whose mechanisms have yet to be unravelled. Among the earliest reactions investigated were those of 2,1-benzoxathiol-3-one-1,1-dioxide (**84**) with PCl_5 and $POCl_3$ as shown in equation 146[205]. However, the most interesting reactions of sultones like (**84**) are those with phenols to give sulphonephthaleins[206], a large group of compounds with acid–base indicator properties. These compounds are extensively reviewed in Breslow and Skolnik's monograph[8]. They can be prepared by heating **84** or similar sultones with phenols, sometimes in the presence of zinc chloride as illustrated in equation 147 for the preparation of thymolsulphonephthalein 'thymol blue' **85**[207]. Orndorff and Cornwell[207] were able to show that formation of **85**

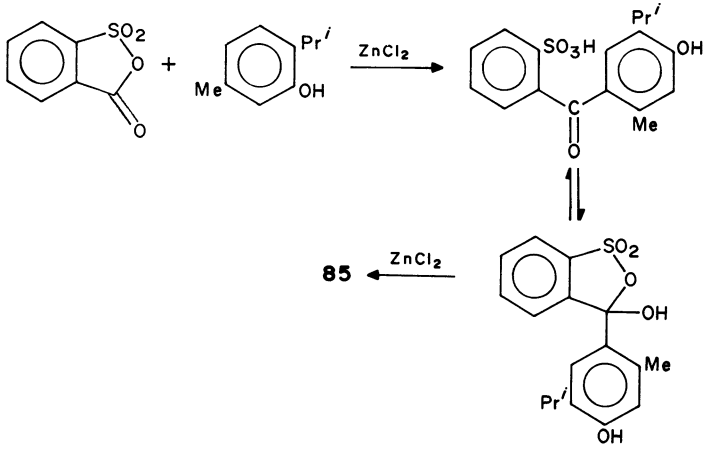


(146)



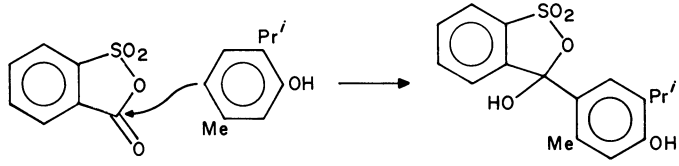
(147)

(**85**)

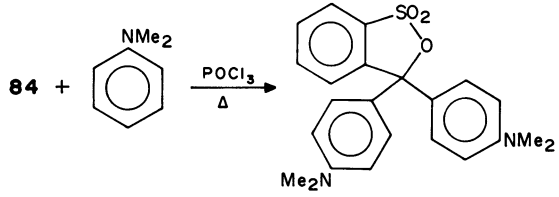


(148)

occurs in two stages (equation 148). They were able to prepare derivatives of both tautomeric forms of the intermediate. It seems likely that the initial step is a nucleophilic attack by the highly activated carbon atom *para* to the hydroxyl group of the phenol on the carbonyl group of **84**, which is highly electrophilic as a result of its proximity to the strongly electron-withdrawing sulphonate group (equation 149). Anilines are capable of similar reactions with **84** as shown in equation 150[208]. The much more recent work of Stachel and his coworkers on β-keto-γ-sultones such as 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide **86** has shown that keto–enol tautomerism plays a leading role in the reactions, where true addition across the carbonyl bond is rarely encountered[209]. The α-hydrogen atoms must exhibit considerable acidity as they are flanked by strongly electron-withdrawing groups (equation 151). Sultone **86** readily undergoes aldol condensation reactions and Mannich reactions as shown in equation 152. Similarly the sodium salt of **86** is readily prepared and easily undergoes O-alkylation, O-acylation and O-sulphonation (equation 153).



(149)



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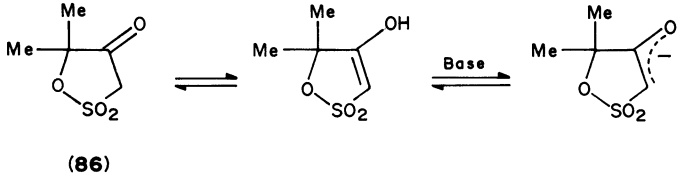
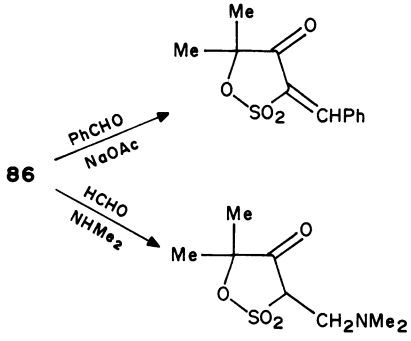


(86)

(151)



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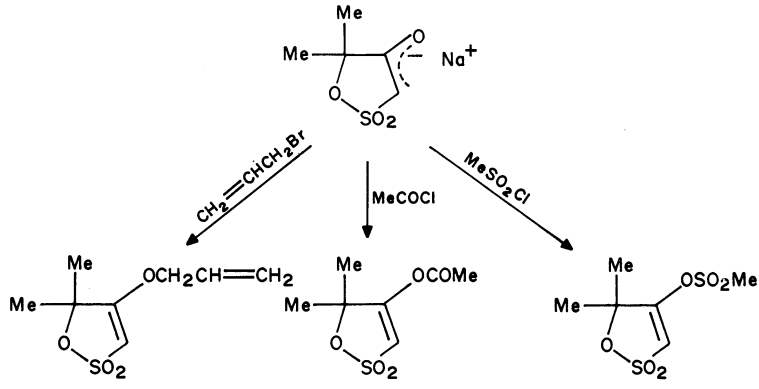
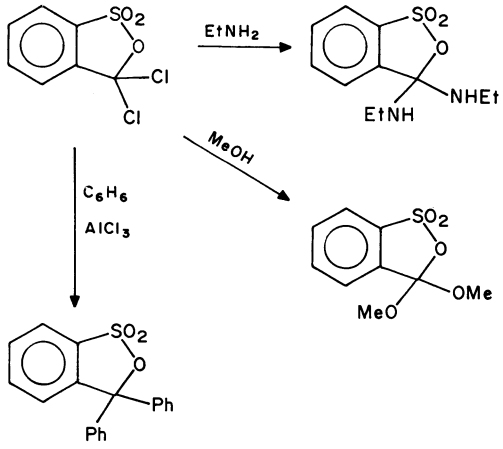


(153)

4. Substitution reactions of aliphatic sultones

It appears that S_N reactions at saturated carbon atoms, free radical substitutions (again at saturated carbon) and S_EAr reactions at unsaturated carbon have all been claimed to occur with aliphatic γ- and δ-sultones, although documentation of evidence seems in some



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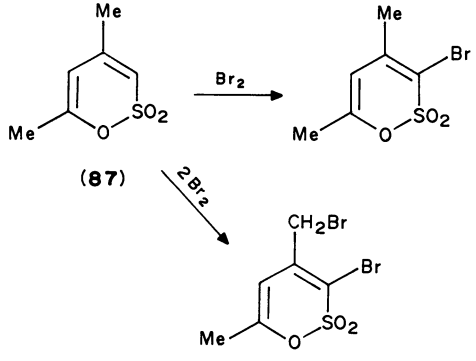
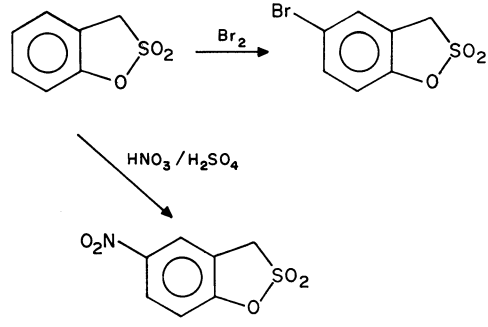


(155)

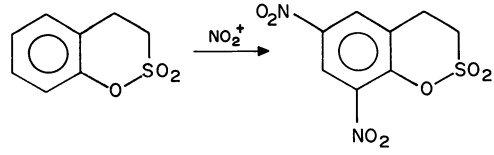
cases to be rather light. Some of the earliest examples involve substitutions in the γ-sultone ring of 3,3-dichloro-2,1-benzoxathiole-1,1-dioxide (equation 154)[74,210-213]. Much more recently, Doss and Abu Zeid, in an extensive study[204] of δ-sultone and δ-sultam bromination, have shown that the major reactions of unsaturated sultones and α,β-di-unsaturated δ-sultones such as **87** are (presumably) electrophilic and free radical substitutions which take place preferentially at the positions shown in equation 155.

5. *Benzenoid ring substitution*

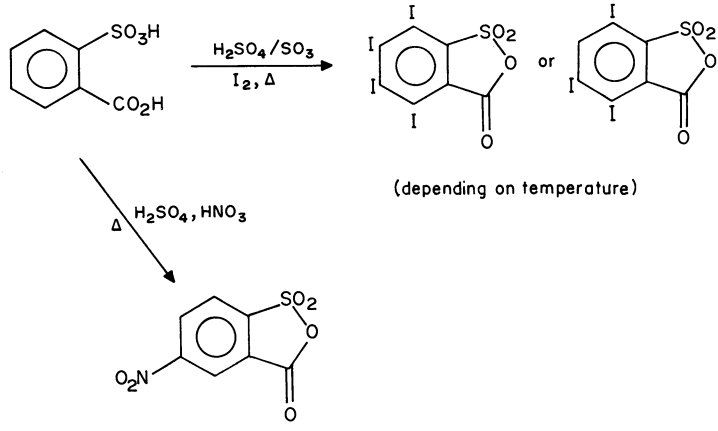
The benzenoid rings of aromatic sultones are known to undergo a number of electrophilic substitution reactions. Their reactivity toward electrophiles appears not to depend to any great extent on whether the sultone ring is connected to the benzenoid ring via the deactivating sulphur atom or the activating oxygen atom of the sulphonyl moiety. Thus 3*H*-1,2-benzoxathiole 2,2-dioxide can be brominated in the absence of bromine



(156)

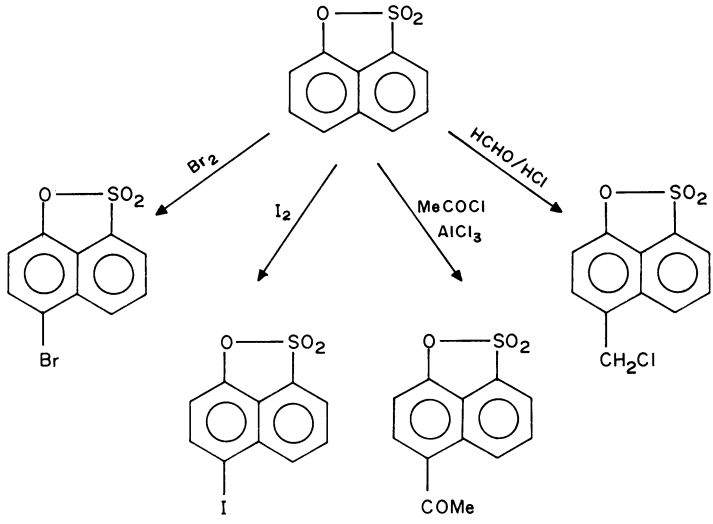


(157)



(158)

carrier Lewis acid catalysts and can also be nitrated under relatively mild conditions (equation 156)[214] with substitution occurring at the *para* position with respect to the sultone ring oxygen atom. Similarly 3*H*-benzoxathiin-2,2-dioxide can be readily nitrated to give the 2′,4′-dinitro derivative (equation 157). Both halogenation and nitration can accompany cyclization of *o*-sulphobenzoic acid (equation 158)[215–217]. Naphthosultones similarly readily undergo electrophilic substitution reactions, with substitution generally occurring at the 6-position. Scheme 7 illustrates the bromination[218], iodination[210], acylation[74] and chloromethylation[219] of 1,8-naphthosultone.

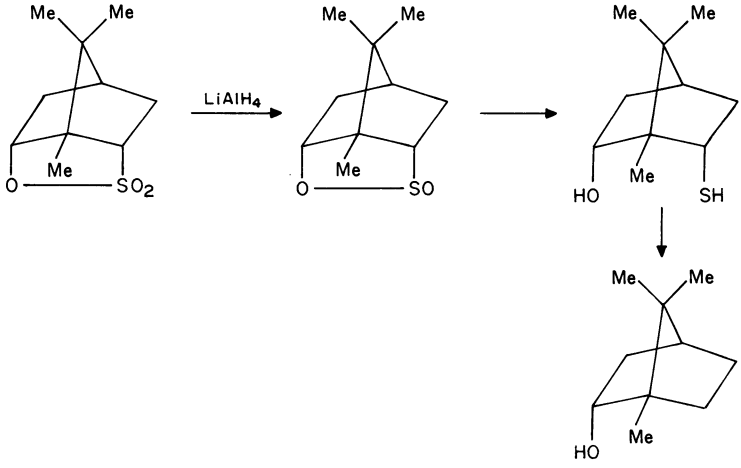


SCHEME 7

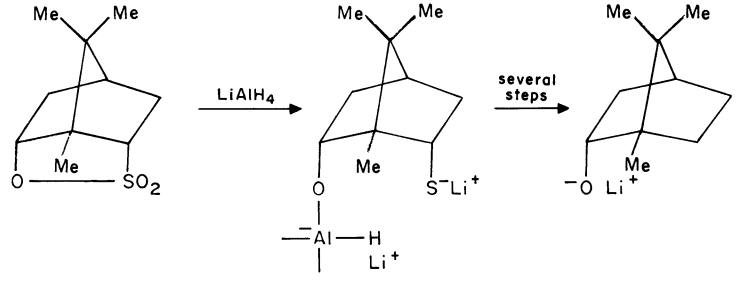
E. Miscellaneous Reactions

1. Reduction

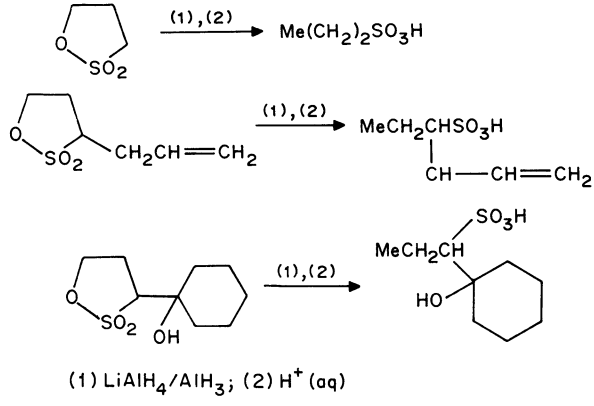
Lithium aluminium hydride (LAH) is easily the most widely studied reagent for the reduction of sultone ring systems. Wolinsky and his group have investigated the reduction of some sultone derivatives of terpenes[220–222]. Reduction appears to occur by S—O bond cleavage after initial reduction to a sultine and the final step involves removal of sulphur illustrated by the reduction of 6-bornyl sultone (Scheme 8). By controlling the concentration of LAH, the temperature and reaction time, any one of the three products shown in Scheme 8 can be made to predominate. A mechanism has been suggested[221] whereby hydride attack at sulphur leads to sulphides and eventually to an alkoxide (equation 159). Smith and Wolinsky have more recently shown that LAH reduction of γ-sultones in the presence of aluminium hydride leads to different products according to the extent of steric hindrance and neighbouring group assistance offered by substituents[222]. When there are no bulky γ- or β- substituents and when substituents are present at the α-position, attack of hydride at the γ-carbon atom predominates, resulting in C—O bond cleavage and the production of sulphonic acids (equation 160). On the other hand, when bulky groups are present at the β- and γ-positions or when there is a suitable non-bulky neighbouring group at the α-position, attack of hydride occurs mainly at the sulphur atom, resulting in S—O bond cleavage and the production of thiols (sometimes desulphuriz-



SCHEME 8

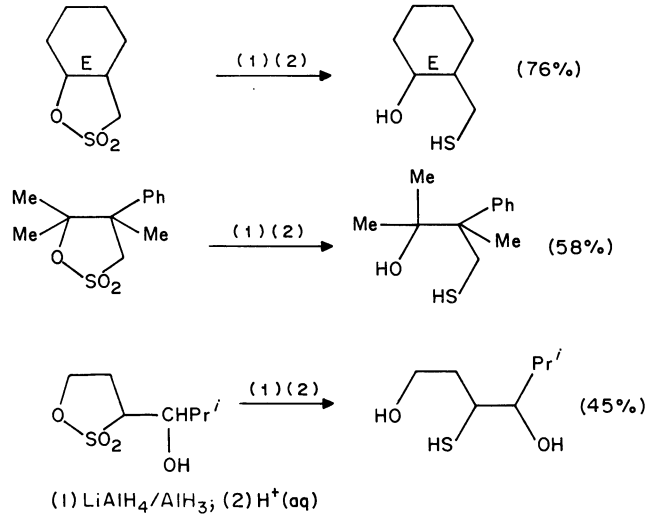


(159)



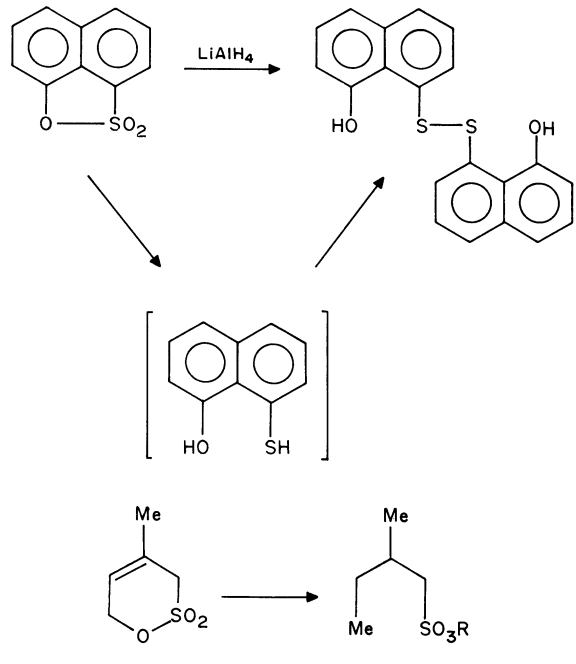
(160)

ation products are obtained) (equation 161). Aromatic γ-sultones such as 1,8-naphthosultone **1** are also reduced by LAH, but the major product in the case of **1** is 1,1-dihydroxy-8,8′-dinaphthyl disulphide, rather than the 1-hydroxy-8-naphthalene. It seems reasonable to suggest that reduction occurs by a similar route to that suggested by Wolinsky and



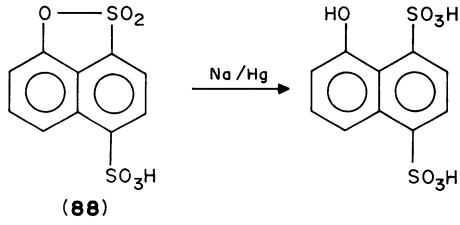
(161)

coworkers, but that the aromatic thiol group readily dimerizes (equation 162). Other reductive methods tend to give sulphonic acids. Mairanovskii and coworkers have reduced δ-sultones by electrochemical methods ($R' = t\text{-}Bu_4N$) and via heterogeneous catalytic hydrogenation ($R' = H$) to give the corresponding sulphonate and sulphonic acid, respectively (equation 163)[224]. Similarly reduction of the naphthosultone (**88**) with sodium amalgam leads to the sulphonic acid (equation 164)[225]. Sulphonephthaleines can be reduced to sulphonic acids by zinc dust (equation 165)[226].

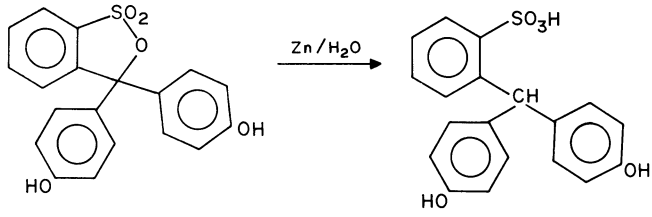


(162)

(163)



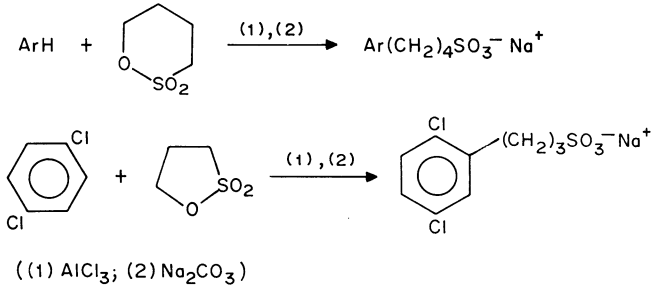
(88) (164)



(165)

2. Friedel–Crafts reactions

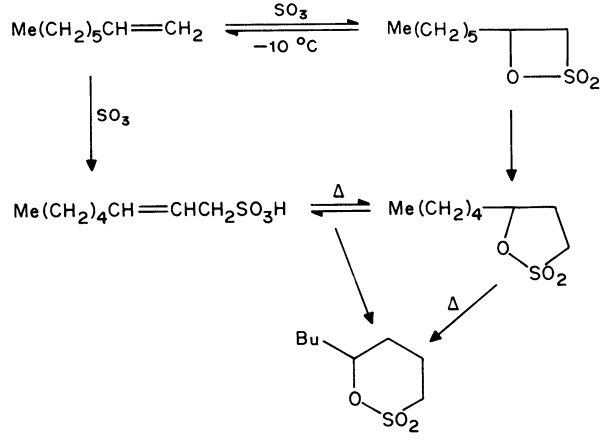
Both γ- and δ-sultones, with highly electrophilic carbon atoms at the γ- and δ-ring positions respectively due to the proximity of the sulphonate ring oxygen atom, readily act as alkylating agents of hydrocarbons in the presence of Lewis acids such as aluminium chloride (equation 166)[163,227]. These reactions provide a useful route to arylalkylsulphonates and have the advantage over the usual Friedel–Crafts alkylations in that skeletal rearrangements do not occur.



(166)

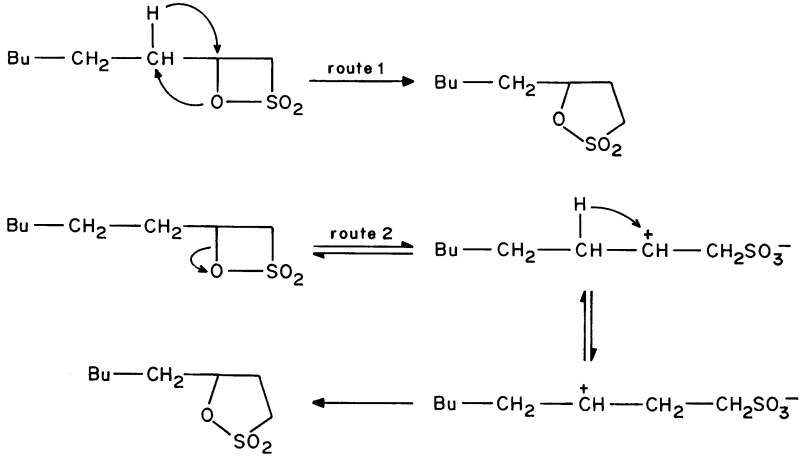
3. Rearrangements

Sultones are, on the whole, very prone to certain types of rearrangement reactions. Of particular interest are the isomerizations of β-, γ- and δ-sultones and these will be discussed first. There is now much evidence[228] that sulphonation of alkenes with sulphur trioxide proceeds largely via the initial formation of β-sultones by (^{2}s + ^{2}s) cycloaddition (see Section II.A.1). The β-sultones then undergo thermal isomerizations to γ- and δ-sultones, as well as to 2-alkenesulphonic acids, although there is the added complication that the latter can be formed directly from the alkene[229] and can also isomerize to γ- and δ-sultones (Scheme 9)[230]. Furthermore, Cerfontain and his coworkers have recently shown that the initial β-sultone formation step is reversible. However, it appears that

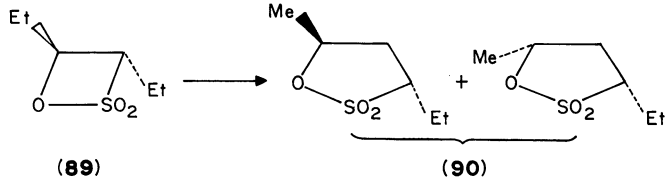


SCHEME 9

direct 2-alkenesulphonate formation is a minor route, particularly that leading to internal alkene sulphonation[229]. The isomerization of β-sultones may occur by a concerted or a stepwise mechanism (involving zwitterionic intermediates) as shown in routes 1 and 2, respectively, of Scheme 10. According to Thaler and du Breul[113] it appears as though isomerization of β-sultones to γ-sultones is not stereoselective, as either (*Z*)- or (*E*)-3,4-



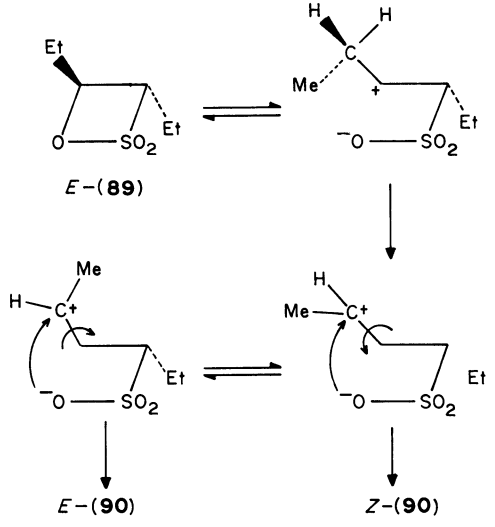
SCHEME 10



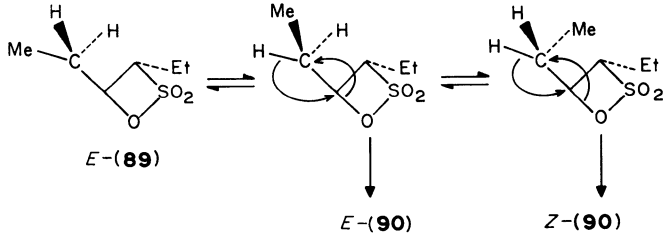
(167)

(89) (90)

diethyl-1,2-oxathietane-2,2-dioxide (**89**) give both (*Z*)- and (*E*)-3-ethyl-5-methyl-1,2-oxathiolane-2,2-dioxide (**90**) as shown in equation 167. Similarly both (*Z*)- and (*E*)-2-ethylbut-2-enesulphonic acid are formed from **89**. These facts are probably more easily explained by a stepwise isomerization process which involves zwitterionic intermediates (Scheme 11a), but a concerted mechanism (Scheme 11b) cannot be ruled out.

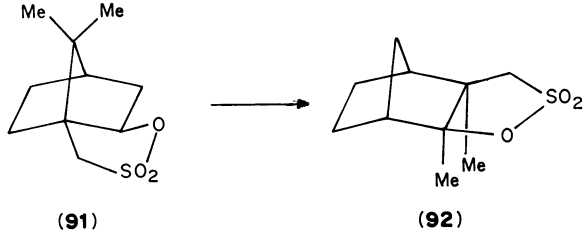


SCHEME 11a

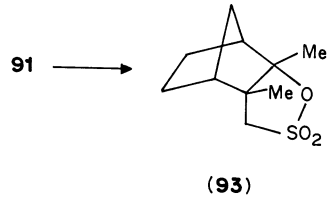


SCHEME 11b

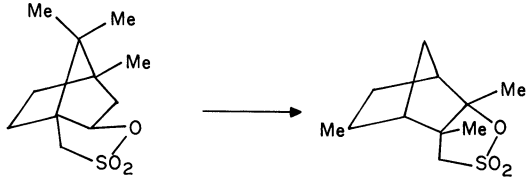
Some spectacular rearrangements of terpenoid γ-sultones were reported by Dimmel and his associates in the late 1960s and early 1970s as illustrated in equations 168–170 for the rearrangement of 10-isobornyl sultone **91** to *exo*-camphene sultone **92**, of **91** to *endo*-



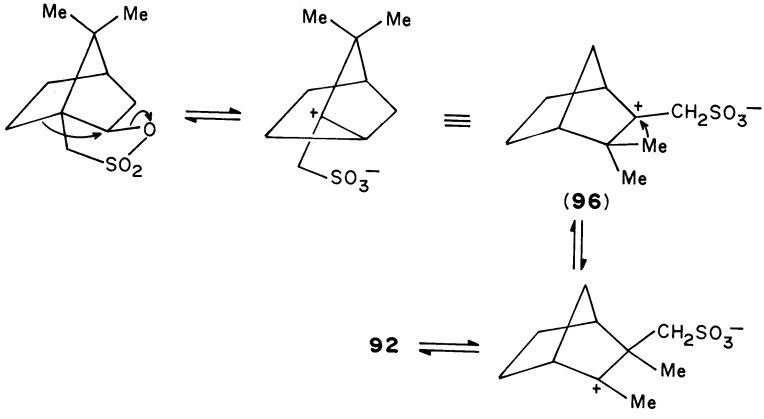
(168)



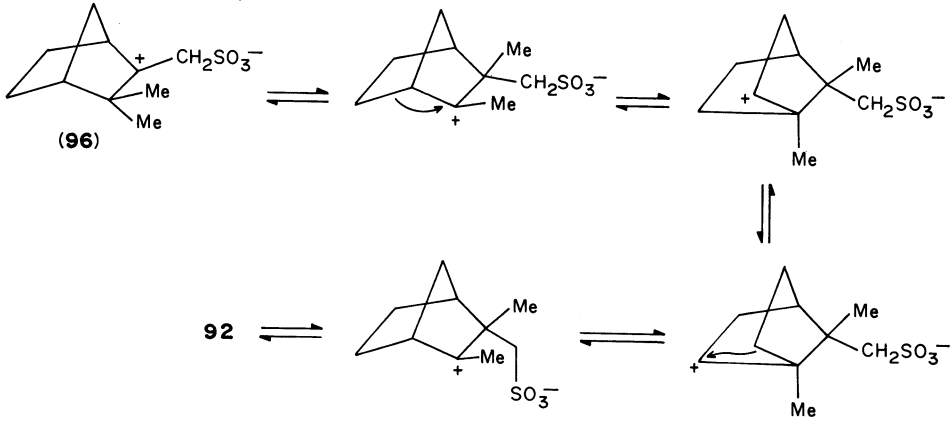
(93) (169)



(94) (95) (170)



SCHEME 12a



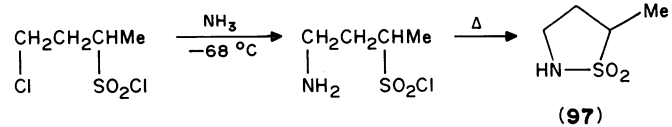
SCHEME 12b

camphene sultone **93** and of 4-methyl-10-isobornyl sultone **94** to *endo*-sultone **95** respectively[231,232]. Two mechanisms were proposed which differ in the nature of a 1,2-methyl migration in the key cation **96** produced by a Wagner–Meerwein rearrangement of **91**, for example. If this shift is *endo*, then product **92** is formed directly (Scheme 12a). However an *exo* 1,2-methyl shift in **96** also leads to **92**, but by a much more indirect route involving a number of rearrangements (Scheme 12b). Studies on the rearrangement of 3,3-[^2H]-**91** suggest the latter to be the main mechanistic route.

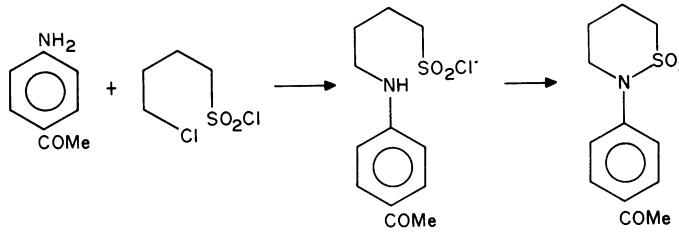
IV. SYNTHESIS OF SULTAMS

A. Cyclization of Aminoalkane- and Alkenesulphonic Acids and their Derivatives

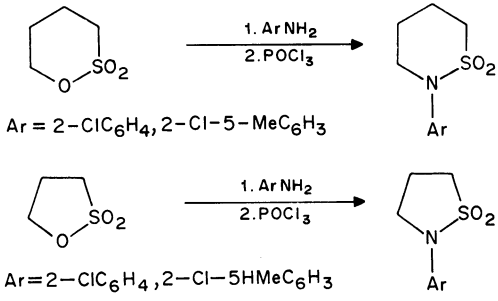
A good general route to a wide variety of β-, γ- and δ-sultams (saturated and unsaturated) is provided by the cyclization of various aminosulphonic acid derivatives. Ring closure is achieved by N—S bond formation resulting from nucleophilic attack of nitrogen on the activated sulphur atom of the sulphonyl group. It is common to prepare and cyclize the immediate sultam precursor *in situ*; there are several ways in which this can be done. Helberger's group succeeded in making γ-sultams like 5-methyl-1,2-thiazolane 2,2-dioxide **97** from α-chlorosulphonyl γ-chloroalkanes (equation 171)[233]. More recently, similar methods have been used by Doss to prepare saturated δ-sultones (equation 172)[234]. The same research group and the equally active group of Zeid have synthesized a number of saturated γ- and δ-sultams via aminolysis of the corresponding sultones (equation 173)[234–236]. In each of these reactions, it is presumed that aminolysis



(97) (171)

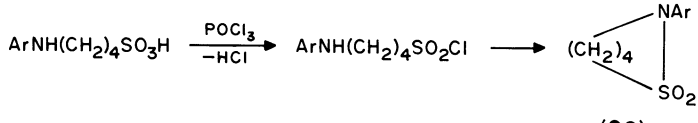


(172)



(173)

leads to the aminosulphonic acid which is then cyclized to the corresponding sultam **98** by conversion to the aminosulphonyl chloride by phosphorus oxychloride (equation 174). Helferich and his coworkers[170] have reported a facile synthesis of α,γ-di-unsaturated δ-sultams such as **99** by reaction of arylamines with α,γ-di-unsaturated δ-sultones (equation 175). A possible mechanism for this reaction is outlined in equation 176, whereby ring opening of the sultone is followed by spontaneous cyclization of the unsaturated aminoalkadienesulphonic acid **100**. Since Helferich's paper a number of other syntheses of α,γ-di-unsaturated δ-sultams by similar routes have been reported[234,235,237] and there is one report of the synthesis of *N*-alkyl β-unsaturated δ-sultams such as **101** (equation 177)[238].



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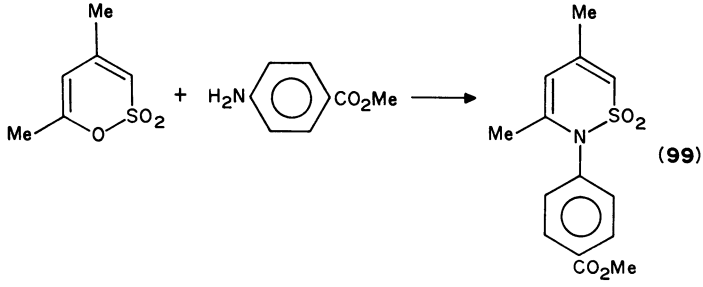
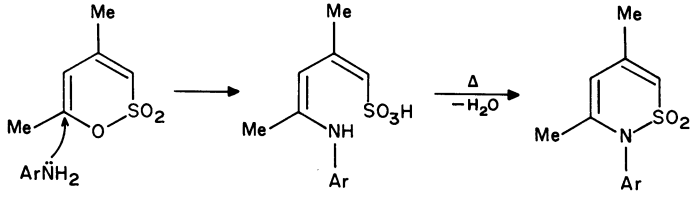
(98)



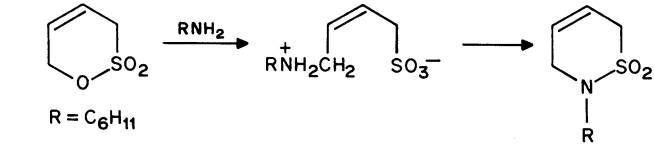
(175)

(99)



(176)

(100)

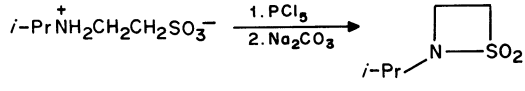


(177)

(101)

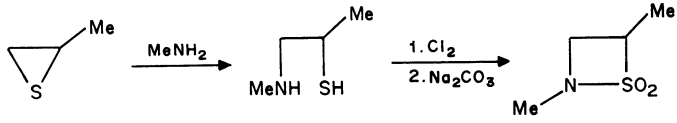
It is in the field of β-sultam chemistry where synthetic pathways involving cyclization of aminoalkanesulphonic acid derivatives have proved to be particularly useful in recent years. Chanet-Ray and Vessiere have included this subject in their extensive review on the synthesis and reactions of β-sultams[239]. A variety of *N*-alkyl and *N*-aryl β-sultams has been prepared[240–243] by a number of research groups via the cyclization of 2-amino-

alkanesulphonyl halides, although routes to these immediate precursors differ quite markedly. Champseix, Chanet-Ray and coworkers[241] have synthesized β-sultams from taurines (2-aminoalkanesulphonates), as shown in equation 178 for the preparation of **102**. 2-Aminothiols can be oxidized to the corresponding sulphonyl chloride by chlorination[241,242] using molecular chlorine or hypochlorous acid. The aminothiols themselves can be prepared via the aminolysis of thiiranes[241] (equation 179) or by reaction of aziridines with hydrogen sulphide (equation 180)[241,242]. Similarly β-aminodisulphides can also be oxidized in this manner (equation 181)[242]. A useful aspect of cyclization of this kind is the conservation of stereochemistry at key diastereoisomeric centres (equation 182)[241]. Otto's group have made particular use of stereochemistry in the synthesis of the parent structure **103** of sulphone penicillin analogues and of its higher analogues



(178)

(102)



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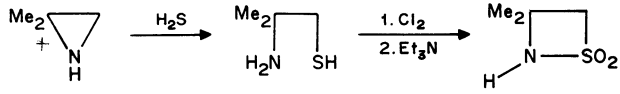

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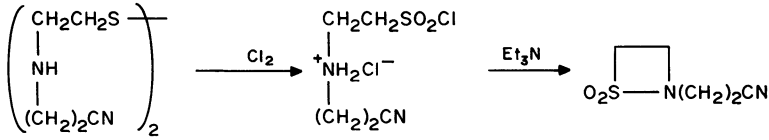

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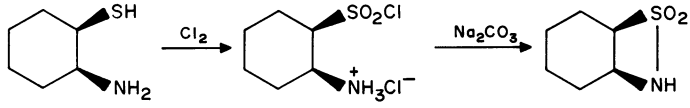
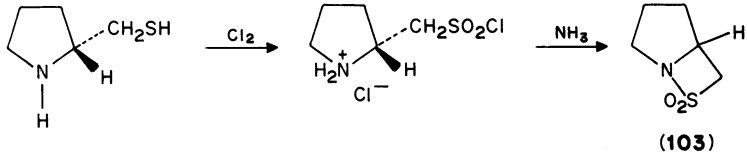


(182)



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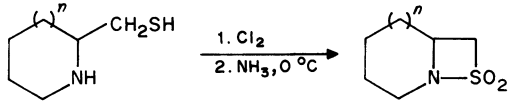
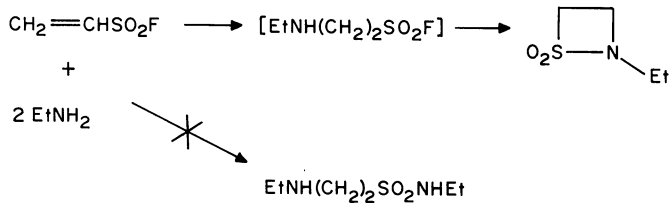


(183)

(n=1,2) (104)

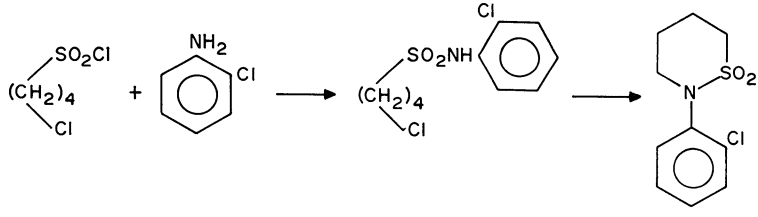
such as **104** (equation 183)[240]. An interesting and useful variation on this method is provided by Champseix, Chanet-Ray and coworkers[241]. They have used 2-aminoalkanesulphonyl fluorides as β-sultam precursors. This method allows introduction of the amine function after the formation of the fluorosulphonyl group, since the fluoride ion is a poor leaving group compared with chloride and hence is less likely to take part in side-reactions. An example is given in equation 184.



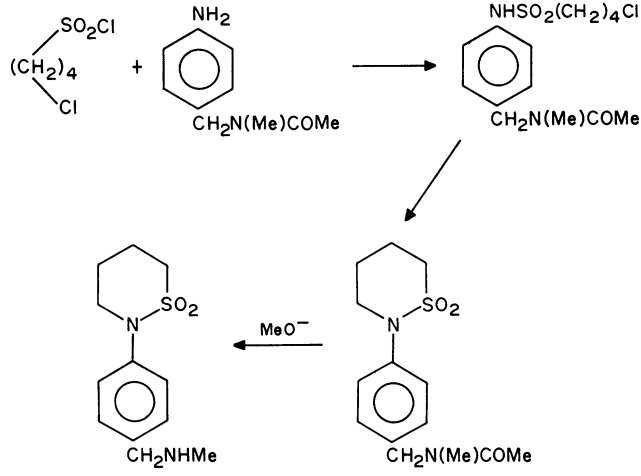
(184)

B. Cyclization of Halogeno- and Hydroxyalkanesulphonamides and Related Compounds

These cyclizations occur via C—N bond formation and have been used for the synthesis of a number of saturated δ-sultams and β-sultams. In particular Helferich, Doss, Zeid and coworkers have reported the synthesis of several, mainly *N*-aryl, saturated δ-sultams via cyclization of chloroalkanesulphonamides as outlined in equations 185–187[236,244,245]. Oppolzer and coworkers have synthesized γ-sultams as part of their work on chiral

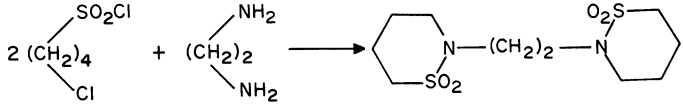


(185)

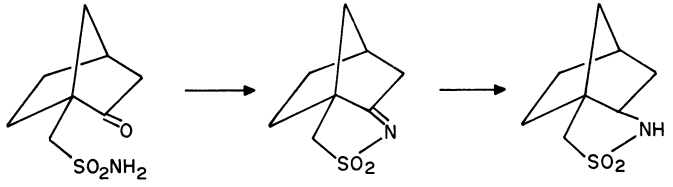


(186)

dienophiles (equation 188)[246]. The sulphonamide **105** is cyclized via nucleophilic attack at carbonyl to the imine **106**, which is then reduced to the corresponding sultam **107**. Thompson has recently shown that cyclization of mesylate esters of β-hydroxysulphonamides leads to β-sultams, in the presence of base (equation 189)[247].

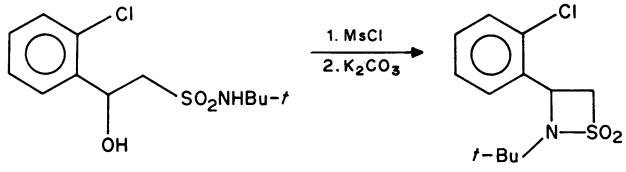


(187)



(188)

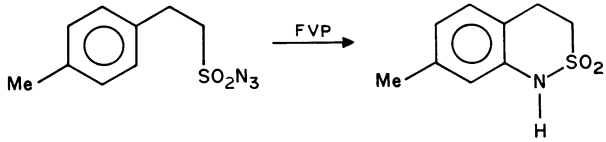
(**105**) (**106**) (**107**)



(189)

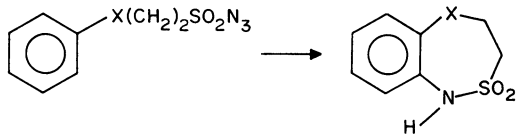
C. Thermal Decomposition of Sulphonyl Azides

Flash vacuum pyrolysis (FVP) of 2-arylethanesulphonyl azides leads to good yields of δ-sultams, such as 4′-methyl-3,4-dihydro-2,1-benzothiazine-2,2-dioxide **108** (equation 190)[248], provided the pyrolysis temperature is no higher than 300 °C and is carried out in Freon 113. More recently, using similar techniques, Abramovitch and coworkers have synthesized unusual seven-membered benzo-sultams[249] from 3-arylpropanesulphonyl azides and 2-aryloxyethanesulphonyl azides, as illustrated in equation 191 for the formation of the ε-sultam 2,3,4,5-tetrahydro[*c*]-1,2-thiazepine 1,1-dioxide (**109**)



(190)

(**108**)

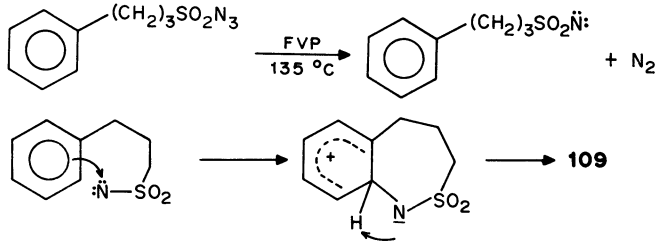


(191)

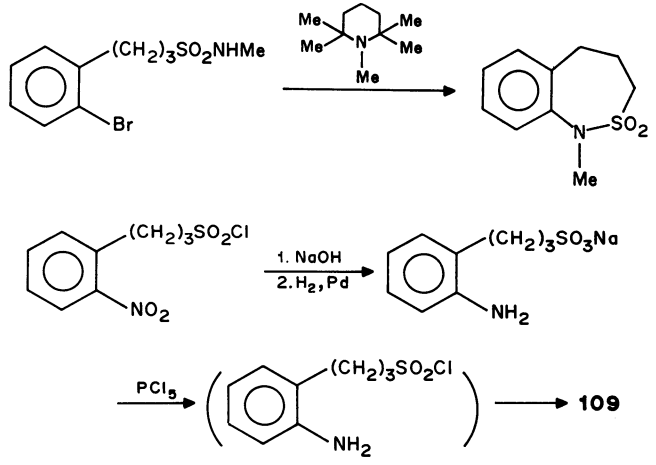
(**109**) X = CH_2

(**110**) X = O

and the oxa derivative (**110**). These reactions are all postulated to proceed via sulphonylnitrenes (Scheme 13). Interestingly, Abramovitch and coworkers[249] used C—N bond-forming cyclizations in independent syntheses of some sultams produced by FVP. Thus N-methylated **109** was made by a route involving an aryne intermediate (equation 192) and **109** itself was synthesized from 3(2-nitrophenyl)-1-propanesulphonyl chloride as shown in Scheme 14.



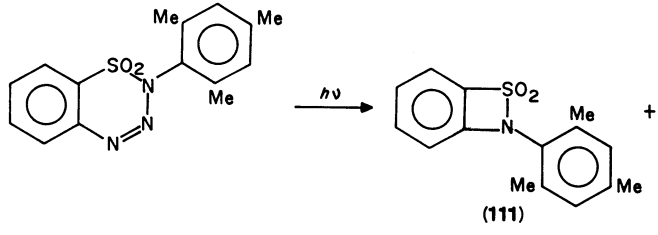
SCHEME 13



SCHEME 14

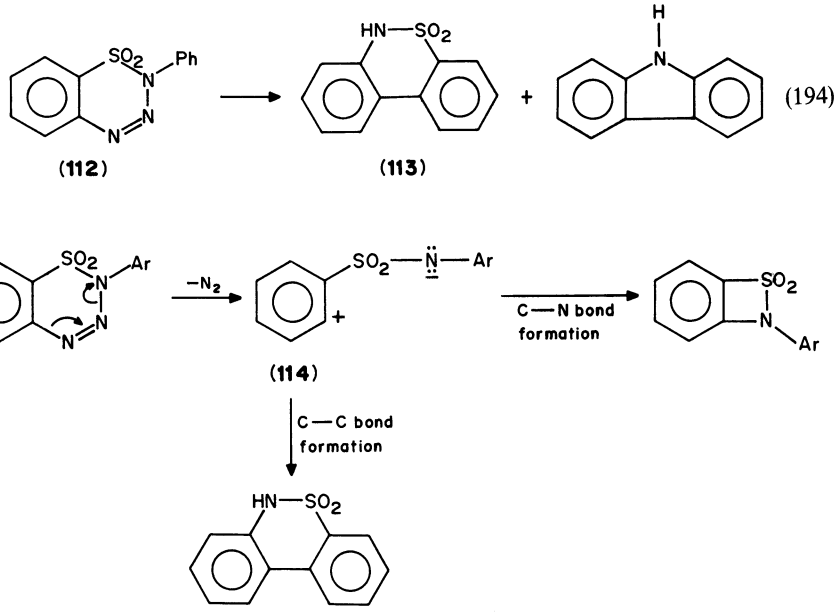
D. Photolysis of 1,2,3,4-Thiatriazine 1,1-Dioxides

Photolysis of 2-mesityl-2H-benzo[*e*]-1,2,3,4-thiatriazine 1,1-dioxide gives the *β*-sultam **111** (equation 193), whereas photolysis of the 2-phenyl analogue **112**, with free



(193)

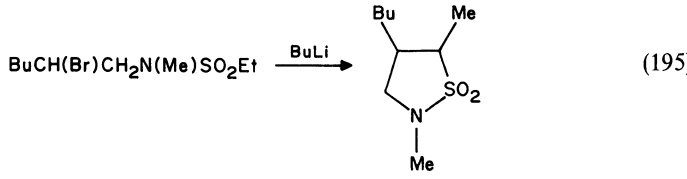
ortho positions on the *N*-aryl group, gives mainly dibenzo-1,2-thiazine 1,1-dioxide (**113**) and carbazole (equation 194)[250]. These reactions can be explained by a mechanism that involves the formation of a phenyl cation-imide zwitterion (**114**) as outlined in Scheme 15.



SCHEME 15

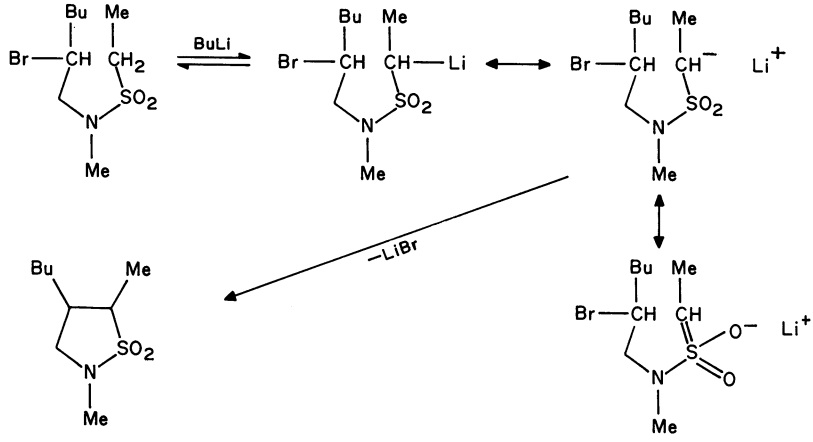
E. Cyclization of *N*-(2-bromoalkyl)-alkanesulphonamides

A variety of γ-sultams have been prepared via metallation (lithiation) of *N*-(2-bromoalkyl)-alkanesulphonamides (equation 195)[251]. Lithiation occurs at the methylene carbon α to the sulphonyl group to give the resonance-stabilized carbanion-like species, which then undergoes nucleophilic attack on the 2-bromoalkyl carbon atom. Thus cyclization is achieved via C—C bond formation (Scheme 16).

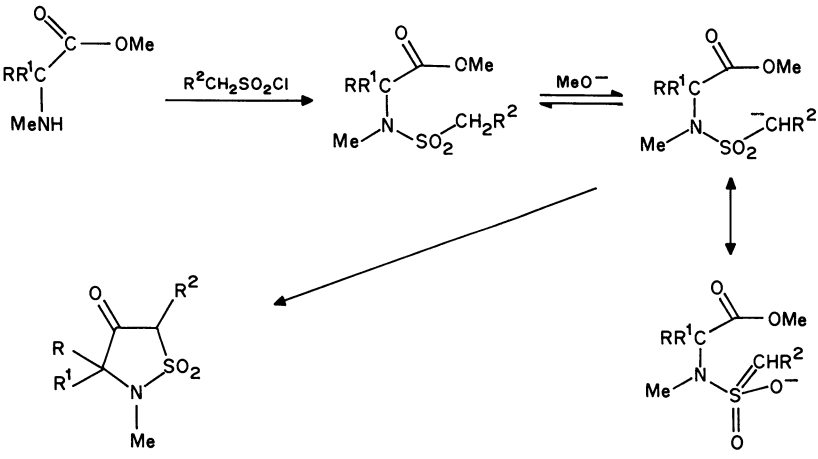


F. Cyclization of *N*-(1-carboxyalkyl)-alkanesulphonamides

Stachel and Drasch have recently synthesised γ-sultams with ketone functions at the ring β position[66]. The synthesis route comprises formation of the title compounds by sulphoacylation of α-amino esters followed by their cyclization, via C—C bond formation, in the presence of base (Scheme 17).



SCHEME 16



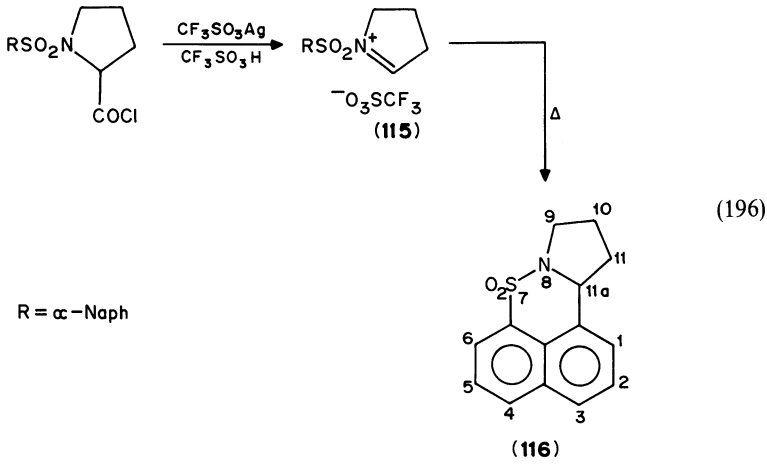
SCHEME 17

G. Cyclization of Iminium Salts

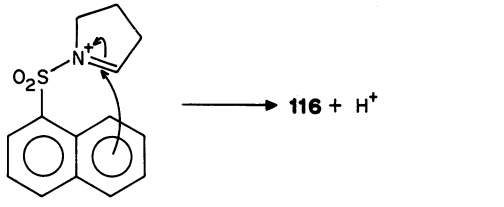
The aromatic δ-sultam, 9,10,11,11a-tetrahydronaphtho[1,8-*d*,*e*] pyrrolo[1,2-*b*]-thiazine-7,7-dioxide (**116**) has been synthesized by Adesogan and Alo by cyclization of the iminium salt **115**, which is itself prepared from *N*-arylsulphonylpropyl chloride by the action of silver triflate and triflic acid (equation 196)[252]. The cyclization step presumably proceeds via C—C bond formation involving electrophilic attack of the activated iminium group carbon atom on the 8-position of the naphthalene ring (equation 197).

H. β-Sultams from Cycloaddition Reactions

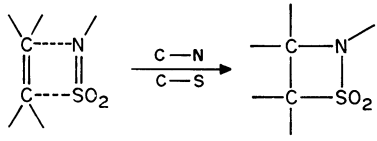
Cycloaddition reactions of heterocumulenes have been much used in the synthesis of β-sultams. The two general methods, emphasizing different synchronous bond formations, are outlined in equations 198 and 199.



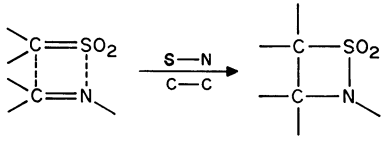
(196)



(197)



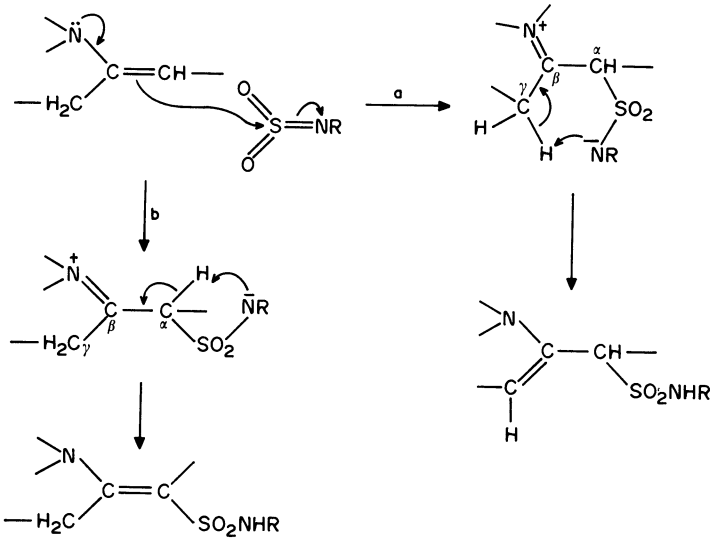
(198)



(199)

1. From N-sulphonylamines

N-Sulphonylamines, such as *N*-sulphonylethylamine **117**, are generated when sulphonyl chlorides are treated with bases such as triethylamine (equation 200). These react with sufficiently nucleophilic alkenes to give *β*-sultams[253–257], the most widely used alkenes being enamines with neither a *γ*-methylene group nor α-hydrogen atoms (equation 201)[253,255], otherwise acylic sulphonamides are formed in competition, as shown in Scheme 18. This is particularly the case when either the nucleophilicity of the alkene or the electrophilicity of the *N*-sulphonylamine are only modest. Formation of *β*-sultams is maximized by using strongly nucleophilic alkenes where *γ*-hydrogen abstraction (route a) is inhibited and strongly electrophilic *N*-sulphonylamines, where α-hydrogen abstraction (route b) is inhibited. Thus *β*-sultam **118** was obtained in good yield

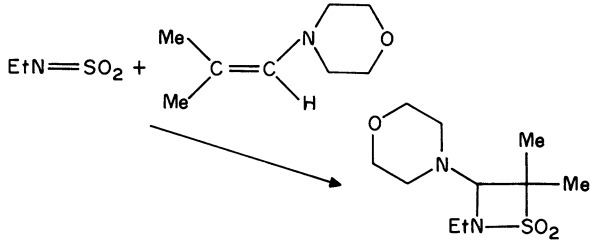


SCHEME 18

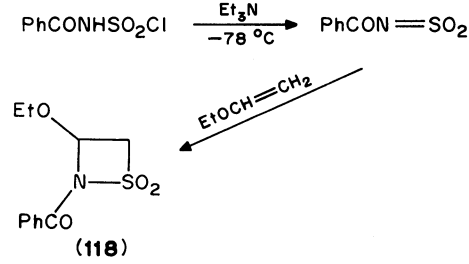
by cycloaddition of *N*-sulphonylbenzamide and ethyl vinyl ether (equation 202)[257]. Similarly *N*-sulphonylmethylcarbamate **119** gives *β*-sultams with weakly nucleophilic alkenes (equation 203)[256]. Some of these reactions have been shown to be stereoselective (equation 204)[258].

$$EtNHSO_2Cl \underset{-78\,^{\circ}C}{\overset{Et_3N}{\rightleftharpoons}} \vec{E}t\ddot{N}{-}SO_2{-}\ddot{C}l \xrightarrow{-Cl^-} EtN{=}SO_2 \qquad (200)$$

(117)

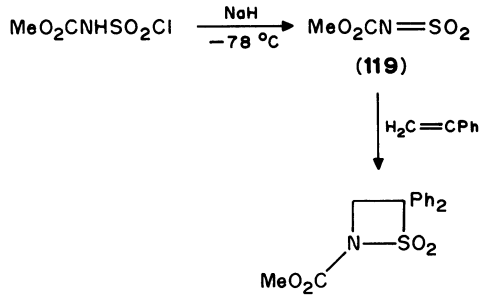


(201)

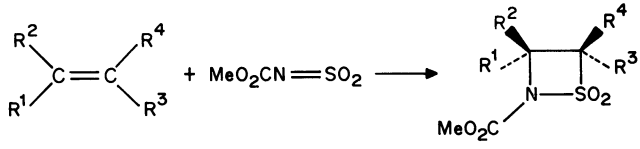


(202)

(118)



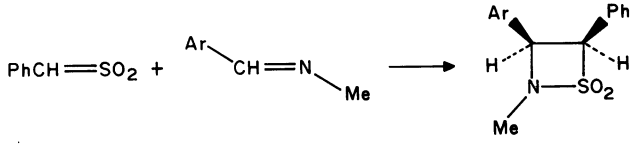
(203)



(204)

2. From sulphene-imines

Sulphenes, generated by reaction with tertiary amines (see Sections II.A.2 and II.B.2), react with Schiff's bases to give β-sultams[258,259]. In all cases so far, *Z*-sultams predominate in the product mixture so that Hirotoka and Kobayashi have suggested a concerted $[\pi^2s + \pi^2s]$ mechanism for the reaction (equation 205)[259].



(205)

Ar = Ph, *p*-ClC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$

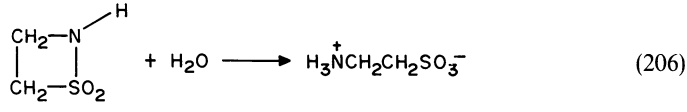
V. REACTIONS OF SULTAMS

Sultams are in general stable, mainly crystalline substances which are readily soluble in alkaline media due to salt formation. This occurs because of the acidic nature of the imino NH group created by the strong electron-withdrawing effect of the adjacent SO_2 group. The water-soluble salts are useful in a variety of synthetic processes. The reactions of sultams have not been so widely studied as those of the corresponding sultones.

A. Hydrolysis

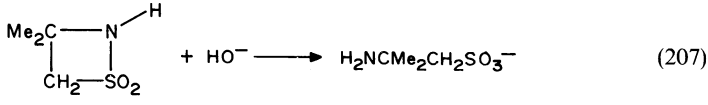
The β-sultams undergo ring opening in water, alkaline solution or in acidic solution. Thus ethane sultam (**120**) slowly decomposes in water to the sultaine taurine (equation 206)[260]. Ring opening of β-sultams in basic solution has been reported in several cases (equations 207, 208)[259,261]. Whilst there have not been any detailed reports of the alkaline hydrolysis of other alicyclic sultams, it has long been known that aromatic sultams like 1,8-naphthosultam and its derivatives undergo ring opening in hot aqueous alkali to give the alkali salts of the corresponding amino sulphonates (equation 209)[262,263]. When fused with alkali, 1,8-naphthosultam forms 8-amino-1-

naphthol[3]. Although the cleavage of sulphonamides in acidic solution (historically a reaction of considerable interest for the Hinsberg method of amine separation[263]) occurs only under rather vigorous conditions, e.g. concentrated hydrochloric acid at 150–200°C[264], Feichtinger and Puschoff reported that propane and *N*-methylpropane sultam were cleaved by HCl in benzene at 25°C[265]. Erman and Kretschmar examined this reaction in some detail and have shown that propane sultam and its *N*-alkyl derivatives are cleaved by hydrogen chloride, hydrogen bromide and acetic acid but not by phenol[266]. Cleavage with methanolic hydrogen bromide or chloride takes place readily at room temperature or below and leads to formation of the sultaines in good yield (equation 210). In ether as solvent, the products are the hydrohalide salts (equation 211). The authors suggested a mechanism analogous to that proposed for the acid-catalysed hydrolysis of sulphonamides (equation 212)[267]. Such a mechanism is supported by the observed substituent effects. *N*-*p*-nitrophenylpropane sultam is not cleaved by anhydrous hydrogen bromide whereas the *N*-*p*-tolyl sultam reacts at a similar rate to *N*-alkylpropane sultams. Ethane sultam is also converted to chlorosulphonyl aminoethane with anhydrous hydrogen chloride[260]. Whilst the cleavage of sulphonamides by concentrated HBr normally leads to oxidation–reduction products, Erman and Kretschmar obtained only sultaines or sulphonyl halide hydrobromides from sultams[266].

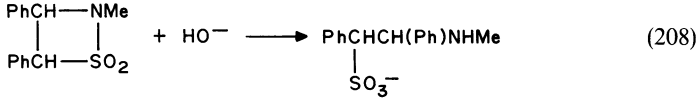


(120)

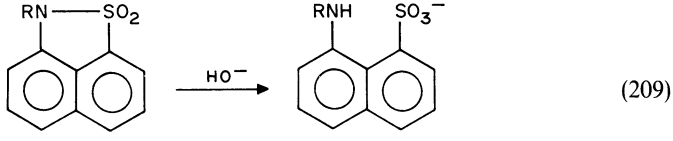
(206)



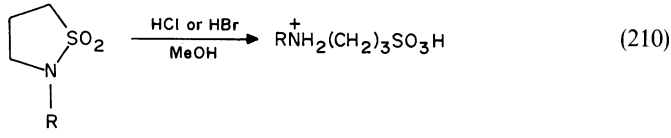
(207)



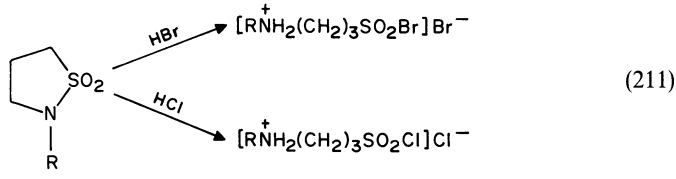
(208)



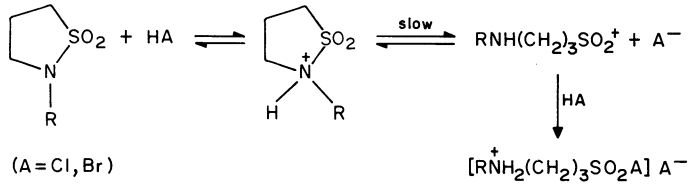
(209)



(210)

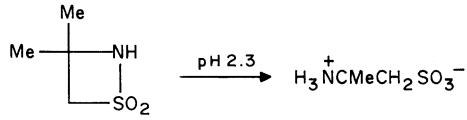


(211)



(212)

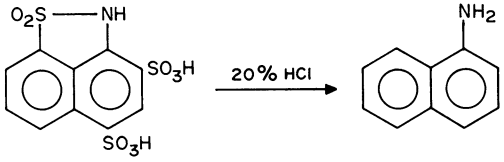
Koller and his coworkers have reported that the sultam **121** rapidly hydrolyses in dilute acid (equation 213)[242]. Helferich and Kleb have reported[268] that whereas *N*-4-acetamidophenylpropane sultam is cleaved by boiling sulphuric acid (16%), the corresponding butane sultam does not react suggesting that the order of reactivity of sultams towards acid hydrolysis is $\beta > \gamma > \delta$.



(213)

(121)

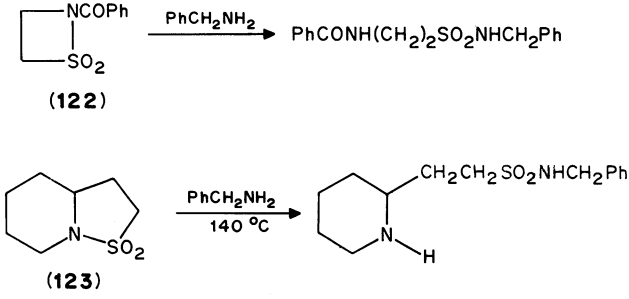
Aromatic sultams are generally resistant to ring opening under acid conditions. When 1,8-naphthosultam-2,4-disulphonic acid is heated in a sealed tube with hydrochloric acid, the sultam ring is opened and elimination of the sulphonate groups occurs (equation 214)[2].



(214)

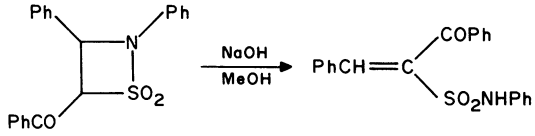
B. Other Nucleophiles

Several reports of the reactions of β-sultams with amines have been recorded. The sultams **122** and **123** are converted by the action of benzylamine to the corresponding sulphonamides (equation 215)[242,269–271]. Functionalized β-sultams often undergo C—N bond fission under nucleophilic/basic conditions as shown in equation 216[258]. Whilst both 1,8-naphthosultam and its *N*-methyl derivative are essentially stable towards

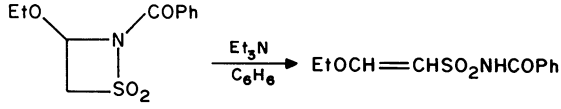


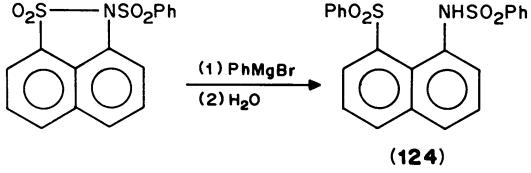
(215)

phenylmagnesium bromide, the *N*-phenylsulphonyl derivative undergoes ring opening to form the sulphonamide **124** (equation 217)[272]. Ring cleavage of simple β-sultams does not occur with sodium borohydride as shown by the fact that in the keto sultam **125** only the carbonyl group is reduced (equation 218)[269]. Whilst the reaction of lithium aluminium hydride on other alicyclic sultams has not been reported, the *N*-benzenesulphonyl derivative of 1,8-naphthosultam is reduced to the disulphide **126** (equation 219)[273].

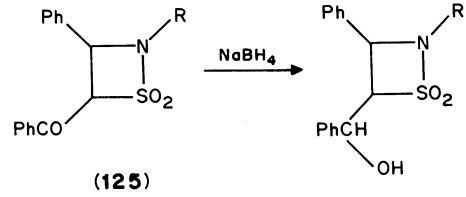


(216)

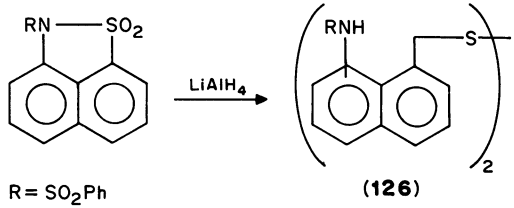




(217)



(218)

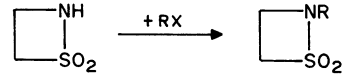


(219)

C. Alkylation and Acylation

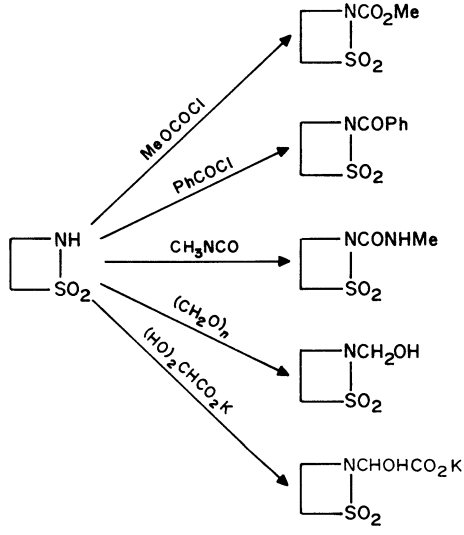
The alkylation of β-sultams has been achieved using the phase transfer method developed for β-lactams (equation 220)[274]. Activated alkyl halides such as alkyl bromides and benzyl bromide react very rapidly, α-bromoacetic esters less so and secondary alkyl halides hardly at all[242]. Although acylation of β-sultams in the 2-position causes

destabilization of the four-membered ring, a large number of such reactions have been reported including those involving reaction with methyl chloroformate, acid chlorides, methyl isocyanate, paraformaldehyde and glyoxylic acid (equation 221)[242]. *N*-methyl and *N*-phenyl butane sultams react rapidly at room temperature with butyllithium in THF–hexane to form α-lithio salts[275]. These have been shown to condense with a variety of electrophiles to form α-substituted derivatives (equation 222). The products formed on

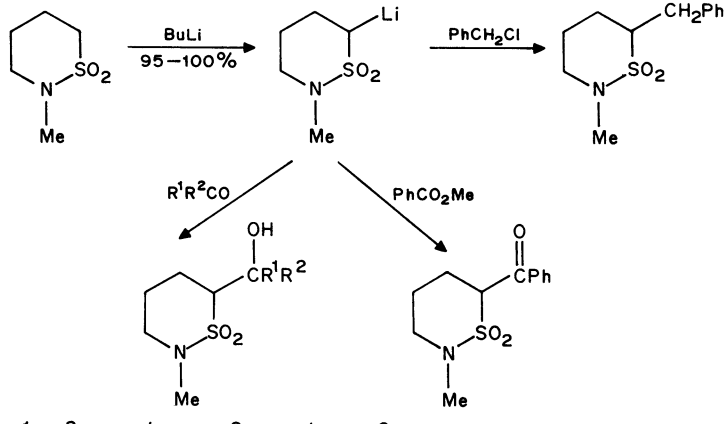


(220)

R=CH_2=$CHCH_2$, $PhCH_2$, $PhCH_2CO_2CH_2$, $EtCO_2CH_2$



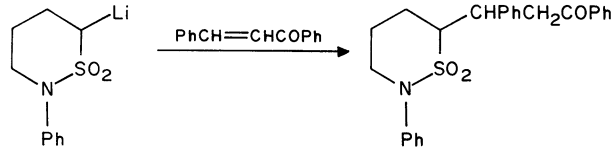
(221)



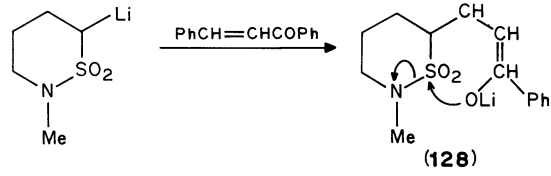
(222)

$R^1=R^2=Ph$; $R^1=Ph$, $R^2=H$; $R^1=H$, $R^2=p\text{-}MeOC_6H_4$

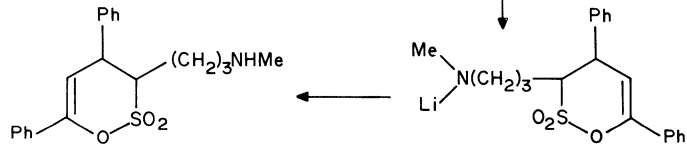
reaction of the α-lithio salts with α,β-unsaturated ketones depend on the *N*-substituent of the sultam. Thus whilst *N*-phenylbutane sultam reacted with chalcone to give the expected ketosultam **127** (equation 223), *N*-methylbutane sultam gave the aminosultam **129**. The authors suggested that this is formed via the 1,4-adduct **128** which then undergoes ring opening and re-closure (equation 224).



(127) (223)

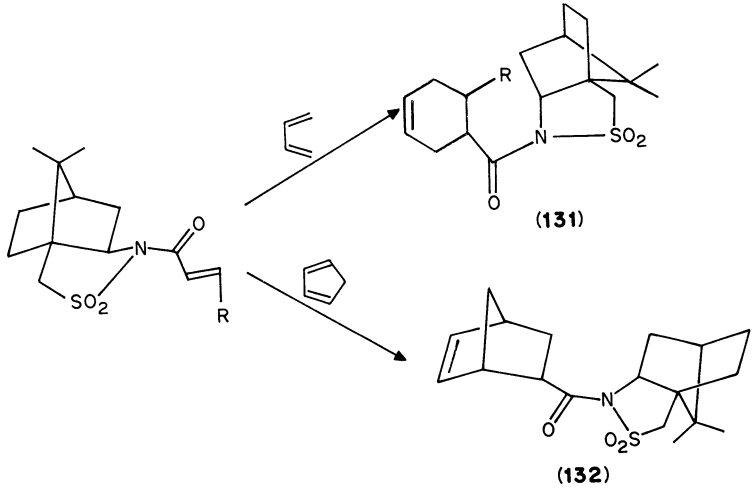


(128)



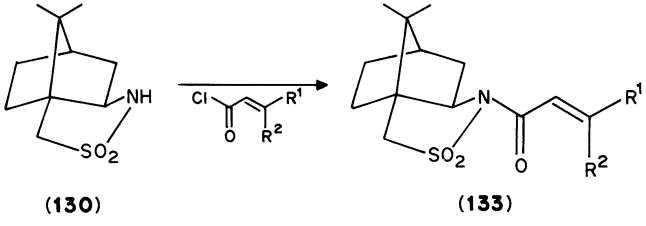
(129) (224)

Oppolzer and his coworkers have made extensive use of the sultam group as a chiral auxiliary[246,276–280]. Thus they were able to achieve efficient Diels–Alder addition of less reactive dienophiles by introducing 2.10-camphor sultam **130** (the enantiomeric



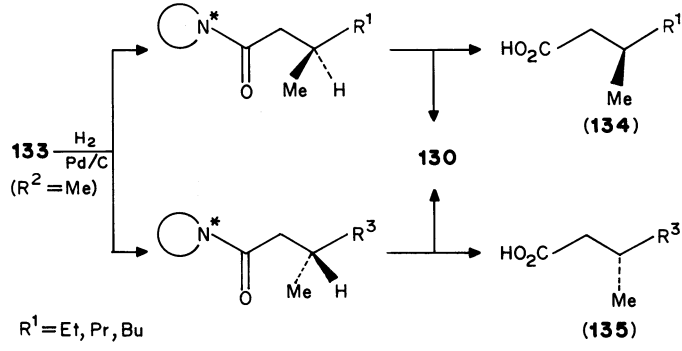
(225)

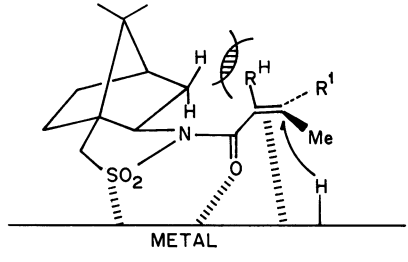
forms of which are commercially available) as an activating group which can subsequently be removed. Lewis-acid-promoted Diels–Alder additions of cyclopentadiene or 1,3-butadiene to the *N*-acryloyl and *N*-crotonyl derivatives of camphor sultam gave the adducts **131** and **132** (equation 225)[246] with high chiral efficiency. Oppolzer also showed that the tri-substituted olefinic double bond of the sultam imide **133** hydrogenated with > 90% diastereoface discrimination to give after saponification the β-substituted carboxylic acids **134** and **135** in good yield (equation 226)[277]. The observed direction and extent of diastereoface differention of reduction was rationalized by assuming that coordination occurs betwen the SO_2— and C=O oxygens as well as the olefinic bond and the metal surface from the sterically less hindered C_α—Re face, followed by H transfer to the same face (**136**). The asymmetric dihydroxylation of enonylsultams also provides a source of enantiomerically pure alcohols or carboxylic acids[278]. Oxidation of the β-substituted (α,β-enonyl) sultams **133** with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide provided the glycols **137** and **138**, which could be converted via the corresponding dimethyl acetals to enantiomerically pure alcohols **139** and **140** (Scheme 19). The formylation of unsaturated δ-sultams has also been reported (equation 227)[281].



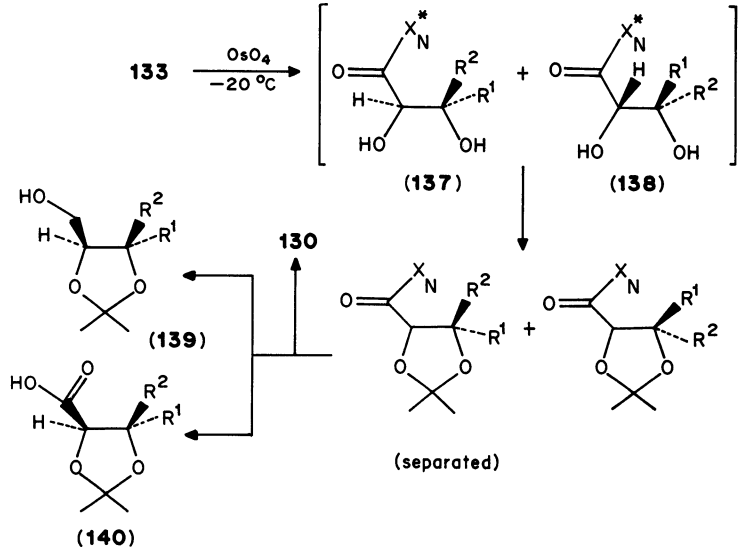
(130) (133)

(226)



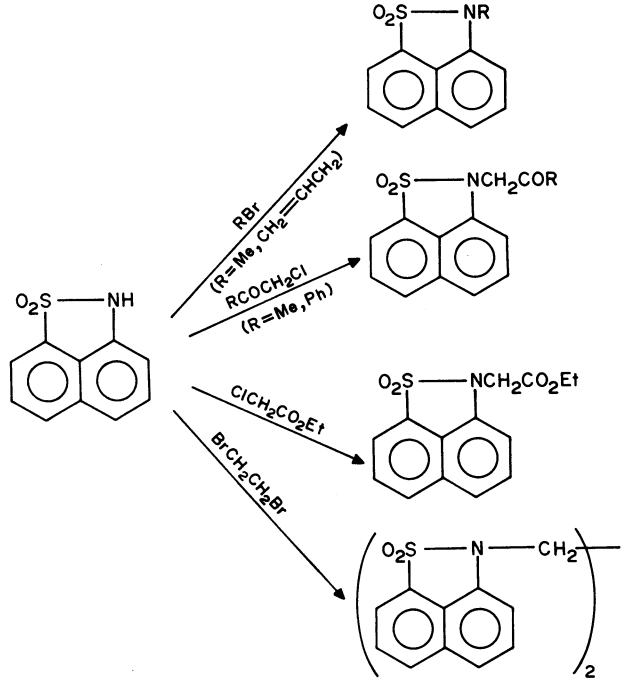


(136)

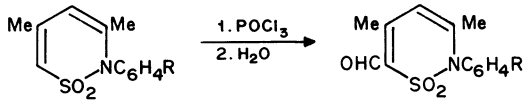


R^1 = Me, R^2 = H; R^1 = H, R^2 = Me; R^1 = Et, R^2 = Me

SCHEME 19



SCHEME 20



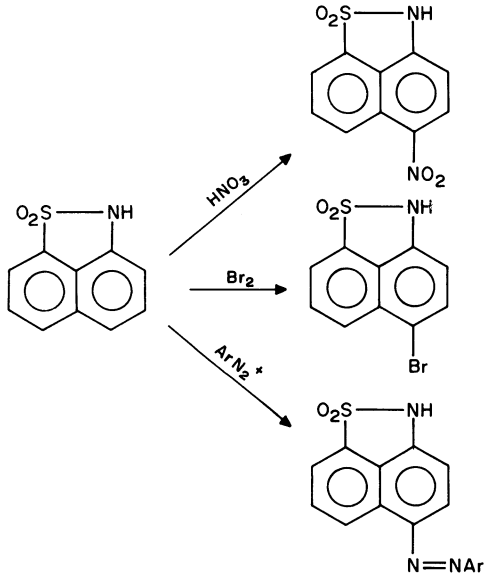
(227)

R = H, *p*-Cl, *p*-Me, *p*-MeO

The alkylation and acylation of aromatic sultams via their sodium salts have been extensively reported[3,262,282,283]. Some typical reactions for 1,8-naphthosultam, including those with alkyl halides and α-haloesters, are shown in Scheme 20.

D. Aromatic Ring Reactions

Aromatic sultams undergo typical electrophilic substitution reactions of the aromatic ring including nitration[3,284], halogenation[283,285–287] and diazotization[3,284,286,288], as shown in equation 228 for naphthosultam. In many cases further substitution may occur. These reactions have been reviewed in some detail by Mustafa[9].

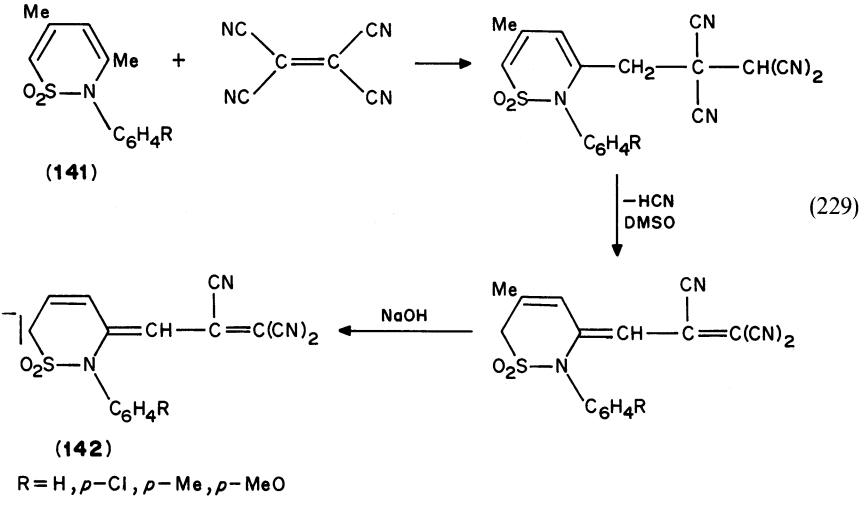


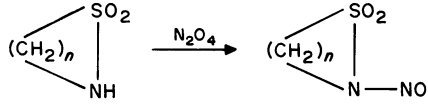
(228)

E. Miscellaneous Reactions

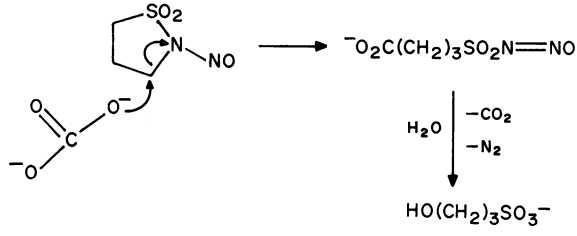
The hydrogens of the 4-methyl group in *N*-aryl-2,4-dimethylbuta-1,3-dien-1,4-sultam **141** are acidic, which facilitates the addition of **141** to tetracyanoethylene[289]. The adducts formed eliminate HCN when dissolved in DMSO to give the unsaturated sultams **142**, which form sodium salts at C-1 (equation 229).

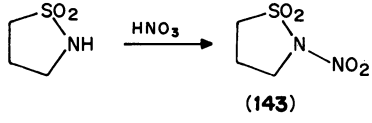
The *N*-nitroso derivatives of propane sultam, butane sultam and pentane sultam were synthesized from the parent compounds (equation 230). *N*-nitrososultams decompose thermally in aqueous solution to form the corresponding sultones. However, just as in the case of sulphonamides, unless bases are present, a variety of reaction products are formed as a result of various (acid-catalysed) side-reactions. Reproducible rates of decomposition





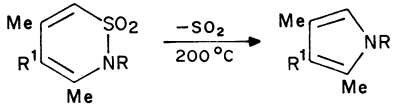
in excess aqueous sodium carbonate could be determined. A displacement mode of decomposition was proposed for the five-membered nitrosopropanesultam (equation 231). It is interesting to note that *N*-nitropropane sultam **143** (equation 232) showed no decomposition after 42 hours at 79 °C.





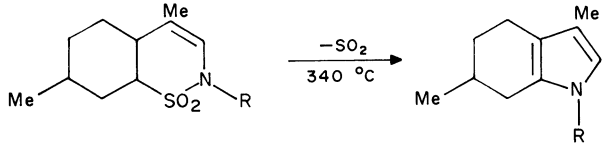
A few reports have appeared on the thermal decomposition of sultams. The thermolysis of unsaturated δ-sultams leads to formation of the corresponding pyrrole and indole derivatives (equation 233 and 234)[291] and resembles the decomposition of the related sultones. The high-temperature pyrolysis of naphthosultam gives a mixture of 2- and 3-cyanoindenes (equation 235)[292]. On the other hand, the *N*-phenyl derivative forms the benzacridine **144** formed by loss of SO_2 and intramolecular trapping of the intermediate which forms (equation 236). Flash vacuum pyrolysis of the bicyclic sultam **145** gave a

mixture of indolines and indoles as products (equation 237)[249]. Both the *cis* and *trans* isomers of the *β*-sultam **146** yield *trans* stilbene and benzaldehyde on pyrolysis (equation 238)[292]. In 1961 Libby reported the polymerization of propane sultam initiated by benzenesulphinyl chloride (equation 239)[293]. Subsequent reports have concentrated on the polymerization of *β*-sultams. Imai and his group showed that polymerization of ethane sultam occurred in aqueous solution at 80 °C[294]. Aminolysis of *N*-benzoylethane sultam give almost exclusively ring-opened product via nucleophilic attack at sulphur (equation 240)[270].



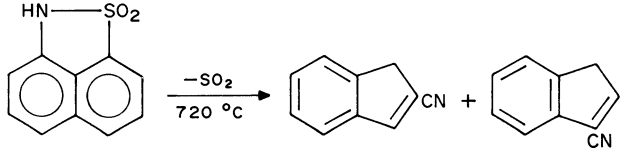
(233)

R=Ph, R^1=H; R=Bz, R^1=H; R=*p*-Tol, R =Me

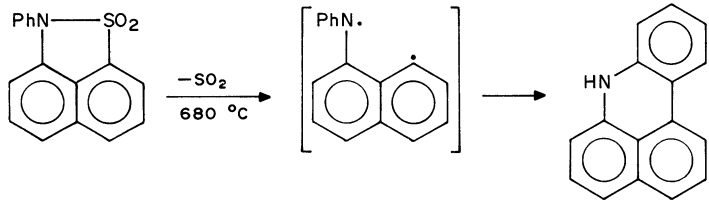


(234)

R=Ph, *p*-MeoC$_6$H$_4$

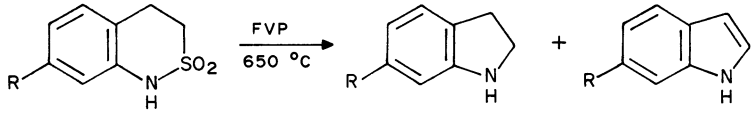


(235)



(236)

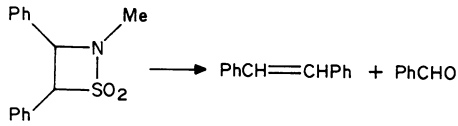
(144)



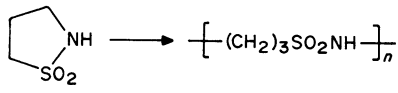
(237)

(145)

R=H, Me, Cl, MeO

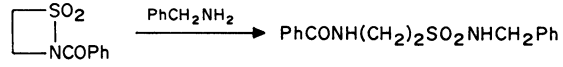


(146)



(239)

Similar ring-opening poly-addition of the bis-sultam monomer **147** occurs with aliphatic diamines (equation 241). Polysulphonamides have also been obtained from the corresponding bis-2,2′-disubstituted keto sultams (equation 242)[295].



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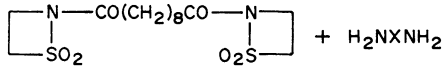
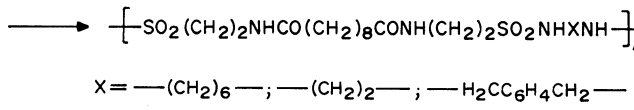


(147)



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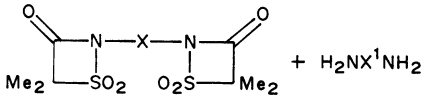

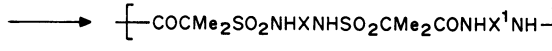

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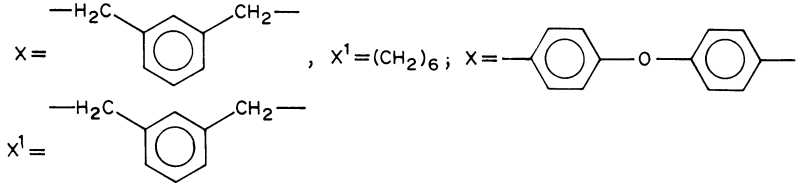

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CHAPTER **20**

Polymers containing SO_3H and related groups

DAVID M. VOFSI

The Weizmann Institute of Science, Rehovot 76100, Israel

LIST OF ABBREVIATIONS

AIBN	azobis(isobutyronitrile)
DC	degree of crystallinity
DMA	dynamic mechanical analysis
DOP	dioctyl phthalate
DS	degree of substitution
DSC	differential scanning calorimetry
E''	tensile loss modulus
EW	equivalent weight
IEC	ion-exchange capacity
meq	milliequivalent
MW	average molecular weight
PE	polyethylene
RO	reverse osmosis

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SAXS	small-angle X-ray scattering
SPPS	sulfonated poly(phenylene sulfide)
SPS	sulfonated polystyrene
SPSF	sulfonated polysulfone
T_g	glass transition temperature
T_m	crystalline melting point
TEM	transmission electron microscopy
TEP	triethyl phosphate
WAXD	wide-angle X-ray diffraction
η_{sp}	specific viscosity

I. INTRODUCTION

Sulfonic-group-containing polymers belong to the family of 'Functional Polymers'. This term is used for macromolecules containing a moiety that is capable of a specific chemical function. In order to do so, the group is usually covalently attached to the polymer backbone either directly, or via an intermediate subgroup.

The sulfonic acid group is strongly acidic, capable of ionic dissociation in aqueous medium. On account of its ion-forming functionality it has been included within the class of so-called 'Ionomers'[1]. Depending on the molar fraction in the polymer as well as on the macromolecular structure, the sulfonic group strongly interacts with water molecules, causing in some cases complete dissolution of the polymer. In other cases, when the polymeric chains are cross-linked or otherwise strongly associated, water is absorbed to different degrees and causes swelling or gel formation. In all of these cases the sulfonic group behaves as a strong acid, capable of exchanging the hydronium ion for other cations.

It is the salt-forming that made these polymers so prominent in industrial and water-treatment applications. Ion-exchange resins for demineralization, membranes for reverse osmosis and for electro- or Donan dialysis, separators in electrochemical cells, membrane devices for alcohol–water separations[2]—all are major 'consumers' of such polymers and are abundantly referred to in the scientific and patent literature. However, their versatility exceeds these most important areas. Being strongly polar, the sulfonic functionality is made use of in such diverse areas as textile-fiber dyeability[3], in thickeners and floccultants[4], rubber modifiers[5] and adhesion promoters[6], to mention only some applications. These references are quoted to indicate briefly the wide range of their use, the detailed description of the various applications being beyond the scope of this chapter.

In addition to ion formation the sulfonic acid group may form other derivatives, such as sulfonyl chlorides, amides, anhydrides, etc. The literature referring to these derivatives is much less extensive and their importance is rather limited. These will be referred to in Section IV.

II. SULFONIC-GROUP-CONTAINING MONOMERS: SYNTHESIS, POLYMERIZATION AND PROPERTIES

The simplest monomer of this group is ethylenesulfonic acid, a member of the vinyl group of monomers. Early synthesis of this monomer was reported by Kohler[7], who obtained the acid in low yield by thermal elimination:

$$ClSO_2—CH_2CH_2—SO_2Cl \longrightarrow CH_2=CH—SO_3H$$

Higher yields are reported by Anthes and coworkers[8], who effected an elimination from sodium hydroxyethyl sulfonate by polyphosphoric acid. A high-purity monomer was obtained by Breslow and Hulse[9] as an oily liquid (bp 125 °C/1 mm). When prevented from

water uptake, it is stable indefinitely at room temperature but can be readily polymerized using free-radical initiators or UV activation[10]. A high-molecular-weight polymer was obtained from its aqueous solution using a persulfate initiator at 55 °C.

Sodium ethylenesulfonate obtained some industrial prominence, mainly as a reactive comonomer in emulsion polymerization. When incorporated in a macromolecule it acts, by virtue of the ionic function, as a 'built in' emulsifying agent and stabilizer of the polymeric emulsion[11].

Breslow and Kutner[12] studied the polymerization of sodium ethylenesulfonate in aqueous solution using the persulfate–bisulfite redox couple as initiator at 5 °C. UV-initiated polymerization at 30 °C was equally effective.

Copolymerization was initiated with azobis(isobutyronitrile) (AIBN) with the following monomers: acrylamide, allyl acrylamide, sodium acrylate, acrylonitrile, methacrylic acid and vinyl acetate. In all these cases, the partner monomer was more reactive and preferentially incorporated in the copolymer. Less-polar or nonpolar monomers, such as styrene and isobutene, failed altogether to copolymerize.

A measure of the relative reactivities of the monomers involved in copolymerization is reflected in their reactivity ratios r_1 and r_2, the subscripts referring to monomers 1 and 2[13]. Thus, when monomer 2 was sodium ethylenesulfonate, r_2 was found to be close to zero while r_1(acrylamide) = 14.9 and r_1(sodium acrylate) = 5.8. A similar sluggishness in copolymerization with less-polar monomers was also found for other sulfonates. Izumi and coworkers studied the copolymerization of sodium allylsulfonate (M_1) with acrylonitrile (M_2) in dimethyl sulfoxide (DMSO) and DMSO–water mixtures. They found considerably lower values for r_2 as compared to r_1 in *aqueous* DMSO and attributed it to 'lack of homogeneity', although no phase separation was observed in this medium[14].

The Q-parameter for the sulfonate monomer, which is indicative of its general reactivity[13], did not change in the range of pH 7–1.5, but the e-parameter, in which the polar effect of the substituent group on the reactivity of the monomer (as well as that of the radical derived from it) is reflected, increased threefold at the low pH value. This was attributed to suppression of ionization at pH 1.5, causing a shift in the e-parameter towards a more positive value.

The monomer styrenesulfonic acid was prepared by dehydrohalogenation of *p*-bromoethylbenzene-sulfonyl chloride with methanolic KOH by Wiley and coworkers[15]. The potassium salt was polymerized in aqueous solution at 45 °C. Depending on initial monomer and initiator concentrations, water-soluble polymers of differing molecular weights were obtained as indicated by their solution viscosities.

The viscosity behavior is characteristic of a charged macromolecule, showing a sharp nonlinear dependence on polymer concentration *in the absence of added salt*. This is shown in Figure 1, where η_{sp}/c is plotted against polymer concentration.

Progressive addition of electrolyte to the solution causes the 'straightening-out' of the η_{sp}/c vs c curve towards linearity[16]. The strong dependence of polyelectrolyte viscosity on its concentration is caused by the sharp change that the macromolecule conformation is undergoing upon dilution. This is shown conceptually in Figure 2. The solid line represents the macromolecule with the attached fixed negative charges. The positively charged dissociated ions (the 'counterions'), as well as negatively charged *free* ions derived from the added salt, are dispersed in its vicinity.

In the higher concentration range, the macromolecules greatly overlap and exist in solution in a coiled-up state, retaining most of their counterions within their domain in the form of nondissociated or nonseparated ion pairs. In such a state they formally do not differ much from an uncharged macromolecule, exhibiting a small dependence of η_{sp}/c against c. However, with increasing dilution, dissociation progressively takes place and, simultaneously, the macromolecule tends to expand on account of electrostatic repulsion caused by the fixed negative charges. The expansion gives rise to a marked change in spatial

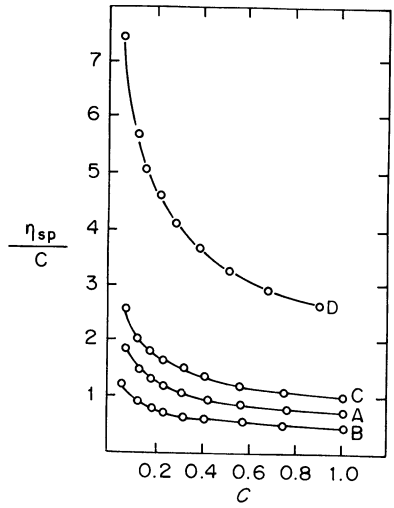


FIGURE 1. Plot of the reduced viscosity against the concentration for potassium *p*-vinylbenzenesulfonate polymers. A,B,C and D are polymers of differing molecular weights. Reprinted with permission from R. H. Wiley, N. R. Smith and C. C. Ketterer. *J. Am. Chem. Soc.*, **76**, 720 (1954). Copyright (1954) American Chemical Society.

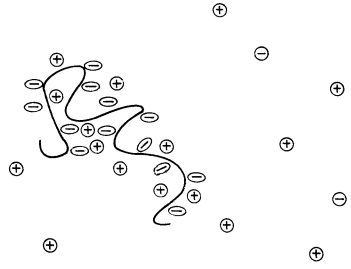


FIGURE 2. Schematic representation of a flexible macroanion in solution. Reproduced by permission from F. A. Bovey and F. H. Winslow. Eds., *Macromolecules*, An Introduction to Polymer Science, Academic Press, New York, 1979.

configuration from a highly coiled-up toward an increasingly extended state, the change being reflected in the sharp increase of solution viscosity.

The increase of solution viscosity is mitigated by addition of salt. The ions of the highly dissociated salt exert a screening effect on the fixed charges of the macromolecule, suppressing its ionization, thereby preventing its uncoiling.

The nonlinear dependence of polyelectrolyte viscosity on concentration has so far eluded satisfactory theoretical treatment to cover the entire range up to extreme

dilution[16]. Fuoss and Strauss[17] have found an empirical relationship for this dependence, which holds up to fairly high dilution:

$$\eta_{sp}/c = \frac{A}{(1 + Bc^{0.5})}$$

A plot of $(\eta_{sp}/c)^{-1}$ vs $c^{1/2}$ is shown in Figure 3, from which extrapolation to $c = 0$ seems justifiable. If so, the constant A represents the intrinsic visocity π_{sp}/c when $c \to 0$. From measurements on other polyelectrolytes (see, e.g., Reference 18) this constant increases with the second power of the molecular weight as measured by a direct method.

Wiley and collaborators also studied the copolymerization of the sulfonate acid and its potassium salt with other monomers[19,20b]. The copolymerization with *p*-sulfamidostyrene was investigated using varying concentrations of di-(*p*-vinylphenyl) sulfone as a difunctional cross-linking monomer, the aim being to produce variable capacity cation-exchange resins[20a]. Synthesis of such resins from the monomers, rather than production of similar materials by sulfonation of a previously prepared cross-linked polystyrene, is important for studying the effect of resin capacity and cross-linking density on the swelling ratio and selectivity coefficients for various cations[21a]. Cross-linked copolymers were also prepared from potassium *p*-styrenesulfonate and divinylbenzene in

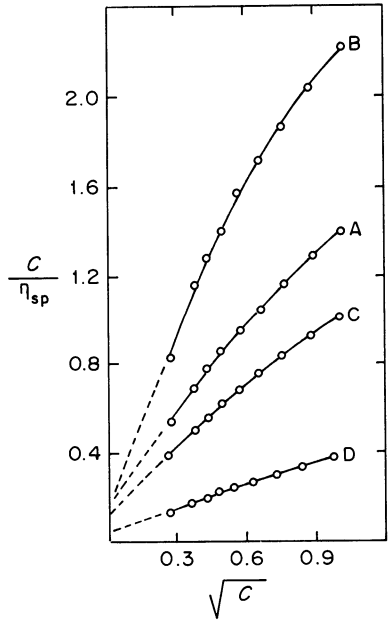


FIGURE 3. Plot of the reciprocal reduced viscosity against the square root of the concentration for potassium *p*-vinylbenzenesulfonate polymers. A,B,C and D are polymers of differing molecular weights. Reprinted with permission from R. H. Wiley, N. R. Smith and C. C. Ketterer, *J. Am. Chem. Soc.*, **76**, 720 (1954). Copyright (1954) American Chemical Society.

dimethylformamide (DMF) at various ratios. It was noted[21b] that at high ratios of the sulfonate to styrene, the tendency of the former to copolymerize was reduced, as was also established for other sulfonates in aprotic solvents or in bulk[12,14].

Gabriel and coworkers studied the copolymerization of sodium sulfonate with many other monomers in aqueous, homogeneous solution and determined the respective r_1(sulfonate) and r_2 values, which turned out to be constant over the entire range of molar ratios. Considerable discrepancies were noted as compared to Wiley's data, obtained in DMF solution[26].

It appears from the above studies that the reactivity ratios and their constancy are dependent on the nature of the reaction medium, since the partner monomers differ much in their mutual compatability (i.e. the solubility parameters) as well as with that of the chosen solvent.

Recently, copolymerization of vinyl-sulfonate esters was reported with vinyl acetate by Tezuka and coworkers. These monomers have closer solubility parameters and their inherent reactivities are the only operating factors in their copolymerization. More evenly distributed copolymers were thus obtained. These were hydrolyzed, or subjected to nucleophilic substitution of the sulfonate moiety, to produce interesting derivatives[22].

III. POLYMER-DERIVED POLYSULFONATES

In contrast to the sulfonate-group-containing polymers described in the previous section, that were formed from their monomers by polymerization, the present section will deal with derivation of such polymers from 'parent' macromolecules by sulfonation.

Various sulfonation reagents and methods to achieve this aim are reported in the literature, chosen to suit the particular substrate to be treated.

A. Aliphatic-chain Polymers

Polyalkanes and polyalkenes have been extensively used as parent macromolecules for polysulfonate synthesis. The sulfonation of various polyethylenes (PE) was effected by first introducing a chlorosulfonic group, using either sulfonyl chloride or a mixture of gaseous sulfur dioxide and chlorine, followed by hydrolysis. This free-radical reaction may be activated by UV light, as reported by De Korosy and Shorr[23a], or by peroxides[24]. The following steps are involved in the kinetic chain (P = polymer, R = radical);

$$\text{Initiator} \longrightarrow R^{\bullet}$$

$$SO_2Cl_2 + R^{\bullet} \longrightarrow RCl + SO_2Cl^{\bullet} \qquad \text{(i)} \qquad \text{Initiation}$$

$$SO_2Cl^{\bullet} \longrightarrow SO_2 + Cl^{\bullet} \qquad \text{(ii)}$$

$$Cl^{\bullet} + PH \longrightarrow P^{\bullet} + HCl \qquad \text{(iii)}$$

$$P^{\bullet} + SO_2Cl_2 \longrightarrow PSO_2Cl + Cl^{\bullet} \qquad \text{(iv)} \qquad \text{Propagation}$$

$$P^{\bullet} + Cl_2 \longrightarrow PCl + Cl^{\bullet} \qquad \text{(v)}$$

The products of this reaction are the chlorinated and sulfochlorinated polymer sites, PCl and PSO_2Cl, in varying ratios, depending on the efficiencies of steps (iv) and (v), and on the ratio of Cl_2 and SO_2 when gaseous reactants are being used.

As may be seen[25], the free-radical attack on PE is not entirely random and is regulated by the type of C—H bond as well as by chain conformation. It was shown by Bikson and coworkers[25a] that tertiary hydrogens (at branching sites) are not prone to sulfochlorination due to steric constraints, while the $—CH_2—$ groups available for substitution are those of gauche sequences, for the same reason[25b].

The heterogeneous sulfochlorination of PE films of various densities (i.e. varying crystallinity) was studied in detail by Bikson and collaborators[25]. In this work the influence of the following factors on the reaction products was investigated:

(i) degree of crystallinity of the PE (i.e. the density),
(ii) degree of orientation (i.e. the draw ratio of the extruded film),
(iii) degree of substitution.

The degree of crystallinity (DC) is the determining factor as regards the ultimate sulfochlorination extent since, as was previously shown by De Korosy[23], substitution of the group takes place exclusively in the amorphous regions of the polymer. Thus, for a low-density PE ($d = 0.916\,g\,cm^{-2}$, DC = 24%), the ultimate sulfonyl chloride content was $3.8\,meq\,g^{-1}$, while under identical conditions, into a high-density material ($d = 0.96$, DC = 54%) only $2.8\,meq\,g^{-1}$ were introduced. A medium-density PE gave an intermediate value.

The rate of sulfochlorination is strongly influenced by prereaction 'conditioning' of the unoriented film. Immersion for 48 hours in CCl_4 at 50 °C greatly increased the rate, but no difference was found in the degree of crystallinity before and after this treatment, although some rearrangement of the crystallites apparently did take place. What seems to be strongly affected is the accessibility of the amorphous regions to the reagent. Moreover, the unaffected crystalline regions remain essentially intact also after alkaline hydrolysis, at least up to an ion-exchange capacity (IEC) of $2.5\,meq\,g^{-1}$. Interestingly, conditioning of the low-density PE films before reaction considerably affected the swelling of the thus obtained ion-exchange membranes, the equilibrated water content increasing from 42 to 59% for the same IEC, and the specific conductivity going up by 60%. These results are attributed to a 'loosening-up' of the amorphous domains, thereby also allowing for better ion mobility.

The degree of chain orientation, as evidenced by birefringence measurement of cold-drawn PE films, also affects the rate of subsequent sulfochlorination, causing a gradual decrease in the rate as the draw ratio increases from 3.2 to 5.2. Since film predrawing has almost no effect on the concurrent chlorination, it is obvious that chain orientation introduces a bigger steric resistance to the incorporation of the larger $—SO_2Cl$ group than to Cl.

The prereaction morphology of the cold-drawn precursor films is at least in part preserved up to fairly high DSs, as shown by polarized IR light measurements. The dichroic character of the relevant bands is preserved, indicating that orientation in the amorphous region remains largely undisturbed by reaction. Chain orientation is preserved also after hydrolysis—up to an IEC of $1.1\,meq\,g^{-1}$. At higher DS values, alkaline hydrolysis does induce increasing disorientation in the amorphous regions, due to enhanced swelling.

Orientation by cold drawing strongly affects the rate of alkaline hydrolysis. For unoriented samples, immersion of the sulfochlorinated films in 1 N NaOH for 24 hours at room temperature causes total hydrolysis, whereas 3 weeks are required to achieve it for some highly oriented samples of the same IEC.

Finally, the birefringence measurements also revealed that the C—S bond of the $—SO_2Cl$ group is perpendicularly placed with respect to the direction of the polymer chains, as induced by drawing[25b].

On account of the domain selectivity of sulfochlorination, the derived PE sulfonates should be regarded as block copolymers, i.e. polyelectrolytes with polyalkane and sulfonated polyalkane alternating sequences of various segmental lengths. This is in contrast to the polyelectrolytes prepared by copolymerization (Section II), where randomization along the chain is possible.

B. Sulfonated Polyalkenes

Sulfonated polyalkenes were conveniently prepared by using a triethyl phosphate–sulfur trioxide 1:1 complex as sulfonation reagent. This complex is versatile in use, as it can be attenuated to a selective reaction by adjusting the ratio of the two components. Thus Rahrig and Macknight[28] used it in chloroform, at room temperature, in preparing sulfonated poly(pentenamers) and their sodium salts ($PPSO_3Na$)

$$\text{-}[(CH_2)_3\text{—}CH\text{=}CH]_n\text{-} \xrightarrow{\text{TEP:SO}_3\ (1:1)} \text{-}[(CH_2)_3\text{—}CH\text{=}CH]_y\text{-} \longrightarrow$$
$$\text{-}[(CH_2)_3\text{—}CH\text{=}C(SO_3Na)]_x\text{-}$$

with sulfonate group content ranging from 1.9 to 17.6%. Sulfonation took place exclusively at the α position to the double bond, without causing any cross-linking of the derived polymers.

Examination of the products revealed that crystallinity in the polymer was completely disrupted in excess of 6.3% sulfonation, and no crystallite melting was evident by DSC measurements. The behavior of the glass-transition temperature, T_g (i.e. the temperature at which a transition occurs from the glassy to the rubbery state), as sulfonation progresses, is seen in Figure 4. T_g is linear up to about 10% sulfonation, but then departs from linearity and sharply increases with extent of reaction. This behavior, which was also observed in other sulfonates[27], differs entirely from what is expected from a random copolymer, where T_g is linear along the whole range of components composition.

Since no cross-linking took place during reaction (the product was soluble in the solvent medium), this cannot account for the sharp increase in T_g. A study of the dynamic-

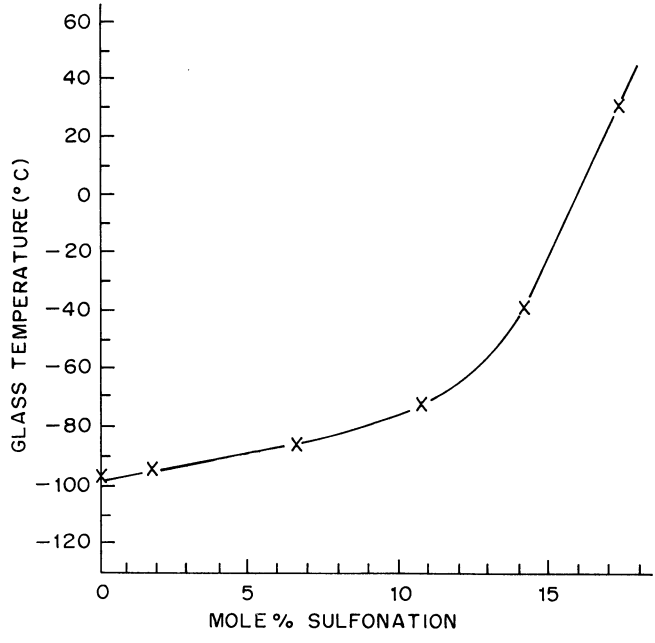


FIGURE 4. Composition dependence of the DSC-determined T_g values for sulfonated poly(pentenamers). Reprinted with permission from A. Eisenberg (Ed.), *Ions in Polymers*, Adv. Chem. Ser. No. 187, ACS, 1980. Copyright (1980). American Chemical Society.

mechanical properties of the $PPSO_3Na$ samples showed that the T_g upswing is caused by the formation of ionic clusters with increase in sulfonate content beyond 10%, separated by hydrophobic domains. The point at which linearity of T_g breaks down corresponds to the critical concentration of pendant sulfonate groups at which separation of the two phases occurs.

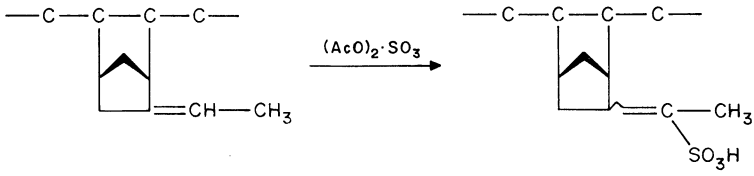
Rahrig and Macknight associated a relaxation process with the ionic domain, termed α-relaxation, that was revealed by plotting the tensile-loss modulus (E'') against temperature[29]. The integral magnitude of this relaxation peak increases with the size of the ionic domain, but the relaxation temperature decreases sharply when water is absorbed by the sample. Thus, for a sample of about 18% sulfonation the relaxation temperature is 12 °C; a drop of 80 °C is observed when the sample is saturated with water, absorbing 84% of its dry weight. The drastic decrease in the relaxation temperature is caused by water migrating into the ionic clusters, thereby exerting a 'plasticizing' effect in these domains, thus increasing segmental mobility. This mobility is depressed with lowering of temperature.

An additional relaxation process, designed β-relaxation, is associated with the hydrophobic domains. The transition temperature for this relaxation rises from −77 °C to −35 °C as the sulfonation content increases from 1.9 to 17.6%. The magnitude of this relaxation decreases with sulfonate content (i.e. with the relative decrease of this phase) but is unaffected by moisture absorbtion. The β-relaxation is associated with the onset of micro-Brownian segmental motion in the amorphous hydrocarbon matrix.

The sharp increase of T_g above a critical sulfonation level coinciding with ionic cluster formation is indicative of a stiffening of the polymer structure in a manner analogous to—but entirely distinct from—a cross-linking process. However, while cross-linking is caused by covalent bonding between chains and is irreversible, ionic clustering is reversible and temperature-dependent. As will be seen below, 'ionic cross-linking' was studied in an attempt to synthesize so-called 'thermoplastic elastomers'[30], a class of materials behaving at ambient temperatures as cross-linked elastomers, but—contrary to the usual rubbers—amenable to thermoplastic processing at elevated temperatures.

Typically, such behavior was demonstrated in sulfonation products of a synthetic rubber, (EPDM, or VISTALON 2504: an ethylene–propylene–norbornene terpolymer produced by EXXON).

Makowsky and coworkers[30] sulfonated this rubber in hexane solution at room temperature using acetyl sulfate, preformed by reacting acetic anhydride with sulfuric acid. As in the case of the TEP:SO_3 complex[28], this attenuated reagent[31] also effected a selective substitution in the α-position to the exocyclic vinyl double bond of the ethylidene–norbornene (EN) moiety, that was present in the rubber samples at a content of 4.4–7.5%.



The neat polysulfonic acids are not markedly associated in clusters and dissolve in hydrocarbon solvents. However their salts, and in particular the Zn and Pb salts, obtained by neutralization with a saturated solution of the corresponding acetates in a hydrocarbon–isopropanol solution, exhibit a distinctly different behavior indicative of strongly associated domains. This is evidenced by measurements of their melt viscosities, showing a steep increase with sulfonate content already at about 1 mol% sulfonate groups.

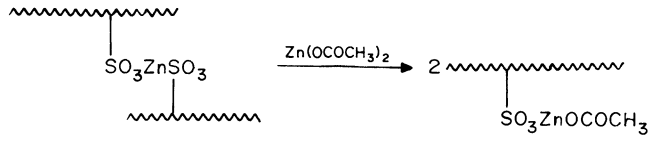
As before[28], the strong rise in viscosity was attributed to association within the ionic clusters.

By proper optimization of the ethylene–propylene–EN ratio in the parent rubber, of its MW and of the sulfonation degree, it was possible to obtain interesting materials that behave as thermoplastic rubbers, capable of thermal relaxation of these ionically 'quasi-cross-linked' domains.

Best results were achieved with the Zn polysulfonates of EPDM. A typical set of properties is summarized as follows:

Melt viscosity (poise $\times 10^{-5}$)	Tensile strength(psi)		Elongation(%)	
at 200 °C	at 25 °C	at 70 °C	at 25 °C	at 70 °C
12.0	1500	270	400	450

The melt viscosity is regarded as still too high for injection molding of these materials. However, an additional option for adjusting their processing conditions is their plastification. An effective means for attenuating ionic association within the clusters is the incorporation of various metal acetates, particularly Zn acetate, which supposedly breaks-up divalent sulfonate linkages:



Moderate amounts of Zn acetate are well compatible with the rubber, and no 'blooming' (i.e. phase separation) was observed.

C. Aromatic Polysulfonates

Sulfonated polystyrene was extensively investigated on account of its important industrial applications. Since 1933, when an early patent on polystyrene sulfonate was obtained by Wullf[32], the subject was covered profusely in the scientific and patent literature.

Water-soluble, high-MW polystyrene sulfonates were obtained by Roth[33] who, in order to avoid cross-linking by sulfone bridges, carried out the sulfonation in carbon tetrachloride solution by addition of SO_3 previously dissolved in sulfur dioxide, at temperatures of -0.5 to 30 °C. Hart and Janssen[36] compared the IR spectra of polystyrene sulfonic acid that was prepared by sulfonation at 100 °C with conc. sulfuric acid, with a product obtained by the polymerization of monomeric *p*-styrenesulfonic acid. The spectra turned out to be identical, confirming that, in the former case, one sulfonic acid group is being introduced per phenyl ring, exclusively in the *para* position.

By carrying out the sulfonation of narrow MW distribution fractions of polystyrene with 100% sulfuric acid, Carrol and Eisenberg[37] proved that no chain scission and no cross-linking is occurring, the molecular weight and distribution of the base polymer being entirely preserved in the derived sulfonation product.

A comparative study of sulfonation methods was carried out by Turbak[38]. To avoid any cross-linking via sulfone groups, he introduced the triethyl phosphate/SO_3 2:1 complex as sulfonation reagent. By using it at room temperature he prepared water-soluble polystyrene sulfonates having MW values in excess of 5×10^6. Complete exclusion of cross-link formation was attributed to substitution by $-SO_3Et$ groups, incapable of reacting with a neighboring chain, contrarywise to $-SO_3H$. Careful hydrolysis of the ester yields the desired product.

Avoidance of any cross-linking in the sulfonation of very high MW substrates is important, as it enables the use of small amounts of the product to produce highly viscous solutions, thus enhancing their efficacy for such applications as flocculants, impregnants, textile sizes, adhesives, etc. These and other potential applications were reviewed by Roth[33], where numerous references are to be found.

The melt behavior of sulfonated polystyrene ionomers was studied by Lundberg and coworkers[41]. As was shown in the case of a sulfonated elastomer[30], sulfonation of polystyrene leads to an increase in the melt viscosity (measured at 250 °C) of the SPS upon neutralization, indicating increased association of the sodium poly-(salt). A sudden jump of the melt viscosity occurs at the point of complete neutralization, where a critical concentration of Na polystyrenesulfonate is reached, apparently resulting in a sharp phase separation between the ionic and hydrophobic domains (Figure 5).

The two-phase coexistence in these poly-(salts) was demonstrated by the use of different plasticizers. It was shown that glycerol, being compatible with the ionic phase, brings about a sharp fall in the melt viscosity already at a weight fraction of 0.02, indicating dissociation in the clusters. On the other hand, dioctyl phthalate (DOP), a conventional plasticizer for the hydrophobic domains, reduces the melt viscosity gradually at very much bigger weight fractions.

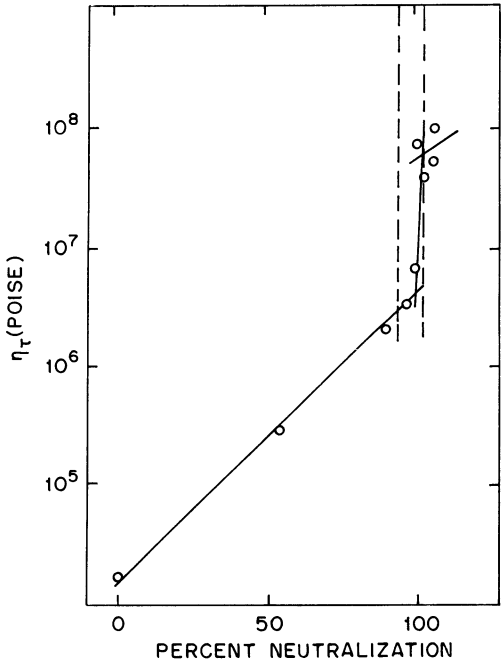


FIGURE 5. Melt viscosity of SPs as a function of % neutralization (average meq NaOH to reach endpoint: ±0.004 or 1.5%; melt index rheometer: 250 °C;—SO_3Na content: 2.5 mol%. Reprinted with permission from R. D. Lundberg, H. S. Makowski and L. Westerman, in *Ion in Polymers* (Ed. A. Eisenberg), Chap. 5, Adv. Chem. Ser. No. 187, ACS, 1980. Copyright (1980) American Chemical Society.

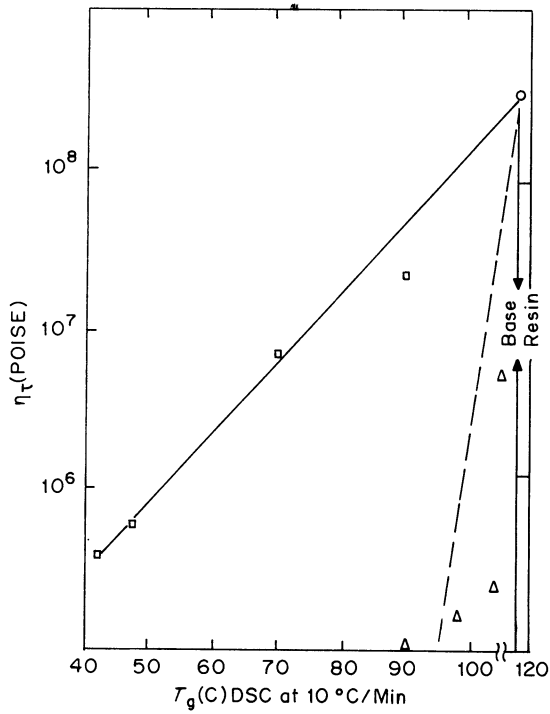


FIGURE 6. Melt viscosity–glass transition relationships for plasticized SPS (1.78 mol%) samples based on various levels of DOP and glycerol: $\tau = 2 \times 10^5$ dyn cm^{-2}, 220 °C; 1″ × 0.05″ capillary; (□) DOP; (△) glycerol. Reprinted with permission from R.D. Lundberg, H. S. Makowski and C. Westerman, in *Ions in Polymers* (Ed. A. Eisenberg), Chap. 5, Adv. Chem. Ser. No. 187, ACS, 1980. Copyright (1980) American Chemical Society.

A plot of the melt viscosity of a typical SPSNa. (1.78 mol% sulfonate) against its T_g value is shown in Figure 6. The viscosity collapse on addition of glycerol causes a sudden drop in T_g, practically eliminating the 'quasi-cross-linking' effect of the ionic clusters. The decrease in T_g upon addition of DOP reflects a classical plasticizing effect on the hydrophobic domains that form the bulk of the polymer[41].

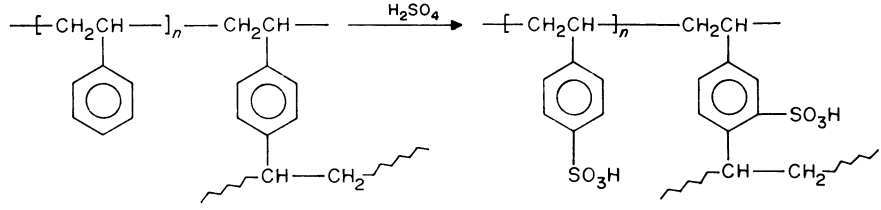
While the melt viscosity of neat SPSNa hardly permits their processing as thermoplastics, appropriate control of the two domains by 'dual plasticization' may lead to a family of sulfonated polymers, covering a wide range of plastomeric and elastomeric behavior[41].

The heterogeneous sulfonation of a cross-linked polystyrene, prepared by polymerizing a styrene–divinylbenzene mixture in an aqueous suspension, is the basis for production of strong-acid cation-exchange resins[34]. Even a superficial treatment of resins of this type would be beyond the scope of the present chapter, and interested readers should consult special treatises on the subject[35a]. Their application as a tool in analytical chemistry is treated elsewhere[35b].

The sulfonation of cross-linked polystyrene beads is being carried out in industry with concentrated sulfuric acid at elevated temperatures. Alternatively, the beads are

preswollen in a chlorinated hydrocarbon and treated with chlorosulfonic acid at room temperature, followed by hydrolysis. The latter method allows for better penetration of the reagent and faster reaction. In either case it is possible to introduce one sulfonic acid group per phenyl ring, corresponding to an IEC of 5.1 meq per g of dry resin.

Schematically, the reaction and resulting product may be described as follows:



where the sulfonate is preferentially introduced in the *para* position to the polymer backbone.

The exchange process of various cations with the sulfonic acid hydrogen ions involves a redistribution of these cations between the solution and the close environment of the negative fixed charge of the sulfonate group in the water-swollen resin,

$$A^+ + BX \xrightarrow{K} AX + B^+$$

$$\text{leading to an equilibrium constant } K = \frac{a_{AX} \cdot a_B{}^+}{a_{BX} \cdot a_A{}^+},$$

a_{AX} and a_{BX} being the activities of ions A and B in the environment close to the fixed anion, and $a_A{}^+$ and $a_B{}^+$ those in solution. The exchanger thus serves as a negatively charged insoluble matrix with which ionic equilibrium is established.

In the case of the alkali metals K depends on the coulombic charge of the cation and its *hydrated* radius, increasing with the strength of the former and decreasing with the latter. Kressman and Kitchener[39] carried out a study of ion affinities of both mono- and divalent cations on a resin, prepared by condensation of a phenol–*p*-phenolsulfonic acid mixture with formaldehyde. They found the following order of adsorption strength for monovalent cations: $Li^+ < Na^+ < NH_4{}^+$, $K^+ < Rb^+ < Cs^+$, and $Mg^{++} < Ca^{++} < Sr^{++} < Ba^{++}$ for divalent ones.

The dependence of the ion-exchange capacity on the hydrated radii of the ions is identical for the various sulfonated aromatic resins and is seen in Figure 7[40].

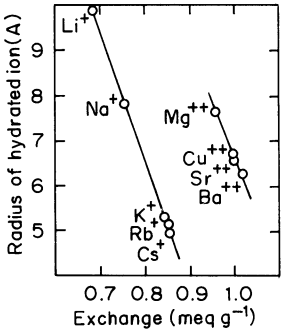


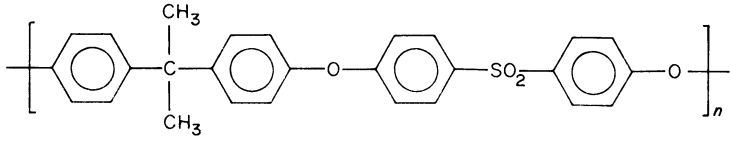
FIGURE 7. Dependence of ion-exchange capacity on the radius of the hydrated. Reprinted with permission from F. C. Nachod and W. J. Wood, *J. Am. Chem. Soc.*, **67**, 629 (1945). Copyright (1945) American Chemical Society.

Ion exchange is an adsorptive process governed by equilibration. However, separation between ions and water may be effected also by a diffusive process through ionically charged membranes, as in the case of dialytic water softening[24] or electrodialysis[44]. Membranes of this kind may also be used for desalination by reverse osmosis, where a combined mechanism of coulombic ion-exclusion and water diffusion under pressure is involved.

In all these processes a dependable membrane material is of decisive importance, expected to perform properly for extended periods, often under adverse conditions of pH, temperature and pressure.

The sulfonation of polyethylene films to produce negatively charged membranes was described above[24]. While adequate for many uses, these aliphatic polysulfonates lack long-term stability under adverse conditions. To improve performance, attention was directed in recent years to sulfonation of so-called 'engineering thermoplastics', a class of film-forming polyaromatics with improved mechanical and thermal properties.

Noshay and Robeson[27] reviewed the extensive patent literature on poly(sulfonated aromatics) and their industrial applications. They carried out the sulfonation of a bisphenol–diphenyl sulfone polycondensate by means of a 2:1 SO_3/TEP complex[38] in



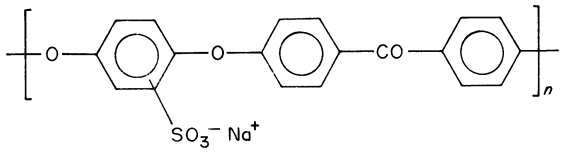
dichloroethane at room temperature. Deactivation of the *m*-position by the sulfone caused the sulfonation to proceed up to 80% in the *m*-position of the bisphenol moiety. Neutralization of the product was effected in isopropanol by sodium methoxide. Polymers thus obtained were injection-moldable up to a content of 0.3 mol sulfonate per repeat unit. Higher content of sulfonate groups causes a linear rise in T_g up to a DS of 1.0, due to increased ionic association.

The structure and properties of Na-sulfonated polysulfone (Na-SPSF) were studied in detail by Macknight and coworkers[45,46]. DSC measurements revealed an essentially linear dependence of T_g on the degree of sulfonation up to 1 sulfonate group per repeat unit, although the slope of the curve for the first 10 mol% sulfonate was markedly smaller. X-ray studies failed to indicate any organized structure, either crystalline or cluster-forming, and any clustering, if present, could account for no more than 10% of the ionic groups, irrespective of the nature of the counterion. It was therefore concluded that one is dealing with a random copolymer of sulfonated and nonsulfonated repeat units as evidenced by the linearity of T_g with composition. The break in the slope of the T_g vs composition curve at about 10% sulfonation is interpreted as an indication that up to this level mainly lone ion-pairs are scattered along the polymer chain. Above this sulfonation level, ionic multiplets increasingly contribute to chain stiffening. However, contrarywise to their previous findings in aliphatic ionomers[28], no formation of ionic domains, and therefore no microphase separation, was evident in this system.

This was corroborated by Shivashinski and Tanny[42], who failed to detect poly-ionic clustering in a domain size above 50 Å up to an IEC of 1.2 meq g^{-1}.

Interestingly, ionic cluster formation was observed in the case of another aromatic ionomer, the Na salt of sulfonated polyether-ketone[47,67].

Apparently, the configuration of the parent polymer does influence the structure of the derived polysulfonate, chain flexibility of the former leading to an easier accommodation of the ionic groups into clusters, while chain stiffness decreases this probability.

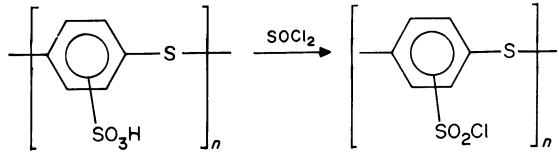


Various sulfonated polysulfones (SPSF) were cast from isopropanol and the resulting membranes were tested in reverse-osmosis desalination of a 0.1% NaCl solution at a pressure of 1500 psi[27]. The results obtained indicated that permeation by molecular water diffusion through the nonsulfonated regions is negligible, although close to 2% water are taken up by the parent polysulfone itself. On the other hand, at an IEC of 2.16 meq g^{-1} and water absorption of 61%, a high water flux was obtained without, however, any concurrent salt rejection. Clearly, permeation is taking place through the water-swollen domains, the salt being 'dragged' along by a Poiseuille-type flow. In the DS region of 0.1–0.5 one obtains an optimal performance of salt rejection coupled with an acceptable water flux. Apparently, salt rejection in such membranes is achieved by anion exclusion due to coulombic repulsion.

A detailed study of SPSF desalination membranes was carried out by Brousse and coworkers[43]. Sulfonation was effected by chlorosulfonic acid on a commercial material (Polysulfone P 1700, Union Carbide), and the products as well as their sodium salts were cast from highly polar solvents. Their performance was compared to that of noncharged cellulose–acetate membranes, largely being used for desalination of brackish water.

The sulfonation of an aromatic polyether, poly-3,5 dimethylphenyl ether, by chlorosulfonic acid was carried out by Kimura[48]. The sulfonated polyether was cast from 2–10% solutions in methanol. Negatively charged membranes of an IEC of up to 5 meq g^{-1} were obtained and evaluated for reverse-osmosis desalination. Their performance is comparable to that of SPSF membranes[42], but their potential use is limited to the treatment of brackish waters of low to medium salinity. Although possessing some advantages over noncharged membranes, such as reduced fouling, long-term dimensional stability and chemical resistance, sulfonated aromatic polymers has not so far merited acceptance in RO desalination, since their combined salt rejection–water flux characteristics are inferior to those of several noncharged membranes in present use. However, their potential in other membrane applications may be of greater interest.

Monteneri and collaborators have prepared polysulfonates from poly-phenylene sulfide (SPPS)[49] and studied their conductance and electrolyte transport properties[50]. The sulfonated products with IEC up to 3 meq g^{-1} were insoluble in any tested solvent except thionyl chloride, in which they converted to the polysulfonyl chlorides



From this solution a film could be cast, and the polysulfonate regenerated by hydrolysis to produce a tough, rather brittle film. The material retained at least one molecule of water persulfonate, even when heated up to the onset of decomposition at 280 °C. Its hydrogenbonded structure is represented as $\dashv SO_3^-(P)H(H_2O)_n^+ \vdash_m$ (P designating the hydrophobic polymer segments).

SPPS is an amorphous polymer, its skeleton rigidity being similar to that of the parent macromolecule. On account of its toughness, complete insolubility and exceptional

thermal stability, it was investigated for potential applications in electrochemical cells operating at temperatures up to 160 °C. Thus, an asbestos(85%)–SPPS(15)% separator membrane was successfully used in 30% KOH solution at 100 °C in an advanced water electrolysis cell. Other SPPS composite membranes were claimed to be quite competitive in performance to Nafion (see below) in industrial brine electrolysis.

D. Perfluorinated Polysulfonates

In the previous section it was suggested that the parent polymer structure considerably influence the physical properties of the derived polysulfonates, imparting to them some of the mechanical and thermal properties of the precursors. This trend is particularly evident in the case of the perfluorinated hydrocarbon polymers. Polymers of this kind, such as e.g., poly(tetrafluoroethylene) (PTFE) are exceptional in their inertness to offensive environment, solvent resistance and high-temperature stability. These considerations led in the sixties to the development of unique sulfonic-acid derivatives of fluorocarbon copolymers by the DuPont Company. While several compositions were disclosed in the patent literature[51], the preferred composition, which is the basis for the commercial Nafion ion-exchange membrane, is a copolymer of tetrafluoroethylene with a perfluorinated vinyl ether/sulfonyl fluoride[52]:

$$n\mathrm{CF_2{=}CF_2} + m\mathrm{CF_2{=}CF{-}O{-}CF_2{-}CF(CF_3){-}O{-}CF_2SO_2F} \longrightarrow$$

$$\mathrm{(CF_2{-}CF_2)_n{-}[CF_2{-}CF(OCF_2{-}CF(CF_3){-}O{-}CF_2SO_2F)]_m} \qquad \text{(Nafion precursor)}$$

The ratio of n to m is designated as the "equivalent weight" (EW) of the polymer and usually has a value of 1000 to 1500.

The polysulfonyl fluoride is soluble in alcohol and moldable by thermoplastic methods. It can be cast into films before or after hydrolysis to produce membranes trade-named NAFION (= Na-fluorinated ion exchanger). In contrast to sulfonated polystyrene-based membranes, that become water-soluble at a sulfonation degree of 25% (i.e. at one sulfonic group per 32 carbons) and have to be cross-linked to prevent their dissolution, Nafion membranes, due to the hydrophobic interaction of the fluorinated segments, are water-insoluble even at a content of one $-SO_3H$ per 20 carbons in the chain.

Typically, a 0.1-mm-thin membrane of EW = 1200 has an IEC of close to 1 meq g^{-1}, a resistance of $3\Omega cm^2$ and a perm-selectivity of 90% of the Nernst potential (measured for 0.5 N KCl against 1 N KCl at 25 °C). Due to an operational capability up to 200 °C, oxidative stability, inertness to strong acids, alkalies and halogens (except fluorine)—coupled with high electrical conductivity and electrolyte permeability—it has gained acceptance as an outstanding membrane material in electrochemical processes such as modern chlor-alkali production[53].

The structural features of Nafion have been the subject of study by many workers[52,54,55]. In a recent review[52] an attempt was made to summarize the results of these studies in what appears as the present state of knowledge on the subject.

The main structural features of Nafion were recently clarified by Kyu and coworkers[56]. Starting with the Nafion precursor membrane, they subjected it to stepwise hydrolysis by diffusion of a sodium-hydroxide solution at 75 °C. Dynamic mechanical analysis (DMA) of the material at intermittent stages up to 90% conversion to Na-Nafion led to the following conclusions:

(i) The Nafion precursor, being nonionic, exhibits 'regular' behavior, characterized by three relaxational modes. The lowest temperature relaxation (δ), occurring at around

$-180\,°C$, is assigned to the $—SO_2F$ group. This mode disappears gradually with progressing hydrolysis. At around $-100\,°C$ a broad peak is seen on the $\log E''$ vs temperature plot[29], associated with the relaxation of the $—CF_2—$ backbone group. This mode is common to all hydrolyzed materials as well as to poly(tetrafluoroethylene) and is uneffected by moisture absorption. Clearly, this is a transition occuring in the hydrophobic matrix. Finally, a sharp peak (α), appearing at *ca* 10 °C, is identified with the glass-transition T_g of the precursor polymer.

(ii) With hydrolysis and progressive conversion to Na-Nafion, the T_g peak (α) of the precursor gradually decreases and is no longer seen at *ca* 10 °C in the 90% hydrolyzed material. It reappears, however, as a sharp transition at around 240 °C. A gradual shift of this transition on the log E'' vs temperature plot toward higher temperatures is taking place with hydrolysis, a phenomenon that was observed for other polysulfonates[29], and identified with progressive ionic association ('quasi-cross-linking') in clusters. In the case of the Ca-Nafion, the T_g peak is shifted to almost 300 °C, where it partially overlaps with the crystalline melting-point T_m.

(iii) Concurrently with this process, another peak (β) is being formed at around 140 °C, which is assigned to the relaxation of the ether-linked pendant side-chains.

The results of the DMA study would thus indicate that—with progressing formation of Na-Nafion—the single T_g of the precursor differentiates into two T_g values in a two-phase system, having two glass transitions, $T_g(\beta)$ of the matrix and $T_g(\alpha)$ associated with the ionic clusters.

The three-phase structure of Nafion (i.e. crystalline and two amorphous phases), as revealed by the DMA study, is consistent with experimental findings by other methods. Evidence for the crystallinity is supplied by wide-angle X-ray diffraction (WAXD) measurements. In the Nafion precursor its extent increases with the EW, as expected, up to 40% for an EW of 1800. With progressing hydrolysis, the crystalline fraction, being confined to the fluorocarbon matrix, remains essentially intact, but small-angle X-ray scattering (SAXS) reveals an increasing peak for Na-Nafion. Contrary to the WAXD result, the SAXS peak decreases with increasing EW (i.e. with decreasing sulfonate fraction)[55a]. Transmission electron microscopy of Ag^{+} and Sn^{2+} Nafion clearly shows a pattern of distinct microdomains scattered within a continuous matrix[55b].

These experimental findings have prompted the development of various models for the supermolecular structure of the Nafion membrane. Apart from describing the morphology, such a model has to account for unique functional characteristics associated with the ionic clusters. Among these, the exceptionally high diffusion coefficient (D) of water ($2.3 \times 10^{-6}\,cm^2\,s^{-1}$), that is only one order of magnitude lower than D for self-diffusion of H_2O[57], should be accounted for. At the same time, the Nafion membrane also excels in OH^- and Cl^- rejection, which usually does not occur together with a high hydraulic permeability. It is these two properties that make it so attractive as a membrane for chlor-alkali production[58].

To account for these phenomena, Gierke and Hsu[55b] proposed the 'inverted Micelle' model, shown schematically in Figure 8.

The diameters of the electrolyte-filled voids are of the order of 30–50 Å with the fixed charges situated within the double-layer regions, from which mobile anions are excluded. The clusters are joined by narrow (10 Å) passages, thus forming a three-dimensional interconnected 'sponge-like' structure, enabling a high water flux to percolate, while anion transport is greatly impaired by the narrow 'gates'.

The model predicts a critical ionic-insulator-to-conductor transition, at which point the interconnection between the clusters is established and above which conductivity is proportional to void volume. Experimentally, the critical void volume is found at a 10% void–volume fraction.

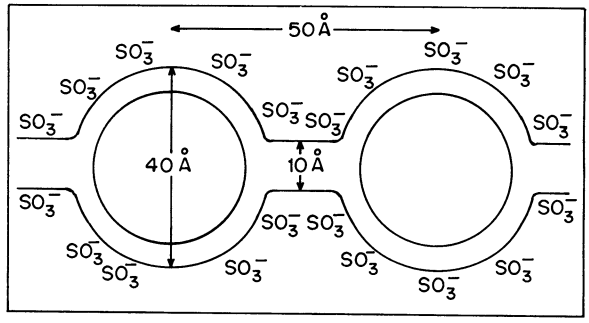


FIGURE 8. Cluster-network model proposed by Gierke. Reprinted with permission from T. D. Gierke and W. Y. Hsu, in *Perfluorinated Ionomer Membranes* (Eds. A. Eisenberg and H. L. Yeager), Chap. 13, ACS Symp. Ser. No. 180, 1980, p. 286. Copyright (1980) American Chemical Society.

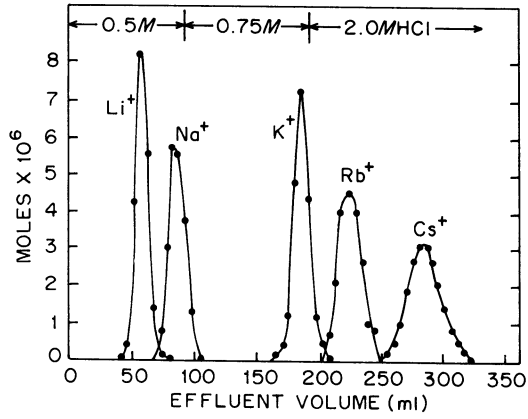


FIGURE 9. Chromatographic separation of alkali metal ions using 1200 EW Nafion at 25 °C. Reprinted with permission from H. L. Yeager, in *Perfluorinated Ionomer Membranes* (Eds. A. Eisenberg and H. L. Yeager), Chap. 3, ACS Symp. Ser. No. 180, 1980, p. 25. Copyright (1980) American Chemical Society.

The utility of Nafion far exceeds application as a membrane material. Yeager[59] studied the selectivity of Nafion ion-exchange resins toward mono- and divalent cations. The equilibrium constants $K(M^+/H^+)$ increase continually with hydrated radius, as was previously found for the polystyrene-sulfonate cation exchangers[39,40]. The differences between the K values enable a facile chromatographic separation of alkali-metal ions, as seen in Figure 9.

Nafion resins in the acid form have been successfully used as catalysts in Friedel–Crafts alkylations and acylations[60] as well as in gas-phase esterifications. In contrast to the batch process, which is slow and produces a low yield, the solid heterogeneous H-Nafion resin catalyst was used in a flow reactor, resulting in close to quantitative yields at contact times of several seconds only[61].

IV. POLYSULFONATE DERIVATIVES

A. Poly(sulfonyl chlorides)

Polysulfonic acid chlorides were mentioned in previous sections as intermediates for the acid form[23,24]. Although the $—SO_2Cl$ group is less prone to hydrolysis than —COCl, polymeric sulfonyl chlorides have not gained importance *per se*. The direct polymerization of vinylsulfonyl chloride by radical initiators proved unsuccessful. The fluoride, however, readily polymerized at 50 °C, resulting in a hydrolytically stable polymer at ambient conditions[62].

A reactive aromatic sulfonyl fluoride monomer, *N*-(fluorosulfonyl)phenyl acrylamide, was prepared by Hart and Timmerman and its copolymerization with other monomers was reported[63]. However, their use as intermediates for the derivation of various sulfonyl- or sulfone-group-containing polymers is widely practiced. Thus, the $—SO_2Cl$ group in a material trade-named Hypalon (DuPont) is used as a 'handle' for the subsequent vulcanization of this elastomer.

Hypalon is based on a low-density polyethylene, subjected to concurrent chlorination and sulfochlorination by the Reed reaction[64,70] under conditions that lead to an elastomer containing 27–30% chlorine and 1.2–1.5% sulfur (i.e. about 18 Cl and one $—SO_2Cl$ groups per 100 chain carbons[67]). The SO_2Cl group can be conveniently used for cross-linking ('vulcanization') reactions, the important ones being with metal oxides and diamines. The preferred oxides are those of lead and magnesium, in conjunction with abietic acid[69]. Cross-linking is presumably of the kind described by Makowsky and Lundberg[66]. Diamines, such as hexamethylene diamine, leading to diamide formation, are used for Hypalon solutions (in tetralin) when the material is used as a coating, and the curing reaction occurs at room temperature[65].

The resulting elastomer has outstanding chemical resistance to strong acids and various solvents, and its mechanical properties are well preserved over a temperature range of −50 to 120 °C[68].

B. Poly(sulfonamides)

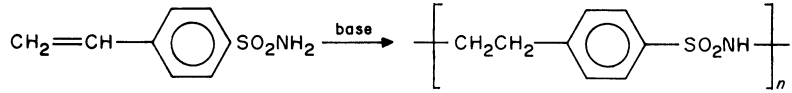
The polymerization kinetics of vinyl sulfonamide were studied by Schultz and Schlessmann[71] using various initiators. Phenyl lithium, a typical anionic polymerization initiator, was the preferred one, a high rate being achieved at −50 °C.

Wiley and coworkers studied the polymerization of ethenesulfonamide by γ-ray initiation at room temperature[72a]. Exceptionally high rates (1.25% per minute!) and yields (up to 98%) were obtained. This was confirmed in later work[72b] with a carefully purified monomer. The reaction rate was essentially independent of temperature in the range of 4 to 50 °C, which is characteristic of an ionic chain-propagation. Such a mechanism is supported by the rate being proportional to the 0.96th ($\sim$1.00) power of the radiation intensity[72c].

The η_{sp}/c vs c plot of the polymer showed typical polyelectrolyte behavior[72a], indicating a weak acidic character of the amide.

The ionic character of the polyamides is more pronounced in aromatic polysulfonamides), as found earlier by Wiley's group[73]. Thus poly(styrene sulfonamide), obtained by radical initiation, titrates as a weak cation-exchange resin of almost theoretical IEC.

While the structure of this polymer contained the amide in the side-chain, polymerization of the monomer by potassium butoxide in DMF produced a high MW polymer of different structure, the sulfonylamide group being part of the main chain:



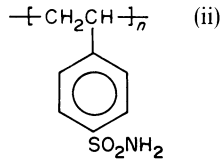
(i)

This polymer has a melting point of 276 °C and is soluble in DMSO, from which clear films could be cast. A proton-transfer polymerization mechanism was suggested by Yoda and Marvel as operative in this case[74], similar to that first proposed by Breslow and coworkers[75] for carbonyl amides, as follows:

initiation $CH_2{=}CHCONH_2 + B \rightleftharpoons CH_2{=}CHCONH^- + BH$

propagation $CH_2{=}CHCONH^- + CH_2{=}CHCONH_2$
$\longrightarrow CH_2{=}CHCONHCH_2C^-HCONH_2$
$\longrightarrow CH_2{=}CHCONH(CH_2)_2CONH^-$ etc.

However, a certain fraction with the sulfonamide in the side-chain,

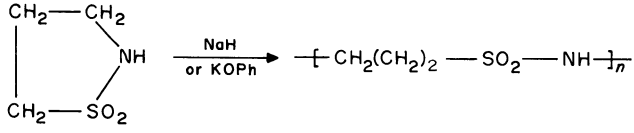


(ii)

is also present.

Structure (ii) was dominant for free-radical initiation, producing a polymer with a mp of 285–288 °C; the difference between the two polymers was evident from NMR and IR spectra[74].

In an analogous manner to lactam polymerization, a high-MW polyamide was obtained by Bliss and collaborators [76] in the ring-opening polymerization of propane sultam under phenoxide or Na hydride catalysis:



Aromatic polysulfonamides were synthesized mainly by polycondensation. The preferred method is interfacial polycondensation, first used by Wittbecker and Morgan[77]. It involves contacting a water phase, containing a diamine with a solution of the disulfonyl chloride, usually in a chlorocarbon solvent, e.g.

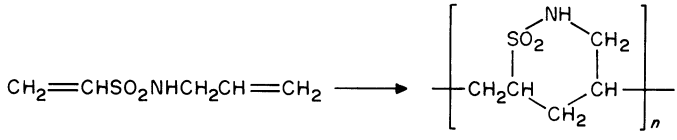
$$ClSO_2\text{—(phenylene)—}SO_2Cl + NH_2(CH_2)_6NH_2 \xrightarrow{Na_2CO_3} \text{-[-phenylene—}SO_2NH(CH_2)_6NH\text{-]}_n$$

(in CH_2Cl_2) (in H_2O)

Various aromatic sulfonyl chlorides were used by Sundet and coworkers in this reaction[78].

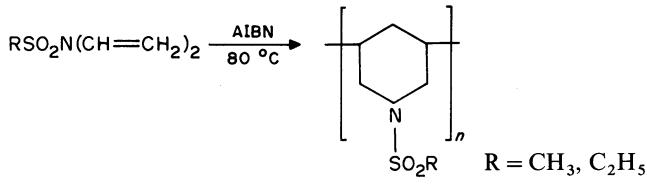
On the other hand, Kwolek and Morgan[79] claimed better yields and high MWs for polycondensation in homogeneous solution. A vigorously stirred stoichiometric mixture of the two components in a solvent and in the presence of $Ca(OH)_2$ as HCl acceptor produced tough, flexible products suitable for film and fiber formation.

A poly(cyclic sulfonamide) was obtained by Goethals and his group[80] in a radical-initiated cyclo-polymerization of a 1,6-diene:



Interestingly, the vinyl as well as the allyl double bonds are both sluggish to polymerize separately in ethene- and allylsulfonates, but in the cyclo-copolymerization, when both moieties are present in the same molecule, they react rather rapidly.

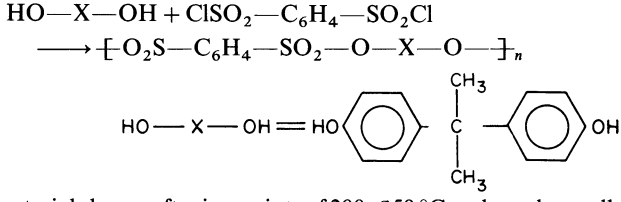
Heterocyclic poly(*N*-sulfonamides) were obtained by Cranshan and Jones[81] by cyclo-polymerization of *N*,*N*-diallylsulfonamides:



$R = CH_3, C_2H_5$

C. Aromatic Esters of Polysulfonates

Main-chain aromatic polysulfonates are disclosed in numerous patents. As in the case of the polyamides, they are mostly prepared by a two-phase polycondensation using an aromatic disulfonyl chloride in a chlorocarbon solvent on the one hand, and an alkaline water solution of a diphenol on the other. The most commonly used diphenol is the industrially available Bisphenol A, in conjunction with aromatic disulfonyl chlorides. Typical cases are reported by Thomson and Ehlers[82], e.g.



These materials have softening points of 200–250 °C and are thermally stable up to 300 °C, above which they decompose with SO_2 evolution.

Clear, transparent films (or fibers) may be obtained by melt extrusion or solvent casting.

Although rather similar in their properties to certain polyesters, they failed to achieve industrial applications.

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CHAPTER **21**

Perfluoroalkanesulfonic acids and their derivatives

WEI-YUAN HUANG and QING-YUN CHEN

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai, 200032, China

The chemistry of sulphonic acids, esters and their derivatives
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I. INTRODUCTION

Perfluoroalkanesulfonic acids belong to one of the most important classes of fluorocarbon derivatives, being the strongest of all known monoprotic organic acids. Perfluoroalkanesulfonic acids and their conjugate bases possess extreme thermal stability and resistance to reductive or oxidative cleavage and to attack by strong nucleophiles. These advantageous features have been a great stimulus to extensive research efforts involving perfluoroalkanesulfonic acids and their derivatives. The simplest member of the group, trifluoromethanesulfonic acid and its derivatives, have been most extensively studied, and the higher analogs, those with a chain of 8–10 carbon atoms, showed excellent surfactant activity under a variety of conditions and found wide commercial applications[1]. The ion exchange membrane manufactured from the copolymer of tetrafluoroethylene with a perfluorovinyl ether containing pendant sulfonate or carboxylate groups has been used in the commercial production of high-purity caustic alkali from the electrolysis of brine[2]. On the other hand, perfluoroaromatic sulfonic acids have not been much studied[3]. Several excellent reviews dealing mainly with trifluoromethanesulfonic acid and its derivatives are available[4–8].

II. SCOPE

The present review concentrates mainly on the recent developments in the field of perfluoro- or polyfluoroalkanesulfonic acids and their derivatives including their syntheses, reactions and synthetic applications. R_f denotes a perfluoroalkyl or a polyfluoroalkyl group.

III. PERFLUOROALKANESULFONIC ACIDS AND THEIR SALTS

A. Preparation of Perfluoroalkanesulfonic Acids

Perfluoroalkanesulfonic acids are mainly prepared by two methods. The first method based on electrochemical fluorination (ECF) in anhydrous hydrogen fluoride (AHF) is the most practical. Although fluorination of the alkanesulfonic acids cannot be carried out directly by ECF[9,10], the alkanesulfonyl fluorides can be successfully fluorinated with fairly high yields. The prefluorinated sulfonyl fluoride produced may then be converted to the corresponding salt by alkaline hydrolysis. The free acids were obtained either by their distillation from a solution of the alkaline metal sulfonate in concentrated sulfuric acid or by treatment of the salt with strong acid-type ion exchange resin (equation 1).

$$RSO_2X \xrightarrow{HF,\ ECF} R_FSO_2F \xrightarrow{NaOH} R_FSO_3Na \longrightarrow R_FSO_3H \qquad (1)$$

$X = F, Cl$

The oxidation of perfluoroalkanesulfinic acids or their salts to the corresponding sulfonic acid derivatives constituted the second general synthetic method. As perfluoroalkanesulfinates can be easily obtained from perfluoroalkyl halides through organometallic intermediates or from the sulfinatodehalogenation process[11–15] (see Section IV), this latter route is particularly useful in the syntheses of perfluoro- and polyfluorosulfonic acids and their derivatives[13–18] (equations 2 and 3).

$$R_FSO_2M \xrightarrow{X_2} R_FSO_2X \quad (X = Cl, Br, I) \qquad (2)$$

$$Cl(CF_2)_nSO_2K \xrightarrow{H_2O_2} Cl(CF_2)_nSO_3K \qquad (3)$$

A α,ω-disulfonyl chloride was prepared in a similar way[19] (equation 4).

$$NaO_2S\text{-}R_F\text{-}SO_2Na \xrightarrow{Cl_2} ClO_2S\text{-}R_F\text{-}SO_2Cl \quad (4)$$

Recently, a mixed sulfonic phosphonic acid was prepared via this route[20] (equation 5). Sodium trifluoromethanesulfonate can be prepared in a similar way[21] (equation 6).

$$(RO)_2P(O)CF_2X \xrightarrow{Na_2S_2O_4,\ NaHCO_3} (RO)_2P(O)CF_2SO_2Na \xrightarrow{H_2O_2,\ 30\%}$$

$$(RO)_2P(O)CF_2SO_3Na \xrightarrow[2.\ \text{Amberlite, IR-120}]{1.\ \text{Conc. HCl}} (HO)_2P(O)CF_2SO_3H \quad (5)$$

$$CF_3Br \xrightarrow[Na_2HPO_4]{Na_2S_2O_4} CF_3SO_2Na \quad (6)$$

The trifluoromethanesulfinate salt thus obtained can be transformed to the sulfonyl chloride by chlorination and to the sulfonic acid by oxidation with hydrogen peroxide.

Another method for the preparation of trifluoromethanesulfonic acid has also been reported[22] (equation 7).

$$CF_3SSCF_3 \xrightarrow{H_2SO_4,\ H_2O_2\ (aq.)} CF_3SO_3H \quad (7)$$

B. Properties of Perfluoroalkanesulfonic Acids

Anhydrous perfluoroalkanesulfonic acids are stable up to a temperature of 400 °C in the absence of air and moisture. Pyrolysis of perfluoropropanesulfonic acid at 500 °C gave C_6F_{14}, C_2F_5COF and other decomposition products (SO_2, COF_2, SOF_2, HF)[23]. On the other hand, a solution of the perfluoroalkanesulfonic anhydride [$(R_FSO_2)_2O$, $R_F = CF_3, C_2F_5, C_4F_9$)] in the perfluoroalkanesulfonic acid decomposes thermally to give the corresponding perfluoroalkyl perfluoroalkanesulfonate ($R_FSO_3R_F$) with liberation of SO_2[24] (see section V.B.) (equation 8).

$$(R_FSO_2)_2O \xrightarrow{R_FSO_3H} R_FSO_3R_F + SO_2 \quad (8)$$

This reaction was developed into a new and facile synthesis of symetrical perfluorosulfonic esters $R_FSO_3R_F$ (equation 9).

$$2R_FSO_3H \xrightarrow{P_2O_5} R_FSO_3R_F + SO_2 \quad (9)$$

The first member of the series of perfluoroalkanesulfonic acids, trifluoromethanesulfonic acid, commonly known as triflic acid, has been most extensively studied. Having an acidity function H_0 value of -14[25], it very readily protonates compounds containing multiple bonds and has been used extensively as catalyst for polymerization/oligomerization of olefins, for isomerization and rearrangement of hydrocarbons, in the modification of polymers containing double bonds, in Friedel–Crafts acylation and alkylation and in the facile cleavage of protecting groups, e.g. in peptide synthesis. CF_3SO_3H has also found application in fuel cell technology, and various diacids such as $HO_3S(CF_2)_nSO_3H$ ($n = 1,3$)[26,27] were also investigated for this purpose. The recently synthesized $(HO)_2P(O)CF_2SO_3H$[20] seems to be a more powerful candidate for fuel cell electrolyte.

There are, of course, a large number of other applications of triflic acid in synthesis, and the interested reader may consult the appropriate reviews for details. A few examples which appeared in the last few years are given below.

A mixed anhydride resulted from the reaction of CF_3CO_2H with CF_3SO_3H in the

presence of P_2O_5 and was found to be a very effective reagent for cleavage of ethers[28] (equations 10–12).

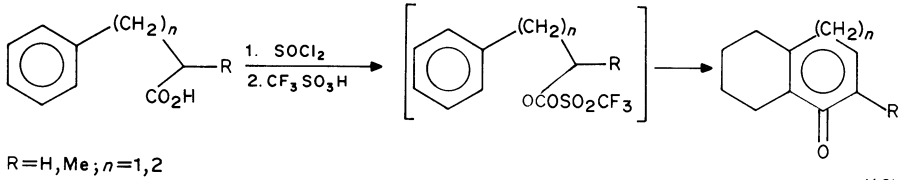
$$(C_2H_5)_2O \xrightarrow{CF_3SO_2OCOCF_3} CF_3SO_3C_2H_5 + CF_3CO_2C_2H_5 \quad (10)$$

$$\xrightarrow{} CF_3CO_2(CH_2)_4OSO_2CF_3 \quad (11)$$

$$PhOCH_3 \xrightarrow{CF_3SO_2OCOCF_3} CF_3SO_3CH_3 + PhOCOCF_3 \quad (12)$$

The reagent was also able to convert carbonyl compounds into enol trifluoroacetates.

3- and 4-phenylalkanoic acids were readily cyclized to 1-indanones and 1-tetralones, respectively, through the intermediary of a mixed anhydride formed with CF_3SO_3H[29] (equation 13).

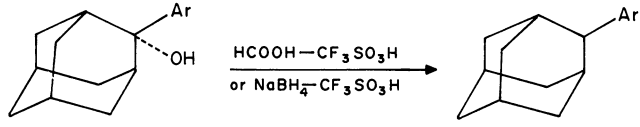


R=H, Me; n=1,2

(13)

Mixtures of CF_3SO_3H and the triflates of B, Al or Ga form a new superacid system, i.e. $CF_3SO_3H_2^+[E(OSO_2CF_3)_4]^-$ (E = B, Al or Ga), which show superior catalytic activity in isomerization of alkanes, in trans-bromination and trans-alkylation of aromatics and in other related Friedel–Crafts reactions as compared with CF_3SO_3H alone[30–33]. The relative reactivity sequence is B > Ga > Al. The triflates $E(OSO_2CF_3)_3$ were prepared from the reaction of EX_3 (X = Br, Cl) with CF_3SO_3H[33].

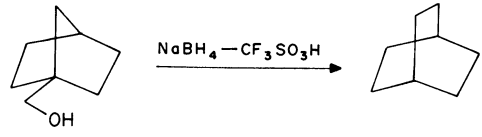
A combination of HCO_2H and CF_3SO_3H showed strong reducing properties and was able to reduce an aryl-substituted tertiary alcohol to the corresponding hydrocarbon[34]. The same reaction also took place with a $NaBH_4$–CF_3SO_3H mixture[34] (equation 14).



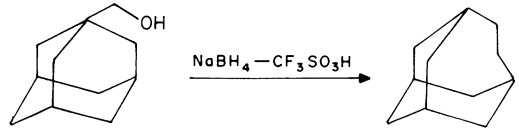
(14)

The latter mixture was shown to possess both the ability to reduce the alcoholic function and to cause a rearrangement of a hydrocarbon[35], as demonstrated in equations 15 and 16.

Unsaturated polycyclics were reduced and isomerized to the saturated polycyclics in a similar way[36] (equation 17).



(15)



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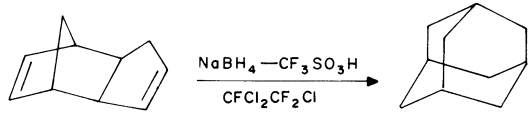


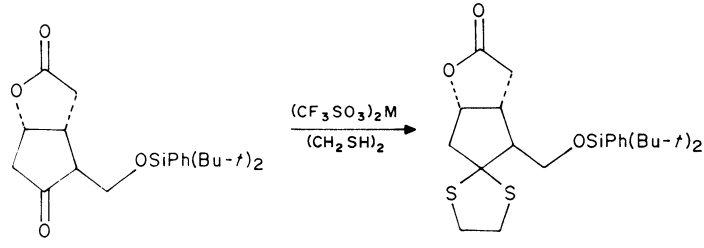
(17)

C. Metallic Salts of R_FSO_3H

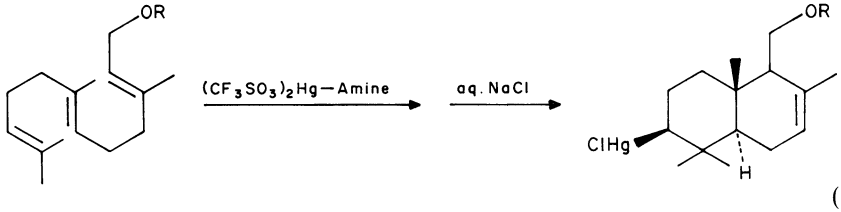
Various metallic salts of CF_3SO_3H, such as those of Na, K, Cs, Cu(I), Ag(I), Mg, Zn, Cd, Ba, B, Al and Ga, are known. Occasionally, salts of some other perfluoro- and polyfluorosulfonic acids are also prepared. These salts are extensively ionized (to ion pairs) even in organic solvents and they show higher solubility in organic solvents than the corresponding salts of other acids. Furthermore, the perfluorosulfonates like perchlorate are very weakly coordinating anions. Consequently, these salts are the reagents of choice in synthetic applications, which were already mentioned in several earlier reviews[4–8]. Some further examples which appeared recently are mentioned in the following paragraphs.

Cupric trifluoromethanesulfonate was found to be an effective reagent for the oxidative coupling reaction of ketone enolates and trimethylsilyl enol ethers[37], for thioketalizations[38], for the cyclopropanation of olefins with diazo compounds[39] and for facile dehydration of alcohols[40a]. Recently, copper(I) trifluoromethanesulfonate was shown to be a useful reagent in the construction of β-lactams from β-amino thiol esters[40b]. Similarly, $(CF_3SO_3)_2M$ (M = Zn, Hg, Mg) were also outstanding as promotors in thioketalization of acid-sensitive or hindered ketones[41], as shown for example in equation 18.

Mercury(II) trifluoromethanesulfonate–amine complex has been used to convert a variety of farnesol derivatives to their cyclization products[42] (equation 19).



(18)

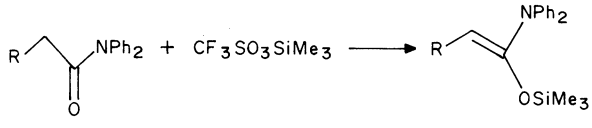


(19)

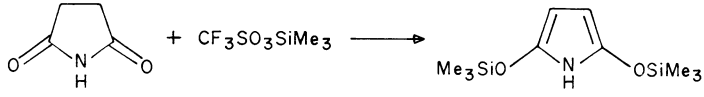
Perfluoroalkanesulfonates of group IIIA elements such as boron, aluminum and gallium triflates were widely used as strong Lewis acids by Olah and coworkers in the generation of stable carbocations and as catalysts in Friedel–Crafts alkylation and acylation[25,30–33]. Thermal cleavage of boron tris(pentafluoroethanesulfonate) and triflate at 200 °C gave boron trifluoride, sulfur dioxide, trifluoroacetyl fluoride(carbonyl fluoride), pentafluoroethanesulfonic(triflic) anhydride, pentafluoroethyl(trifluoromethyl) pentafluoroethylsulfonate(triflate) and boric acid[43].

Triflates of some group IVA elements were also successfully applied in organic synthesis. $CF_3SO_3SiR_3$ is a group of highly reactive silylating agents and strong Lewis acids and has been reviewed recently in great detail[5,7]. Some further applications are reported below.

Investigation of trimethylsilyl triflate as a powerful silylating agent continues to be reported[44] and is demonstrated in equations 20 and 21.

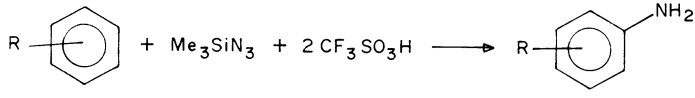


(20)



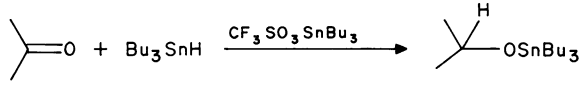
(21)

Combination of CF_3SO_3H with Me_3SiN_3 was used as a reagent for electrophilic amination of alkylbenzenes and halobenzenes[45] (equation 22).



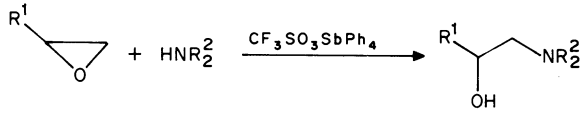
(22)

Bis(trimethylsilyl)peroxide/triflic acid was similarly used in electrophilic aromatic hydroxylation[45], whereas $CF_3SO_3SnBu_3$ served as a catalyst to promote the reduction of the carbonyl function by Bu_3SnH[46] (equation 23).



(23)

Other salts of perfluorosulfonic acid have found special application in synthesis. For example, $CF_3SO_3SbPh_4$ was used as a catalyst for the regioselective opening of epoxide by amines where the attack of the amine took place predominately or exclusively on the less hindered carbon[47] (equation 24).



(24)

Interestingly, reaction of amides and ureas with $(CF_3SO_2)_2O$ resulted in the formation of a new type of stabilized dicarbonium salt[48] (equation 25).

$$2R^1R^2C{=}O + (CF_3SO_2)_2O \longrightarrow R^1R^2C^+{-}O{-}C^+R^1R^2{\cdot}2CF_3SO_3^- \quad (25)$$

$R^1{=}NH_2$, NMe_2, CH_3, Ph; $R^2{=}NH_2$, NMe_2, NEt_2, $C_5H_{10}N$

$(CF_3SO_2)_2O$ reacted with phosphoryl derivatives in a similar way to give dicationic compounds[49] (equations 26 and 27).

$$[Me_2N]_3PO + (CF_3SO_2)_2O \longrightarrow [Me_2N]_3P^+{-}O{-}P^+[NMe_2]_3{\cdot}2CF_3SO_3^- \quad (26)$$

$$Ph_3PO + (CF_3SO_2)_2O \longrightarrow Ph_3P^+{-}O{-}P^+Ph_3{\cdot}2CF_3SO_3^- \quad (27)$$

IV. PERFLUOROALKANESULFONYL HALIDES

A. Synthesis

1. *Perfluoroalkanesulfonyl fluorides R_FSO_2F*

The most important method for the preparation of a R_FSO_2F is the electrochemical fluorination of an alkanesulfonyl halide in anhydrous HF (equation 28). Since many

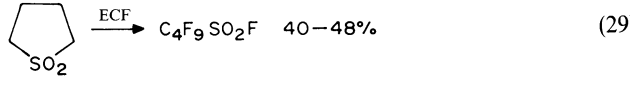
$$RSO_2X \xrightarrow[ECF]{HF} R_FSO_2F \quad (28)$$

X=F, Cl

products of great commercial value can be manufactured from perfluoroalkanesulfonyl fluoride, much effort has been invested in the development of the ECF method, the so-called Simon's process. This has been reviewed in a recent monograph in which more efficient ECF preparation and higher yields of perfluoroalkanesulfonyl fluoride have been reported[1].

The yields of the perfluoroalkanesulfonyl fluorides fall off rapidly with increasing chain length of the starting material.

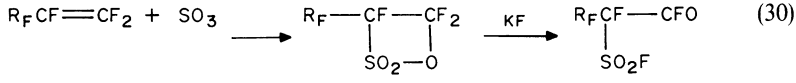
Alternatively, tetramethylene sulfone and its derivatives have been used as the starting materials, as demonstrated in equation 29.



(29)

The ECF method has been developed into a successful process for the production of various R_FSO_2F, such as CF_3SO_2F and $C_8F_{17}SO_2F$.

Certain types of R_FSO_2F can be prepared chemically. For example, telomerization of C_2F_4 using SO_2ClF as telogen gave $Cl(C_2F_4)_nSO_2F$[50] and the sultone resulting from the addition of SO_3 to a perfluoroalkene can be rearranged to sulfonyl fluoride (equation 30)[51,52].



(30)

Reaction of tetrafluoroethane sultone or its rearranged product with an alkaline metal fluoride and perfluoroalkene in the presence of halogen resulted in the formation of ω-

$$\begin{array}{l} CF_2—CF_2 \\ | \quad\quad | \\ SO_2—O \end{array} + C_2F_4 + KF + I_2 \xrightarrow{DG} I(CF_2)_2O(CF_2)_2SO_2F \qquad (31)$$

halo-oxaperfluoroalkanesulfonyl fluoride[53,54] (equation 31). The product has been further converted to a series of oxaperfluoroalkanesulfonyl fluorides.

Recently, R_FSO_2F was prepared from the reaction of the corresponding sulfonyl chloride with KF[55].

2. *Perfluoroalkanesulfonyl chlorides R_FSO_2Cl*

R_FSO_2Cl is usually prepared from either the corresponding sulfonic[56] or sulfinic acid[13,57] derivatives[56] (equations 32 and 33).

$$R_FSO_3Na + PCl_5 \longrightarrow R_FSO_2Cl \qquad (32)$$

$$R_FSO_2Na + Cl_2 \longrightarrow R_FSO_2Cl \qquad (33)$$

Perfluoroalkanesulfinic acids or their salts were prepared from the reaction of R_FX (X = I, and sometimes Br) with metals and SO_2, the various metals used including Mg[58], Zn[59], Zn–Cu[60], Fe, Co, Ni[61], Cd[20], etc., and the intermediary metallic sulfinates were converted directly into R_FSO_2Cl (equation 34).

$$R_FI + Zn \longrightarrow R_FZnI \xrightarrow{SO_2} R_FSO_2ZnI \xrightarrow{Cl_2} R_FSO_2Cl \qquad (34)$$

Recently, various R_FSO_2Na salts were prepared in good to excellent yields through the economic and convenient alternative sulfinatodehalogenation process[11,12] (equations 35[13] and 36[14,15]).

$$R_FX + Na_2S_2O_4 \xrightarrow{NaHCO_3} R_FSO_2Na \qquad (35)$$

X = I, Br

$$R_xCCl_3 + Na_2S_2O_4 \longrightarrow R_xCCl_2SO_2Na \qquad (36)$$

$R_x = R_F$, Cl, F

Perfluoalkanesulfonyl chlorides were also prepared in high yields by a direct chlorination of these R_FSO_2Na[13].

3. *Perfluoroalkanesulfonyl bromides R_FSO_2Br*

Trifluoromethanesulfonyl bromide has been prepared by a multistep synthesis, which involved the disproportionation of CF_3SOBr[62] (equation 37). However, the general method for the preparation of this class of compounds was the reaction of R_FSO_2Na with Br_2 in CCl_4[17,63] or, more conveniently, in water[17] (equation 38).

$$2CF_3SOBr \longrightarrow CF_3SO_2Br + CF_3SBr \qquad (37)$$

$$R_FSO_2Na + Br_2 \xrightarrow{CCl_4 \text{ or } H_2O} R_FSO_2Br \qquad (38)$$

4. *Perfluoroalkanesulfonyl iodides R_FSO_2I*

Perfluoroalkanesulfonyl iodides were unknown until recently. It was impossible to get R_FSO_2I by the usual method of treating R_FSO_2Na with I_2, but a good yield of the

thermally unstable R_FSO_2I was obtained by the low-temperature reaction of either R_FSO_2Ag and I_2 in CH_2Cl_2[18,64] (equation 39) or of $(R_FSO_2)_2Cu$, KI and excess $CuSO_4$ in ether[65] (equation 40).

$$R_FSO_2Ag + I_2 \xrightarrow{-30\,^\circ C,\ CH_2Cl_2} R_FSO_2I + AgI \tag{39}$$

$$(R_FSO_2)_2Cu + 2KI + 3CuSO_4 \xrightarrow[\text{ether}]{-30\,^\circ C} 2R_FSO_2I + 2Cu_2SO_4 + K_2SO_4 \tag{40}$$

B. Properties of R_FSO_2X

The difference in the atomic radii, the electronegativities of the halogen atoms and the S—X bond strengths resulted in a gradual change in the properties of the four sulfonyl halides which are manifested in the following paragraphs.

1. *^{19}F NMR of $—CF_2SO_2X$*

The ^{19}F NMR spectra of perfluoroalkanesulfonyl fluorides, chloride and bromide $CF_3(CF_2)_3SO_2Cl$, $Cl(CF_2)_6SO_2X$, X = Cl, Br were recorded by using their corresponding pure samples at room temperature. However, the ^{19}F NMR spectrum of $Cl(CF_2)_6SO_2I$ was only recorded by using its freshly prepared solution in dichloromethane at low temperature (e.g. $-50\,^\circ C$)[18,64]. The chemical shifts are given below:

X =	F	Cl	Br	I
$\delta(CFCl_3)$	107.8	104.1	103.3	105.3

2. *Thermal stability and homolytic cleavage of S—X bonds*

The thermal decomposition of R_FSO_2X to R_FX and SO_2 was shown to occur homolytically. However, the ease of the decomposition varied greatly with the nature of X.

Thus, R_FSO_2F was stable at 250 °C and decomposed in a flow reactor above 460 °C[24] in the presence of copper[66]. No addition reaction with alkene has been reported. R_FSO_2Cl decomposed at about 150 °C[67], and the reaction was also initiated by actinic radiation or by free radical initiators or by Cu[67,68]. The reaction had been utilized to bring about the addition of a perfluoroalkyl group to an alkene (equation 41), and a free radical chain-mechanism was suggested[67,68].

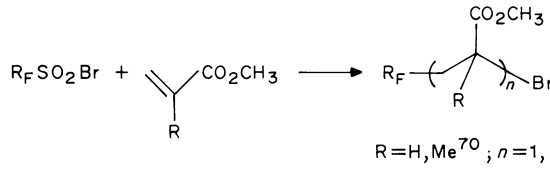
$$R_FSO_2Cl + \text{CH}_2\!=\!\text{CH}—R \xrightarrow{\text{Peroxide or UV}} R_F\text{CH}_2\text{CHClR} + SO_2 \tag{41}$$

R_FSO_2Br decomposed around 80–100 °C in acetonitrile or acetic acid, but it did not decompose in boiling water, CCl_4 or benzene[69]. However, R_FSO_2Br reacted with various olefinic compounds in two different ways[17]. One is a spontaneous addition, after loss of SO_2 to electron-rich olefins, e.g. equation 42.

$$R_FSO_2Br + \text{CH}_2\!=\!\text{CH}—\text{CH}_2—O—\text{CH}_2—\text{CH}\!=\!\text{CH}_2 \xrightarrow{-SO_2} R_F\text{CH}_2\text{CHBrCH}_2\text{OCH}_2—\text{CH}\!=\!\text{CH}_2 \tag{42}$$

In the reaction of perfluoroalkanesulfonyl bromides with styrene, only the 1:1 adducts were formed in good yields, and the reactions were not sensitive to added hydroquinone

or *p*-dinitrobenzene. Hence, a nonradical mechanism has been proposed to account for the results[17]. The second reaction is addition to acetylenes or to electron-poor olefinic compounds proceeding by initiation with a free radical initiator or by light which always forms some telomers together with the 1:1 adduct (equation 43).



$$R_FSO_2Br + \underset{R}{\overset{CO_2CH_3}{\diagup\!=\!\diagdown}} \longrightarrow R_F\text{-}\left(\underset{R}{\overset{CO_2CH_3}{C}}\right)_n\text{-}Br \qquad (43)$$

$R = H, Me$[70]; $n = 1, 2$

These reactions were used to synthesize perfluoroalkyl-substituted amino acids[70].

The sulfur-iodine bond appears to be very weak. R_FSO_2I were unstable at room temperature and decomposed spontaneously to give R_FI and SO_2. These compounds cannot be isolated in a free state but their solutions in CH_2Cl_2 at $-30\,^{\circ}C$ have been prepared and used directly[18,64]. The sulfonyl iodides were found to react spontaneously with multiple bonds in three ways: (i) by addition to electron-rich olefins without elimination of SO_2, (ii) by addition to acetylenes and electron-poor olefins to give adducts with loss of SO_2 and (iii) by reaction with $CH_2{=}CHCOR$ (R = H, Me) to give $R_FSO_2CH_2CH_2COR$.

It is believed that the thermal-induced decomposition and the addition of perfluoroalkanesulfonyl iodides to unsaturated compounds follow a free radical chain-mechanism. The strongly electron-withdrawing R_F group causes the perfluoroalkanesulfonyl radical to be electrophilic, and consequently the addition of $R_FSO_2\cdot$ to the electron-rich carbon–carbon double bonds to give the normal 1:1 adducts without losing SO_2 is favored. In contrast, in the spontaneous addition of R_FSO_2I to alkynes or alkenes substituted with electron-withdrawing substituents, the reactivity of the perfluoroalkanesulfonyl radical is sufficiently reduced, thus allowing the $R_FSO_2\cdot$ radical to decompose to the $R_F\cdot$ radical before addition to the multiple bond. Indeed, the intermediary $R_FSO_2^{\bullet}$ or $R_F^{\bullet}$ radicals were trapped by 2-methyl-2-nitrosopropane during the additions of R_FSO_2I to these olefins, and studied by ESR spectroscopy[18,64].

3. *Reactivity toward nucleophiles*

R_FSO_2F reacts invariably with nucleophiles at the sulfur atom to give the corresponding sulfonyl derivatives[4] as shown in equations 44–46.

$$R_FSO_2X \xrightarrow{H_2O \text{ or } OH^-} R_FSO_3H \text{ or } R_FSO_3^- \qquad (44)$$

$(X = F, Cl)$

$$R_FSO_2F + ROH \xrightarrow{NEt_3} R_FSO_3R \qquad (45)$$

$$R_FSO_2F + RR'NH \longrightarrow R_FSO_2NRR' \qquad (46)$$

R_FSO_2Cl reacted in a similar fashion with most nucleophiles, e.g. to give esters or amides with alcohols or secondary amines. However, in the reaction with a primary amine, such as $C_2H_5NH_2$, the expected amide was not formed, but a chlorophilic reaction apparently occurred to give the salt $R_FSO_2^-\ N^+H_3R$ as the sole product in many solvents, and a mixture of the sulfinate and the expected amide, e.g. $R_FSO_2NHC_2H_5$ was formed in $PO(OCH_3)_3$[55].

In the case of R_FSO_2Br and R_FSO_2I, no product resulting from nucleophilic attack on sulfur has been observed, and reactions with various nucleophiles invariably involved a

halophilic attack to give perfluoroalkanesulfinate, R_FSO_2M[17,18,64] e.g., equation 47. The behaviour of R_FSO_2Br and R_FSO_2I is reminiscent of that of CCl_3SO_2Cl[71].

$$R_FSO_2Br + EtOH \longrightarrow R_FSO_2H + HBr + [CH_3CHO] \quad (47)$$

In the reactions of perfluoroalkanesulfonyl halide with carbonyl containing nucleophiles, such as ketones or aldehydes, the reactivity difference of the various R_FSO_2X was readily observed. R_FSO_2F was inert toward these compounds, whereas R_FSO_2Cl was shown to chlorinate the active methylene group in acetoacetic esters or malonic esters under light irradiation[72], but simple ketones did not react. R_FSO_2Br behaved as a powerful brominating agent, and reacted readily with compounds containing an active methylene group and even with simple ketones and aldehydes containing α-hydrogen atom to give the corresponding α-bromo derivatives in good to excellent yields without the aid of actinic radiation or added catalyst[17] (equation 48).

$$R_FSO_2Br + \geq CH—CO— \longrightarrow R_FSO_2H + \geq CBrCO— \quad (48)$$

R_FSO_2I was also able to iodinate spontaneously compounds containing an active methylene group as well as simple carbonyl compounds containing an α-hydrogen atom, such as acetone[18,64].

V. PERFLUOROALKANESULFONIC ESTERS

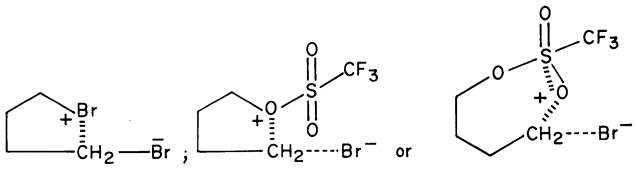
Perfluoroalkanesulfonic esters are among the most important derivatives of perfluoroalkanesulfonic acids, and they have been extensively studied both in theory and in synthetic applications. An excellent and detailed summary has been presented by Stang and coworkers in 1982[6]. Since then, numerous results in this area have been accumulated. We do not intend to include in this chapter all the material reported but will give only a brief review with emphasis on more recent developments.

A. Alkyl Perfluoroalkanesulfonic Esters

One convenient method for the preparation of alkyl perfluoroalkanesulfonates is the reaction of alkyl halides with the silver salts of the perfluoroalkanesulfonic acids[6a]. A recent work[6b] showed that the reaction of bromoalkanes with silver triflate is sensitive to the structure of the reactants, the solvent characteristics and the reaction conditions. For example, in CCl_4 at room temperature 1-bromopropane or 1-bromobutane reacted with AgOTf to give predominantly the rearranged 2-propyl and 2-butyl triflate together with the unrearranged products. However, α,ω-dibromoalkanes, e.g., 1,4-dibromobutane produced only the unrearranged primary 4-bromobutyl triflate and 1,4-butaneditriflate under the same conditions (equation 48a).

$$\begin{aligned} BrCH_2CH_2CH_2CH_2Br &\xrightarrow{AgOTf} T_fOCH_2CH_2CH_2CH_2Br \\ &\xrightarrow{AgOTf} T_fOCH_2CH_2CH_2CH_2OT_f \end{aligned} \quad (48a)$$

The lack of rearrangement was ascribed to a neighboring bromine group participation in the first step and to the rare formation of an intermediate with a bridging triflate group in the second step, as shown below.



In benzene, depending upon the reaction temperature, α,ω-dibromoalkanes, $Br(CH_2)_nBr$ (n = 2–6, 10) can be transformed to the mono-triflate $Br(CH_2)_nOTf$ and/or the ditriflate $TfO(CH_2)_nOTf$. The reaction in benzene provides a good one-step synthesis of ditriflates. It was found that the lithium and n-butylammonium salts of triflic acid, instead of the silver salts, can also react with alkyl iodides in the presence of oxidants, such as chlorine gas, *m*-chloroperbenzoic acid or H_5IO_6 to give the corresponding triflates in 20–50% yields[73] (equation 49).

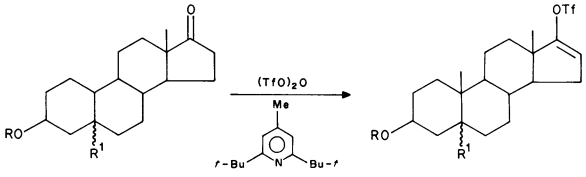
$$CH_3(CH_2)_nI + CF_3SO_3^-M^+ \xrightarrow{\text{oxidant}} CH_3(CH_2)_nOSO_2CF_3 \qquad (49)$$

$n = 0\text{–}5$; M = Li, $(n\text{-}Bu)_4N$

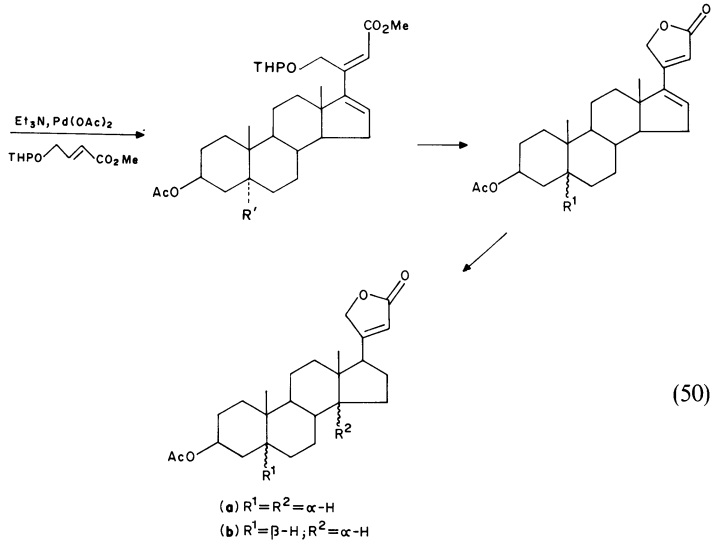
This is an example of a reaction of a very weak nucleophile with the carbocation generated by oxidation of alkyl iodides[74].

The most convenient and widely used method for preparing esters of triflic acid consists of reacting the appropriate alcohol or enol with triflic anhydride in the presence of alkylated pyridines, although 2,6-lutidine or 2,4,6-collidine readily react alone with triflic anhydride[75].

As a good example, the cardenolides can be synthesized from 3β-hydroxy-5α-androstan-17-one acetate and its 5-epimer by a four-step sequence[76] (equation 50).



(a) R = CH_3CO; R^1 = α-H
(b) R = CH_3CO; R^1 = β-H
(c) R = CF_3CO; R^1 = α-H
(d) R = CF_3CO; R^1 = β-H

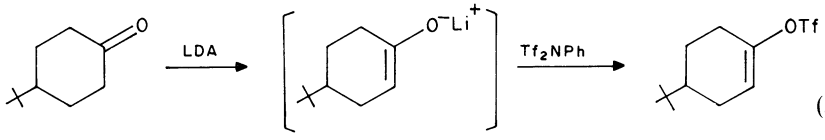


(50)

(a) $R^1 = R^2$ = α-H
(b) R^1 = β-H; R^2 = α-H

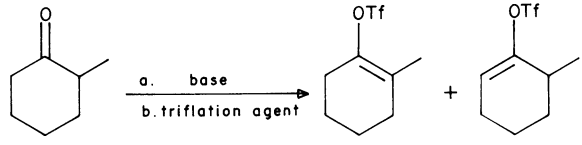
The enol triflates are prepared by treatment of the ketones with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in 55% and 46% yields, respectively. Interestingly, improved yields (over 71% and 76% yields, respectively) can be obtained by using the 3-trifluoroacetates rather than the 3-acetates in the triflating step, then removing the 3-trifluoroacetate group with potassium carbonate followed by reacetylation of the resulting alcohols. Thus, the trifluoroacetate group appears to be a valuable protecting group of the alcoholic function in the preparation of enol triflates from hydroxyketones.

Another general method of enol triflate synthesis is by conversion of a ketone into its enolate ion followed by trapping. For example, the enolate ion prepared by deprotonation of 4-*tert*-butylcyclohexanone with lithium diisopropylamide (LDA) was trapped by *N*-phenyltriflimide, but not by triflic anhydride, to give the corresponding enol triflate in 82% yield[8,77] (equation 51).



(51)

The most important feature of the enolate-trapping method is its ability to define the regiochemistry of the enol triflate, as exemplified by the selective formation of either the thermodynamically or the kinetically controlled enol triflate from 2-methylcyclohexanone by choice of the reaction conditions[77] (equation 52).



(52)

a	b			
LDA	Tf_2NPh	1	:	19
$(i\text{-}Pr)_2NMgBr$	Tf_2NPh	19	:	1
Na_2CO_3	Tf_2O	3	:	1

A series of 1-cyclobutenyl nonafliates(nonafluoro-n-butanesulfonates) and 1-cyclohexenyl triflates has been synthesized from the corresponding ketones and their solvolyses were also investigated[78–80].

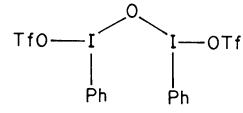
In recent years Katsuhara and DesMarteau have discovered a new series of perfluoroalkanesulfonyl hypochlorites and bromites which can be used to synthesize many useful fluorinated compounds (*vide infra*) including ditriflates[81] (equation 53). Attempts to obtain tritriflates and tetratriflates from $CHCl_3$ and CCl_4 with trifluoromethanesulfonyl hypochlorite were unsuccessful.

$$2CF_3SO_2OX + Cl(CH_2)_nCl \longrightarrow CF_3SO_3(CH_2)_nO_3SCF_3 + 2XCl \quad (53)$$

$X = Cl, Br; n = 1,2,3$

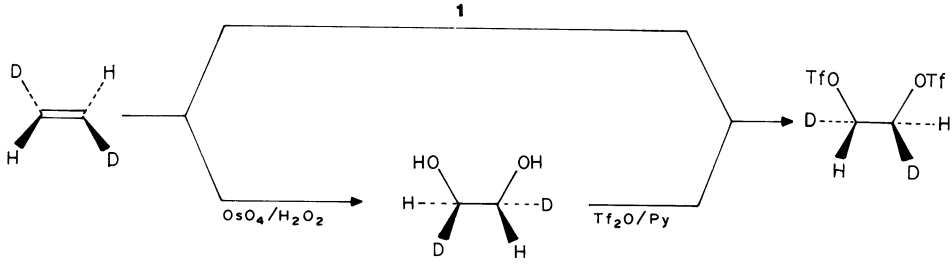
Preparation of the appropriately labeled and stereochemically pure vicinal ditriflates

from triflic anhydride and diols requires a stereochemically pure *meso*- and *dl*-1,2-ethanediol-1,2 d_2 derivatives. Recently a new reagent μ-oxobis[(trisfluoromethanesulfonato) (phenyl)iodine] (**1**) was reported to convert olefins stereospecifically to vicinal



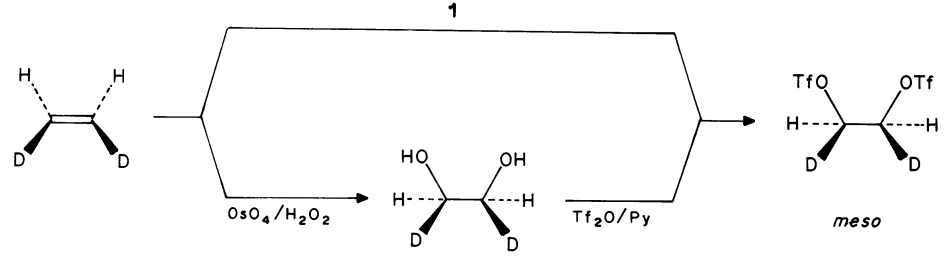
(**1**)

ditriflates in a mild one-pot procedure[82,83]. For example, the reagent reacts with cyclohexene to give *cis*-1,2-cyclohexane ditriflate. The specificity of this *syn*-addition is > 99%. Reaction of reagent 1 with *cis*- and *trans*-ethylene-1,2-d_2 provided vicinal-1,2-ditriflates-1,2-d_2. The stereochemistry was deduced by comparison with the samples of *meso*- and *dl*-ethane-1,2-ditriflate-1,2-d_2 prepared by the OsO_4/Tf_2O route (equations 54 and 55).



dl

(54)



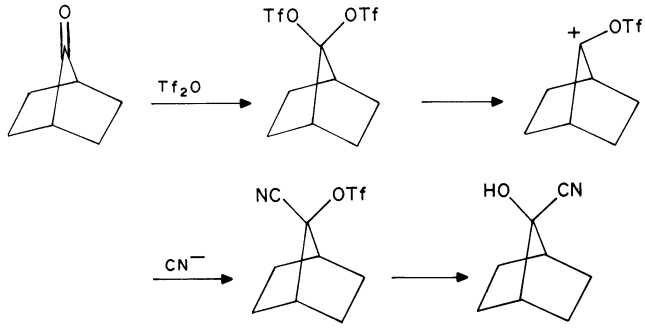
meso

(55)

Judging from the magnitudes of the coupling constants of these ethanediyl bistriflates, the more stable rotamer has *gauche* triflate groups.

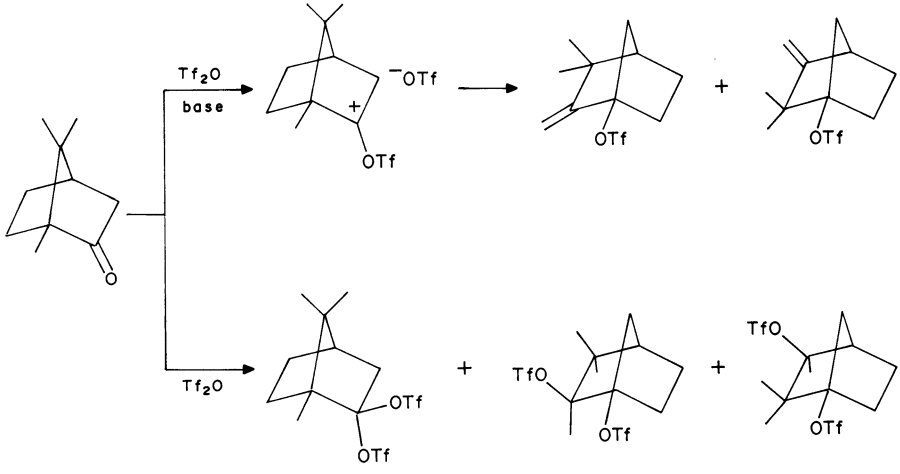
A relatively stable *gem*-ditriflate, $CH_3CH(OTf)_2$, has been prepared from CH_3CHI_2 and silver triflate[84].

The *gem*-ditriflate, prepared from the difficult-to-enolize 7-norbornanone and triflic anhydride[85], reacts with metal cyanides in dipolar aprotic solvents giving 7-cyano-7-norbornyl triflate, which affords 7-cyano-7-hydroxynorbornane[86] (equation 56).



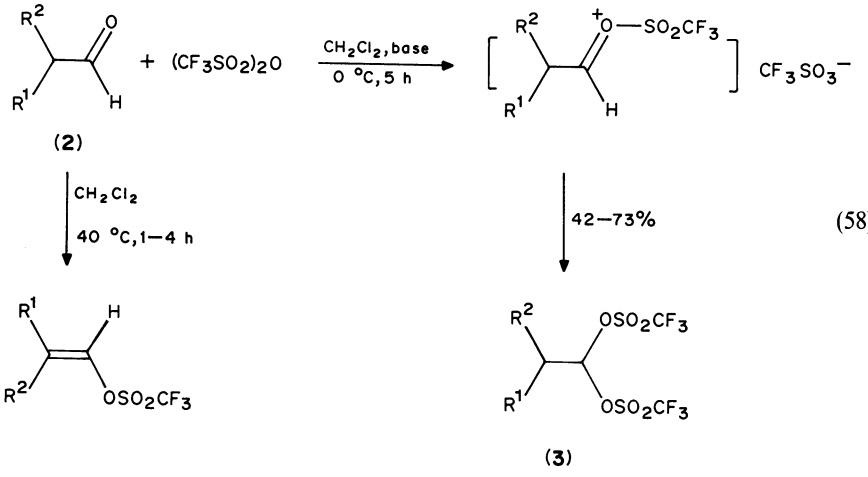
(56)

Camphor reacts with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine or Na_2CO_3, affording two compounds via the triflyloxycarbenium ion, which undergoes a Wagner–Meerwein rearrangement, followed by a Nametkin rearrangement[87,88]. However, in the absence of base a mixture of 2,2-bis(trifluoromethylsulfonyloxy) camphane and 1,2- and 2,4-bis-(trifluoromethylsulfonyloxy)-*endo*-isocamphane is obtained[88b] (equation 57).



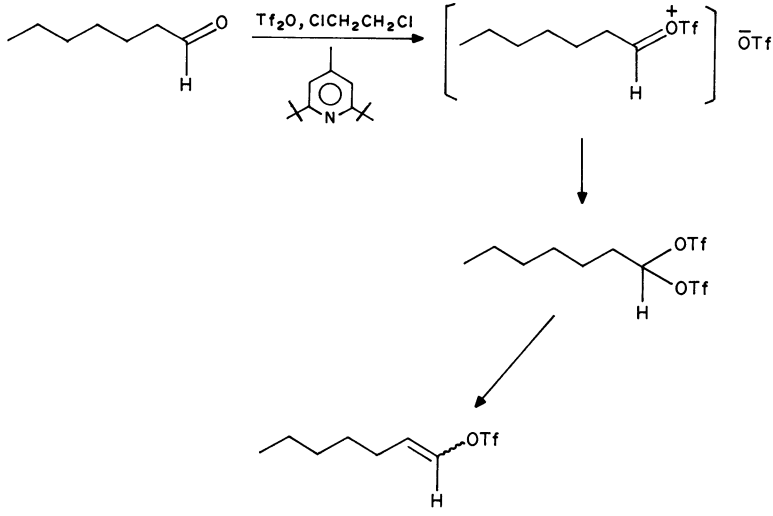
(57)

Aliphatic aldehydes and ketones, both acyclic and cyclic, react with triflic anhydride in the presence of inorganic or organic base to give the corresponding vinyl triflate[6]. For example, the aliphatic aldehyde **2** reacts with triflic anhydride at 0 °C in the presence of 2,6-di-*t*-butyl-4-methylpyridine or 2,6-lutidine giving the *gem*-bistriflate **3** in good yields[88] (equation 58). However, only vinyl triflates could be isolated by carrying out the reaction at 40 °C for 1–4 h (equation 58). A complex mixture of products, including the vinyl triflate (20%), is obtained if the reaction is conducted without adding the organic base. However, a recent work[89] showed that aldehydes with low steric hindrance, e.g. heptanal, reacted with a freshly redistilled Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine or a polymer-bound 2,6-di-*tert*-butylpyridine[90] in refluxing 1,2-dichloroethane for 2 h giving two vinyl triflates with an *E*/*Z* ratio of 1/4 and no aldol-type product. When the same



(58)

reaction was carried at 0 °C in dichloromethane, the major product isolated was the *gem*-bis(triflate). However, neither elevated temperature alone nor the chlorinated solvent alone can produce good yield of the vinyl triflate, although the combination of the two parameters works well (equation 59). The formation of the *gem*-bis(triflate) from the linear



(59)

aldehydes is crucial for the success of the reaction and it requires both a polar solvent such as $CHCl_3$ or 1,2-dichloroethane and an elevated temperature. The subsequent thermal conversion of the *gem*-bis(triflate) to the vinyl triflate also requires the same reaction conditions.

Aliphatic ketones do not form any *gem*-bis(triflate) under the same conditions or even at

low temperature, unless the elimination of triflic acid is hindered stereoelectronically as in the case of the bicyclic ketones mentioned above[88a].

As a result of easy access to perfluoroalkanesulfonyl fluorides in recent years, variety of esters have been synthesized by their reactions with fluorinated alcohols and phenols. The first example is the preparation of polyfluoroalkyl triflates, reported by Burdon and McLaughlin, who carried out the reaction in the presence of one equivalent of triethylamine in dichloromethane at $-30\,^{\circ}C$[91] (equation 60). Excessive base had to be avoided in the reaction, otherwise the nonvolatile quaternary ammonium salt, instead of the desired triflate, was obtained.

$$R_fCH_2OH + CF_3SO_2F \longrightarrow CF_3SO_2OCH_2R_f \tag{60}$$

Using this method a series of polyfluoroalkanesulfonates have been synthesized in high yields[92] (equation 61). The sulfonate esters $YCF_2SO_3CH_2(CF_2)_2H$ ($Y = Me_2CHOCO$, n-C_3F_7)[93] and $C_4F_9SO_3CH(CF_3)CR_3$ ($R = H$, F)[94] were similarly prepared. In the reactions with the fluorinated alcohol, both the reaction temperature and the amount of base used are important in controlling the yield of the products, while the temperature is the most critical factor[92]. However, with phenols, polyfluoroalkanesulfonates can be prepared in 60–70% yields in the presence of excessive triethylamine, which is used both as a base and a solvent[95] (equation 62).

$$XOCF_2CF_2SO_2F + ROH \xrightarrow[-20\text{ to }30\,^{\circ}C]{CH_2Cl_2,\ NEt_3} XOCF_2CF_2SO_3R \tag{61}$$

$R = C_6H_5$, $H(CF_2)_nCH_2$, n = 2,4;
$X = CH_3$, Cl_2CFCF_2, ICF_2CF_2, $ClCF_2CF_2$, $H(CF_2)_n$ $n = 2,4$

$$R_fSO_2F + HOC_6H_4X \xrightarrow[\text{r.t.}]{Et_3N} R_fSO_3C_6H_4X \tag{62}$$

$R_f = H(CF_2)_2O(CF_2)_2$, $Br(CF_2)_2O(CF_2)_2$ $X = o$-Cl, m-OCH_3, H, 2,6-Me_2

Tetrafluoroethane-β-sultone, formed from tetrafluoroethylene and sulfur trioxide, readily reacts with 2 equivalents of lithium polyfluoroalkoxides at 0 °C giving the corresponding mixed esters[96] (equation 63).

$$2R_fOLi + \begin{array}{l} CF_2—CF_2 \\ | \quad\quad | \\ O——SO_2 \end{array} \longrightarrow R_fOC(O)CF_2SO_3R_f + 2LiF \tag{63}$$

$R_f = CF_3CH_2$, $(CF_3)_2CH$ 65%

The mixed ester can also be prepared with a comparable yield from the preformed $(CF_3)_2CHOCOCF_2SO_2F$ and polyfluoroalkoxides[96].

As mentioned above, a series of polyfluoroalkanesulfonyl fluorides were synthesized from tetrafluoroethylene, tetrafluoroethane-β-sultone and halogens. The corresponding sulfonic esters can be obtained from the reaction of the anhydrides with alcohols in the usual way[97] (equation 64).

$$\begin{aligned} CFXYCF_2OCF_2CF_2SO_2F &\longrightarrow CFXYCF_2OCF_2CF_2SO_3H \\ &\longrightarrow (CFXYCF_2OCF_2CF_2SO_2)_2O \\ (ICF_2CF_2OCF_2CF_2SO_2)_2O + ROH &\longrightarrow ICF_2CF_2OCF_2CF_2SO_3R \end{aligned} \tag{64}$$

$XY = Cl_2$, FCl, FH, FI
R = Me, i-Pr, $ClCH_2CH_2$, CF_3CH_2, $H(CF_2)_2CH_2$
$H(CF_2)_4CH_2$, C_6F_5, 2,4-$(NO_2)_2C_6H_3$

B. Perhaloalkyl Perfluoroalkanesulfonic Esters

Considerable progress in the synthesis of perhalo perfluoroalkanesulfonic esters has been made since the publication of a recent review[6].

Taylor and Martin have summarized the synthesis of trifluoromethyl triflate (TFMT)[98] in equations 65–71. We discuss here only the last three methods in more detail. By utilizing

$$2CF_3SO_3H \xrightarrow{-2e} [CF_3SO_2O-OSO_2CF_3] \xrightarrow{10\,^\circ C} CF_3SO_3CF_3 + CF_3CF_3 + SO_3 \quad (65)$$

2 67%

$$CF_3SO_3H + FSO_3H \xrightarrow{165\,^\circ C} CF_3SO_3CF_3 + FSO_3CF_3 \quad (66)$$

19%

$$CF_3I + AgOSO_2CF_3 \xrightarrow[200\,^\circ C]{C_6H_6} CF_3SO_3CF_3 + AgI \quad (67)$$

86%

$$B(OSO_2CF_3)_3 + CF_3SO_3H \longrightarrow CF_3SO_3CF_3 + BF_3 \quad (68)$$

$$CF_3SO_2OCl + CF_3Br \xrightarrow{-111\,^\circ C} CF_3SO_3CF_3 + BrCl \quad (69)$$

95%

$$CF_3SO_3H + P_2O_5 \longrightarrow CF_3SO_3CF_3 + H_3PO_4 \quad (70)$$

$$(CF_3SO_2)_2O + SbF_5\ (cat) \xrightarrow{25\,^\circ C} CF_3SO_3CF_3 \quad (71)$$

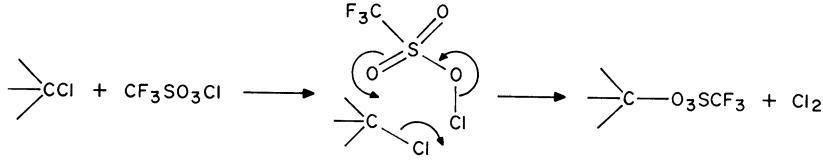
94%

perfluoroalkanesulfonyl hypochlorites or bromites, polyfluoroalkyl perfluoroalkanesulfonates can be synthesized from polyfluoroalkyl halides[99,100] as shown in equations 72 and 73. These reactions proceed readily to give high yields of mono-substituted esters and

$$CF_3SO_2OBr + C_3F_7Br \xrightarrow{-110\,^\circ C} CF_3SO_3C_3F_7 \quad (72)$$

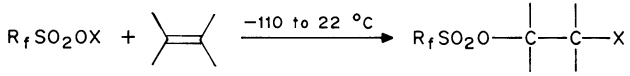
$$CF_3SO_2OCl + (CF_2Br)_2 \xrightarrow{-80\text{ to }30\,^\circ C} CF_3SO_3CF_2CF_2Br + (CF_3SO_3CF_2)_2 \quad (73)$$

lower yields of disubstituted ones. A complete retention of configuration of the alkyl group was observed in the reaction of CF_3SO_3Cl with *erythro*- and *threo*-$CF_3COOCFHCFHCl$, each yielding a single stereoisomer. This suggests a substitutive electrophilic dehalogenation reaction via an S_Ei-type mechanism (equation 74).



(74)

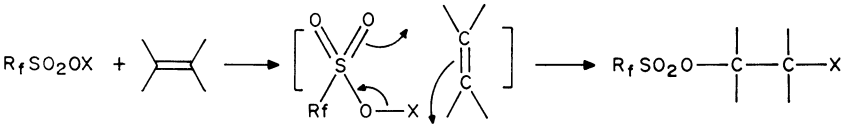
A variety of haloalkyl esters of perfluoroalkanesulfonic acids was also obtained in high yields by the addition of R_fSO_2OBr or R_fSO_2OCl to alkenes[100,101] (equation 75).



(75)

$R_f = CF_3$, n-C_4F_9; X = Cl, Br. Alkene = $CF_2{=}CF_2$, $CF_2{=}CFCl$, $CF_3CF{=}CF_2$, *cis*-CHF = CHF, *c*-C_5F_8, $CF_2{=}CH_2$, $CF_2{=}CCl_2$, *trans*-CHCl=CHCl, $CH_2{=}CH_2$

When excess alkene is employed, the addition of the hypohalite to the alkene takes place more readily than the above-mentioned substitutive electrophilic dehalogenation reaction. Based on the structures of stereoisomers obtained from the reactions of hypochlorite with *cis*- and *trans*-CHF=CHF and *trans*-CHCl=CHCl a regio- and stereospecific *syn*-addition mechanism was suggested (equation 76). Methyl and trifluoromethyl esters of



(76)

Nafion® (a perfluorosulfonic acid type ion exchange resin, Du Pont) have also been synthesized from CH_3Br and CF_3Br, respectively, with Nafion-Br in a similar way[102] (equation 77).

$$\text{Nafion-H} + \text{ClF} \xrightarrow{-110 \text{ to } -30\,^\circ\text{C}} \text{Nafion-Cl} \xrightarrow[-50 \text{ to } 0\,^\circ\text{C}]{\text{BrCl}} \text{Nafion-Br}$$

$$\xrightarrow{CF_3Br} \text{Nafion-}CF_3 \qquad (77)$$

Some reactions of trifluoromethanesulfonyl hypochlorites and bromites with inorganic compounds, such as SiF_3Br, POF_2Br, SF_5Br, $COCl_2$, $SiCl_4$, $SiBr_4$, BBr_3, $SOCl_2$, CrO_2Cl_2, $VOCl_3$, SO_2 and PF_3, were also reported[103].

A practical method developed by Commeyras and coworkers for preparing perfluoroalkyl perfluoroalkanesulfonates is the acid-catalyzed decomposition of perfluoroalkanesulfonic anhydrides, formed in turn by dehydration of the acids[24,104] (equation 78). Similarly, long-chain polyfluoroalkyl perfluoroalkanesulfonates are obtained from the corresponding acids[105] (equation 79).

$$6R_fSO_3H + P_2O_5 \longrightarrow 3R_fSO_3R_f + 3SO_2 + 3H_3PO_4 \qquad (78)$$

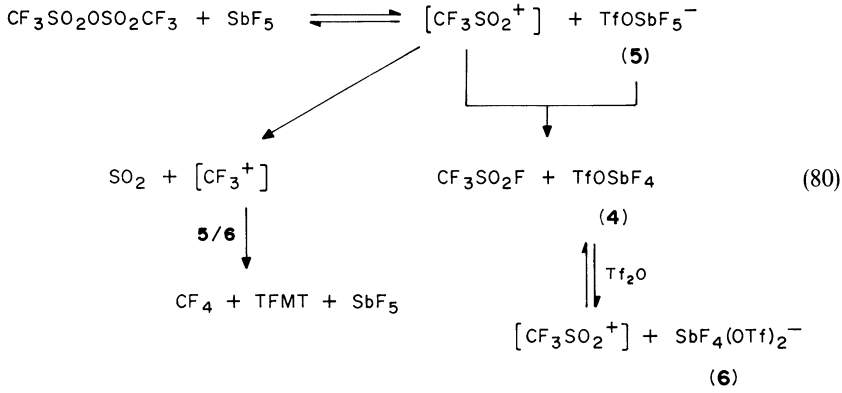
$R_f = CF_3$, C_2F_5, n-C_4F_9

$$XCF_2O(CF_2)_2SO_3H + P_2O_5 \longrightarrow XCF_2O(CF_2)_2SO_3(CF_2)_2OCF_2X \qquad (79)$$

$X = ICF_2$, $ClCF_2$, HCF_2, Cl_2CF

In order to obtain the esters rather than the anhydrides, the addition of a small amount of P_2O_5 and slower distillation are required. The yields of the pure esters are good. On heating a mixture of an anhydride with another acid, e.g. $(CF_3SO_2)_2O/C_2F_5SO_3H$ or $(C_2F_5SO_2)_2O/CF_3SO_3H$, a mixture of the esters $R_fSO_2OR_f$, namely, $CF_3SO_2OCF_3$, $C_2F_5SO_2OC_2F_5$ and $C_2F_5SO_2OCF_3$ but no $CF_3SO_2OC_2F_5$ is obtained. Their relative proportions depend on the initial conditions[24,104]. Recently, Taylor and Martin developed a new synthetic method for preparing trifluoromethyl

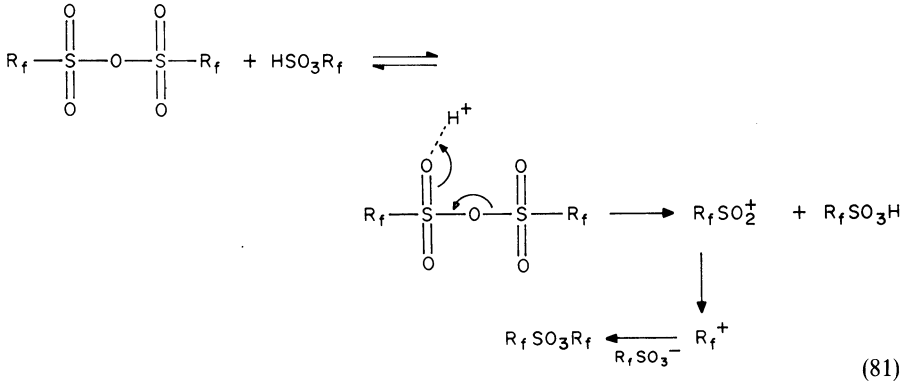
triflate (TFMT) and discussed the mechanism of its formation in more detail[98]. Utilizing catalytic amounts of antimony pentafluoride, TFMT can be obtained from Tf_2O in 94% yield. In addition to TFMT and sulfur dioxide, minor amounts of CF_4, CF_3SO_2F and COF_2 are also produced in the reaction. A new and strong Lewis acid catalyst $F_4SbOSO_2CF_3$ (**4**) is also found to react with triflic anhydride at room temperature to give TFMT in excellent yield. A mechanism involving the assisted ionization of Tf_2O by SbF_5, and generation of the catalyst **4** is proposed in equation 80.



(80)

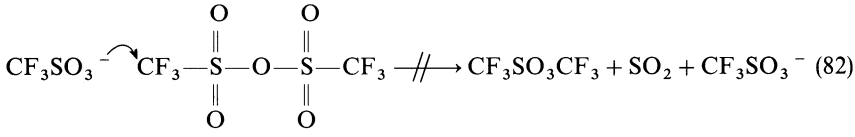
The main points of the mechanism are that the ionization of Tf_2O by SbF_5 produces the (trifluoromethanesulfonyloxy) pentafluoroantimonate anion **5** and the trifluoromethanesulfonyl cation $CF_3SO_2^+$. Subsequent reaction of $CF_3SO_2^+$ with **5** occurs either by electrophilic attack at a fluoride ligand of **5** to yield CF_3SO_2F and catalyst **4** or by liberating SO_2 to give CF_3^+. The reaction of **4** with Tf_2O also generates $CF_3SO_2^+$ (and then CF_3^+) and catalyst **6**. The reactive CF_3^+ formed reacts with **5** and **6** to yield TFMT[98].

In connection with the method for preparing the esters from reaction of the perfluoroalkanesulfonic anhydrides with the parent or other acids, it seems reasonable to assume that the mechanism is quite similar to that of equation 80. P_2O_5 or the acid promotes ionization of the acid anhydride to give the unstable cation $R_fSO_2^+$ and then R_f^+ reacts with the sulfonate anion to produce the desired ester[104] (equation 81). The previously postulated ionic bimolecular mechanism for the formation of the esters

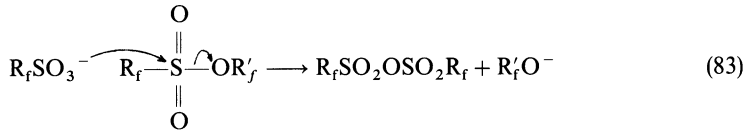


(81)

involves the nucleophilic attack of the highly non-nucleophilic triflate anion at the CF_3 group of anhydride[104] (equation 82) seems therefore unlikely[98]. Furthermore, it was shown that perfluoroalkanesulfonate anion undergoes nucleophilic attack on sulfur atom of the formed ester[106] (equation 83).

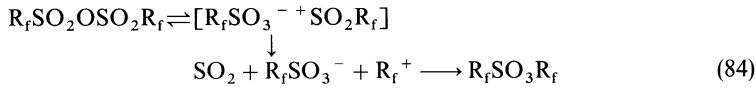


$$CF_3SO_3^- + CF_3{-}S(=O)_2{-}O{-}S(=O)_2{-}CF_3 \not\longrightarrow CF_3SO_3CF_3 + SO_2 + CF_3SO_3^- \quad (82)$$



$$R_fSO_3^- + R_f{-}S(=O)_2{-}OR'_f \longrightarrow R_fSO_2OSO_2R_f + R'_fO^- \quad (83)$$

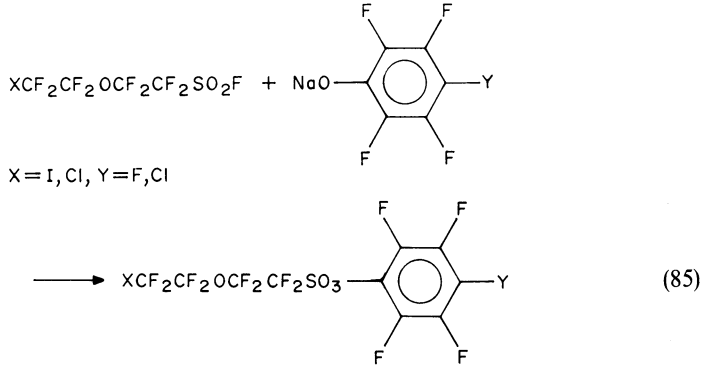
An alternative mechanism for the formation of the esters is the dissociative mechanism involving $R_fSO_2^+$ and R_f^+ which was considered to be unlikely[104] because of failure to detect R_f^+ directly and the observation of only a symmetrical anhydride upon the equilibration of a mixture of perfluoroalkanesulfonic acid and triflic anhydride, or a mixture of triflic acid and a perfluoroalkanesulfonic anhydride. However, recent work showed that the unsymmetrical anhydride indeed exists[98]. The preferential formation of trifluoromethyl esters in the reactions of mixtures of triflic and other perfluoroalkanesulfonic anhydrides in the presence of the corresponding sulfonic acids is consistent with the dissociation mechanism, since trifluoromethyl cation is much more easily formed than its higher analogues. Therefore, the dissociative mechanism (equation 84) cannot be ruled out unequivocally.



$$R_fSO_2OSO_2R_f \rightleftharpoons [R_fSO_3^- {}^+SO_2R_f] \downarrow SO_2 + R_fSO_3^- + R_f^+ \longrightarrow R_fSO_3R_f \quad (84)$$

C. Polyfluorophenyl Perfluoroalkanesulfonates

The only perfluorophenyl perfluoroalkanesulfonate recorded in the literature before our work was $CF_3SO_3C_6F_5$, prepared from the reaction of CF_3SO_2Cl with C_6F_5OK in a sealed tube[107]. We found that polyfluoroalkanesulfonyl fluorides readily react with polyfluorophenoxide ions in diglyme, giving the corresponding sulfonates in high yields[108] (equation 85).



$$XCF_2CF_2OCF_2CF_2SO_2F + NaO\text{-}C_6F_4\text{-}Y \quad (X = I, Cl;\ Y = F, Cl) \longrightarrow XCF_2CF_2OCF_2CF_2SO_3\text{-}C_6F_4\text{-}Y \quad (85)$$

D. Nucleophilic Reaction of Perfluoroalkanesulfonates

The nucleophilic substitution reaction on a sulfonate ester is an interesting subject, since the attacked site of the ester can be either the sulfur (with S—O scission) or the alkyl carbon (with C—O scission) or both. Early information about the modes of cleavage of fluorinated sulfonates reported by Johncock[109] is that the ratios of sulfur–oxygen versus carbon–oxygen scission are 40–70%:4–10% in 1*H*,1*H*-perfluoroalkyl triflates ($CF_3SO_3CH_2R_f$, R = CF_3, n-C_3F_7) using fluoroalkoxides ($R_fCH_2O^-$) or ethoxide as the nucleophiles. However, it was found[92] that the analogous triflates (*vide ante*) react with amines and halides, isocyanate and alkoxides ions to give only the products of C—O cleavage (equation 86) and even with ethoxide and

$$XOCF_2CF_2SO_3CH_2R_f \xrightarrow{Nu^-} XOCF_2CF_2SO_3^- + NuCH_2R_f \qquad (86)$$

$X = I(CF_2)_2$, Me, Cl_2CFCF_2, $H(CF_2)_2CH_2$
$R_f = H(CF_2)_n$, n = 2 – 4
Nu = I, CNS, F, NR_2

$CH_3OCH_2CH_2O^-$; the C—O cleavage predominates and only a very minor proportion of S—O bond cleavage is observed. However, with phenyl fluorosulfonate the primary step must be the S—O bond cleavage due to the inability of attack on a nonactivated sp^2-hybridized aromatic carbon (equation 87).

$$XOCF_2CF_2SO_3CH_2R_f + RO^- \begin{cases} \xrightarrow{\text{C—O Cleavage}} R_fCH_2OR \\ \xrightarrow{\text{S—O Cleavage}} XOCF_2CF_2SO_2OR + R_fCH_2O^- \end{cases}$$

$$XOCF_2CF_2SO_2OR + R_fCH_2O^- \xrightarrow{RO^-,\ \text{C—O Cleavage}} ROR + XOCF_2CF_2SO_3^-$$

R = Et, $CH_2CH_2OCH_3$

$$XOCF_2CF_2SO_3CH_2R_f + R_fCH_2O^- \xrightarrow{\text{C—O Cleavage}} (R_fCH_2)_2O + XOCF_2CF_2SO_3^-$$

$$XOCF_2CF_2SO_3Ph \xrightarrow{RO^-} XOCF_2CF_2SO_3R \begin{cases} \xrightarrow{PhO^-} ROPh \\ \xrightarrow{RO^-} ROR \end{cases} \qquad (87)$$

$X = I(CF_2)_2$, Cl, CCF_2
$R = H(CF_2)_2CH_2$

Tri- and hexafluoroisopropyl nonafluoro-n-butanesulfonates (nonaflates, NfO) react with halide anions in acetylacetone to give the synthetically interesting fluorinated isopropyl halides[94] (equation 88).

$$NfOCH(CF_3)CR_3 + X^- \longrightarrow CF_3CHXCR_3 \qquad (88)$$

R = H, F; X = Cl, Br, I

The only information existent before our work about nucleophilic substitution of fully fluorinated sulfonates was that TFMT reacted with N-cyclohexenylpiperidine and dilute NaOH to give ketosulfone and salts, respectively[24,110,111].

We have systematically investigated the nucleophilic substitution of perfluoroalkyl perfluoroalkanesulfonates and found that they behave quite differently from $R_fSO_3CH_2R_f$[105]. The former react with nucleophiles to give exclusively the S—O cleavage products, i.e. nucleophiles always attack the sulfur atom of the sulfonates (equation 89).

$$XCF_2O(CF_2)_2SO_3(CF_2)_2OCF_2X \xrightarrow{Y} XCF_2O(CF_2)_2SO_2F + XCF_2OCF_2CFO$$

$$X = ICF_2, ClCF_2, HCF_2, Cl_2CF$$
$$Y = F^-, Cl^-, Br^-, I^-, CNS^-, Et_3N, CF_3CO_2^-, AcO^- \qquad (89)$$

$$XCF_2O(CF_2)_2SO_3(CF_2)_2OCF_2X \xrightarrow{RO^-} \begin{cases} \rightarrow XCF_2O(CF_2)_2SO_3^- + R_2O + XCF_2OCF_2CO_2R \\ \qquad R = Et,\ H(CF_2)_2CH_2 \\ \rightarrow XCF_2O(CF_2)_2SO_2OR + XCF_2OCF_2CO_2R \\ \qquad R = Ph,\ C_6F_5 \end{cases}$$

Catalytic amounts of KF in diglyme cause a quantitative decomposition of the ester even at $-50\,^\circ C$ to give the corresponding sulfonyl and acetyl fluorides (Y = Z = F), but KCl reacts similarly only at $100\,^\circ C$ and KBr only partially at $160\,^\circ C$. These results indicate the following relative reactivity sequence: $F \gg Cl > Br$. However, KI reacts anomalously, i.e. it readily induces a complete decomposition of the ester at room temperature to the same products which are accompanied by a small amount of iodine. The finding that addition of *p*-dinitrobenzene to the reaction system inhibits the formation of iodine but not of other products indicates that iodide ion reacts with the ester through an ordinary S_N2 reaction on sulfonyl sulfur and probably also by a single electron-transfer pathway. Since all the nucleophiles used attack the sulfur atom without exception to cause S—O bond cleavage with generation of F^-, the reaction products are derived from attack of the original nucleophile and of the F^- generated during the course of the reaction on the ester (equation 90). The relative amounts of the various products depend upon the relative reactivities and the difference in concentration of the nucleophiles[105] (equation 90).

$$Cl(CF_2)_2O(CF_2)_2SO_3(CF_2)_2O(CF_2)_2Cl + CH_3CO_2^- \quad (7)$$
$$\longrightarrow CH_3CO_2SO_2(CF_2)_2O(CF_2)_2Cl + Cl(CF_2)_2OCF_2COF + F^- \quad (8) \qquad (90)$$
$$\mathbf{8} + F^- \longrightarrow CH_3COF + Cl(CF_2)_2O(CF_2)_2SO_3^-$$
$$\mathbf{7} + F^- \longrightarrow Cl(CF_2)_2O(CF_2)_2SO_2F + Cl(CF_2)_2O(CF_2)_2COF$$

The recent observation of COF_2 and CF_3SO_2F or $PhSO_2Ph$ and PhCOPh in the reactions of TFMT with pyridine and phenyllithium[98] supported the conclusion of exclusive S—O bond scission of perfluoroalkyl perfluoroalkanesulfonates by nucleophiles.

Yoshida and coworkers[110] ascribed the S—O bond cleavage in these sulfonates to the effect of the strong electronegativity of the R_f group, whereas Umemoto and Kuriu[112] ascribed this scission to the fact that R_fO^- is a better leaving group compared with $R_fSO_3^-$. However, as shown in equations 91–93, the sulfonates react readily with I^- whereas ethers do not. Therefore $R_fSO_3^-$ should be a better leaving group than R_fO^-. We explain the phenomenon by the shielding effect of the lone pairs of electrons of two

fluorine atoms and the perfluoroalkyl group even when the compound possesses a very good leaving group, such as $R_fSO_3^-$. This constitutes an additional example of the nonreactivity of highly fluorinated sp^3-hybridized carbon toward S_N2 attack[113].

$$R_fSO_3CH_2R_f + R_fO^- \rightleftharpoons R_fSO_3^- + R_fCH_2OR_f \quad (91)$$

$$R_fSO_3CH_2R_f + I^- \longrightarrow R_fSO_3^- + ICH_2R_f \quad (92)$$

$$R_fOCH_2R_f + I^- \not\longrightarrow R_fO^- + ICH_2R_f \quad (93)$$

In order to test this effect, difluoromethyl perfluoroalkanesulfonates have been synthesized and investigated. Difluoromethyl triflate was synthesized earlier from the insertion of difluorocarbene, generated by photolysis of difluorodiazirine into the O—H bond of triflic acid[114] (equation 94). By using HCF_2SO_3H as a difluorocarbene precursor, difluoromethyl perfluoroalkanesulfonate can be obtained in 30–50% yields[115] (equation 95).

$$CF_3SO_3H + CF_2N_2 \xrightarrow{h\nu} CF_3SO_3CF_2H \quad (94)$$

$$R_fSO_3H + HCF_2SO_3H \xrightarrow[120\,^\circ C]{P_2O_5} R_fSO_3CF_2H + HCF_2SO_3CF_2H \quad (95)$$

A more convenient method for preparing these esters involves utilizing readily available FO_2SCF_2COOH as a difluorocarbene source in the presence of an inorganic salt[116] (equation 96).

$$R_fSO_3H + FO_2SCF_2COOH \xrightarrow[70-100\,^\circ C,\ 2-3\,h]{Na_2SO_4} R_fSO_3CF_2H \quad 40\text{–}50\% \quad (96)$$

The difluoromethyl sulfonates react with halide X^- or ehtanol giving only HCF_2X and HCF_2OEt, respectively, which result from C—O bond cleavage. Other reagents, such as RCO_2^- (R = CF_3, CH_3) or PhS^-, can attack the carbon or sulfur of the ester to give the corresponding product of C—O and S—O cleavage, respectively, as shown in equation 97.

$$R_fSO_3CF_2H + RCO_2^- \begin{cases} \xrightarrow{\text{C—O scission}} R_fSO_3^- + RCO_2CF_2H \\ \xrightarrow{\text{S—O scission}} HCF_2O^- + R_fSO_2OCOR \xrightarrow{} (RCO)_2O \end{cases} \quad (97)$$

$$HCF_2O^- \rightarrow HCFO \qquad R_fSO_2OCOR \rightarrow R_fCOF$$

$R_f = CF_3, I(CF_2)_2O(CF_2)_2, Cl_2CFCF_2O(CF_2)_2, ClCF_2CF_2O(CF_2)_2$

The reaction of difluoromethyl sulfonates with KF is *ca* 40 times slower than that of methyl triflate. All these results indicate that the shielding effect caused by the two fluorine atoms in the difluoromethoxy carbon of the difluoromethyl sulfonates to some extent prevents the nucleophilic attack on this carbon, although due to the presence of a hydrogen atom the shielding is not as complete as in perfluoroalkanesulfonates[117].

With regard to the scission position of perfluoroaryl perfluoroalkanesulfonates, it was found that they react with nucleophiles such as halides or alkoxides with lower rates and give S—O cleavage products, except with PhS^-[108] (equation 98).

$$X(CF_2)_2O(CF_2)_2SO_2OC_6F_4Y\text{-}p \xrightarrow{Nu^-} X(CF_2)_2O(CF_2)_2SO_2Nu + p\text{-}YC_6F_4O^- \quad (98)$$

X = I, Cl; Y = F, Cl

The relative reactivity in nucleophilic substitution on the sulfur atom of the fluorinated ester decreases on decreasing the electron-withdrawing properties of the alkoxy or aryloxy group in the following order:

$$R_fSO_3Ar < R_fSO_3Ar_f < R_fSO_3R_f$$

In order to compare the relative nucleophilic reactivity of perfluorophenyl perfluoroalkanoates and sulfonates, both polyfluorophenyl perfluoroalkanoates (**9**) and bis(perfluorophenyl) diesters (**10**) were synthesized from the reaction of the corresponding acid fluorides with sodium polyfluorophenoxide in monoglyme[118].

$R_fCO_2C_6F_4X$-*p* (**9**) p-$XC_6F_4O_2CCF_2SO_3C_6F_5$ (**10**)

R_f = n-$C_3F_7OCF(CF_3)$, FSO_2CF_2; X = F, Cl

The relative reactivity toward nucleophiles is established as follows:

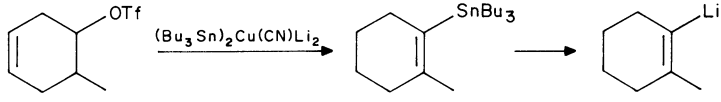
$$C_6F_5O_2CCF_2SO_3C_6F_5 \geqslant R_fCO_2C_6F_5 > R_fSO_3C_6F_5$$

E. Coupling Reactions of Vinyl and Aryl Triflates with Organometallics

Vinyl and aryl triflates have been much studied as important intermediates for the carbon–carbon bond formation, in addition to the use of vinyl triflates as a source of vinylic cations and unsaturated carbenes[6]. A recent good survey dealing with olefin synthesis via organometallic coupling reactions of enol triflates which covers the literature up to 1986 has appeared[8] and here we intend only to add some new material.

A palladium-catalyzed coupling reaction of enol triflates with a variety of organostannanes carrying alkyl, vinyl, acetylenic and allyl groups in the presence of LiCl has been developed as a general method for carbon–carbon bond formation[8,75]. Since it is possible to regioselectively prepare vinyl triflates from unsymmetrical ketones, a regioselective vinylic stannane can be obtained from hexamethyldistannane with the enol triflates. These vinylic stannanes are then able to be further converted into vinyl iodides or vinyl lithium reagents. However, attempts to form vinylic stannanes by a palladium-catalyzed coupling of enol triflates with hexabutydistannane[75,119] or diethyl(trimethylstannyl) aluminum[120] were unsuccessful.

An improved method that uses stannyl cuprates instead of hexabutyldistannane and which react even with hindered vinyl triflates and give the coupling products in good yields[121] is exemplified in equation 99.

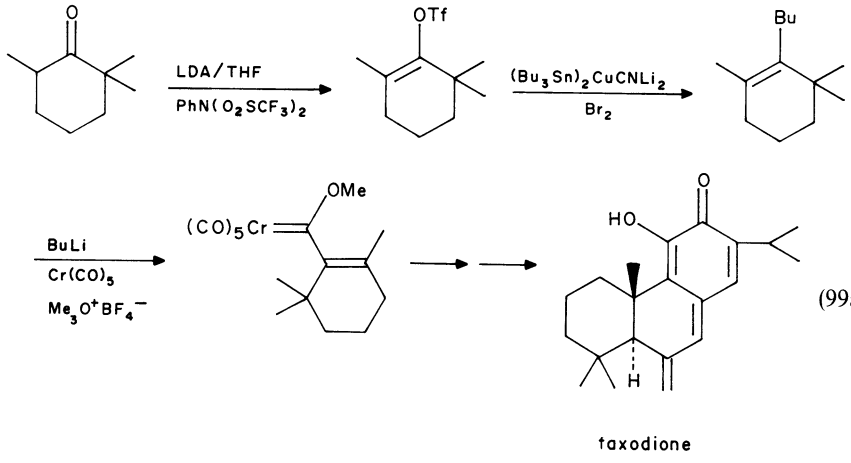


(99)

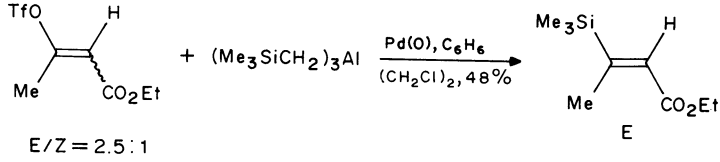
This method has been applied to the synthesis of taxodione and related diterpenes through cyclohexadienone annulations of a chromium-carbene complex which was prepared from a hindered vinyl triflate[121b] (equation 99a).

In connection with the failure to convert vinyl triflates to allytrimethylsilanes with tetrakis[(trimethylsilyl)methyltin], $Sn(CH_2SiMe_3)_4$, a tris(trimethylsilyl)methyl aluminum $[Me_3Si(CH_2)]_3Al$, conveniently generated in situ from (trimethylsilyl)methyl lithium and $AlCl_3$, was found to be a good chemoselective and stereospecific coupling reagent[121c] (equation 99b).

In addition, another alane, i.e. [(trimethylsilyldimethyl aluminium methyl)]

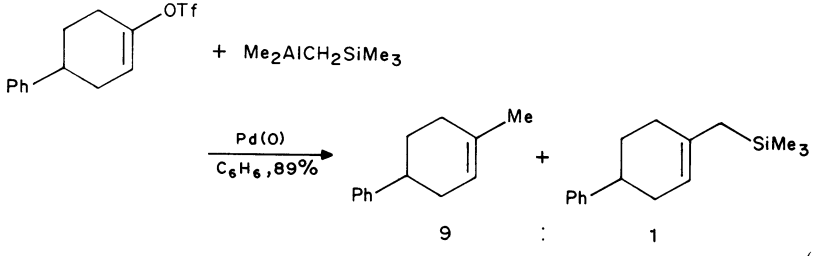


(99a)



(99b)

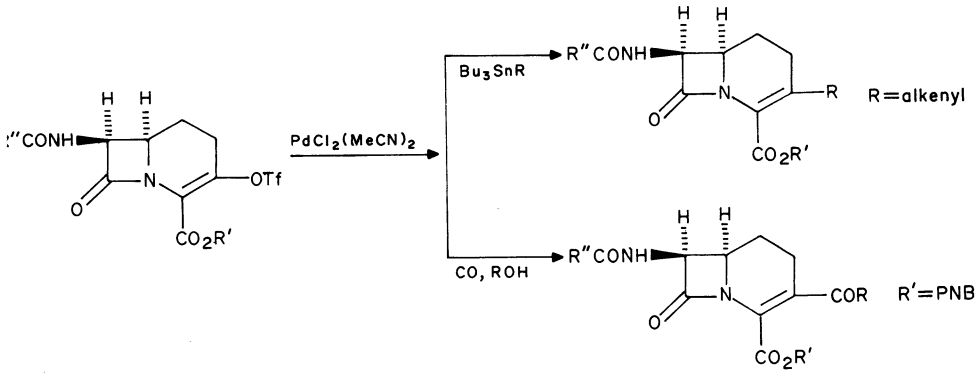
$Me_2AlCH_2SiMe_3$, prepared in situ from Me_3SiCH_2Li and Me_2AlCl, reacted with enol triflates, e.g. 4-phenylcyclohexen-1-ol triflate, to give a 9:1 mixture of olefins, showing that Me transfers in preference to CH_2SiMe_3 (equation 99c).



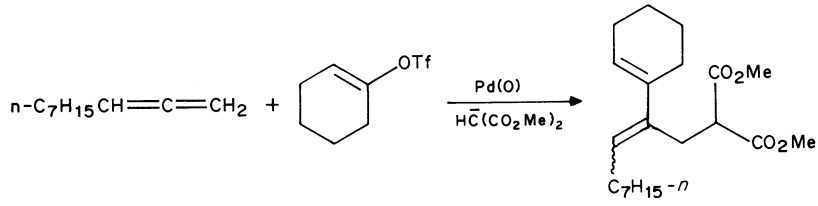
(99c)

A vinyl triflate derived from a complex β-lactam nucleus reacted with unsaturated stannanes in the presence of a "ligandless catalyst", i.e., bis(acetonitrile)palladium(II) chloride, rather that $(PPh_3)_4Pd$, to give high yield of the coupling product. Alkoxycarbonylation of this triflate with CO and an alcohol (except t-BuOH) in the presence of $PdCl_2(MeCN)_2$, LiCl and Et_3N occurred effectively[121d] (equation 99d).

Enol triflates react with olefins and alkynes in a palladium-catalyzed Heck olefination reaction, which is characterized by a small effect of the nature of the enol triflate on the reaction rate and by high configurational stereoselectivity in the formation of the double bond of the final product[8]. A recent report[122] showed that enol triflates react with allenic hydrocarbons and the anion of dimethyl malonate in the presence of a $Pd(PPh_3)_2$ catalyst leading to conjugated dienes in good yields with E/Z of 9:1 (equation 100).

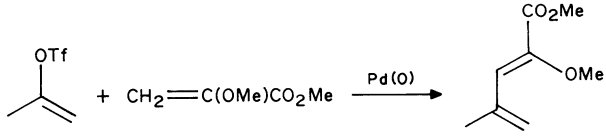


(99d)



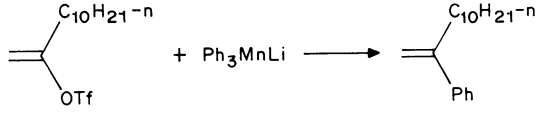
(100)

Vinyl triflates, rather than aryl triflates, and palladium(0) species undergo reaction with methyl α-methoxyacrylate under phase-transfer conditions to form enol ethers of β,γ-unsaturated α-keto esters of *Z* configuration[123] (equation 101). This method has been applied in steroid chemistry.



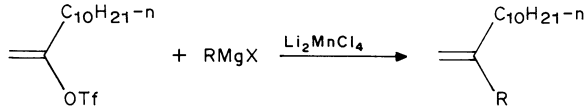
(101)

Enol triflates, unlike phosphates, react with trialkylmanganates R_3MnLi derived from equivalent Li_2MnCl_4 and RLi in the absence of Pd(0) to give mainly the coupling product[124a] (equation 102). Furthermore, the reaction of enol triflates with certain



(102)

Grignard reagents can be catalyzed by Li_2MnCl_4 to afford the same coupling products (equation 103). This finding, together with the observation of an S—O cleavage product rather than the desired coupling product in the reaction of CH_3Li with the enol triflate even in the presence of catalytic amounts of Li_2MnCl_4, shows that organomanganese

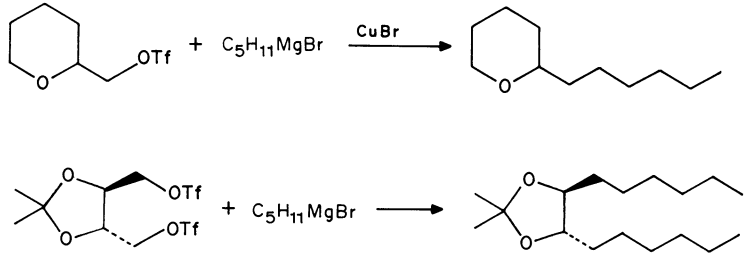


(103)

R=Ph, $PhCH_2$, allyl

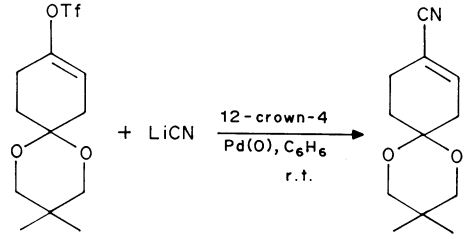
compounds, like diorganocuprates[6], can be used to induce a C—O cleavage rather than an S—O cleavage of enol triflates in the nucleophilic substitution[124a].

Indeed, a recent work[124b] showed that a variety of triflates containing a β-oxygen functionality reacted successfully with Grignard reagents in the presence of copper(I) bromide to afford the corresponding coupling products (equation 103a).



(103a)

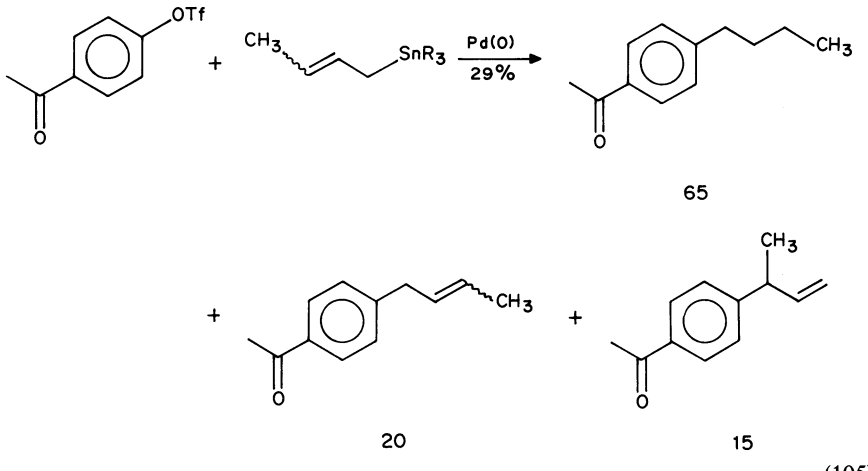
However, very recently, an efficient conversion of an enol triflate into an α,β-unsaturated nitrile has been accomplished by nucleophilic substitution on the vinyl carbon using lithium cyanide in benzene in the presence of Pd(0)[124c] (equation 104).



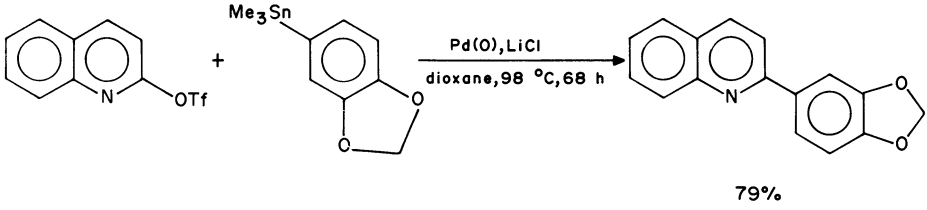
(104)

Aryl triflates mimic their vinylic counterparts in many reactions. Thus, aryl triflates undergo the palladium-catalyzed coupling reaction with alkyl, vinyl, alkynyl and aryl tin reagents in the presence of lithium chloride under mild conditions to form a new carbon–carbon bond. Many functional groups are tolerated, both on the aryl triflate and on the organotin reagents, including alcohol, ester, nitro, acetal, ketone and aldehyde groups[125]. Vinyl, alkyl, aryl and alkynyl substituents on tin reagents are all transferred in good yields. Hexamethyldistannane can be used to provide aryltrimethylstannanes. However, allyltrialkyltin reagents gave lower coupling yields and unselective transfer of the allyl group was observed (equation 105).

The cross-coupling of aryl triflates with vinylstannanes gave a good yield of styrene derivatives with retention of the double-bond geometry in most cases. The reaction was applied to a synthesis of the quinoline alkaloid dubamine[125] (equation 106). Other



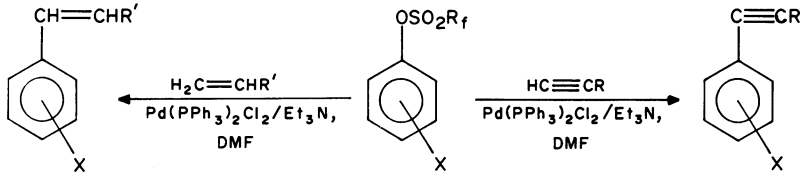
(105)



(106)

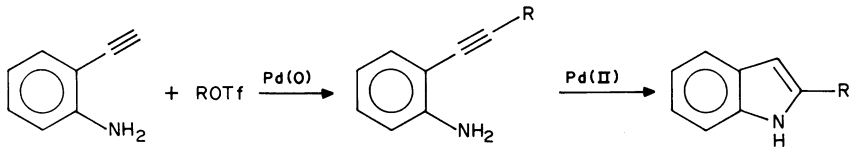
fluoroalkanesulfonates besides triflates also react with allyltributyltin giving allylbenzenes in good yields[126] (equation 107). These fluoroalkanesulfonates also undergo the palladium-catalyzed Heck olefination and alkynation to give the coupling products[127a] (equation 108). Similarly aryl, heteroaryl and vinyl triflates reacted with 2-ethynylaniline in the presence of Pd(0) giving the corresponding 2-alkylnyl and 2-arylethynyl anilines, which in turns could be cyclized with a palladium(II) catalyst to yield the functionalized 2-substituted indoles[127b] (equation 109).

$$ArOSO_2R_f + Bu_3SnCH_2CH{=}CH_2 \longrightarrow ArCH_2CH{=}CH_2 \qquad (107)$$
$$R_f = CF_3,\ H(CF_2)_2O(CF_2)_2,\ H(CF_2)_4O(CF_2)_2$$



(108)

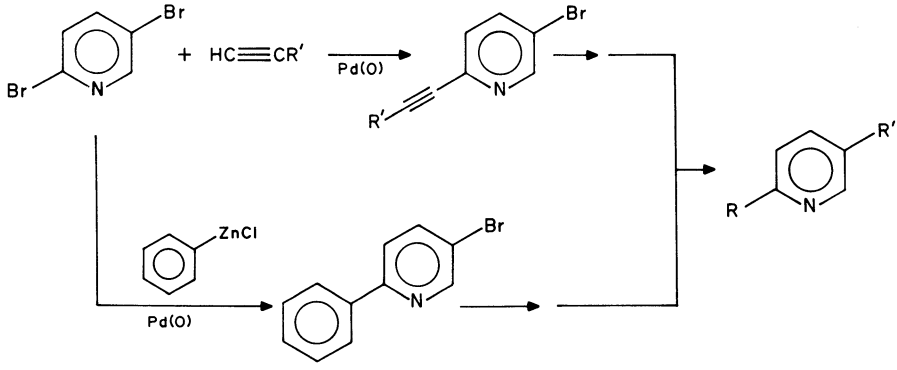
$R_f = CF_3,\ H(CF_2)_2O(CF_2)_2,\ Br(CF_2)_2O(CF_2)_2;$
$R = Ph,\ SiMe_3;\qquad R' = CO_2Et,\ CN.$



R = vinyl, aryl, heteroaryl

(109)

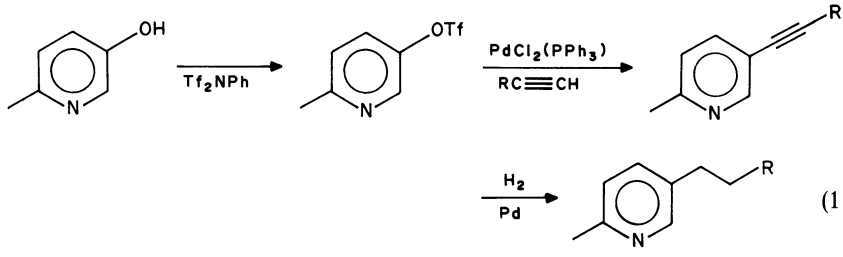
Recently, a new regioselective synthesis of 2-alkyl and 2-aryl 5-substituted pyridines was reported[128]. It involved the chemoselective reaction of commercially available 2,5-dibromopyridine with terminal acetylenes or phenylzinc chloride in the presence of Pd(0) (equation 110). However, this method does not allow the preparation of 2-methyl-5-



R = alkyl, aryl; R ≠ R'

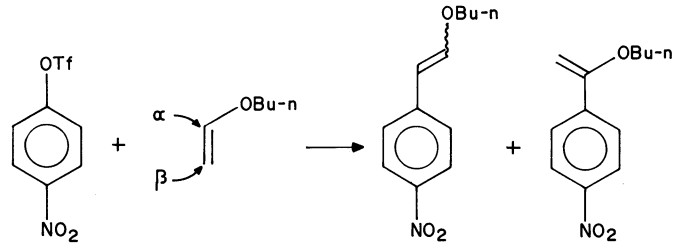
(110)

substituted pyridines. These were synthesized indirectly by coupling of 2-methyl-5-pyridinyl triflates with terminal alkynes[128] (equation 111).



(111)

The regioselectivity of arylation of the electron-rich olefin, n-butylvinyl ether with 4-nitrophenyl triflate has been investigated[129]. Without added lithium salt the regioselectivity was low (β:$\alpha = 1.5$) whereas addition of a lithium halide in DMF strongly promotes β-arylation ($\beta/\alpha = 13$) and addition of tetrabutylammonium halide in CH_3CN gave a somewhat lower regioselectivity ($\beta/\alpha = 8$) (equation 112).



(112)

Another new method for carbon–carbon bond formation is the cross-coupling reaction of aryl perfluoroalkanesulfonates with organozinc reagents in the presence of catalytic amounts of Pd(0) to give the corresponding alkylbenzenes in good yields[130] (equation 113). A novel synthesis of alkyl and alkenyl aromatics can also be achieved by reacting fluoroalkanesulfonates with organoaluminum reagents in the presence of Pd(0)[131]. For example, *E*-1-alkenyldibutylaluminum reacts smoothly with aryl fluoroalkanesulfonate to afford a substituted *E*-1-alkenylbenzene (equation 114). Surprisingly, the substituted isobutylbenzene is also obtained in the same reactions and is sometimes the sole product; this has not been encountered in nickel-catalyzed coupling reaction of alkenylalane with aryl halides[132]. Aryl fluoroalkanesulfonates as well as aryl bromides react with triisobutylaluminum under similar conditions to give isobutylbenzenes[133].

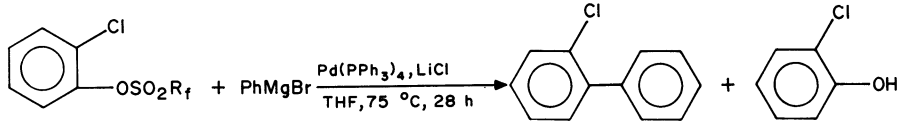
$$YC_6H_4OSO_2R_f + RZnX \xrightarrow[LiCl,\ DMF]{Pd(PPh_3)_4} YC_6H_4R \qquad (113)$$

Y = H, *p*-Cl, *o*-Cl, *p*-NO_2, *m*-OCH_3, *p*-OCH_3

$R_f = CF_3$, $H(CF_2)_2O(CF_2)_2$, $H(CF_2)_4O(CF_2)_2$
R = $PhCH_2$, $EtO_2CCH_2CH_2$, $C_4H_9C{\equiv}C$, $MeOCH_2C{\equiv}C$, $PhC{\equiv}C$

$$YC_6H_4OSO_2R_f + E\text{-}RCH{=}CHAlBu_2 \xrightarrow[LiCl,\ THF,\ 80\,^\circ C]{Pd(0)} E\text{-}YC_6H_4CH{=}CHR + YC_6H_4Bu\text{-}i \qquad (114)$$

Using organolithium reagents or Grignard reagents as nucleophiles, the reactions are unsatisfactory since they proceed with poor conversion and low regioselectivity. The sulfur–oxygen cleavage products, ArOH, are also obtained from the attack of the organometallic reagent on the sulfur atom of the fluoroalkanesulfonate[133] (equation 115).



$R_f = H(CF_2)_2O(CF_2)_2$

(115)

A carbon–phosphorus bond formation can be accomplished by the reaction of fluoroalkanesulfonates with *o,o*-dialkyl phosphonates in the presence of Pd(0)[134,135] (equation 116). The method has been used to replace the phenolic OH in tyrosine by a diethoxyphosphinyl group[135].

$$YC_6H_4OSO_2R_f + (RO)_2P(O)H \xrightarrow[Et_3N]{Pd(0)} YC_6H_4P(O)(OR)_2 \qquad (116)$$

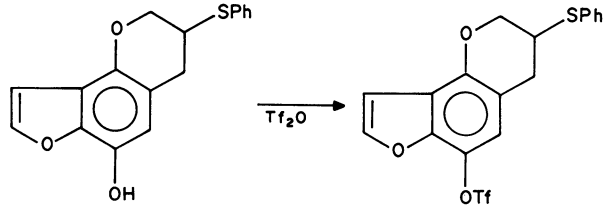
$R_f = CF_3$, $Cl(CF_2)_2O(CF_2)_2$; R = Et, Me_2CH, n-Bu
Y = H, 2-Cl, 4-OCH_3, 4-Cl, 2-$OOCH_3$, 3-Br, 4-NO_2

Like enol triflate, aryl triflates can be readily reduced to arenes; this provides a useful general method for conversion of phenols to arenes. Chen and coworkers[136] and Cacchi and coworkers[137] have developed independently the reduction of aryl triflates and fluoroalkanesulfonates with triethylammonium formate in the presence of catalytic amounts of Pd(0) (equation 117).

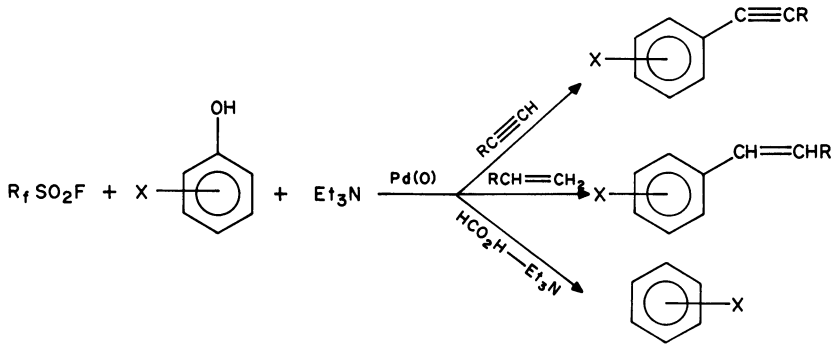
$$ArOSO_2R_f \xrightarrow[Bu_3N\text{–}HCO_2H,\ DMF]{Pd(PPh_3)_2Cl_2 \text{ or } Pd(PPh_3)_4} ArH \qquad (117)$$

$R_f = CF_3$, $H(CF_2)_2O(CF_2)_2$

The reduction of aryl triflates with electron-withdrawing substituents works well also with sodium borohydride, but for systems with electron-donating substituents the use of triethylammonium formate is much better[138]. The method has been applied to synthesize angelicin through the sequence of equation 118.



(118)

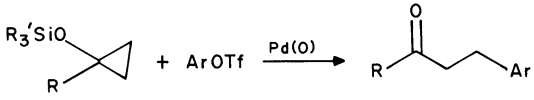


$R_f = n\text{-}C_8F_{17}$, $H(CF_2)_2O(CF_2)_2$, $H(CF_2)_6O(CF_2)_2$, $CF_3CF_2O(CF_2)_4O(CF_2)_2$

(119)

A simple one-pot conversion of phenols to arenes by the reaction of fluoroalkanesulfonyl fluoride with phenols, i.e. without isolating aryl fluoroalkanesulfonates, in the presence of alkenes, alkynes or triethylammonium formate, can be accomplished in good yields[139] (equation 119).

Palladium-catalyzed arylation of siloxycyclopropanes with aryl triflates results in carbon-chain elongation[140] (equation 120).

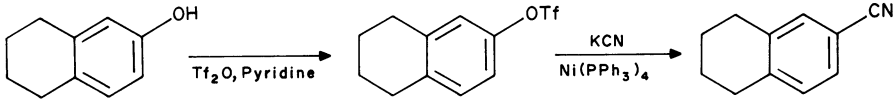


(120)

$R'_3Si = Me_3Si$, t-$BuMe_2Si$; R = alkoxy, alkyl, H

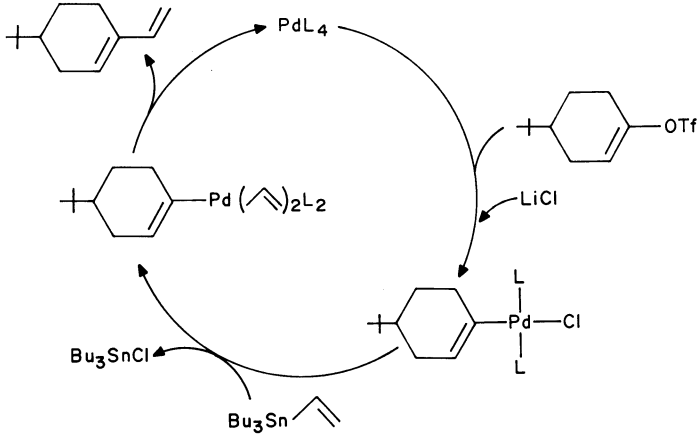
Palladium-catalyzed carbonylation of aryl triflates in the presence of an alcohol[141] or amine[142a] provides a good method for preparation of arenecarboxylic esters and amides from phenols (equation 121). However, palladium-catalyzed cyanation of 5,6,7,8-tetrahydro-2-naphthyl triflate with potassium cyanide failed completely whereas the more reactive tetrakis(triphenylphosphine)nickel(0) could catalyze the same reaction which gives the nitrile in a good yield[142b] (equation 122).

$$ArOTf \xrightarrow[CO, ROH \text{ or } R_2NH]{Pd(0)} ArCOX \qquad X = OR, NR_2 \tag{121}$$



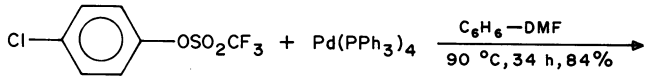
(122)

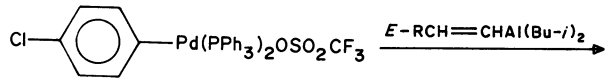
Finally, it is worth mentioning the mechanism of the palladium-catalyzed coupling reaction of enol and aryl triflates. Scott and Stille[75] proposed that a plausible working mechanism involves the initial oxidative addition of the triflate to the palladium(0) catalyst to afford an organopalladium(II) complex. Transmetallation with other organometallic reagents then generates the bis(organo)palladium(II) complex, which rapidly undergoes reductive elimination to form the coupling product and regenerates the palladium(0) catalyst. An example is given in equation 123.



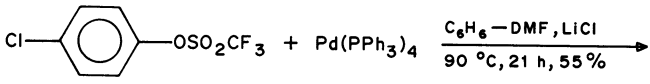
(123)

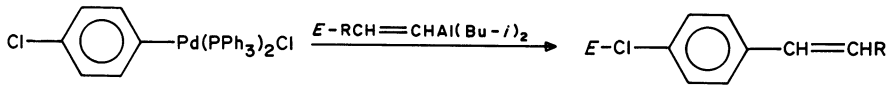
Evidence for this mechanism is the observation that the reaction of an enol triflate with $Pd(PPh_3)_4$ in the presence of LiCl forms a *trans*-organopalladium(II) chloride complex which is able to catalyze the coupling of the enol triflate with tributyl(vinyl)tin to afford the expected product[75]. For *p*-chlorophenyl triflate, both *trans*-organopalladium(II) triflate and chloride complexes were isolated[131,133] (equations 124 and 125).





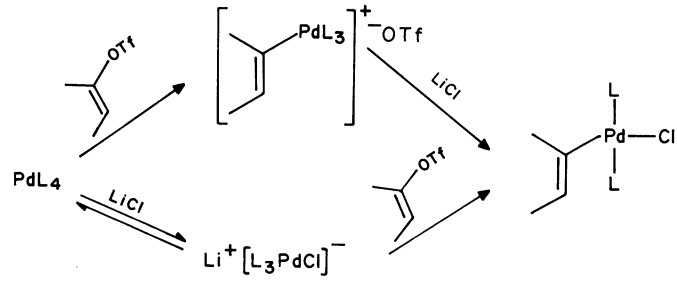
(124)





(125)

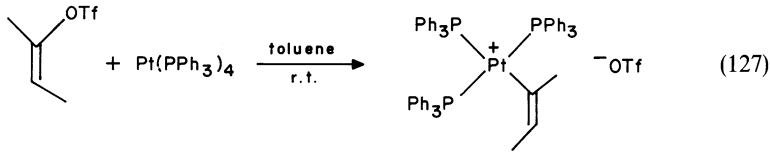
As indicated in the literature[75], lithium chloride is a necessary component in the coupling reactions. This is confirmed by the fact that reaction of the triflate complex alone with alkenyldiisobutylalane gives no coupling product (equation 124). However, as expected, the chloride or the triflate complex reacts with the organoaluminum reagent or with tributylallyltin in the presence of LiCl giving the corresponding coupling products in good yields (e.g. equation 125). Therefore, there is little doubt that both vinyl triflates and aryl triflates react with organometallics in the presence of Pd(0) and LiCl to form a *trans*-organopalladium(II) chloride complex, which then rapidly undergoes reductive elimination to form the coupled products. The question is how to form the chloride complex. Scott and Stille[75] have proposed two approaches: oxidative addition to give the organopalladium(II) triflate complex is followed by exchange with chloride ion, or alternatively the LiCl form a complex with the palladium prior to the oxidative addition (equation 126).



(126)

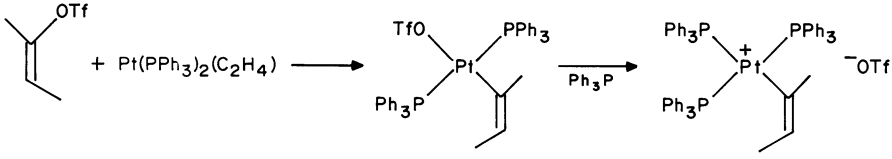
Very recently a further mechanistic investigation of the vinyl cross-coupling reactions, involving oxidative addition and reductive elimination of a vinyl triflate with Pt(0), was

reported by Stang and his coworkers[143,144]. They have isolated and fully identified a series of crystalline σ-vinyl cation complexes from vinyl triflates and $Pt(PPh_3)_4$ in toluene at room temperature[143] (equation 127).



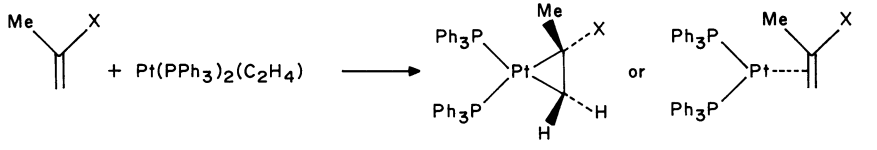
(127)

A single-crystal X-ray diffraction of σ-(*trans*-2-butenyl triphenylphosphine) Pt(II) triflate complex was also obtained. This compound reacted with PPh_3 to form the cationic complex mentioned above (equation 128).



(128)

From the kinetic data, the stereochemistry and structure of the σ-complex, the mechanism of formation of the σ-complex involves a rate-determining formation of a π-alkene Pt complex, followed by a rapid rearrangement rather than a single electron transfer, a three-centered concerted addition or a free radical pathway. However, attempts to prepare a π-complex from 2-propenyl triflate and $Pt(PPh_3)_2(C_2H_4)$ failed but, two π-alkene-Pt halide complexes were fully characterized, (equation 129).

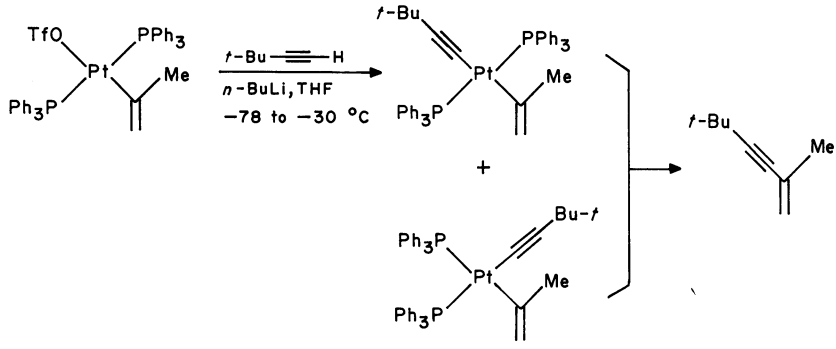


X=Cl, Br

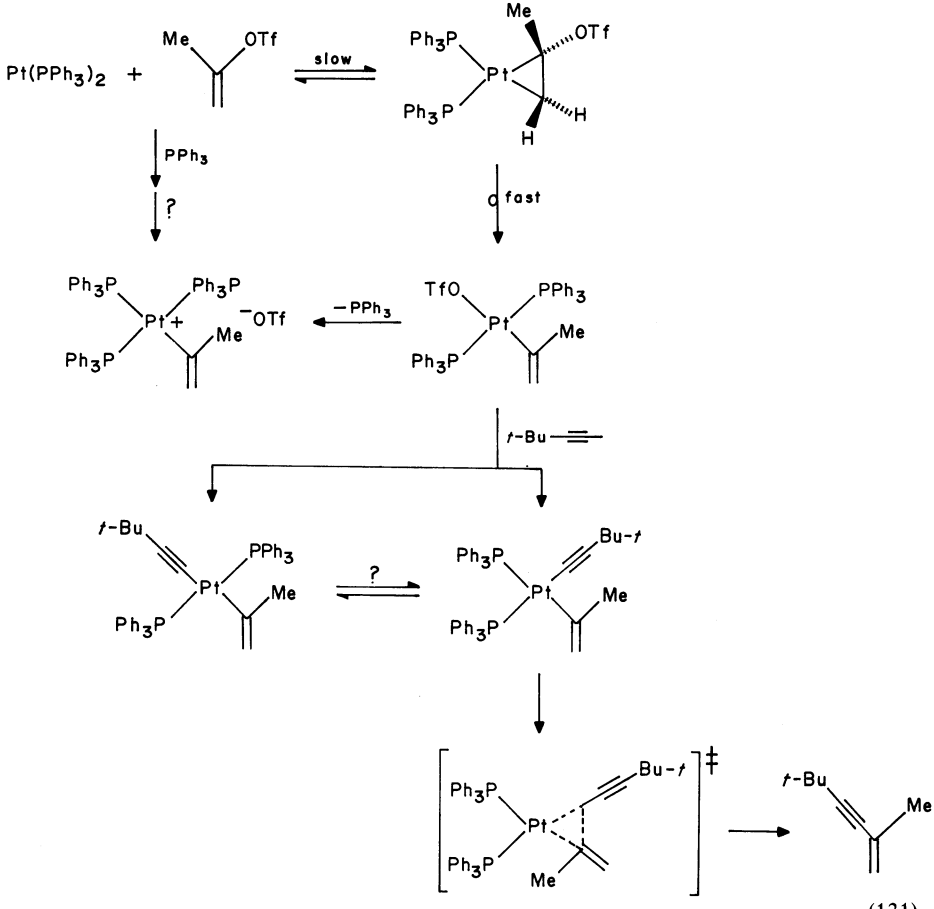
(129)

The reductive reaction of $CH_2{=}C(CH_3)Pt(PPh_3)_2(OTf)$ with RC≡CLi results in the formation of *cis* and *trans* (σ-alkynyl) (σ-vinyl)platinium(II) complexes. The *cis* isomer is the kinetically controlled product and the *trans* isomer the thermodynamically stable isomer. Added Ph_3P essentially inhibits the reductive elimination of the *trans* isomer, but has little effect upon the coupling reaction of the *cis* isomer. The *cis* isomer undergoes reductive elimination at a much lower temperature than the corresponding *trans* isomer (equation 130). The conclusion is that the *trans* isomer undergoes reductive coupling by a prior dissociative pathway, whereas the *cis* isomer reacts by a concerted process[144].

As a whole, the mechanism of oxidative addition and reductive elimination of the Pt-mediated vinyl cross-coupling reaction with vinyl triflates may be described as in



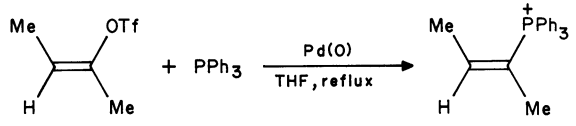
(130)



(131)

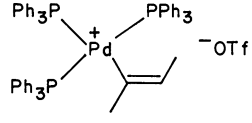
equation 131. The oxidative addition of vinyl triflates affords σ-vinyl complexes, via the rate-determining formation of π-complex intermediates. The σ-complexes undergo transmetalation with organometallic reagents, such as t-BuC≡CLi, to give both thermodynamically controlled and kinetically controlled σ-alkynyl σ-vinyl products. Reductive elimination of the conjugated enyne occurs from both isomers[143,144].

The interaction of $(PPh_3)_4Pt$ with alkylnylvinyl triflates results in formation of σ-enynyl and σ-butatrienyl cationic Pt(II) complexes and their reactions were also reported[145,146]. Vinyl triflates reacted with PPh_3 in the presence of catalytic amounts of Pd(0), with formation in good yields of vinyl phosphonium salts with high stereospecificity as shown in equation 132.



(132)

Similarly to the Pt(0)-σ-vinyl cation complex, a Pd(0) complex **11** formed from the vinyl triflate and Pd(0) is supposed to be the oxidative addition intermediate[147].



(11)

VI. (PERFLUOROALKYL)PHENYLIODONIUM TRIFLUOROMETHANESULFONATES (FITS) AND THEIR ANALOGUES

In the last ten years Umemoto and his co-workers have developed a series of effective perfluoroalkylating agents, i.e. perfluoroalkylphenyliodonium trifluoromethanesulfonate (FITS, **12**) reagents. We very briefly summarize below their synthesis and reactions.

FITS reagents are synthesized in high yields from oxidation of perfluoroalkyl iodides by trifluoroperacetic acid [60% $H_2O_2 + (CF_3CO)_2O$] or by elementary fluorine followed by treatment with benzene or fluorobenzene in the presence of triflic acid in 1,1,2-trichlorotrifluoroethane or CF_3COOH at 0 °C to room temperature[148] (equation 133).

$$\begin{array}{l} R_fI + CF_3CO_3H \longrightarrow R_fI(OCOCF_3)_2 \xrightarrow{TfOH} R_f\text{-I-OTf} \\ \text{or } CF_3COOH + F_2 \qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Ar \end{array} \qquad (133)$$

FITS (**12**)

$R_f = C_nF_{2n+1}$, $H(CF_2)_n$, $Br(CF_2)_n$, $n = 2$–10
Ar = C_6H_5, p-FC_6H_4

Perfluoroalkyl-, α,ω-bisaryliodonium triflates (**13**) and (1*H*, 1*H*-perfluoroalkyl) aryliodonium triflates (FMITS, **14**) are prepared in a similar fashion[149].

(13)
$x = 3, 8$ FMITS (14)

12 and **14** are considered to be cationic perfluoroalkylating agents which, by reaction with nucleophiles such as Grignard reagents, alkyl lithium, thiolate anion, etc., give perfluoroalkylated compounds[112] (equation 134 and 135).

$$\mathbf{12} + Nu^- \longrightarrow R_fR \tag{134}$$

Nu = alkyl, allyl, benzyl, α-nitroalkyl, alkynyl, RS, etc.

$$\mathbf{14} + Nu^- \longrightarrow R_fCH_2R \tag{135}$$

Nu = $CH(CO_2R)_2$, R, OPh, OR, SR, etc.

Both reagents react with phenols giving mainly *o*, *p*-perfluoroalkylated products[150,151] and **14** reacts with amines affording 1*H*, 1*H*-perfluoroalkylated amines or ammonium salts[152] (equations 136–139).

$$\mathbf{14} + RNH_2 \longrightarrow R_fCH_2NHR \tag{136}$$

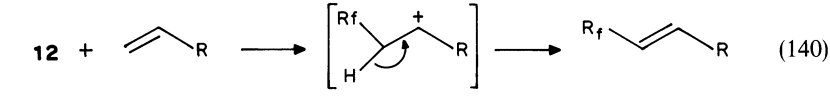
$$\mathbf{14} + RR'NH \longrightarrow R_fCH_2NRR' \tag{137}$$

$$\mathbf{14} + R^1R^2R^3N \longrightarrow R_fCH_2N^+R^1R^2R^3TfO^- \tag{138}$$

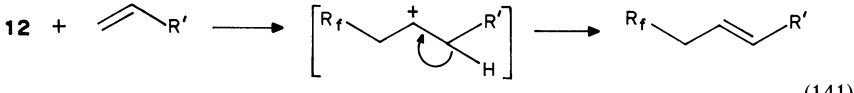
$$\mathbf{14} + HCON(CH_3)_2 \longrightarrow \left[\begin{matrix} Me \\ Me \end{matrix}\!\!>\!\overset{+}{N}\!=\!C\!<\!\begin{matrix} OCH_2R_f \\ H \end{matrix}\right] \xrightarrow{H_2O} HCO_2CH_2R_f \tag{139}$$

12, but not **14**, reacts with alkenes, alkynes and dienes in different ways which depend upon the substrates used[153]. The initial step is always an electrophilic attack of the R_f group on the least hindered site of the multiple bond, followed by other reactions of the formed carbocation such as elimination or trapping by the nucleophile (equations 140–144).

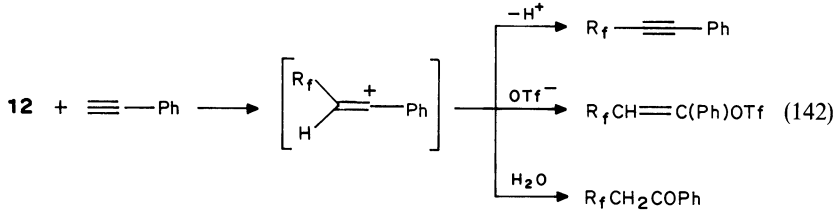
(1) Elimination[153]



(140)

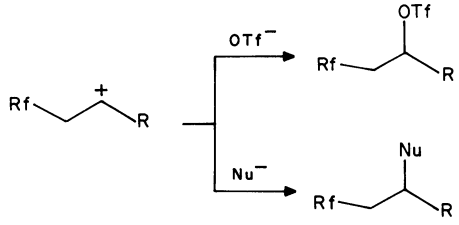


(141)



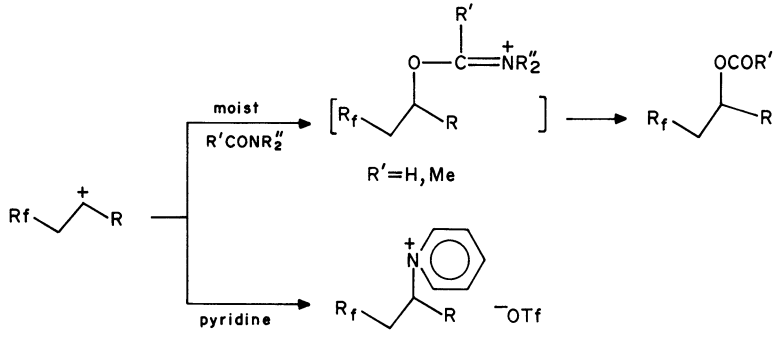
(142)

(2) Trapping of the cationic species formed either by the reagent or by nucleophiles[153]



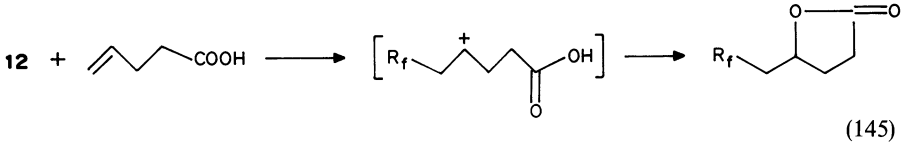
(143)

Nu=OMe,HCO_2,Cl,OH or OAc

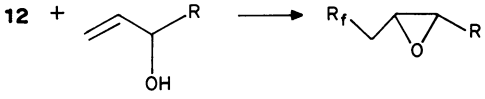


(144)

With nucleophiles containing functional groups such as hydroxy or carboxy, a product of intramolecular nucleophilic attack is obtained (equations 145 and 146).

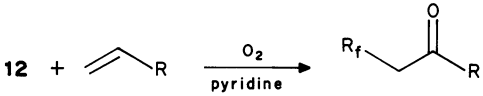


(145)



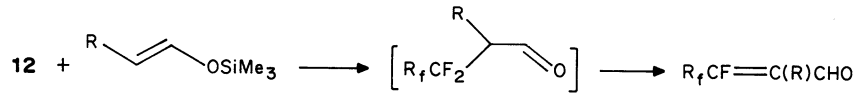
(146)

(3) Other reactions of **12** are shown in equations 147–149[154,155].



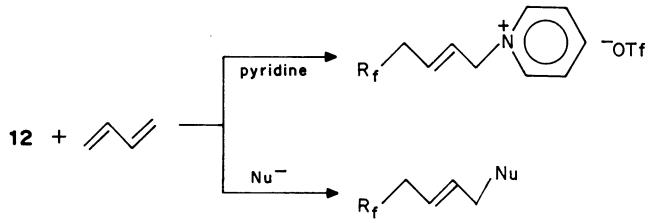
(147)

(148)



(149)

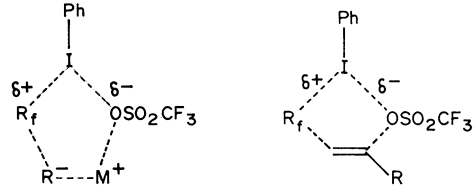
1,3-Dienes react with **12** in a similar way to give 1,4-adducts[154], as demonstrated in equation 150.



(150)

In reactions with aliphatic alkynes, such as $CH_3(CH_2)_5C{\equiv}CH$, besides the addition–elimination product, $CH_3(CH_2)_5C{\equiv}CR_f$, a reduction product $CH_3(CH_2)_5CH{=}CHR_f$ was also formed, whereas with 4-octyne the only product isolated was $CH_3(CH_2)_2C(R_f){=}CH(CH_2)_2CH_3$[156].

These reactions of **12** and **14** have been explained to proceed through the cyclic transition states **15** and **16**[112,153]. However, whether or not a single electron transfer process is involved remains to be clarified.



(15) **(16)**

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CHAPTER **22**

Sulphamic acid and derivatives

G. A. BENSON

Department of Physical Sciences, Regional Technical College, Sligo, Ireland

and

WILLIAM J. SPILLANE

Chemistry Department, University College, Galway, Ireland

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I. INTRODUCTION

Eleven years ago we reviewed the general area of sulphamic acid (**1**) chemistry and its N-substituted derivatives, particularly sulphamic acids, sulphamide, sulphamoyl halides, esters, azides and amine–sulphur trioxide complexes[1]. Around the same time an important review entitled *Acyclic Sulphur–Nitrogen Compounds* appeared[2]. This covered a wider range of sulphur–nitrogen compounds and included some short sections on sulphamic acid and derivatives. Somewhat larger sections on the area of interest appeared in the Gmelin Handbook on sulphur–nitrogen compounds[3]. A very short but useful review (18 references) has appeared in *Comprehensive Organic Chemistry*[4] and a more lengthy and industrially orientated review (61 references) on sulphamic acid and sulphamates is available in an encyclopedia of chemical technology[5].

$$H_2NSO_3H$$
(1)

Our earlier review covered the literature up to about the end of 1978[1]. A very substantial body of work has been reported on sulphamic acid and derivatives since then and accordingly it was felt to be timely to now review the period from 1978 to the present. Both *Chemical Abstracts* and the major journals have been covered up to approximately mid-1989. Some types of compound have been excluded[6] since they were felt to be of peripheral interest and in some cases are of sufficient importance to have merited reviews in their own right, e.g. heparin[7], chlorosulphonylisocyanate, $ClSO_2NCO$[8], sulphonyl isocyanates and isothiocyanates[9] and heterocycles containing the sulphamide moiety (i.e. cyclic sulphamides)[10]. Some topics covered in this review have been the subject of reviews elsewhere and these are noted in the appropriate sections.

II. SULPHAMIC ACID

A. Physical Studies

1. X-ray

Crystal data[11] and later the crystal structure[12] of anhydrous sodium sulphamate H_2NSO_3Na (**2**) has been reported by Indian workers. An Australian group have carried

out X-ray crystallographic studies on *N*-methylsulphamic acid (**3**)[13], *N*,*N*-dimethylsulphamic acid (**4**)[14] and the potassium salts of the latter[15]. The structure of the *N*-methyl compound **3** is analogous to that of the *N*,*N*-dimethyl compound **4** and to sulphamic acid (**1**)[13]. All three compounds exist as zwitterions with tetrahedral configuration about the nitrogen atoms and comparable bond distances and angles. The N–S distances (in Å) are 1.779 (*N*-methyl), 1.76 ($NH_3{}^+SO_3{}^-$), 1.79 (*N*,*N*-dimethyl) and 1.84 (potassium salt of *N*-methyl). More recently the crystal structures of two sweet aromatic sulphamates, namely phenyl (**5**) and *m*-chlorophenyl (**6**), have been partially reported[16] though the full data are available from the Cambridge Crystallographic Data Centre. The N–S distances (in Å) in these compounds are significantly shorter, being 1.67 and 1.66, respectively.

$RR'NSO_3H$

(**3**) R = H; R′ = Me

(**4**) R = R′ = Me

m-$XC_6H_4NHSO_3{}^-Na^+$

(**5**) X = H

(**6**) X = Cl

Though, strictly speaking, they are outside the scope of the review, a number of other interesting structures have been reported recently. They include potassium hydroxylamine-*N*,*N*-disulphonate (**7**)[17] and the sulphonylated sulphamate cyclohexyl *N*-benzyl-*N*-(*p*-bromophenylsulphonyl)sulphamate (**8**)[18].

$HON(SO_3K)_2$ (**7**)

p-$BrC_6H_4SO_2N(CH_2C_6H_5)SO_3C_6H_{11}$-*c* (**8**)

2. *Raman and IR spectroscopy*

An Indian group have reinvestigated the polarized Raman spectra of a single crystal of sulphamic acid (**1**) in the internal mode region and find Fermi resonances at around 680 and 1060 cm^{-1}. Medium strength hydrogen bonding is indicated from the N—H stretching mode which shows a substantial shift of 280 cm^{-1}. There is a weakening of the N—S bond compared to that in sulphamate salts[19]. Another study of sulphamic acid (**1**) has focussed on the factors responsible for the half widths of the NH_3 Raman torsional band[20]. Some Raman studies of torsional vibrations in sulphamic acid (**1**) as a function of temperature and pressure have been reported[21]. Combined polarized IR, low-temperature and isotopic dilution studies have been reported on single crystals of sulphamic acid containing 5% D[22].

Ten papers have appeared on Raman/IR studies of various sulphamate salts[23–32]. All lattice modes except two were observed in the room temperature polarized Raman spectra of H_2NSO_3K (**9**) single crystals which were investigated in the region 30–3400cm^{-1} using laser excitation[23]. A normal coordinate analysis of the sulphamate ion using the laser Raman frequencies of a single crystal of potassium sulphamate indicates some double bond character in the N—S bond[24].

The same group have reported room temperature polarized laser Raman spectra for single-crystal sodium sulphamate (**2**)[25,26] and IR spectra in the region 50–400 cm^{-1} for the polycrystalline material[26]. Results of studies of Raman and IR spectra of lithium (**10**)[27], calcium (**11**)[28], barium (**12**)[28,29], strontium (**13**)[30] and ammonium sulphamates (**14**) have been reported. A Russian group have reported IR and Raman spectra of **9** and D_2NSO_3K (**15**) and full assignments have been made[32].

3. Magnetic resonance spectroscopy

ESR studies of copper(2+) doped barium sulphamate (**12**) single crystals show well-resolved hyperfine spectra of ^{63}Cu superimposed with superhyperfine lines due to ^{14}N nuclei[33].

^{1}H and ^{15}N NMR studies of sulphamic acid (**1**), ammonium sulphamate (**14**), ammonium imidodisulphate $HN(SO_3NH_4)_2$ (**16**) and nitridotrisulphate $N(SO_3NH_4)_3$ (**17**) have been reported[34]. Spin lattice relaxation times have been measured for sulphamic acid[35].

The electron nuclear double resonance method (ENDOR) has been used to obtain greatly enhanced NMR signals for the deuterium nuclei in D_3NSO_3 (**18**) single crystal at 4.2 K[36]. The N—D angles obtained are in good agreement with those reported from neutron diffraction data at 78 K. ENDOR has also been used more recently by another group to study features of sulphamic acid structure[37].

4. Ionization and thermal studies

Thermodynamic parameters for the solution and ionization of sulphamic acid and the aminosulphonic acids $H_2N(CH_2)_nSO_3H$ ($n = 1,2$) (**19** and **20**) and sulphanilic acid (**21**) were determined in dimethyl sulphoxide and water[38]. The three aliphatic acids are much weaker ($2.1 \leqslant \Delta pK_a \leqslant 5.5$) in dimethyl sulphoxide than in water and their heats of ionization are *ca* 30 kJ mol^{-1} more endothermic in dimethyl sulphoxide. Sulphamic acid (**1**) and the other acids are present principally as zwitterions in dimethyl sulphoxide just as in H_2O.

The sulphamate equilibria in equation 1 have been studied by potentiometric and ^{13}C NMR. pK_a values for step a have been determined as *ca* 12 for five compounds. pK_a values for step b have been determined for 19 sulphamates including seven hetero sulphamates which contain an additional nitrogen atom. The pK_a s for the sulphamates in equilibrium b were in the range 1.05 to 2.35. Step c was studied in H_2SO_4 for three sulphamates and the pK_as obtained were approximately -1.40 from the Bunnett and Olsen equation[39].

$$R\bar{N}SO_3^- + H^+ \overset{a}{\rightleftharpoons} RNHSO_3^- + H^+ \overset{b}{\rightleftharpoons} R\overset{+}{N}H_2SO_3^- + H^+ \overset{c}{\rightleftharpoons} R\overset{+}{N}H_2SO_3H \qquad (1)$$

The ionization constants at various temperatures and thermodynamic functions for sulphamic acid and several other aminosulphonic acids have been determined in formamide from electromotive force measurements[40]. The initial thermoelectric power (TEP) for hydrogen electrode thermocells has been determined for aqueous solutions of sulphamic acid at 29 °C over the concentration range 0.001 to 0.01 molal[41].

Three papers dealing with differential scanning calorimetry (DSC) of sulphamates and various related systems have appeared[42–44]. Studies by (DSC) of ammonium sulphate, ammonium hydrogen sulphate and ammonium sulphamate (**14**) have been described[42,43]. The series of binary systems: $NH_3{}^+SO_3{}^-$–$NH_2SO_3NH_4$ (**15**), $NH_3{}^+SO_3{}^-$–$(NH_4)_2SO_4$ (**22**), $NH_3{}^+SO_3{}^-$–NH_4HSO_4 (**23**), $NH_2SO_3NH_4$–$(NH_4)_2SO_4$ (**22**), $NH_2SO_3NH_4$–NH_4HSO_4 (**23**) and $(NH_4)_2SO_4$–NH_4HSO_4 (**24**) have been investigated by DSC[44]. The thermal behaviour (DTA) of hydrazinium sulphamates has been reported[85].

5. Miscellaneous

Osmotic and activity coefficients have been reported for solutions of sodium[45], potassium[45], lithium[46] and tetramethylguanidinium sulphamates (**25**) and for sulphamic acid[45].

Isothermal ternary sections of the system H^+, $NH_4{}^+//SO_4{}^{2-}$, $NH_2SO_3{}^-$, H_2O were

constructed from electrical conductivity and tie-line data[47]. In a subsequent paper[48] the complete solid–liquid phase diagram was established at 25 °C. A new double salt $(NH_4)_2SO_4 \cdot 3H_2SO_4$ was formed.

Later studies were carried out at 40 °C, 60 °C and 80 °C[49]. The same workers have made conductiometric studies of the ternary system ammonium sulphamate (**14**), ammonium sulphate (**22**) and water[50].

The kinetics of the electrochemical reduction of sulphamic acid giving sulphite ion and ammonium hydroxide have been studied polarographically in aqueous solution in the presence of various salts[51]. The electrodissolution of lead sulphide, prepared by fusion or by sintering in sulphamic acid, has been measured by cyclic voltammetric, potentiodynamic and potentiostatic methods[52].

A study of the reorientational motions of NH_3 groups in polycrystalline sulphamic acid by quasi-elastic neutron scattering and heat capacity measurements have been reported[53].

The absorption of sulphamate ions (**26**) on Hg electrodes was studied by measuring the double layer capacitance in solutions of ammonium sulphamate maintained at constant ionic strength with ammonium fluoride[54].

Ab initio calculations for sulphamic acid and sulphur trioxide with three bases show that d functions centered on sulphur have a large influence on the optimized geometries[55a]. *Ab initio* MO studies at the STO-3G and 4-31G levels have been reported for neutral sulphamic acid and *N*-methyl sulphamate[55b] and later the same group performed calculations for zwitterionic sulphamic acid[55c].

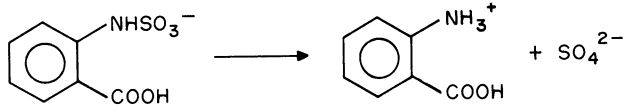
The coprecipitation of barium and lead sulphates from homogeneous solutions using sulphamic acid has been studied using electron microscopy and diffraction methods[56]. The reaction crystallization of sulphamic acid from urea and fuming sulphuric acid has been investigated[57].

B. Kinetics of Formation, Solvolysis, Sulphation and Photochemistry

The kinetics of formation of sulphamic acid (**1**) from urea (**27**) and fuming sulphuric acid (equation 2) at 50 °C–70 °C and the rate constant was found to be proportional to the excess concentration of SO_3[58]. Formation of the salt $[(H_2N)_2COH]^+[HS_2O_7]^-$ (**28**) takes place and its decomposition occurs in the slow step.

$$\underset{(\mathbf{27})}{H_2NCONH_2} + SO_3 + H_2SO_4 \longrightarrow \underset{(\mathbf{1})}{NH_2SO_3H} + CO_2 \qquad (2)$$

Complete hydrolysis of the salts $Fe(NH_2SO_3)_3$ (**29**), $Cu(NH_2SO_3)_2$ (**30**) $Fe(NH_2SO_3)_2$ (**31**) and $Zn(NH_2SO_3)_2$ (**32**) to sulphate takes three hours in aqueous solution at temperatures of 130 °C, 160 °C, 175 °C and 185 °C, respectively. Under these conditions sulphamic acid hydrolyses at much lower temperatures[59]. The hydrolysis of sulphamic acid in 0–30% aqueous H_2SO_4 involves a slow step in which a monomolecular transformation of the zwitterion occurs. At > 30% H_2SO_4 the slow step is the reaction of water with the decomposition products of the zwitterion[60].

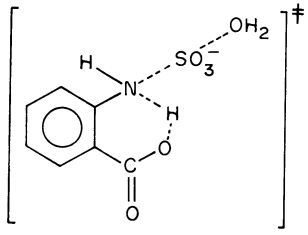


(3)

(**33**)

William's group[61] has studied both intramolecular and intermolecular mechanisms in the transfer of sulphonate groups from arylsulphamates using *N*-(1-naphthyl) and *N*-(2-

carboxyphenyl)sulphamates (**33**) as substrates. Their results favour a proton transfer concerted with water attack of the sulphamate group in the intramolecular mechanism.

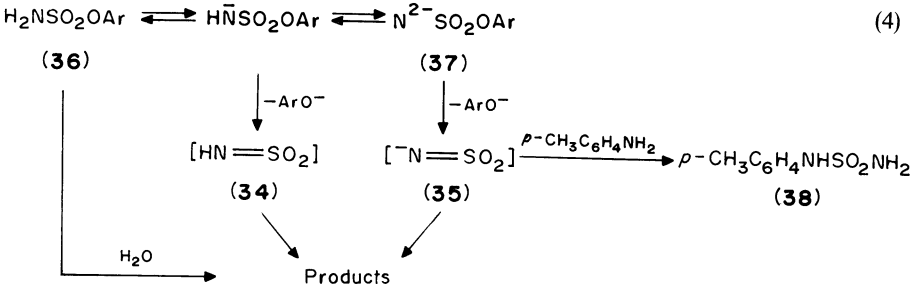


(**33**)

Intermolecular acid catalysis using a series of mainly carboxylic acids involves reaction of N-protonated naphthyl sulphamate with carboxylate anions in the rate-determining step. The β_{nuc} value for attack (0.33) is similar to that reported by the same group for the reaction of phenolate ions with tertiary amine sulphonate (0.23). Stereoelectronic effects are suggested as governing the type of mechanism operating in these systems.

Some years ago[62] Williams demonstrated the existence of the neutral sulphonylamine intermediate $[HN{=}SO_2]$ (**34**) in the hydrolysis of sulphamate esters. In recent work[63] on esters he has confirmed the existence of this sulphonylamine and also found evidence for an anionic sulphonylamine (**35**).

The alkaline hydrolysis of arylsulphamate esters (**36**) follows good first-order kinetics up to at least 80% reaction and the pathway involving bimolecular attack by H_2O and the formation and decomposition of the sulphonylamine, $[HN{=}SO_2]$ (**34**) have been established. At high pH the pathway involving the dianion **37** is important and it decomposes unimolecularly to give **35** in a slow step. The activation parameters are $\Delta H^{\ddagger} = 15.2\,\text{kcal mol}^{-1}$ and $\Delta S^{\ddagger} = 11.6\,\text{cal mol}^{-1}\,\text{K}^{-1}$ at 25 °C for 4-nitrophenylsulphamate indicating a dissociative mechanism. The rate constant is very sensitive to the pK_a of the leaving group (ArO^-)($\beta_{lg} = -1.79$) indicating considerable negative charge on the oxygen in the transition state. Finally, added *p*-toluidine converts all the sulphamate into *N*-*p*-toluenesulphamide (**38**) (see Equation 4).



(4)

In another sulphation study the kinetics of the reaction of sulphamic acid with 2-octanol to give *sec*-octylsulphate were found to be first order in sulphamic acid with energies and entropies of activation of $3.1 \pm 0.6\,\text{kcal mol}^{-1}$ and 15 ± 2 e.u. (in DMF) and $33.7 \pm 1.0\,\text{kcal mol}^{-1}$ and 17 ± 3 e.u. (in dimethyl sulphoxide)[64]. In dimethylformamide the mechanism involves the slow formation of $DMF{\cdot}SO_3$ followed by its rapid reaction with the alcohol to give $ROSO_2ONH_4$.

Photolysis at 254 nm of sodium *N*-phenylsulphamate (**39**) gives three isomeric anilinesulphonic acids, viz. orthanilic, methanilic and sulphanilic acids and aniline[65]. The involvement of an intramolecular radical cage mechanism is supported by the absence of a substrate concentration effect and a considerable lowering of sulphamic acid yields in the presence of a radical scavenger. Stern–Volmer plots have provided evidence for involvement of two triplets in the reaction.

C. Synthesis

1. *Sulphamic acid, ammonium sulphamate, etc.*

A number of improvements in the preparation of sulphamic acid have been patented[66–69]. The formation of ammonium sulphate has been minimized in the preparation of sulphamic acid from NH_3 and SO_3 (followed by hydrolysis) by using a modified work-up procedure[66]. The same reaction has been improved in Russian work[67], In other Russian work an improved yield of sulphamic acid in the reaction of urea with fuming H_2SO_4 and the simplification of the process has been achieved by using 60–65% fuming acid and 50–55% H_2SO_4 for mixing[68]. Suspensions of $HN(SO_3NH_4)_2$ in molten $NH_2SO_3NH_4$ were reacted with NH_3 at 5–9 bar and 200–50 °C[69]. The molten reaction product is hydrolysed in aqueous acid and sulphamic acid is precipitated.

Four German patents[70–73] and two Japanese[74,75] patents deal with the preparation of ammonium sulphamate. Three patents[70–72] deal with the reaction of NH_3 and SO_3 leading to ammonium sulphamate. Another patent[73] considers the reaction of NH_3 and SO_2 to give ammonium sulphite, which is subsequently converted to ammonium sulphamate via the reaction of sulphite with N_2O_3, isolation of the ammonium nitrilotrisulphonate and its reaction with NH_3 at 5–11 bar and 200–220 °C gives the ammonium sulphamate.

The formation of ammonium sulphamate by oxidation of aqueous ammonium thiosulphate is the subject of two patents[74,75]. Ammonium sulphamate has been produced in 97% purity from the effluent of a wet redox desulphurization process containing 5–20% $(NH_4)_2S_2O_3$, 5–20% NH_4SCN and 0.5–1.0% NH_3[76]. Production of good quality ammonium sulphamate from sulphamic acid and sodium hydroxide has been described.[77] Ammonium salts of sulphamic acids were obtained by the reaction of a nitroligomer of SKI-3 isoprene rubber with NH_4HSO_3 at 40–70 °C and pH 6 to 7[78]; 91% pure sodium sulphamate has been prepared from 40–95% pure ammonium sulphamate containing ammonium imidosulphate and sulphate by treatment with NaOH[79].

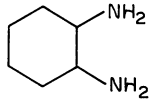
There have been five papers dealing with guanyl sulphamates[80–84]. Three Japanese patents deal with the preparation of guanidine sulphamate. $H_2NC(:NH)NH_2 \cdot NH_2SO_3H$ (**40**). Batch reactions of sulphamic acid with dicyanodiamide, $NH_2C(:NH)NHCN$ (**41**) in the presence of NH_3 have been employed[80,81] and the reaction of ammonium sulphamate with the dicyano compound in NH_3 has been used[82]. A series of sulphamoyl guanidines (**42**) have been prepared by reaction of sulphuryl chloride and dialkylcyanamides and subsequent aminolysis with trimethylsilylamines (**43**)[83]. Guanylurea sulphamate $H_2C(:NH)NHCONH_2 \cdot H_2NSO_3H$ has also been prepared[84].

$$R^1{}_2NC(NR^2R^3)=NSO_2NR^2R^3 \qquad R^2R^3NSi(CH_3)_3$$
(**42**) (**43**)

Hydrazinium sulphamate, $NH_2N^+H_3{}^-SO_3NH_2$ (**44**) and several other hydrazinium salts have been prepared by the reaction between the appropriate ammonium salts and hydrazinium hydrate[85]. The thermal behaviour of the sulphamates and the other salts has been investigated.

2. Aliphatic, alicyclic and aromatic sulphamates

A 90% + yield of *N*-methylsulphamic acid (**45**) has been reported from the reaction of $(CH_3NH)_2CO$ with 40% oleum[86]. Sodium *N*-cyclohexyl sulphamate (cyclamate) (**46**), the non-nutritive sweetener, has been prepared by reaction of cyclohexylamine with sulphamic acid in xylene at 132–139 °C[87]. A series of polymer-containing pendant cyclamate units have been prepared starting from 1,2-cyclohexanediamine (**47**), which was monosulphamated to give sodium *N*-(2-aminocyclohexyl)sulphamate (**48**). Some reactions of **48** gave vinyl derivatives of types **49** and **50** in yields of 29% and 35%, respectively. These compounds could be polymerized or copolymerized with *N*-vinyl-2-pyrrolidone[88].



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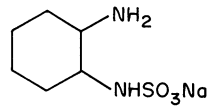

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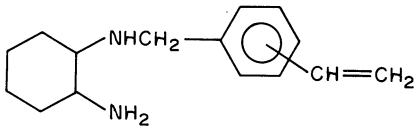

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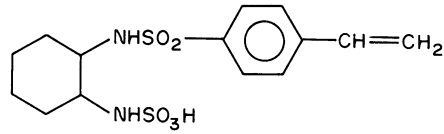
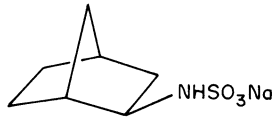


(50)

A useful practical review (48 references) on cyclamate and its use has appeared[89]. Most of the work of this review concentrates on the sweetness aspect of cyclamates. The structure–taste relationships of a wide variety of sulphamates has been studied by many groups. Pautet's group in a series of papers[90–94] have synthesized various sodium sulphamates including some with second functionalities[93] and some esters of type *c*-$C_6H_{11}NHSO_2OR$ (R = alkyl, alicyclic)[92]. This work has led to the establishment of some new and important structure–taste relationships for sulphamates and has added greatly to the data base of sulphamates that have been assessed for sweetness properties.

In an important paper de Nardo and co-workers have synthesized a number of alicyclic and heterocyclic (see below, Section II.C.3) sulphamates and the corresponding sulphamoyl chlorides[95]. Two of the sulphamyl chlorides are sweet and the corresponding sodium sulphamates are also sweet. Sodium *exo*-bicyclo[2.2.2]heptan-2-ylsulphamate (*exo*-2-norbornyl sulphamate) (**51**) is reported to be 5 times as sweet as sodium cyclamate. This is an important discovery since cyclamate was heretofore the sweetest sulphamate reported. The Italian group also found that the *endo*-compound **52** is tasteless. Another Italian group have prepared an extended series of norbornyl sulphamates[96].



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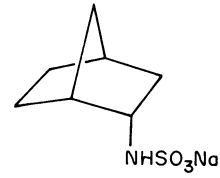
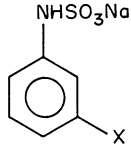


(52)

A semi-quantitative structure–taste relationship has been derived[97] and extended[98] for carbosulphamates using Corey–Pauling–Koltun (CPK) space-filling models for measurements of parameters. Structure–taste relationships for heterosulphamates were developed

using CPK models and molecular connectivities and the technique of linear discriminant analysis[99]. These relationships have also been extended recently[98]. A short review of other carbo- and hetero-sulphamates structure–taste relationships has appeared[100].

The important discovery that simple *meta*-substituted phenylsulphamates (**53**) are sweet, but not their *ortho* and *para* isomers, has been made recently[16]. Since the discovery of sulphamate sweeteners over 40 years ago it had been tacitly assumed, on the basis of the synthesis and tasting of a few aromatic sulphamates, that phenylsulphamates in which the $-NHSO_3$ moiety is directly attached to the aromatic ring are not sweet. The sweetness of these compounds has been simply explained using CPK models and a recently developed theory of sulphamate sweetness[90,91] has not proved adequate to explain the sweetness of these novel, new, sweet sulphamates[16].



X = F, Cl, Br, CH_3, CN

(**53**)

A QSAR for sulphamate taste has been developed[101] based on limited earlier data. The equation is

$$\log 1/C = 0.68 \pm (0.45) \log P + 0.05 \pm (0.61)$$

where C is the taste threshold in water for 7 sulphamates and P is the n-octanol–water calculated partition coefficient of the sulphamate. The correlation coefficient (R) and the standard deviation (s) were 0.86 and 0.33, respectively.

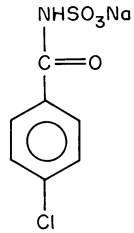
Pattern recognition methods have been used successfully to classify sweet and non-sweet carbosulphamates[102]. For the fifty carbosulphamates studied the average recognition rate was 80–93% of the sweet and 67% of the non-sweet being correctly classified. In a second paper these authors using similar methods correctly classified 87% of acyclic compounds and 81% of the cyclic compounds studied[103].

From analysis of 'third sites' for different sweeteners, inter-class relationships have been developed by a Dutch group for the sweet classes: oximes, nitroanilines, sulphamates, dipeptides and isocoumarins[104].

In vivo and *in vitro* studies with some sulphamate sweeteners show a partial correlation[105]. *Trans*- and *cis*-*N*-(2-methylcyclohexyl)sulphamates (**54**) and *trans*- and *cis*-*N*-(2-isopropylcyclohexyl)sulphamates (**55**) and *trans*-*N*-(2-ethylcyclohexyl)sulphamate (**56**) have been synthesized and used to check on the stereochemical requirements of cyclamate metabolism[106].

Sodium *N*-*p*-chlorobenzoyl sulphamate (**57**) has been synthesized and observed to produce potent hypolipidemic activity in rodents[107]. In a structure–activity study of the antihyperlipidemic activity in mice, eleven different *ortho*-, *meta*- and *para*-substituted benzoylsulphamates (including **57**) have been synthesized and in the same study four benzylsulphamates (**58**) have been reported[108].

Kanetani[109] has prepared for the first time free arylsulphamic acids, $ArNH_2{}^+SO_3{}^-$ (**59**) where Ar = C_6H_5, 4-$CH_3C_6H_4$, 3,5-$(CH_3)_2C_6H_3$, 4-HOC_6H_4, 2-$HO_2CC_6H_4$, 3-$CH_3COC_6H_4$-, 1- and 2-naphthyl, etc., by adding concentrated hydrochloric acid to a cold aqueous solution of the corresponding ammonium salts. The significance of this work lies in the fact that phenylsulphamic acid, though postulated as an intermediate in the sulphonation of aniline by H_2SO_4 and in the 'baking process' for the sulphonation of aniline, has not hitherto been isolated. Thirteen free acids have been prepared. In



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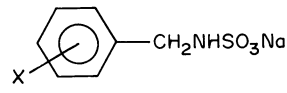
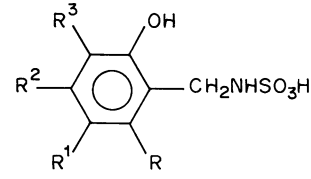


(58)

$XC_6H_4N(SO_3M)_2$

(60)

X = H, 2-, 3-, 4-CH_3, 2-, 3-, 4-Cl; M = Na, K



(61)

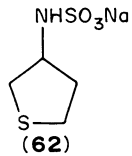
later work Kanetani[110] has prepared seven arylimidobissulphates (**60**). The intermediacy of the latter (**60** with X = H, M = H) in the sulphonation of aniline has been suggested (*loc. cit.* in Reference 110).

The sulphamic acids **61** have been prepared by an unusual route: for example, reaction of 2-HO-5-$(CH_3)_3CC_6H_3CHO$ with ammonium sulphamate gave, after reduction with sodium borohydride and treatment with HCl, the compound **61**, $R = R^2 = R^3 = H$, $R^1 = (CH_3)_3C$[111].

3. *Heterosulphamates*

As in the previous section much of the work here has been motivated by the desire to establish new structure–taste relationships for sweeteners.

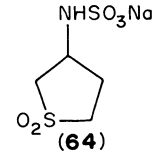
Oxa-1-cyclopentyl-2-sulphamate is reported to have been made and is not sweet[91]. However, the two sulphur compounds **62** and **63** were sweet, while the same workers found that the sulphone derivative **64** was not sweet[93]. Other compounds made by the same group, such as **65** ($n = 2,3$), **66** ($n = 1,2$), **67**, **68** ($n = 2,3$) and **69**, were not sweet. Interestingly, the carbon analogues of these heterocompounds and of **62**, **63** and **64** are all sweet[93].



(62)

$CH_3SCH_2CH_2NHSO_3Na$

(63)



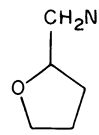
(64)

$HO(CH_2)_nNHSO_3Na$

(65) $n = 2,3$

$(CH_3O)_nCH_{3-n}CH_2NHSO_3Na$

(66) $n = 1,2$



(67)

$NaO_2C(CH_2)_nNHSO_3Na$

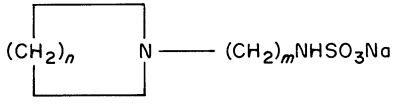
$n = 2, 3$

(68)

$(CH_3)_2NCH_2CH_2NHSO_3Na$

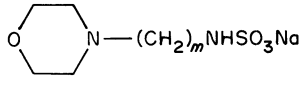
(69)

Italian workers[95] have made various nitrogen and oxygen (**70**–**77**) heterocyclic sulphamates and their corresponding sulphamoyl chlorides and they found that none of these materials is sweet. The non-sweet heterosulphamates **78**–**85** have also been reported[99]. The same group also prepared **70** ($n = 4$, $m = 2$), **73** and **71** ($m = 3$).



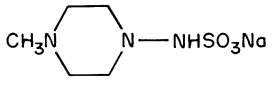
(70)

$n = 4, m = 2$; $n = 5, m = 2$; $n = 4, m = 0$;
$n = 5, m = 0$; $n = 6, m = 0$



(71)

$m = 0, 2$



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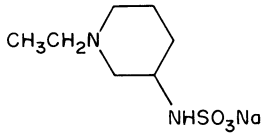

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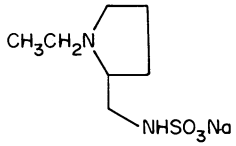

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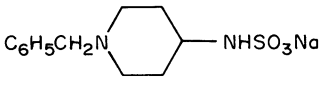

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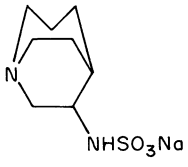

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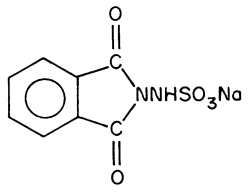
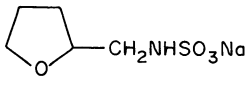


(77)

The heterocyclic sulphamate **86** has been synthesized[96]. The sulphamates **87**–**92** were synthesized to help probe and extend the existing taste relationships in this field[98]. The mono- and di- sodium salts of antipyrine sulphamate (**93**) have been prepared by the reduction of nitrosopyrine with a sulphite–bisulphite mixture[112].



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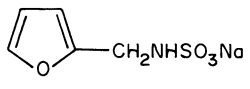

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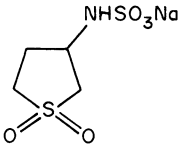

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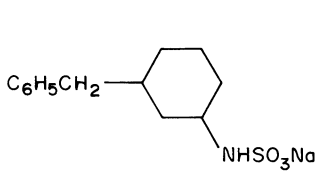

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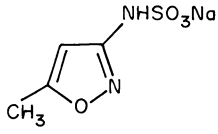

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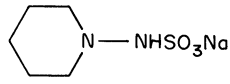


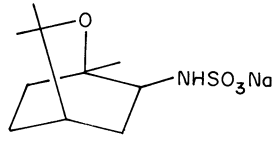
(83)

$(CH_3)_2CHO(CH_2)_2NHSO_3Na$

(84)

$(CH_3)_2N(CH_2)_3NHSO_3Na$

(85)



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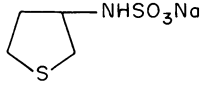

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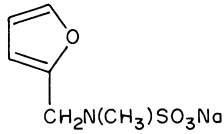

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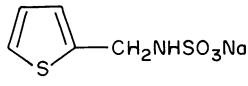

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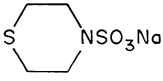

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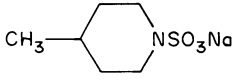
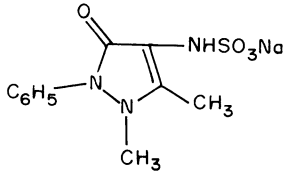


(91)

$CH_3CH_2O(CH_2)_3NHSO_3Na$

(92)



(93)

4. Halosulphamates

Potassium *N*-oxyl *N*-trifluoromethylsulphamate $F_3C—N(—O\cdot)SO_3K$, prepared by reaction of trifluoronitrosomethane $F_3C—NO$ with bisulphite, reacts with halosubstituted ethylenes to give 2:1 adducts of type **94**[113].

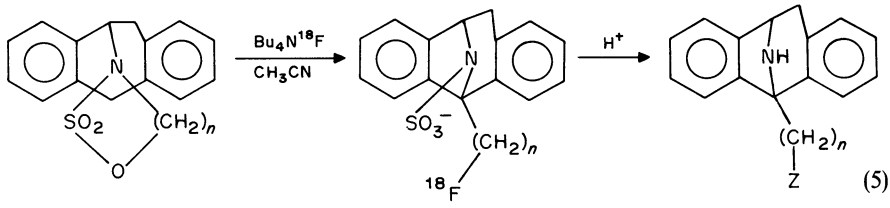
$$^{-}O_3S(CF_3)NOCX_2CYZON(CF_3)SO_3^{-}$$

(**94**)

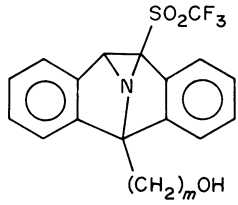
(X = Y = Z = F; X = Y = F, Z = Cl; X = Y = F, Z = H)

Cyclic sulphamates **95** appear to have a role as substrates in ^{18}F-radiochemistry. Nucleophilic substitution by ^{18}F occurs readily and cleavage of the N—S bond by acid gives the [^{18}F] fluoro analogues of MK 801 (**96**), Z = ^{18}F (equation 5)[114]. MK 801

(**96**), $n = 1$, Z = H is the most potent non-competitive antagonist of the NMDA receptor, but it is not easily labelled for studies, hence the importance of this work which leads to 25–30% radiochemical yield. The basis for this work was laid a few years earlier by another group[115] who demonstrated that **97** gave **96** (Z = F) via the sulphamate on similar treatment.



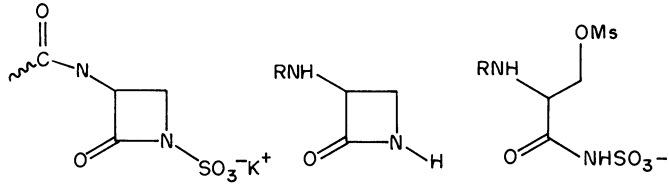
(**95**) (**96**) (5)



(**97**)

5. Monobactams

The simultaneous and independent discovery by US[116] and Japanese[117] groups, that 3-acylamino-2-oxoazetidine-1-sulphonates (**98**), called monobactams, are monocyclic β-lactam antibiotics active against gram-negative bacteria, has provided a powerful stimulus to synthetic efforts in this area. The two major routes to the monobactams are (i) sulphamation of an azetidinone (**99**) with SO_3 complexes and (ii) the important manufacturing route, which involves cyclization of an acylsulphamate (**100**).

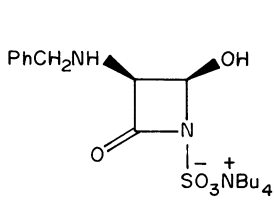


(**98**) (**99**) (**100**)

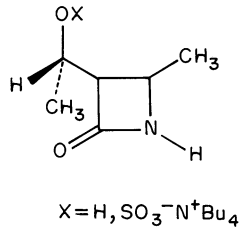
Several reviews of monobactams have appeared. One 1981 review describes the screening of the monobactams[118] and another details their isolation and structural determination[119]. Another review published in 1982 deals with the isolation, structure, synthesis and microbiological activity of the monobactams[120]. A very short but stimulating review by Cimarusti and Sykes appeared in 1983[121] and more recently Cimarusti has reviewed the synthesis of monobactams[122].

Synthesis in this field in recent times includes the synthesis of 4-alkylated monobactams[123], of **101**, a precursor of the antibiotic carumonam[124], of monobactams

lacking the 3-acylamino side-chain, e.g. **102**[125], of the 3-amino-2-oxoazetidine-1-phosphonic acids (**103**)[126], of the 4-fluoromethyl-1-sulpho-2-azetidinones (**104**)[127] and of the 3-(2-amino-2-phenylacetamido)-2-methyl-4-oxo-1-azetidine sulphonic acid (**109**)[128].

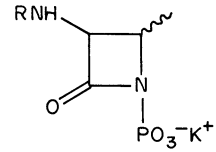


(**101**)

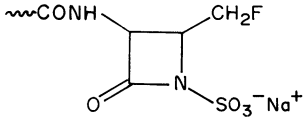


X=H, $SO_3^-N^+Bu_4$

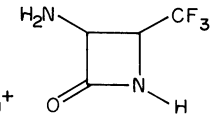
(**102**)



(**103**)



(**104**)



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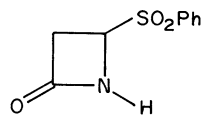
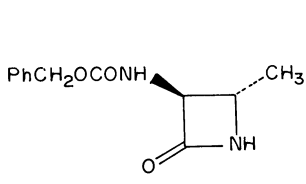
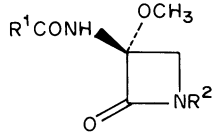


(**106**)

An improved synthesis of *trans*-3-amino-4-trifluoromethyl-2-azetidinone (**105**), a precursor of several monobactams, has been achieved[129]. 4-Phenylsulphonyl-2-azetidinone (**106**) has been used to synthesize the monobactam intermediates **107** and **108**[130]. The utility of the imidazolylsulphonate group in the synthesis of monobactams has been demonstrated[131]. 6-Sulphoaminopenicillanic acid (**110**) has been both isolated and synthesized (from 6-aminopenicillanic acid)[132].



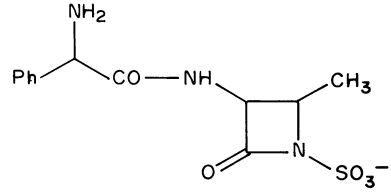
(**107**)



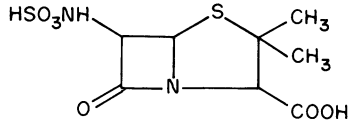
R^1=$PhCH_2O$, R^2=H

R^1=CH_3CO, R^2=$SiBu^t(CH_3)_2$

(**108**)



(**109**)



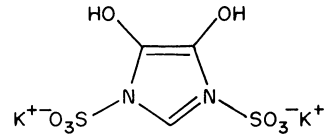
(**110**)

6. Use of sulphamic acid and sulphamates for sulphation and sulphonation

There are several reports of the use of sulphamic acid for sulphation of fatty acid monoglycerides[133], higher secondary alcohol ethoxylates[134,135] and the hydroxyethy-

lated alkylphenols p-$RC_6H_4O(CH_2CH_2O)_nH$ with R = C_6—C_{15} alkyl, $n = 2$–16[136]. Sulphation of secondary alcohols with SO_3 has also been reported[137].

Reaction of aniline with sulphamic acid at 160 to 170 °C for 1 hour gave a mixture of orthanilic, sulphanilic and 2,4-anilinedisulphonic acids and a little 2,4,6-anilinetrisulphonic and phenylsulphamic acids[138]. The reaction of formaldehyde with potassium sulphamate at 25–30 °C and subsequent reaction of the product with glyoxal at 35–45 °C gave dipotassium 4,5-dihydroxyimidazoline-1,3 disulphonate (**111**)[139].



(**111**)

D. Sulphamate–Metal Bonds

The rate of reduction of the sulphamato ruthenium complex, $RuNH_2SO_3^{-2}$, by titanium(III) was found to increase with increasing [Ti(III)] and to decrease with the $[H^+]$ decreasing. Both Ti^{+3} and $TiOH^{+2}$ are reduced by an outer-sphere mechanism[140]. The association of thallium(I) with acetate and sulphamate has been found from potentiometric studies to be much weaker than with ClO_4^-[141]. The chromium(III) complex **112**, which contains three bridging OH groups, has been synthesized. In aqueous solution **112** is in equilibrium with the mononuclear complex, $Cr(en)_3(SO_3NH_2)_3$, and structures are proposed for both on the basis of IR spectra[142].

$Cr_2(OH)_3en_3(SO_3NH_2)_3 \cdot 3H_2O$

(**112**)

$M(NH_2SO_3)_2 \cdot xH_2O$
(M = Co, Ni, Zn, Cu)

(**113**)

An ESCA study of the metal sulphamate complexes (**113**) and of sodium sulphamate and sulphamic acid has been reported[143]. For **113** (M = Co, Ni, Zn) pure O- and N-bonded isomers can be obtained.

The metal sulphamates of Co, Ni and Cu have been prepared by reaction of sulphamic acid with the metal in the presence of H_2O_2[144].

The effect of pH on the electrochemical reduction of Ni complexes for sulphamate baths has been studied[145].

The preparation of the tributyltin sulphamate **114** has been reported[146]. It undergoes slow hydrolysis to tributyltin sulphamate **115**, which can be prepared under controlled conditions from the reaction of sulphamic acid with $(Bu_3Sn)_2O$. In the same reaction at higher temperatures tributylstannylation of both the hydroxyl and amino groups occurs[146].

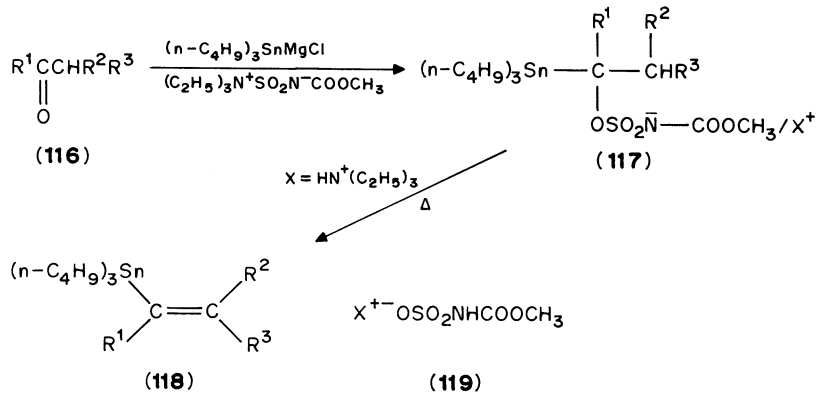
$[(n\text{-}C_4H_9)_3Sn]_2NSO_3Sn(C_4H_9\text{-}n)_3$

(**114**)

$(n\text{-}C_4H_9)_3SnSO_3NH_2$

(**115**)

Various alkyltributyltin sulphamates (**117**) were prepared as shown. Decomposition of these triethylammonium *N*-carbomethoxysulphamates occurs smoothly to give ≈60% yields of vinyltributyltin derivatives (**118**) and the water-soluble *N*-carbomethoxysulphamic acid (**119**)[147]. This procedure allows a new route to substrates having a tin atom on the more substituted carbon. The reaction may be regioselective with the exclusive formation of the least substituted olefin (equation 6).



(116) (117) (118) (119) (6)

In a series of papers[148–150] a Russian group has examined the reactions of platinum and rhodium sulphamate complexes. Potassium permanganate oxidation of *cis*- and *trans*-$K_2[Pt(NH_2SO_3)_2Cl_2]$ gave H_2SO_4, gaseous N_2O and a Pt(IV) complex which gave H_2PtCl_6 after treating with HCl. Different mechanisms are involved in the oxidation of the two isomers[148]. Further studies on the H_2O_2/Ce(IV) oxidation of *cis*-$[Pt(NH_3)_2(NH_2SO_3)Cl]$ and $KnMnO_4$ oxidation of *trans*-$K_2[Pt(NH_2SO_3)_2Cl_4]$ and $K_2[Rh(NH_2SO_3)Cl_5]$ have been described[149]. The reaction of *trans*-$K_2[Pt(NH_2SO_3)_2Cl_2]$ and *cis*-$K_2[Pt(NH_3)_2(NH_2SO_3)Cl]$ with chlorine has been examined[150].

The rhodium complexes **120** and **121** were prepared by reaction of $Na_3(RhCl_6)$ with sulphamic acid in aqueous KCl solution. **121** isomerizes thermally at 190 °C to *trans*-$K_3[RhCl_4(NH_2SO_3)_2]\cdot xH_2O$ ($n = 1,2$) which gives chloro-bridged $K_4[Rh_2(NH_2SO_3)_2Cl_8]$ at 225 °C[151].

$K_3[RhCl_5(NH_2SO_3)]\cdot H_2O$ (**120**)

cis-$K_3[RhCl_4NH_2SO_3)_2\cdot 2H_2O$ (**121**)

Some crystallochemical characteristics of complex iridium sulphamates have been reported[152]. A series of lanthanide sulphamates (**122**) have been prepared[153], by reaction of the lanthanide carbonate and sulphamic acid, isolated as solids and examined by infrared, X-ray diffraction and thermography. The sulphamates have a higher solubility in water than other alkali or alkaline earth sulphamates.

$M(NH_2SO_3)_3\cdot nH_2O$
(M = La, Ce, Pr, Nd, Sm, Eu, Gd, Ho, Er, Tm, Yb, Lu; $n = 2,3$)
(**122**)

E. Analysis of Sulphamic Acid and Sulphamates

The use of cyclohexylsulphamic acid (**46**) as a sweetening agent and food additive in the fifties and sixties stimulated interest in the analysis of sulphamates in general. The analytical techniques and procedures used up to the late seventies have been reviewed[1]. Subsequent to this review, two major monographs have appeared, which describe the evaluation of the carcinogenic risks of cyclamates and also describes a survey of analytical methods for the estimation of cyclamates in food. Page and Conacher[154] have reviewed a wide range of analytical techniques including gravimetric, titrimetric, chromatographic and spectroscopic methods for the estimation of cyclohexylsulphamate in foods. In addition, clean up procedures including extraction, ion exchange, dialysis, precipitation

and column chromatographic techniques for sample preparation prior to analysis are detailed. The international agency for research on cancer (IARC) have also evaluated the carcinogenic risk of cyclamates[155].

A kinetic analytical procedure for the estimation of trace levels of sulphamate ion has been reported by Wei[156]. The procedure is based on the ability of the sulphamate ion to inhibit the oxidation of ferrous ion by nitric acid. A linear relationship between the log of the inhibition time and concentration of the sulphamate ion over the range 6×10^{-3} to 4×10^{-1} g l^{-1} with deviations less than ± 0.03 mg was assessed. No interference by SO_4^{2-}, Ni^{2+}, Co^{2+}, Cu^{2+} and Mn^{2+} ions on the estimation of the sulphamate was reported.

A recently reported ion-selective electrode, specific for cyclamate **46**, has provided a new and rapid method for its estimation in food[157]. The electrode prepared from polyvinyl chloride and trioctyl dodecyl ammonium iodide was found to exhibit a Nernstian response to cyclamate anions from 8×10^{-6} M to 1×10^{-2} M with a slope of 58mV/decade (27 °C). By using acidified water, pH 4, memory effects are eliminated. Sulphamic acid itself has been used to determine free chlorine in air. The procedure involves scrubbing the chlorine into a sulphamic acid solution to which iodide reagent is added and the liberated triodide is estimated by ion-selective methods[158,159]. Smith and Cochram[160] reported, however, that the electrodes were subject to drift and developed a spectrophotometric procedure based on a strong sharp absorption band at 298 nm. Good linearity between 0.1 μg ml^{-1} to 10 μg ml^{-1} was observed. The percent relative standard deviation for 10 replicates at the 1 μm l^{-1} level by the spectrophotometric and the electrode procedure was 1.4% and 5.3%, respectively. Interference from oxidizing agents such as nitrogen dioxide, hydrogen peroxide, ozone, chlorates and iron(III) compounds was observed with both procedures. Calorimetric determination of the reaction of chlorine and chlorine dioxide with sulphamic acid has been used for the continuous determination of chlorine and chlorine dioxide in cellulose pulp bleaching processing[161].

Spectrophotometric analysis of cyclohexylsulphamic acid (**46**) and its salts has been carried out. The procedure involves conversion of the cyclamate to *N*,*N*-dichloro-cyclohexylamine (**123**) using excess hypochlorite. **123** is determined by measuring its UV absorption at 314 nm. Two collaborative studies have been reported using this analytical technique for the determination of cyclamate in soft drinks, desserts and jams[162,163]. The first study reports the results of nine laboratories assaying 3 soft drinks with cyclamate levels of 0.36–0.37 g kg^{-1} and 3 jams with cyclamate levels of 1.23–1.50 g kg^{-1}. Average recoveries of cyclamate were 99.7% in the soft drinks and 103.8% in the jams with reproducibility coefficients of variation of 6.7% and 4.4%, respectively. The second study involved determination of cyclamates at much lower concentration levels, namely 90–311 mg l^{-1} and 202–526 mg kg^{-1}. The results from 15 collaborators gave cyclamate recoveries of 97.5% in soft drinks with relative standard deviations from 4.7% to 6.5%. The recovery from desserts was 98.6% with relative standard deviations of 6.9% to 8.5%.

N-Nitrosocyclohexylsulphamic acid (**124**) has been isolated from gastric juice and urine in humans and is probably formed by the *in vivo* reaction of cyclamate with sodium nitrite. Kinawi and Luth[164] have studied the effect of **124**, when administered orally to rats, on the respiration of rat liver and the activity of alkaline phosphatase in serum. The sulphamate was estimated using an indirect technique, which involved measuring the absorbance at 250 nm after addition of hydrochloric acid to an aqueous solution of the residue from a methanol extract of the serum. The oral administration of **124** to rats resulted in an increase in the activity of alkaline phosphatase in serum of the rat but no increase in liver respiration.

A spectrophotometric procedure for the estimation of metallic impurities Pb, Zn and Cu in a wide range of artifical sweeteners, including cyclamate, has been reported[165]. The Pb and Zn were determined at 525 nm and 540 nm, respectively, by reaction with dithizone.

The Cu was determined by reaction with oxalic acid bis(cyclohexylidene hydrazide) and absorption readings measured at 600 nm. Concentration ranges of the metals studied in the cyclamate were 10 to 50 mg kg^{-1}.

Gas chromatography was used to determine cyclohexylsulphamic acid in beverage and confectionery samples[166]. The procedure involved initial treatment of the sample with 20% sulfosalicylic acid followed by centrifugation; the supernatant containing the cyclamate was converted to its corresponding cyclohexylamine by hydrolysis using 6N HCl and 30% H_2O_2 in boiling water for one hour. The mixture was extracted with dichloromethane and analysed on a 10% Carbowax column 20M with 2.5% NaOH on Chromosorb P NAW using cycloheptylamine as an internal standard. The procedure was also extended to detect and estimate the presence of impurities such as cyclohexylamine, dicyclohexylamine and aniline. Gas liquid chromatography has also been used to monitor the metabolism of the sweet sulphamates cyclooctylsulphamate and 4-methylcyclohexylsulphamate[167]. The purpose of the study was to probe the effect of structural modification of the cyclamate, i.e. cyclohexyl nucleus on the stability of these compounds in the body. The average % conversions in Wistar albino rats for cyclooctylsulphamate (**125**) to cyclooctylamine, cyclooctanone and cyclooctanol were 0.127, 0.08 and 0.092%, respectively. The average % conversions for 4-methylcyclohexylsulphamate (**126**) to 4-methylcyclohexylamine and 4-methylcyclohexanone were 0.007 and 0.0013%, respectively. No *cis*- or *trans*- 4-methylcyclohexanol metabolites were found. A sensitive gas chromatographic determination of the new antitumour agent, the sulphamic acid diester (sulphamic acid 1,7-heptanediyl ester) **127** (*loc. cit.* in Reference 263), has been described based on its conversion to 1,7-diiodoheptane in the presence of excess sodium iodide. The derivative was detected using electron capture[168]. The assay is linear up to 1 μg ml^{-1} sulphamic diester and has a lower limit of detection of 25 ng ml^{-1} from plasma. The analytical technique has been used to monitor the stability of **127** in buffers and in blood and its metabolism in the beagle and dog[169].

High-performance liquid chromatography has been used recently to separate the sodium salts of arylsulphamic acids using reverse-phase techniques with UV detection[170]. The effect of ten strong electrolytes, dissolved in the mobile phase, on the retention times of the sodium salts of arylsulphamic acids is described. The retention times were found to be independent to a large extent of the nature of the electrolyte but dependent on the concentration. Separations were achieved using both methanol and acetonitrile mobile phases. Ion-pair reverse-phase high-performance liquid chromatography has been used to separate phenylsulphamic acid and isomeric arylamino-mono- and disulphonic acids[171]. Ion-pairing techniques with tetrabutylammonium *p*-toluenesulphonate using indirect photometric detection methods on reverse-phase columns have been used to analyse cyclohexylsulphamate in the presence of other sweeteners in food samples. Detection limits of 50 ppm have been reported[172]. High-performance ion chromatographic (conductometric detection) methods have been used to assay cyclamate in the presence of saccharin and acesulphame -K using aqueous sodium bicarbonate mobile phases with potassium bromide as an internal standard[173]. The response for sodium cyclamate was linear for the concentration range 0.0010–0.0508 mg.ml^{-1}. Common inorganic anions such as nitrite, fluoride, phosphate or sulphate do not interfere with the determination except for chloride.

Three papers have appeared on the isolation and purification of the 2-deoxy-D-glucoside-2-sulphamate sulphohydrolase (**128**) from liver[174–176]. The enzyme has been purified 40,000-fold utilizing four chromatographic steps. The purification procedures were followed using a specific substrate isolated from an acid hydrolysate of heparin. The subunit molecular weight (M_r) of the enzyme isolated from liver, kidney and placenta was assessed to be 56,000 using SDS/polyacrylamide-gel electrophoresis and the native enzyme results from the dimerisation of the subunits.

F. Amine–Sulphur Trioxide Complexes

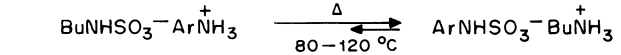
1. Synthesis, physical, theoretical and analytical aspects

A convenient synthesis of the triethylamine–sulphur trioxide complex $Et_3N{\cdot}SO_3$ (**129**) has been reported by Nair and Bernstein[177]. A 75% yield of **129** was obtained by the reaction of triethylamine with chlorosulphonic acid. Reaction of quinuclidine N-oxide with SO_2 yield a stable colourless, non-hygroscopic material which was identified by X-ray and elemental analysis to be the quinuclidine–sulphur trioxide complex **130**[178]. The complex was exceedingly stable and its hydrolysis in water even at 86 °C was very slow, 280 times slower than the analogous rate for triethylamine–sulphur trioxide (**129**). A single X-ray structure determination of the complex showed a sulphamic acid type co-ordination of SO_3 to the quinuclidine nucleus [N–S = 1.831 (6) Å].

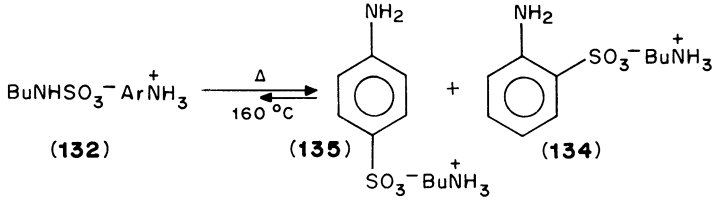
An *ab initio* study of the interaction of sulphur trioxide and ammonia has been carried out[179]. The adduct is the zwitterionic form of sulphamic acid. A partially optimized structure [$R_{N-S} = 2.55$ Å, ϕ (OSO) = 117°] gives a net energy of complex formation of -17.8 kcal mol^{-1}, showing SO_3 to have unusually high Lewis acidity. A Russian group has characterized the products of the reaction of SO_3 and NH_3 under a variety of experimental conditions. Using elemental analysis, X-ray diffraction and IR spectra the compounds were shown to be $NH(SO_3NH_4)_2$, $(NH_4)N(SO_3NH_4)_2$ and $N(SO_3NH_4)_3$[180]. The 1:1 complexes of sulphur trioxide with ammonia, pyridine and methylamines have been isolated in nitrogen matrices[181]. The complexes are characterized by their infrared spectra, in particular by the red shift of the SO_3 antisymmetric stretching vibration at 1354 cm^{-1} of the $NH_3{\cdot}SO_3$ adduct. The $NH_3{\cdot}SO_3$ complex was sensitive to annealing; the other complexes were quite stable, however.

Sieh and Dunham have described an analytical procedure for the estimation of the active sulphur trioxide in pyridine–sulphur trioxide (**131**) complex. The hydrolysis of the latter when added to water, is completed in one hour. However, when the complex is dissolved in 0.1% water in pyridine solution, complete hydrolysis takes place in 5 minutes. This increased rate of hydrolysis allow the estimation of the complex by Karl Fischer titration with good precision. The reaction was extended to the determination of the active sulphur trioxide in the trimethylamine–sulphur trioxide complex[182]. A solid adduct of SO_3 and dimethylformamide has been used as a titrant for the conductiometric titration of aliphatic, aromatic and cyclic amines[183].

In his studies of the reaction of amines and sulphur trioxide Kanetani and his group[184] have studied the thermal reactions of anilinium, dimethylanilinium and trimethylanilinium salts of butylsulphamic acid (**132**). When the reaction was carried out between



(**132**) (**133**) (7)



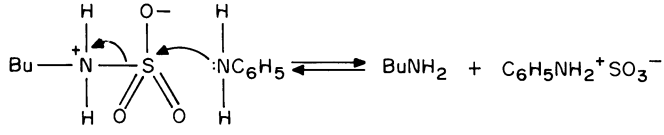
(**132**) (**135**) (**134**) (8)

80 °C and 120 °C, phenylsulphamates (**133**) and sulphophenylsulphamates were the main compounds formed (equation 7). Increasing the temperature leads to the formation of ring mono (**134, 135**) and di-sulphonates (equation 8). The sulphonate group migrated to the *ortho* and/or *para* positions (**134, 135**) to the amino group; in no case was any *meta* product detected. The anilinium salts **132** are considered to dissociate into the free acid ($BuNHSO_3H$) and the salt forming base $ArNH_2$. An S_N2-type mechanism is preferred to account for the transsulphonation reaction over an S_N1 type dissociative mechanism under the non-solvolytic conditions of the reaction. Kanetani considers a variety of mechanisms to account for the rearrangements which occur at higher temperatures. However, an S_N2 intermolecular pathway involving nucleophilic attack by a substrate amine at the tetracoordinate sulphur atom of the zwitterion to form σ complexes leading to *ortho* and *para* sulphonates (**134, 135**) (equations a–c) is favoured. The reaction of anilinotrimethylsilane (**136**) with a variety of sulphonating agents such as SO_3, $ClSO_3Si(CH_3)_3$ (**137**) and dioxane–sulphur trioxide showed that SO_3 can be inserted into the N—Si bond to yield the trimethylsilyl phenylsulphamate which, on treatment with acetic acid and trifluoroacetic acid, yield the free arylsulphamic acids (equation 10)[185]. The reaction of aniline with $ClSO_3Si(CH_3)_3$ in a 2:1 molar ratio at -10 °C yielded the anilinium salt of phenylsulphamic acid in 87% yield. Chromatographic analysis showed the absence of ring sulphonation products and negative chloride analysis leads to the possibility of reaction occurring according to equation 11.

Thermal Dissociation

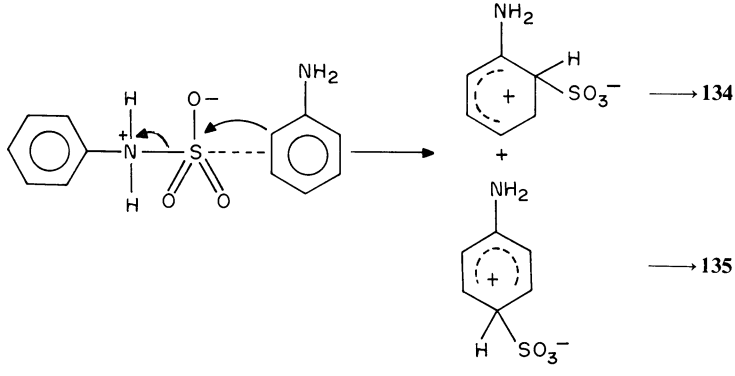
$$BuNHSO_3^-C_6H_5NH_3^+ \underset{\text{Fast}}{\overset{\Delta}{\rightleftharpoons}} BuNHSO_3H + C_6H_5NH_2 \qquad (9a)$$

Transsulphonation at lower temperatures

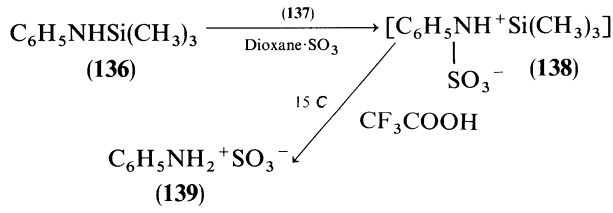


(9b)

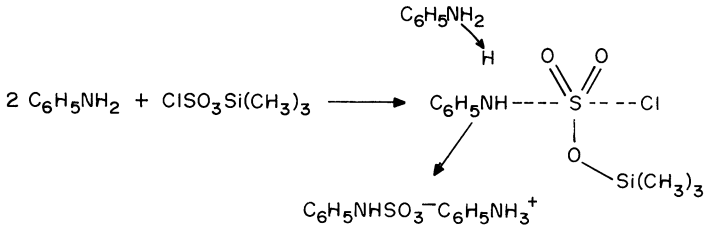
Rearrangement at higher temperatures



(9c)

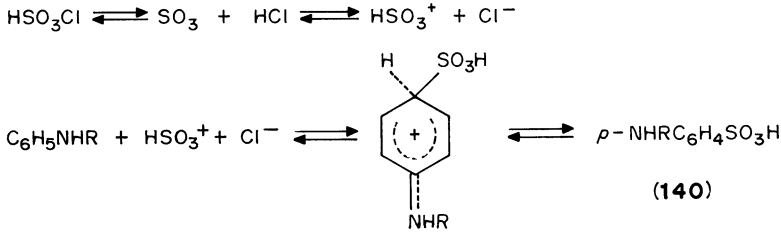


(10)



(11)

Khelevin[186] studied the kinetics of the sulphonation of aniline and *N*-alkylanilines and also *N,N*-dialkylanilines with chlorosulphonic acid. The reaction with aniline and *N*-alkylanilines follows second-order kinetics for irreversible reactions; this, coupled with a similarity of activation energies for the reaction with the energies reported for the sulphonation of unprotonated anilines with sulphuric acid, has led to the proposal that the *N*-alkylanilines are sulphonated by the participation of HSO_3^+ ions (equation 12) to give the sulphonated anilines **140**. The sulphonation of *N,N*-dialkylanilines with chlorosulphonic acid is found to follow a first-order rate equation and to form almost exclusively the *p*-aminosulphonic acid. A comparison of the rate constants and activation energies of this reaction with those for the rearrangement of dialkylaniline sulphur trioxides to *p*-aminosulphonic acids show them to be similar. This led to the conclusion that the sulphonation of *N,N*-dialkylanilines using chlorosulphonic acid takes place with the fast formation of the amine sulphur trioxide complex **141**, the rearrangement of which controls the sulphonation reaction (equation 13).

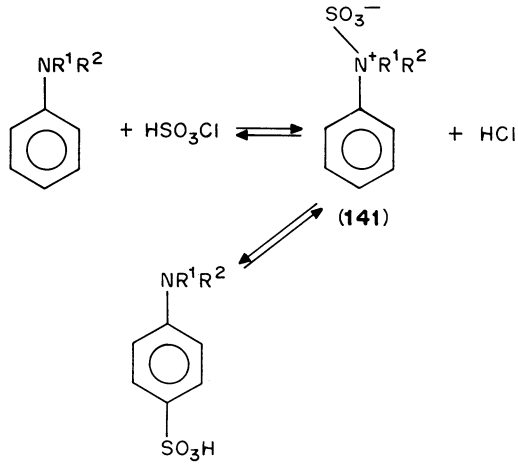


(12)

Hopkins and Williams[187a] in their study of the hydrolysis of isoquinoline sulphonate concluded that free sulphur trioxide is absent as an intermediate in the hydrolysis of the sulphonate. In other work they have reported on the transfer of the sulphonate group from pyridines to phenols[187b], isoquinolines to pyridines[187c,d] and from pyridines to pyridines[187e].

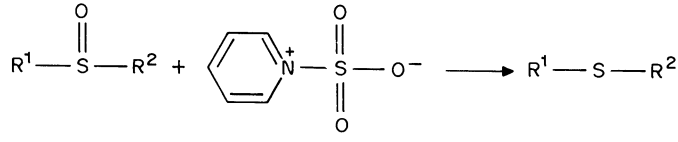
2. *Uses in synthesis*

Deoxygenation of sulphoxides to sulphides has been achieved using sodium iodide/pyridine sulphur trioxide complexes in yields of excess of 80% (equation 14)[188].

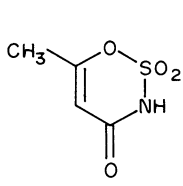


(13)

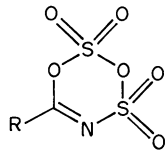
Cyclocondensation and other reactions with SO_3 and adducts of SO_3 has led to the synthesis of a wide range of compounds including 1,2,3-oxathiazin-4-one dioxides (**142**)[189], cyclic sulphur trioxide adducts (**143**)[190], piperidinone (**144**)[191] and *N*-isopropyl-*N'*-2-carbomethoxy sulphamide (**145**)[192].



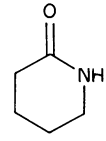
(14)



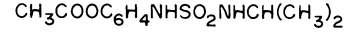
(**142**)



(**143**)

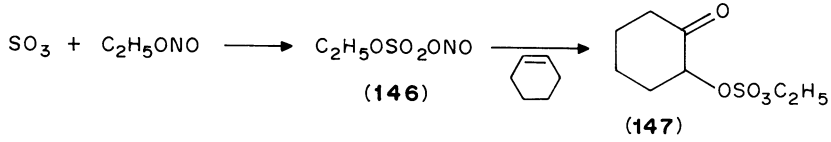


(**144**)



(**145**)

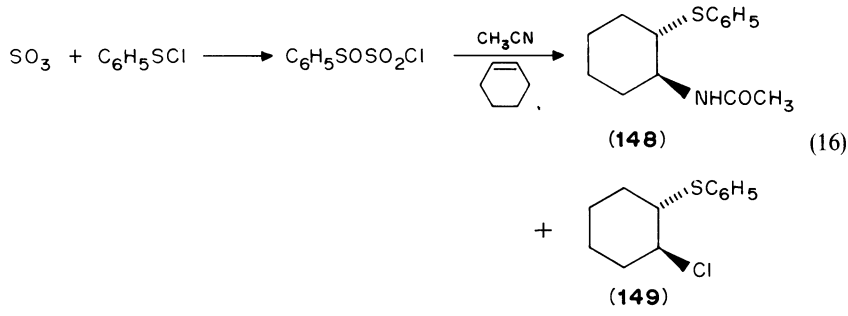
Zeifirov's group has reported on the activation of the electrophilic reagents ethyl nitrite and phenylsulphenyl chloride by insertion of SO_3 into the molecules and has subsequently described their reactions with olefins. The reaction of activated ethyl nitrite (**146**) with cyclohexene yields ethyl 2-oxocyclohexylsulphate (**147**) (equation 15)[193] while the reaction of activated phenylsulphenyl chloride in acetonitrile with cyclohexene gives the *trans* amide **148** in 62% yield and 28% yield of the chlorosulphide **149** (equation 16)[194].



(**146**)

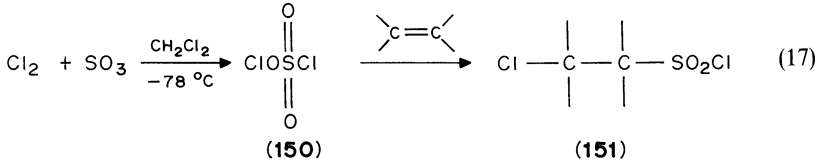
(**147**)

(15)



3. Uses in sulphation

The reaction of chlorine and sulphur trioxide in dichloromethane at $-78\,^{\circ}C$ gives a highly electrophilic reagent, chlorine chlorosulphate (**150**) which adds across olefins to form β-chloroalkyl chlorosulphates (**151**) (equation 17)[195].



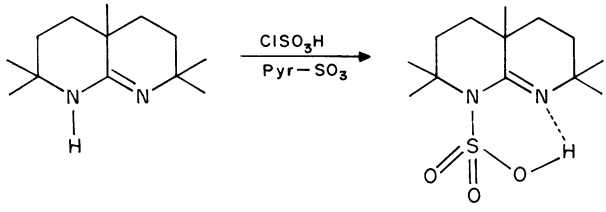
The use of dioxane–SO_3, pyridine–SO_3 and triethylamine–SO_3 complexes has been described to prepare benzyl and allyl hydrogen sulphates[196] and *tert*-alkyl sulphate ester salts[197]. The kinetics and mechanism for the sulphation of alcohols has been reported by a Russian group[198,199], and the mechanism of sulphation by SO_3 complexes using water or amines is considered to involve ligand replacement at the central S atom via a trigonal bipyramidal transition state.

The sulphation of cellulose using Lewis-base SO_3 complexes in the presence of *N*,*N*-dimethylacetamide yields sodium cellulose sulphate with a degree of substitution of 0.35[200]. Two other reports describe the preparation of cellulose sulphates. One reports the sulphation of amidodeoxycellulose with the DMF·SO_3 complex[201] and the IR spectra showed the chemical structure of the sulphated cellulose to be similar to sodium heparinate. The second report[202] details the synthesis using DMF·SO_3 of sulphated cellulose and reports on its anticoagulating action.

4. Uses in sulphonation

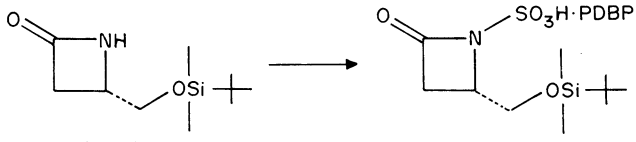
The novel amidine-*N*-sulphonic acid (**153**), prepared from 3,3,6,9,9-pentamethyl-2,10-diazbicyclo[4.4.0]-1-decene (PDBD) (**152**) and chlorosulphonic acid, has been found useful in N- and O-sulphonation reaction[203]. An example of this is the N-sulphonation of azetidinone **154** with **153** and isolation of the product **155** as its PDBD salt by column chromatography in 99% yield.

A Russian group have studied the use of dioxane–SO_3 complexes in the sulphonation of imidazole and benzimidazole; using a 3-fold excess of SO_3 4(5)-imidazolesulphonic acid and 5(6)-benzimidazolesulphonic acid were isolated[204]. The same group also reported on the sulphonation of substituted azoles with SO_3[205]. Using a 1:1 ratio of SO_3 to azole yields the adducts **156**, while increasing the ratio to three parts SO_3 to azole led to the formation of the sulphonated azoles **157**. Aromatic sulphonic acids were prepared by



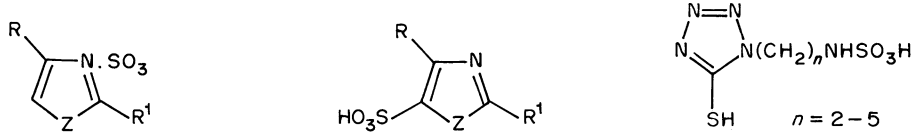
(152) (153)

(18)



(154) (155)

sulphonation of the aromatic compounds with arylnitrile–sulphur trioxide adducts in a chlorinated hydrocarbon solvent[206]. Another group have prepared a series of SO_3–imide adducts by reaction of SO_3 with a series of imides $RCONR^1COR^2$[R,R^2 = substituted C_6H_5; R, R^2 = (un)substituted 1,2 phenylene; R^1 = alkyl, cycloalkyl, $CH_2C_6H_5$] which were subsequently used to sulphonate biphenyl[207]. Sulphamoylation has also been achieved using the trimethylamine–SO_3 complex to prepare sulphaminoalkyltetrazole thiols (**158**), which were useful as intermediates in cephalosporin preparation[208].



(156) (157) (158)

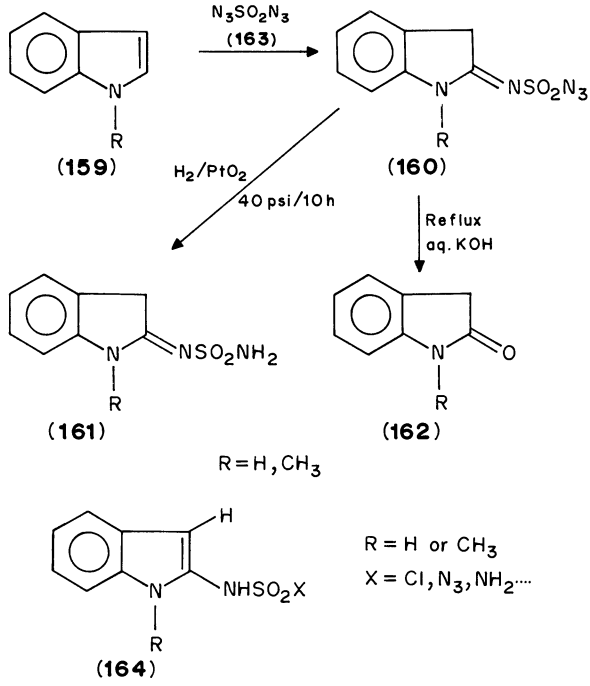
R = H, CH_3, R^1 = H, CH_3, Br, OH Z = NH, S

The kinetics and mechanism of sulphonation of thiophene with SO_3 complexes of ether, dioxane, THF and DMF has been reported by Shustareva and Druzhinina[209]. The sulphonating activity of the complex decreased with increasing basicity of the electron donor. An S_E2 mechanism is postulated to account for the reaction.

III. SULPHAMOYL AZIDES, ESTERS AND HALIDES

A. Sulphamoyl Azides

Obafemi[210] has reported on the chemistry of 2-azidosulphonyl iminoindoline and 4-azidosulphonylimino-1-methylindoline (**160**) which can be considered to be a type of sulphamoyl azide. The compounds were prepared by the reaction of sulphural azide (**163**) with indole (**159**; R = H) and 1-methylindole (**159**; R = Me) (equation 19). NMR, IR and mass spectral studies of the compounds confirmed the imino structure of the products **161** as written and not as in **164**. Hydrolysis of **160** in aqueous KOH yielded the oxindoles **162** while hydrogenation over platinum oxide leads to the formation of the iminosulphonamides **161**.



(19)

B. Sulphamoyl Esters

1. Synthesis

The synthesis of esters of sulphamic acids is generally achieved by the reaction of the corresponding sulphamoyl halides with an alkoxide or alcohol according to equation 20. A large variety of such esters have been prepared and the synthetic procedures and their properties have been reviewed[1]. The present work describes the synthetic procedures which have been developed since 1980 to incorporate the sulphamoyl ester moiety (NSO_3R) into molecules and to look at the general reactivity of sulphamate esters.

$$R^1R^2NSO_2Cl + R^3OH \longrightarrow R^1R^2NSO_3R^3 \qquad (20)$$

One of the major problems in the synthesis of sulphamoyl esters is the low yield of ester from the reaction. Phase transfer catalysis has been used to substantially increase ester yields under mild experimental conditions. Spillane and coworkers[211] using liquid/liquid and liquid/solid phase transfer methods (equations 21 and 22) prepared in high yield a wide range of sulphamoyl esters of the type $R^1R^2NSO_3R^3$ (**165**), $RNHSO_3R^3$ (**166**) and $H_2NSO_3R^3$ (**167**).

The order of catalytic activity of the phase transfer agents (Pta) in the reaction is tetraoctylammonium bromide > tetrabutylammonium bromide > benzyltriethylammonium chloride.

$$R^1R^2NSO_2Cl + R^3OH \xrightarrow[50\,^\circ C,\ C_6H_6]{\text{Pta, 30\% NaOH}} R^1R^2NSO_3R^3 \qquad (21)$$

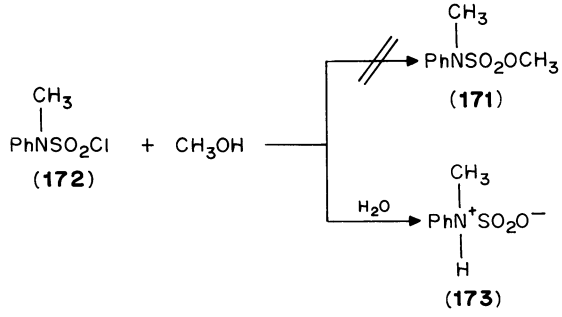
$R^1 = R^2 = Me$, Et; R^3 = Alkyl, Aryl (**165**)

$$RNHSO_2Cl + R^3OH \xrightarrow[20\,^\circ C,\ \text{anhydrous } Na_2CO_3]{\text{Pta, } CH_2Cl_2} RNHSO_3R^3 \qquad (22)$$

$R = H,\ c\text{-}C_6H_{11},\ R^3 = \text{Alkyl, Aryl}$ **(166 & 167)**

The phase transfer catalysis process has also been extended to synthesize the alkyl and aryl esters (**170**) of *N*-aryl sulphamic acids[212] (equation 23). If the ratio of aliphatic alcohol (**169**) to sulphamoyl chloride (**168**) is increased from 1:1 to 2:1, then *N*-alkyl-*N*-arylsulphamate esters (**171**) with similar alkyl groups are obtained together with considerable amounts of *N*-arylsulphamic acid esters (**170**). The exclusive formation of the *N*-alkyl-*N*-arylsulphamate esters (**171**) can be achieved by employing longer reaction times. A second approach to the synthesis of **171** would be to react the *N*-methyl-*N*-phenyl sulphamoyl chloride (**172**) with the alcohol. This was attempted, but the ester failed to form even under forcing conditions. The corresponding *N*-alkyl *N*-arylsulphamate ion (**173**) was isolated (equation 24); hydrolysis to the acid was considered to occur as opposed to nucleophilic displacement of the chloride by the methanol.

$$\underset{\textbf{(168)}}{PhNHSO_2Cl} + \underset{\textbf{(169)}}{ROH} \longrightarrow \underset{\textbf{(170)}}{PhNHSO_2OR} + \underset{\textbf{(171)}}{\begin{matrix} R \\ | \\ PhNSO_2OR \end{matrix}} \qquad (23)$$



(24)

The preparation of *N*-alkyl-*N*-aryl and *N*,*N*-dialkylsulphamic esters $R^1R^3NSO_2OR^2$ (**174**) where R^1 = aryl and $R^3 \neq R^2$ is a problem. The lack of reactivity of *N*-alkyl-*N*-arylsulphamoyl halides (equation 24) makes this an impractical synthetic route. One group[213,214] prepared a series of the esters (**174**) in very low yields by reaction of the appropriate secondary aromatic amines and alkyl chlorosulphates. Another approach is to alkylate the methyl *N*-phenyl sulphamates (**170**) using alkylating agents. Lwowski[215] successfully ethylated methyl *N*-phenyl sulphamate (**170**; R = CH_3) using ethyl bromide, but self-alkylation to give *N*-methyl-*N*-phenyl sulphamate (**171**) also occurred (equation 25).

$$\underset{\textbf{(170)}}{\begin{matrix} H \\ | \\ PhNSO_2OCH_3 \end{matrix}} \xrightarrow{C_2H_5Br} \underset{\textbf{(174)}}{\begin{matrix} C_2H_5 \\ | \\ PhNSO_2OCH_3 \end{matrix}} + \underset{\textbf{(171)}}{\begin{matrix} CH_3 \\ | \\ PhNSO_2OCH_3 \end{matrix}} \qquad (25)$$

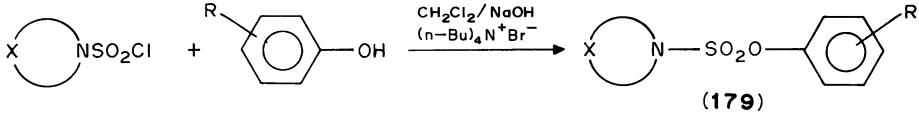
Solid-liquid phase transfer catalysis[216] has been successfully employed to prepare *N*-alkyl-*N*-aryl and *N*,*N*-dialkylsulphamic esters (**174**) in high yield (equation 26). When

R^1 = phenyl in compound **170**, the acidity of the amino hydrogen is such that deprotonation is easily achieved using sodium carbonate as a base. Where R^1 is aliphatic or alicyclic, a stronger base mixture of sodium hydroxide/potassium carbonate is used. Self-alkylation reactions of the esters **170** was avoided by using excess of the alkylation reagents **175** and high yields are generally achieved.

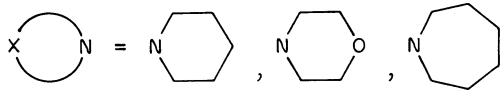
$$\underset{\textbf{(170)}}{\begin{matrix}R^1\\H\end{matrix}\!\!>\!NSO_2OR^2} + \underset{\textbf{(175)}}{R^3X} \xrightarrow{\substack{Na_2CO_3 \text{ or } K_2CO_3/NaOH\\(C_2H_5)_3{}^+NCH_2Ph\ Cl^-,\ 20\ ^\circ C}} \underset{\textbf{(174)}}{\begin{matrix}R^1\\R^3\end{matrix}\!\!>\!NSO_2R^2} \qquad (26)$$

Reduction of aryloxysulphonyl azides (**176**) using phase transfer conditions has been used to synthesize in high yield the aryl esters (**177**) of free sulphamic acid NH_2SO_3H[217] (equation 27). The reaction is carried out at 0 °C and is generally accompanied by the evolution of nitrogen. In the same paper the synthesis of aryl esters of cyclic N-substituted sulphamic acids (**179**) by reaction of the phenoxide ion with N-cyclic sulphamoyl halides under phase transfer conditions is reported. Yields in excess of 90% are obtained using tetrabutylammonium bromide or benzyltriethylammonium chloride as phase transfer agents. The choice of phase transfer reagent does not significantly affect the yields in the reaction (equation 28).

$$\begin{aligned} &Q^+Br^- + NaBH_4 \longrightarrow Q^+BH_4{}^-\\ &Q^+BH_4{}^- + \underset{\textbf{(176)}}{4PhOSO_2N_3} \longrightarrow (PhOSO_2NH)_4B^-Q^+ + 4N_2\\ &Q^+ = Bu_4N^+ \qquad\qquad Q^+OH^- + B(OH)_3 + \underset{\textbf{(177)}}{PhOSO_2NH_2} \end{aligned} \qquad (27)$$



(179)

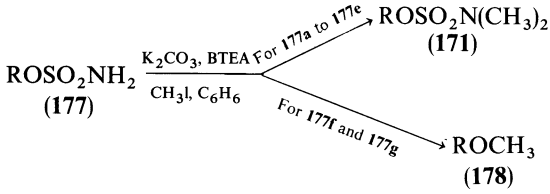


(28)

R = H, *p*-Me, *p*-Cl, *p*-Ph

N-Alkylation of N-unsubstituted arylsulphamic esters (**177**) gives the aryl esters of *N*,*N*-dialkylsulphamic acids (**171**). Beji and Hedayatullah[218] have shown that this reaction occurs under phase transfer conditions for a wide range of the aryl esters **177** (equation 29). It is interesting to note that when 2,4,6-trichlorophenyl and pentachlorophenyl sulphamate esters **177f** and **177g** were reacted, the corresponding sulphamate esters **171f** and **171g** were not formed. Instead cleavage of the O—SO_2 bond occurred which resulted in the formation of 2,4,6-trichloroanisole (**178f**) and pentachloroanisole (**178g**). However, the esters **171f** and **171g** could be prepared by reacting the appropriate phenol under phase

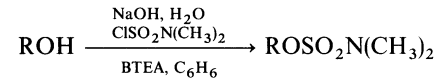
transfer conditions with dimethylsulphamoyl chloride (equation 30).



(29)

(**a**) R = C_6H_5
(**b**) R = 4-$MeOC_6H_4$
(**c**) R = 2,5-$(MeO)_2C_6H_3$
(**d**) R = 2,3,5-$Me_3C_6H_2$
(**e**) R = 2,6-di-Pr_2-C_6H_3
(**f**) R = 2,4,6-$Cl_3C_6H_2$
(**g**) R = C_6Cl_5

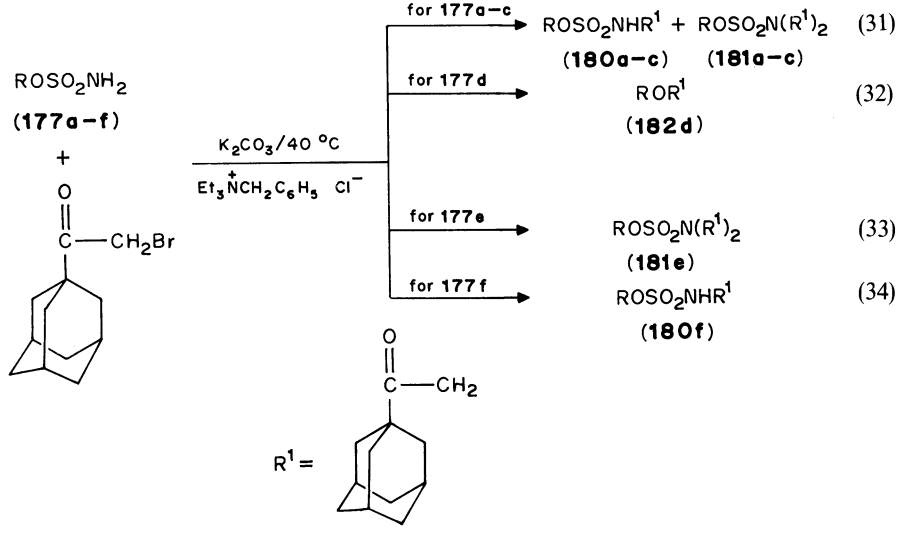
(**178f**) R = 2,4,6-$Cl_3C_6H_2$
(**178g**) R = C_6Cl_5

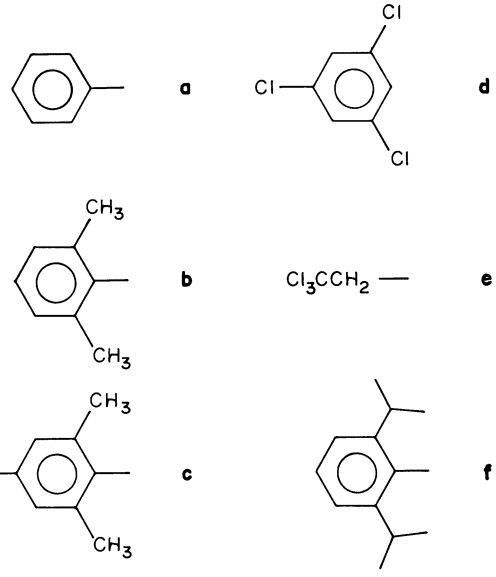


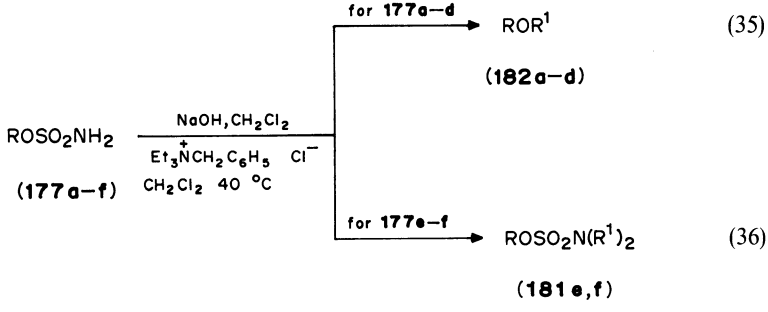
(30)

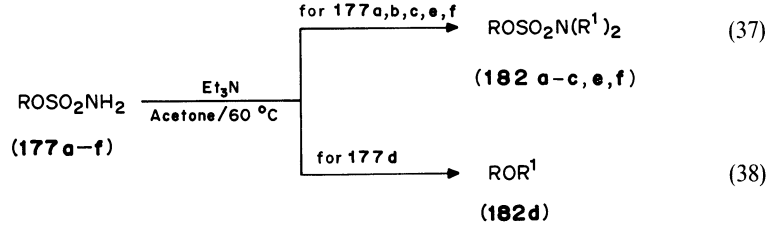
(171f, g)

The introduction of the adamantyl group into a sulphamate ester has been achieved by an extension of the reaction in equation 29[219]. The unsubstituted esters **177a–f** were alkylated under solid–liquid (equations 31–34), liquid–liquid (equations 35 and 36) phase transfer catalysis conditions and in a homogeneous medium (equations 37 and 38) by reaction with 1-adamantyl bromomethyl ketone.







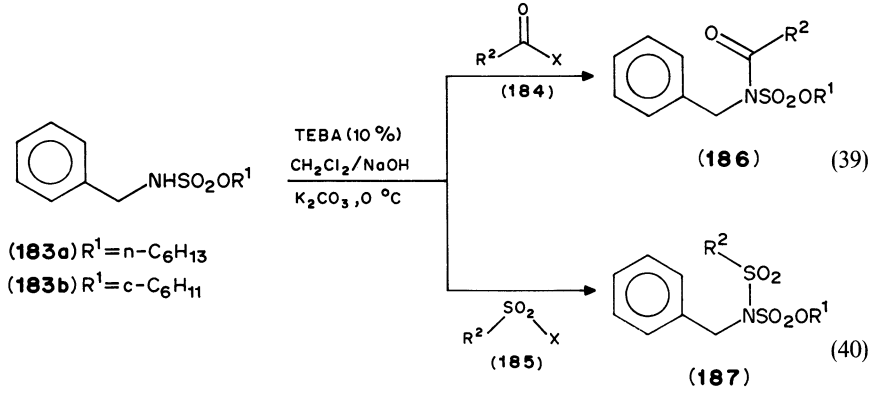


Sole monoalkylation occurs when 2,6-di-i-PrAr ester (**177f**) is the starting ester (equation 34) while complete *N*,*N*-dialkylation to give **181** (equation 33) is obtained when trichloroethyl sulphamate is used. The starting esters (**177a–c**) give mixtures of *N*-alkyl (**180**) and *N*,*N*-dialkyl esters (**181**) (equation 31). When 2,4,6-trichlorophenyl sulphamate (**177d**) is used, cleavage of the S—O bond occurs yielding the ether **182d**.

When liquid–liquid phase transfer conditions are employed (equations 35, 36), compounds **177a–d** result in no ester formation, cleavage of the S—O bond occurs with ether formation (**182a–d**) (equation 35) dominating. Dialkylation occurs to give **181e, f** when 2,6-di-*i*-PrAr (**177f**) and trichloroethyl (**177e**) sulphamates are used (equation 36). Homogeneous reaction of **177a–f** with 1-adamantyl bromomethyl ketone yields the *N*,*N*-dialkylated adamantyl esters **182a–c, e, f** (equation 37). Use of the 2,4,6-trichlorophenyl sulphamate (**177d**) again results in S—O cleavage to give the ether **182d** (equation 38).

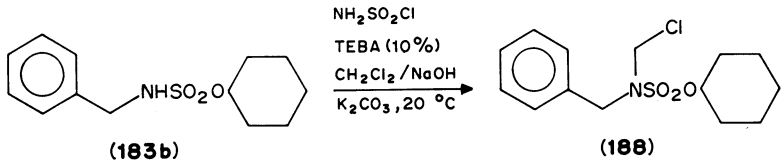
Phase transfer catalysis has greatly extended the range and type of sulphamate esters which can be prepared. Alkylation of the nitrogen atoms in the esters is readily achieved under very mild experimental conditions. Acetylation, benzoylation and sulphonation of the nitrogen atom of sulphamate esters has been reported. The functionality formed on acetylation and benzoylation of sulphamate esters —$CONHSO_3$— is well known when the sulphamate carries a negative charge[220–222], when it occurs in ring systems, as in the oxathiazinone dioxide (acesulfam) sweeteners[223–225] or in the ester form[226].

Phase transfer catalysis has been used successfully to prepare *N*-acetylated (**186**) and *N*-sulfonylated (**187**) esters of *n*-hexyl and cyclohexyl esters of benzylsulphamate[227] (**183a, b**) (equations 39 and 40). Attempts to achieve *N*-sulphamoylation of **183** using either *N*,*N*-dimethylsulphamoyl chloride or sulphamoyl chloride did not succeed, and in the case of the reaction of **183b** with sulphamoyl chloride it would seem that the chloride is hydrolysed and that the solvent dichloromethane acts as an alkylating agent yielding the *N*-substituted 2-chloromethyl ester **188** (equation 41). The presence of an acetyl group on the nitrogen atom in **186a** enhances its effectiveness as an alkylating agent and it has been used to *N*-alkylate both **183a** and **183b** (equation 42). However, when it is used to *N*-alkylate **183b**, formation of the desired product, **189b** is accompanied by formation of **189a** (equation 42). This is accounted for by a process of *N*-deacetylation of **186a** to form **183a**, which is then further alkylated by **186a**. Where the nitrogen atom is joined directly to an aromatic ring, as in an alkyl ester of phenylsulphamic acid, the reaction in equation 43 does not occur. Sulphonylation (equation 43) or acetylation (equation 44) of **190** yields the sulphonamide **191** or the acetanilide **192**. It is considered that both of these reactions involve *N*-alkylation of **190** to give the *N*-sulphonated and *N*-acetylated esters which are unstable under the experimental conditions. N—S cleavage yields the stable sulphonamide **191** and anilide **192**. It was possible to extend the acetylation reaction to prepare **195**, a precursor of acesulfame, K, by reaction of 4-chlorophenylsulphamate **194** with diketene **193** (equation 45).

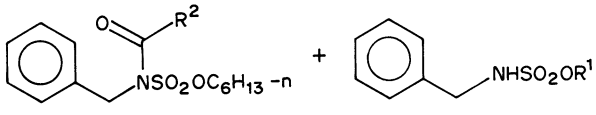


(39)

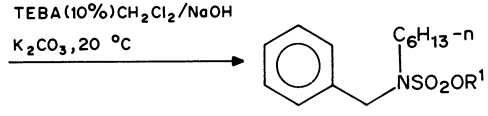
(40)



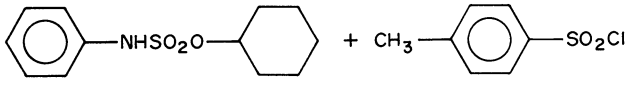
(183b) (188) (41)



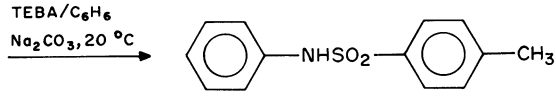
(186a) (183a,b) (42)



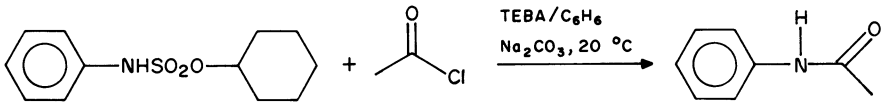
(189a) $R^1 = n\text{-}C_6H_{13}$
(189b) $R^1 = c\text{-}C_6H_{11}$



(190) (185)



(191) (43)

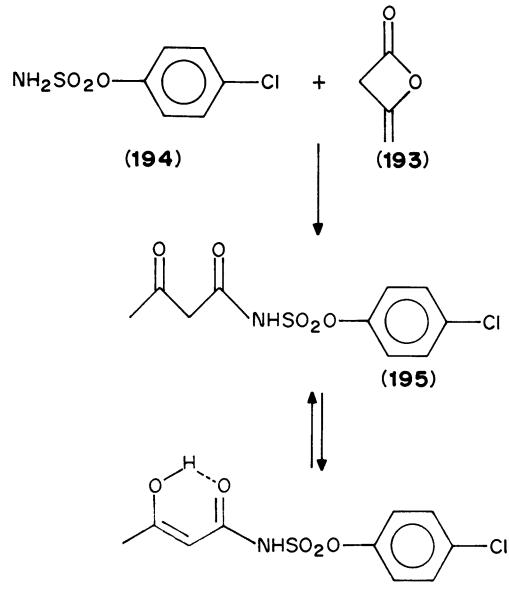


(190) (184) (192)

(44)

The crystal structure of a sulfonylated sulphamate, cyclohexyl-*N*-benzyl-*N*-(*p*-bromophenylsulphonyl)sulphamate (**8**) has been reported[17].

Chlorosulphonyl isocyanate when reacted with phenols has proven useful in the synthesis of aryl sulphamates[228,229] (equation 46). Hydrolysis and decarboxylation of

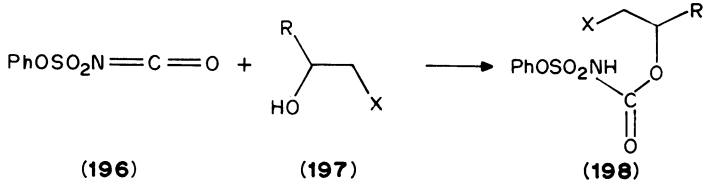


(45)

the aryloxysulphonyl isocyanates (**196**) yields the *N*-unsubstituted aryl suphamates (**177**).

$$\mathrm{ArOH} + \mathrm{ClSO_2{-}N{=}C{=}O} \longrightarrow \underset{(196)}{\mathrm{ArOSO_2N{=}C{=}O}} \xrightarrow[-CO_2]{H_2O} \underset{(177)}{\mathrm{ArOSO_2NH_2}} \tag{46}$$

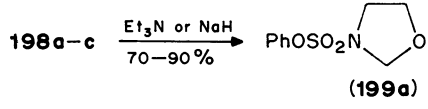
The intermediates **196** have been reacted with ω-halogeno-alcohols (**197**) to give *N*-carboxylsulphamates (**198**) (equation 47)[230]. Cyclization of **198** can occur very easily in the presence of triethylamine to give a new family of 2-oxazolidones (**199**) (equations 48 and 49).



(47)

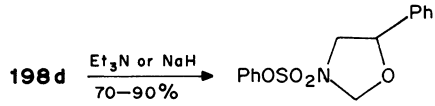
(196) (197) (198)

(**a**) R = H, X = Cl
(**b**) R = H, X = Br
(**c**) R = H, X = I
(**d**) R = Ph, X = Br



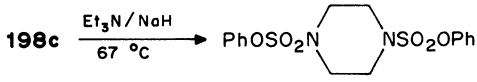
(48)

(199a)



(49)

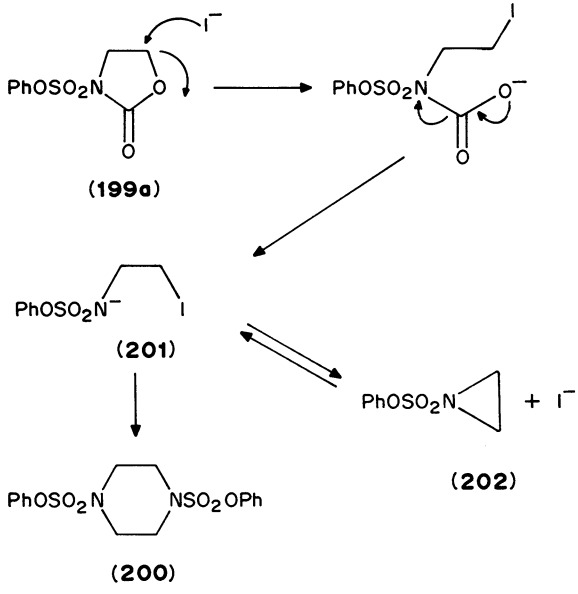
(199b)



(50)

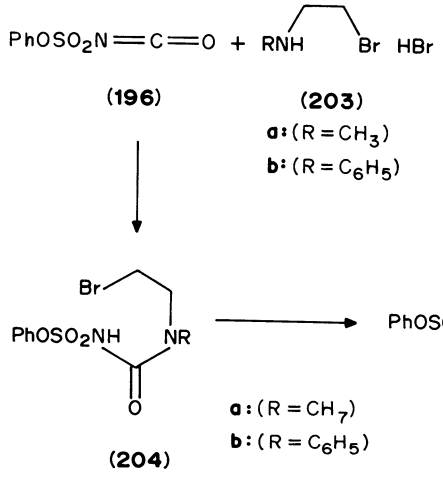
(200)

When the cyclization of **198c** was carried out with sodium hydride at 67 °C in THF, the corresponding 2-oxazolidone (**199a**) was not formed but the *N,N'*-di-(aryloxysulphonyl)-piperazine (**200**) was isolated from the reaction (equation 50). The 2-oxazolidone (**199a**) is considered to be formed initially, but nucleophilic attack by the liberated iodide ion leads to C—O cleavage and ring opening. This is followed by decarboxylation to give the intermediate **201**, which is considered to be in equilibrium with the aziridine type structure **202**. Cyclodimerisation of the open-chain intermediate **201** gives the piperazine derivative **200**. Support for this mechanism comes from the fact that when the oxazolidone (**199a**) is heated with sodium iodide at 67 °C (**200**) is formed (equation 51). When the phenoxysulphonyl isocyanate **196** is reacted with the β-halogeno ethylamines **203**, the phenoxysulphonyl-3 imidazolidinones-2 (**205a, b**) are isolated in high yield. The intermediate sulphamate esters **204** were not isolated from the reaction (equation 52). The reactivity of phenoxysulphonyl isocyanate (**196**) has also been used to introduce the adamantyl group into sulphamate esters[231]. The difference in reactivity of a secondary alcohol and a tertiary alcohol towards the phenoxysulphonyl isocyanates is shown in equations 53 and 54. Reaction of adamatan-1-ol with **196** leads to *N*-alkylation

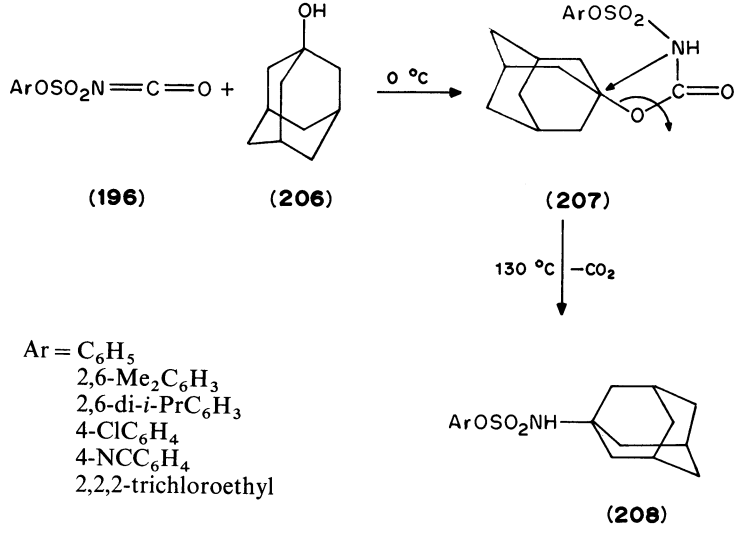


(51)

and the synthesis of the heretofore inaccessible *N*-adamantyl esters (**208**). The *N*-acyl intermediates **207** are reacted at 130 °C and decarboxylation leads to the formation of **208**. Attempts to prepare these compounds by *N*-alkylation of the esters of sulphamic acid $ArOSO_2NH_2$ (**177**) using 1-chloro and 1-bromo adamantane were unsuccessful. Reaction of adamatan-2-ol with the isocyanates leads to the *N*-acylated adamantyl derivatives **209**, heating the compounds to 130 °C does not result in decarboxylation to the *N*-alkylated esters **210**. The secondary hydrogen atom in the intermediate is considered to prevent through steric hindrance the decarboxylation process (equation 54). High yields in excess of 90% were obtained both for the *N*-alkylated esters **208** and the *N*-acylated esters **209**.

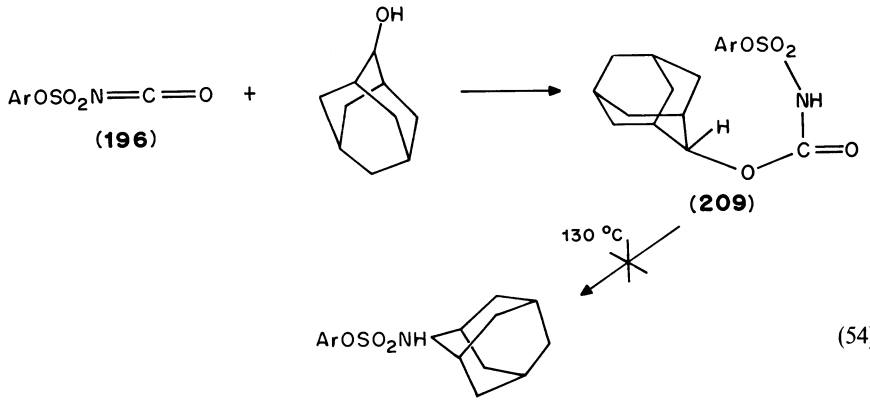


(52)



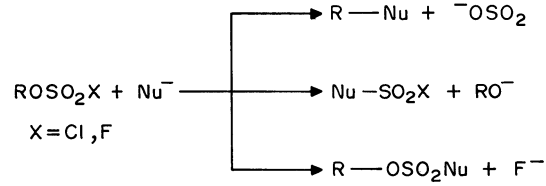
(53)

Ar = C_6H_5
2,6-$Me_2C_6H_3$
2,6-di-*i*-PrC_6H_3
4-ClC_6H_4
4-NCC_6H_4
2,2,2-trichloroethyl



(54)

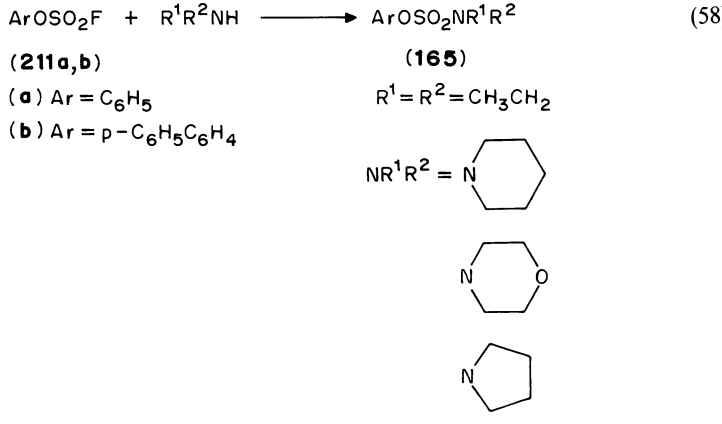
Arylhalosulphates are considered to have three reactive sites and can react with nucleophiles in three different ways (equations 55–57). The nucleophile can attack at the carbon which results in the cleavage of the O—C bond, yielding sulphuryl halides and an aryl nucleophile product (equation 55). The nucleophile can attack the sulphur atom followed by cleavage of the S—O atom leading to the corresponding sulphonyl halides (equation 56). The third reaction involves attack by the nucleophile leading to rupture of the S—F atom with the expulsion of the fluoride ion (equation 57). Hedaytullah[232] has found that when arylfluorosulphates (**211**) are reacted with amines, expulsion of the fluoride ion occurs leading to the formation of aryl esters of alkylsulphamic acids **165** (equation 58).



(55)

(56)

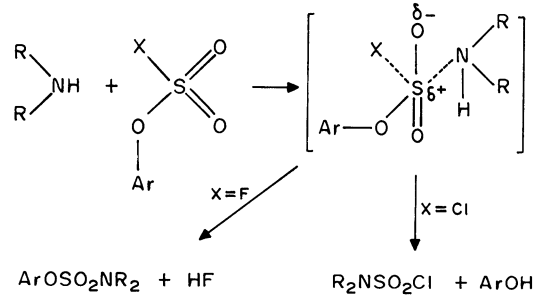
(57)



(58)

The reaction of arylchlorosulphates (**212**) with amines fails to yield the sulphamate esters (**165**). The amine attacks the sulphur atom and this is followed by cleavage of the S—O bond with expulsion of the phenol, leading to the formation of the sulphamoyl chloride. This sulphamoyl compound reacts with a second mole of amine and a tetra-substituted sulphamide is formed (equation 59). The difference in reactivity between arylfluorosulphates (**211**) and arylchlorosulphates (**212**) towards amines is explained with the aid of the hard and soft acid base theory; the nitrogen atom of the amine coordinates with the sulphur atom to give a trigonal bipyramidal structure as an intermediate. The nature of the halogen atom then dictates the course of the reaction with the hardest nucleophile (X = F) being eliminated with S—F cleavage to give the ester **165**. When X = Cl, the phenoxy group is expelled which yields the sulphamoyl chloride as the product of the reaction (equation 60).

$$\underset{\textbf{(212)}}{ArOSO_2Cl} + R_2NH \longrightarrow R_2NSO_2Cl + ArOH \xrightarrow{R_2NH} \underset{\textbf{(165)}}{R_2NSO_2NR_2} \qquad (59)$$



(60

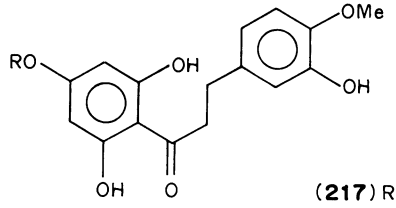
Polyfluoroalkyl fluorosulphates $ROSO_2F$ (**213**) also react with hard nucleophiles such as amines, the S—O bond remains intact and cleavage of the sulphur and fluorine bond occurs, leading to the formation of polyfluoroalkyl sulphamates (**214**)[233,234] (equation 61).

$$\underset{\textbf{(213)}}{ROSO_2F} + R^1R^2NH \longrightarrow \underset{\textbf{(214)}}{ROSO_2NR^1R^2} \qquad (61)$$

$R = CF_3CH_2$, $(CF_3)_2CH$, $CF_3CH(CH_3)$, $CF_3C(CH_3)_2$, $(CF_3)_2CH$

$R^1 = R^2 = CH_3$; $R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH_3$

The non-nutritive sweetening properties of the salts of certain aliphatic and alicyclic sulphamic acids are well known. DuBois[235] considered that the sulphamic acid salt (**215**) of the dihydrochalcone (**216**) should be sweet. Known sulphamation methods of **217**

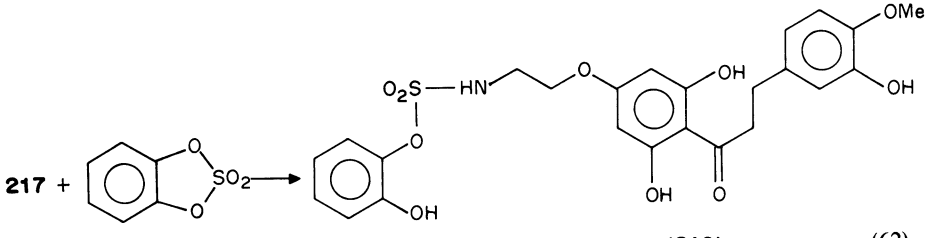


(**216**)

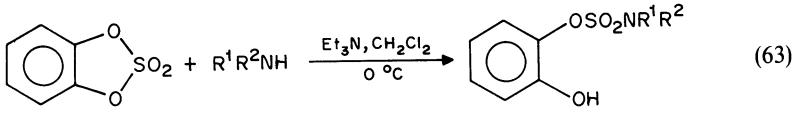
(**217**) $R = CH_2CH_2NH_2$

(**215**) $R = CH_2CH_2NHSO_3K$

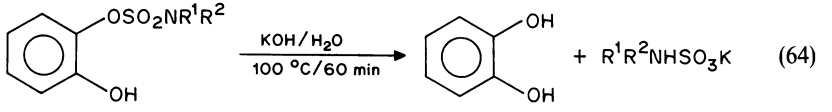
gave only low yields of **215**. However, when **217** is reacted with catechol sulphate (**218**) ring opening via sulphur oxygen bond cleavage occurs to yield the *ortho*-hydroxyphenyl sulphamoyl ester (**219**)[236] (equation 62). The reaction is general for aliphatic amines and leads to the formation of a wide range of hydroxyphenyl esters of the type **219a** in high yields (equation 63). The amines used include $PhCH_2NH_2$ and c-$C_6H_{11}NH_2$. The hydrolysis of the esters procedes cleanly to give the salts of the sulphamic acids (equation 64). Compound **215** exhibited a sweet taste 352 times more than the taste of sucrose.



217 + **(218)** → **(219)** (62)

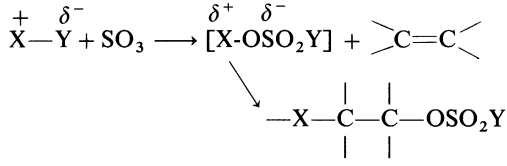


(218) + R^1R^2NH → **(219a)** (63)



(219a) → **(215)** + $R^1R^2NHSO_3K$ (64)

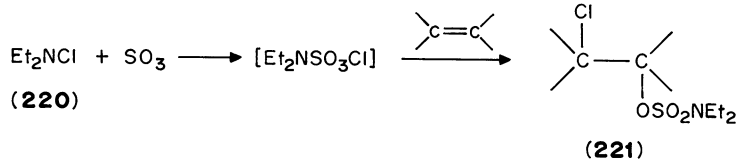
The study of the electrophilic addition of activated electrophiles across the alkene functional group by Zefirov and coworkers[237] has led to the synthesis of a wide range of sulphamate esters. The general approach involves the insertion of SO_3 into a weak electrophile which generates an activated electrophile that adds readily across carbon–carbon double bonds of olefins (equation 65).



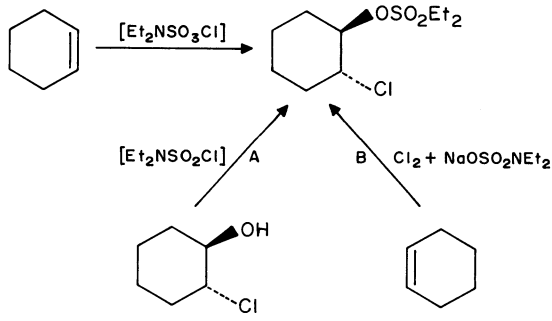
(65)

When sulphur trioxide is added to dialkylchloramines R^1R^2NCl (**220**), where $R^1 = R^2 = Et$ (**220a**), R^1, $R^2 = (CH_2)_5$ (**220b**), R^1, $R^2 = O(CH_2CH_2)_2$ (**220c**), at $-70\,^{\circ}C$ followed by olefin addition and then allowing the temperature to rise to ambient the process results in the formation of the β-chloroalkyl sulphamate esters **221** (equation 66). The addition across the double bond occurs in accordance with the Markovnikov rule and leads to the *trans* configuration. This is shown for cyclohexene in equation 67 and the *trans* structure is confirmed by independent synthesis by reaction of *trans*-cyclohexanol with

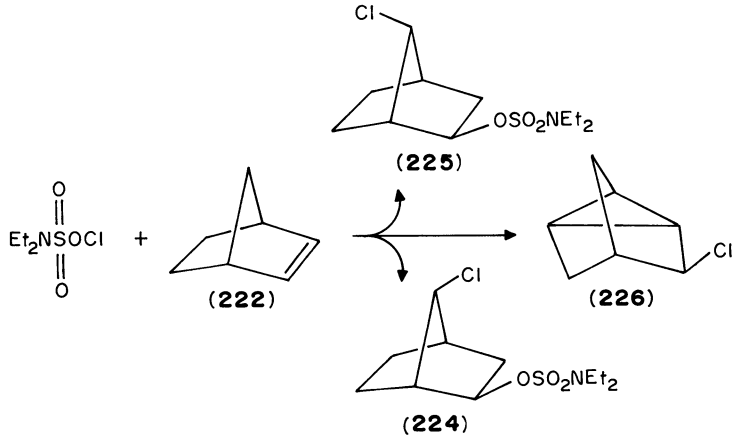
diethylsulphamoyl chloride (path A) and the chlorination of cyclohexene in the presence of the sodium salt of diethylsulphamic acid (path B). The strained olefins norbornene (**222**) and norbornadiene (**223**) were also studied to give an insight into the skeletal rearrangement and homoallylic participation of the second double bond in electrophilic addition reactions[238]. The main product of the reaction is the ester **224** with the *syn, exo* configuration of the substituents and this arises via a normal Wagner–Meerwein rearrangement. A small amount of the *anti, exo* ester (**225**) which arises via a Wagner–Meerwein rearrangement followed by a 1,6 hydride shift is formed also. 3-Chloronortricyclene (**226**) is also formed in 6% yield (equation 68). The reaction of norbornadiene (**223**) with the activated electrophiles obtained from **220a, b** with SO_3 yielded three new types of sulphamate esters **227**, **228** and **229** (equation 69). The ester **229** is the product of a Wagner–Meerwein rearrangement without the participation of the second double bond. The products **227** and **228** have a nortricyclene skeleton and result



(**220**) (**221**) (66)

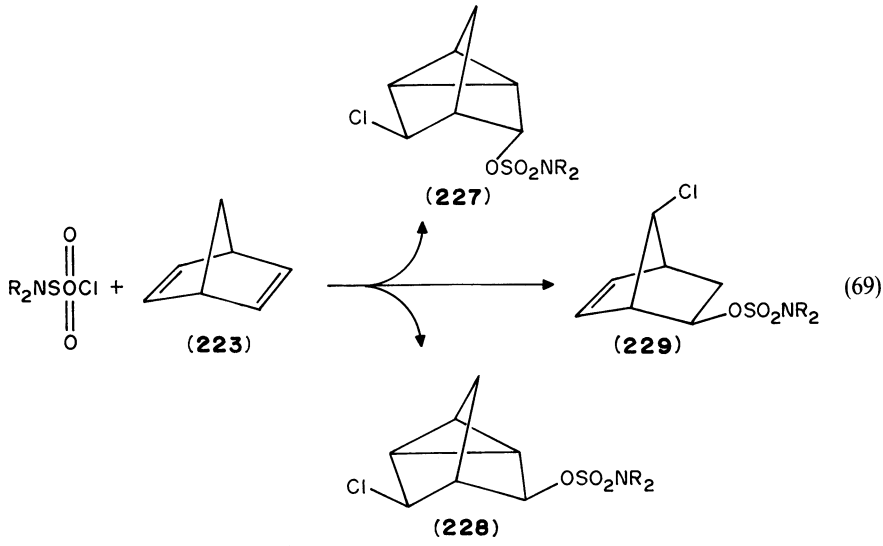


(67)



(**225**) (**222**) (**226**) (**224**) (68)

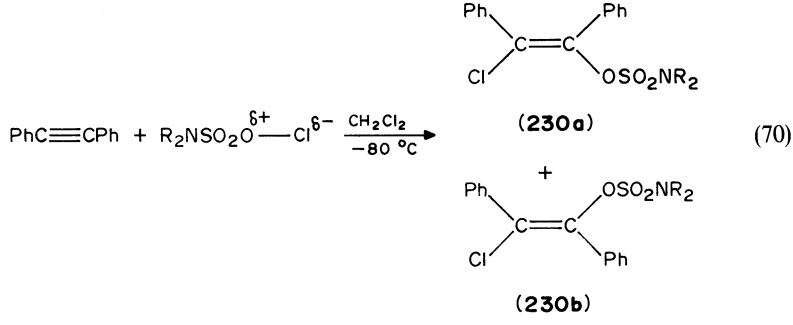
from the involvement of the homoallylic double bond. The counter anion $R^2NSO_2O^-$ in the final step of the electrophilic addition reacts non- stereo-specifically to give both epimeric product **227** and **228**.



(69)

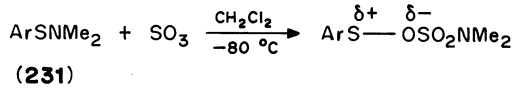
Acetylenes have also been used as substrates for reaction with the same activated electrophilic reagents. Addition to diphenylacetylene yields the corresponding esters **230a** and **230b** in 60% yield with *Z* to *E* isomers in the ratio of 2:1 (equation 70)[239]. Reaction of *N*,*N*-dimethyl- and *N*,*N*-diethylbenzenesulphenamides (**231**) with SO_3 at $-80\,^{\circ}C$ in CH_2Cl_2 and olefins yields phenylthioalkyl *N*,*N*-dialkylsulphamate esters smoothly[240–242]. The reaction with cyclohexene yields the *trans*-2(phenylthio)cyclohexyl sulphamate (**232**), which subsequently undergoes acid-catalysed nucleophilic substitution with hydrogen bromide and organic acids to yield the (phenylthio)cyclohexyl compounds **233** (equation 71)[243].

$$R_2NCl + SO_3 \xrightarrow[-80\ ^{\circ}C]{CH_2Cl_2} R_2NSO_2O^{\delta+}—Cl^{\delta-}$$

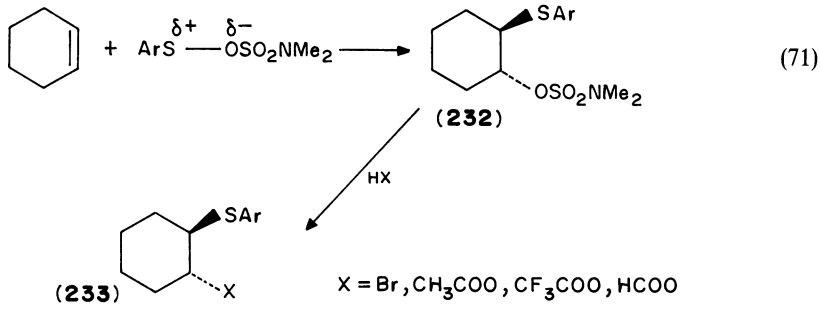


(70)

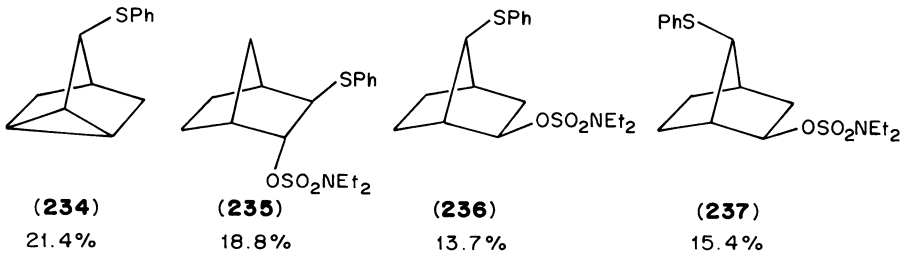
The reaction conditions used in the electrophilic addition reactions across olefins to yield the sulphamate esters (equations 65 to 70) involve low temperatures ($-80\,^{\circ}C$) and



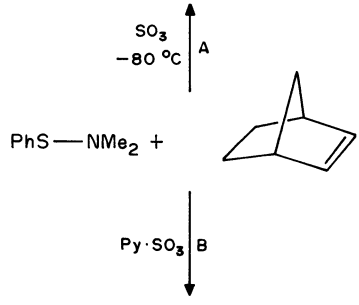
(231)



(71)



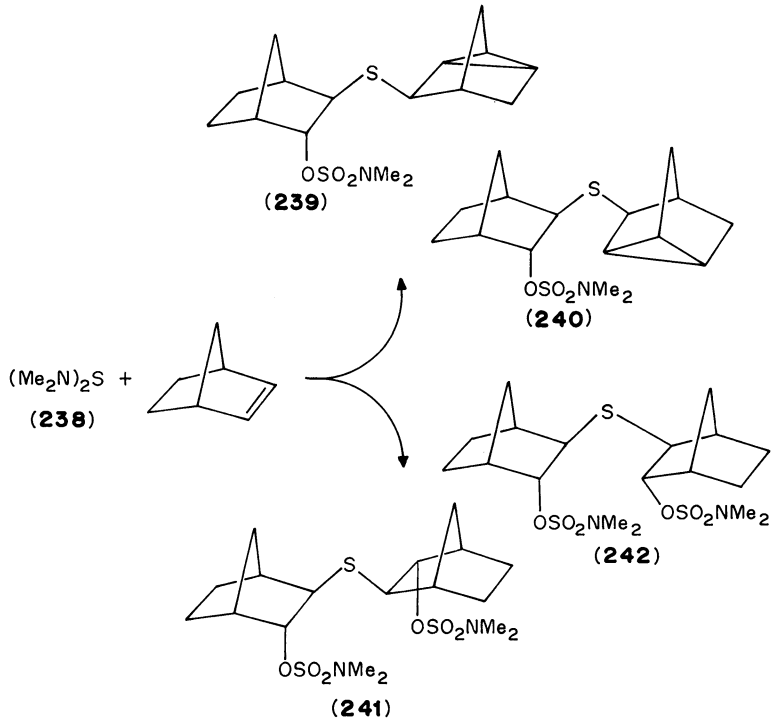
(234) 21.4% (235) 18.8% (236) 13.7% (237) 15.4%



(234) 29% (235) 34% (236) 9% (237)

(72)

necessitate the use of freshly distilled sulphur trioxide, and yields are sensitive to the presence of acidic impurities. The use of pyridine–sulphur trioxide avoids these reaction conditions and allows the activation of *N*-chloramines and sulphenamides and reaction with olefins to form sulphamate esters at room temperature[244,245]. A comparison of the two electrophilic addition pathways and the yields of the esters **235**, **236**, **237** and the phenylthionortricyclene (**234**) are shown in equation 72 for the addition of *N*,*N*-dimethylbenzenesulphenamide across the double bond of norbornene. The low temperature route, path A, gives yields of 18.8%, 13.7% and 15.4% of the normal *trans* sulphamate (**235**), *syn*-7-phenylthiobicyclo[2.2.1]hept-exo-2-yl diethylsulphamate (**236**) and *anti*-7-phenylthiobicyclo[2.2.1]hept-*exo*-2-yl diethylsulphamate (**237**), respectively, while room temperature reaction of norbornene, path B, gives much higher yields of the normal *trans* addition sulphamate and much lower yields of the *syn* (**236**) and *anti* sulphamate isomers (**237**). The insertion of SO_3, mediated by pyridine–sulphur trioxide at 20 °C, has been extended to activate thiobisdimethylamine (**238**) and reaction with norbornene gives a mixture of two pairs of diastereomeric sulphamate esters, [**239** + **240**] and [**241** + **242**], which were separated by column chromatography (equation 73). Similar results were obtained when the reaction was carried out using thiodimorpholine[246].



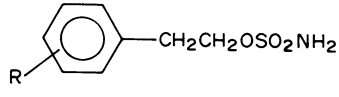
(73)

A large number of sulphamate esters have been prepared and tested for a wide range of properties including uses as herbicides, pharmaceutical agents and artificial sweeteners. A series of sulphamates (**243**) of diols have been prepared and an evaluation of their male antifertility properties has been reported. The compounds were prepared by treating the appropriate glycol salt with sulphamoyl chloride or by cleavage of a *t*-butylsulphamate of

the glycol with trifluoroacetic acid (equation 74)[247]. Three sulphamates, namely 1,2-ethanediyl sulphamate, 1,3-propanediyl sulphamate and 1,4-butanediyl sulphamate, when administered orally to male rats, caused a decrease in the number of pregnant females and/or implantation coupled with increased embryonic and fetal resorption.

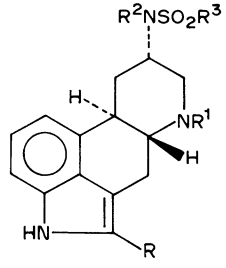
$$(CH_2OH)_2 \xrightarrow{NH_2SO_2Cl} (CH_2OSO_2NH_2)_2 \quad \textbf{(243)} \quad \xleftarrow{CF_3COOH}$$
$$(CH_2OH)_2 \xrightarrow[NaH]{ClSO_2NHBu\text{-}t} [CH_2OSO_2NHC(CH_3)_3]_2 \qquad (74)$$

N-unsubstituted sulphamates of the type **244** have been prepared by the reaction of the appropriate alcohol with sodium hydride in DMF with sulphamoyl chloride at 0–5 °C[248]. The compounds are reported to have anticonvulsant activity and are considered to be potential agents for the treatment of epilepsy. In addition, carbonic anhydrase activity was reported for the compounds and they are considered to be useful in the treatment of glaucoma. A series of 8α-substituted ergoline derivatives (**245**) were shown to have anti-Parkinson activity and inhibited prolactim secretion[249].



(244)

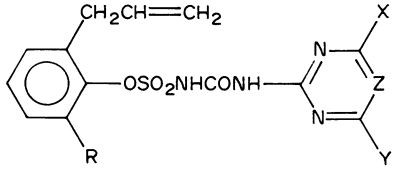
R = halogen
alkyl
alkoxy
CF_3
NO_2



(245)

R = H, Cl, Br
R^1 = Me, Et,
R^2 = H, C_{1-4} alkyl
R^3 = C_{1-4} alkyl mono-, di- or trihaloalkyl
Ph, alkoxyphenyl, halophenyl,

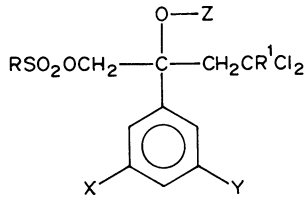
The reaction of a series of *o*-allylphenols with chlorosulphonyl isocyanate yields a series of *o*-allylarylsulphonyl isocyanates which, when reacted with 2 amino-4,6-dimethoxy pyrimidines in dioxane at 20 °C, yielded the sulphamates **246**. These compounds exhibited



(246)

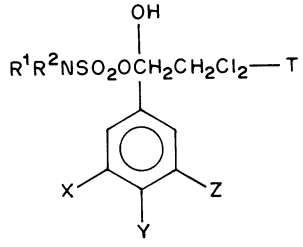
R = H, Halogen
X = Me, MeO
halogen
Y = Me, MeO;
Z = N, CH

herbicidal activity without causing damage to rice[250]. Glycol sulphamate esters (**247**) were found to act as enhancers of the herbicidal phytotoxicity of triazines against giant foxtail[251]. A series of related 2-hydroxybutyl or 2-hydroxypentyl sulphamates **248** possessing herbicidal activity were prepared by treating the corresponding epoxide using a proton source[252].



(247)

R = NR^2R^3
R^2 = H, alkyl
R^3 = H, alkyl, Ph
naphthyl or benzyl
Z = COMe, COEt, $COCF_3$



(248)

T = F, Cl, Br, CH_3, CF_3 or $CONH_2$
X, Y, Z are independently H, F, Cl, Br, Me, Et or CF_3

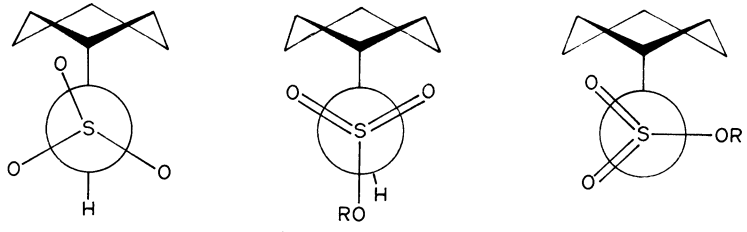
R^1 and R^2 are each independently H, C_1—C_4 alkyl, C_1—C_4 haloalkyl and C_3—C_6 alkoxyalkyl provided: that if either is C_1—C_4 hydroxyalkyl, the other must be H

The sweetening properties of the sodium and potassium salts of *N*-cyclohexylsulphamic acid are well known. Pautet and coworkers[92] have studied the sweetening properties of a series of alkyl esters of cyclohexylsulphamic acid. In all cases the compounds prepared were found to exhibit no sweetness. The loss of activity, when passing from acid salts to esters, is explained in terms of the unfavourable conformations of these molecules.

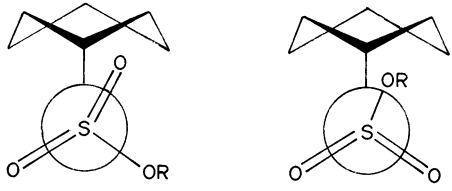
The synclinal conformation ($\phi = 60°$) between N—H and S=O bonds seems to be essential for sweetness (structure A) for the salts of cylohexylsulphamic acid. Where the synperiplanar conformation is the preferred one ($\phi = 0°$) the synclinal conformation is excluded with the resulting loss of sweetness. This is seen if one considers the possible conformations of the amino and sulphonyl groups of the ester. Conformation **E**, which has the synclinal conformation, would be correct for sweet activity but steric constraints prevent this conformation; conformations **B**, **C**, **D** have reduced steric constraints, but **B** has not the necessary synclinal N—H and S=O conformation. Conformation **C** cannot interact with the receptor site due to the steric effect of the alkyl group R and hydrogen bonding by the oxygen atom to the receptor site cannot take place. The same arguments are considered to operate for conformation **D** due to steric constraints.

2. *Sulphamate esters of monosaccharides and nucleosides*

The sulphamation of monosaccharides is generally carried out by treating the alcoholate of the partially protected monosaccharide with *N*,*N*-dialkylsulphamoyl chlorides[253]. Deryabin[254] has shown that the alcoholate of the monosaccharide is generated by dissolving the sugar in DMSO followed by the addition of methanolic

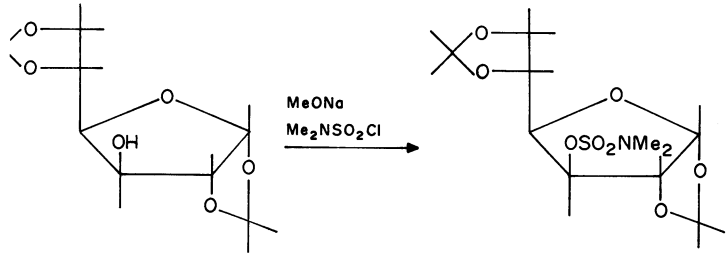


(A) (B) (C)



(D) (E)

MeONa and *N*,*N*-dimethylsulphamoyl chloride is then added to the mixture. A series of monosaccharide derivatives (**249**) with protecting groups, which are stable towards bases, were successfully and selectively converted to sulphamate esters (**250**). The monosaccharides used were 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (**249a**), methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside (**249b**), 1,2-*O*-isopropylidene-α-D-glucofuranose (**249c**), methyl α-D-glucopyranoside (**249d**) and methyl α-D-galactopyranoside (**249e**). The reaction for **249a** is outlined in equation 75. The product 3-dimethylsulphamoyl-1,2,5,6-



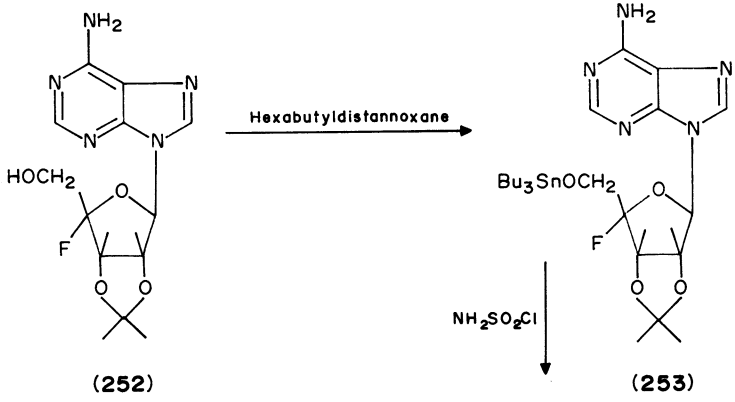
(75)

(**249a**) (**250a**)

di-*O*-isopropylidene-α-D-glucofuranose (**250a**) was obtained in 75% yield, $[\alpha]_d = -74°$ and has a melting point 95–96 °C after recrystallization from methanol. A series of novel sugar sulphamates, including 2,3:4,5-*bis*-*O*-(1-methylethylidene)-β-D-fructopyranose sulphamate, have been prepared and found to have anticonvulsant properties.[255]

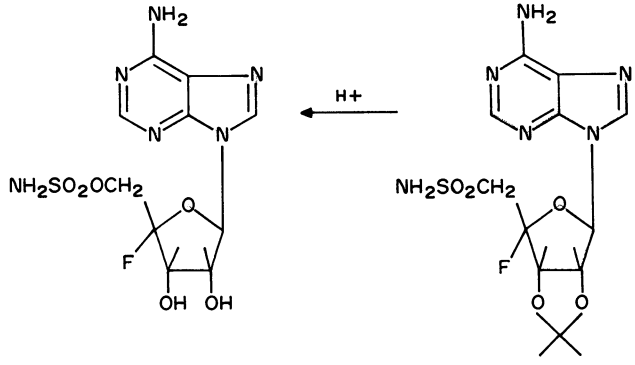
Nucleocidin 4′-fluoro-5′-*O*-sulphamoyladenosine[256] (**251**) was isolated from *Streptomyces calvis* and was shown to exhibit a broad antibacterial spectrum and to be particularly active against trypanosomes. Moffatt's group[257] has carried out the total synthesis of this compound. The introduction of the sulphamoyl moiety into the nucleoside system was achieved by reaction of 4′-fluoro-2′,3′-*O*-isopropylideneadenosine

(**252**) under reflux with hexabutyldistannoxane. This gives the 5′-*O*-tributyltin ether **253**, which was not isolated but allowed to react smoothly with excess sulphamoyl chloride at 5 °C to give the crystalline 4′-fluoro-2′,3′-*O*-isopropylidene-5′-*O*-sulphamoyladenosine (**254**) in 83% yield. Removal of the isopropylidene group using trifluoroacetic acid led to the formation of the nucleocidin **251** (equation 76).

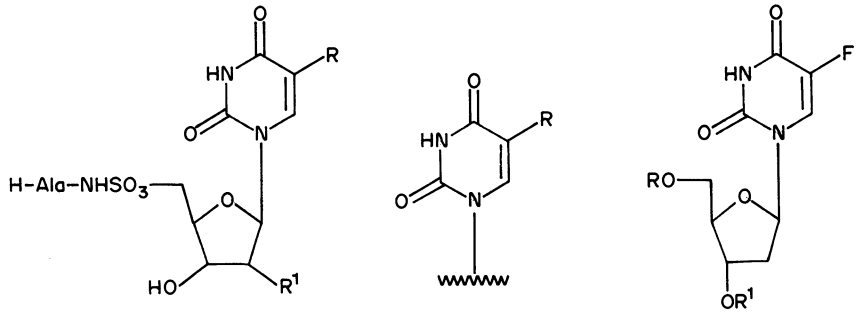


(252) (253)

(76)



(251) (254)

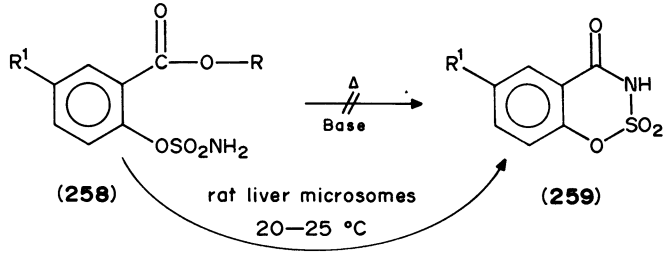


(255) (256) (257)

A series of pyrimidine nucleoside sulphamate esters have been prepared and their antibiotic and antiviral activity has been reported[258,259]. Ascamycin [5′-*O*-[*N*-(L-alanyl)sulphamoyl]-2-chloroadenosine] analogues **255** and **256**, in which the 2-chloroadenosine moiety has been replaced by uridine, thymidine, cytidine and 2′-deoxy-5-methylcytidine, have been prepared by selective aminoacylation of the N-substituted nucleosidic sulphamates using Boc-Ab-OSu (Boc = Me_3CO_2C, Su = succinimido), followed by removal of the Boc group. A similar procedure[260] is also used to prepare 2′-deoxy-5′-(aminoacyl)sulphamoyl-5-fluoridines (**257**), which have been found to be useful as low-toxic antitumour agents.

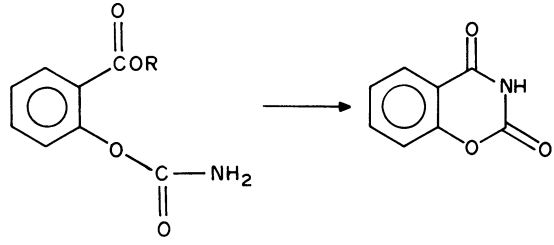
3. Reactions

Thermal cyclization of 2-(sulphamoyloxy)benzoates (**258**) in an attempt to synthesize 4-oxo-3,4-dihydro-1,2,3-benzoxanthine 2,2-dioxides (**259**) resulted in the cleavage of the OSO_2 linkage[261] (equation 77). Cyclization of **258** using bases such as triethylamine



(77)

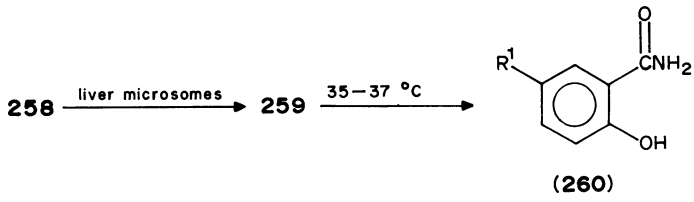
and pyridine also failed to produce **259**. The catalytic activity of enzymes was successful in the cyclization of 2-(carbamoyloxy)benzoates to 1,3-benzoxazines-2,4-diones[262] (equation 78). Incubation of various alkyl- and aryl-substituted 2-(sulphamoyloxy)-



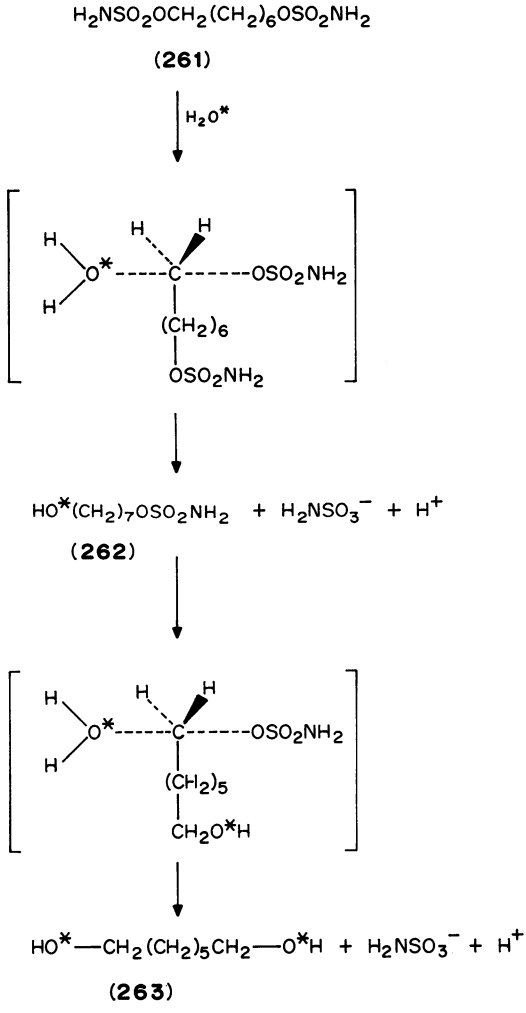
(78)

benzoates (**258**) with rat liver microsomal fractions gave the cyclized products in yields from 66 yo 78%. When the temperature of the incubation was raised to between 35 °C and 37 °C the major products isolated from the reaction were 2-hydroxy substituted benzamides (**260**). Mechanistically, the formation of **260** is expected to take place via the cyclic sulphamate ester **259**, and this has been confirmed by reaction of **258** with rat microsomes at temperatures of 22 °C to 25 °C for 18 hours; a sample after this time showed that **259** was the main product. When the temperature was raised to between 35 °C and 37 °C and incubated for a further 7 hours, work-up of the mixture gave predominantly the 2-hydroxybenzamides **260** (equation 79).

Sulphamic acid 1,7-heptanediyl ester **261** is a weak alkylating agent which has exhibited cytotoxicity and has an effective shelf-life (*t* 90%) of 9.3 days. A mechanistic investigation


258
liver microsomes
259
35–37 °C
R1
O
CNH2
OH

(260) (79)

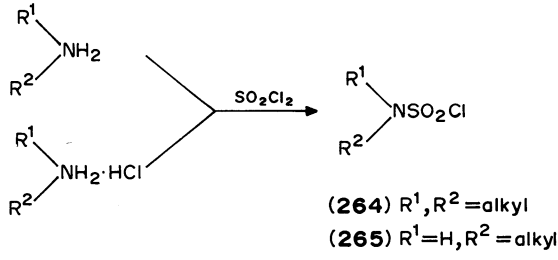

H2NSO2OCH2(CH2)6OSO2NH2
(261)
H2O*
H
O*
C
OSO2NH2
(CH2)6
OSO2NH2
HO*(CH2)7OSO2NH2 + H2NSO3− + H+
(262)
(CH2)5
CH2O*H
HO*—CH2(CH2)5CH2—O*H + H2NSO3− + H+
(263)

has been carried out to elucidate the degradation pathway and to gain an insight into the mechanism of action of **261** as an alkylating agent[263]. The degradation of **261** was carried out in water and ^{18}O-enriched water at 47 °C. The hydrolysis was first order with a mean observed rate constant of $2.38 \pm 0.6 \times 10^{-3}\ h^{-1}$. The reaction was independent of pH (2.5 to 8.0) and showed no significant buffer catalysis. Mass spectrometry of the ^{18}O reaction mixtures showed that exclusive C—O fission was observed. Chromatographic and spectral analysis showed that **261** degrades to 7-hydroxy heptane sulphamate ester **262** and subsequently to 1,7-heptanediol **263**. The results from the studies were considered consistent with an S_N2 mechanism where the water molecule and the carbon atom are aligned in an early transition state with no appreciable bond formation between the oxygen of the water molecule and the carbon atom of **261**. The same process is considered to operate for the degradation of **262** to yield the final degradation product. The proposed S_N2 mechanism is shown.

C. Sulphamoyl Halides

1. Synthesis

Dialkylsulphamoyl (**264**) and monoalkylsulphamoyl (**265**) halides have been prepared by the reaction of amines or amine hydrochlorides with sulphuryl chloride (equation 80)[264–269]. Sulphuryl chloride also reacts with dialkylsulphamides to give sulphamoyl halides **266** (equation 81)[270].



(80)

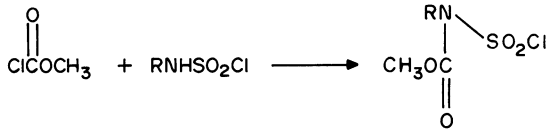
$$RNHSO_2NHR \xrightarrow{SO_2Cl_2} \underset{(\mathbf{265})}{2RNHSO_2Cl} \qquad (81)$$

Alkylsulphamic acids have been used as starting materials for the synthesis of alkyl sulphamoyl chlorides with a variety of chlorinating agents (equation 82)[271–274]. Kloeck

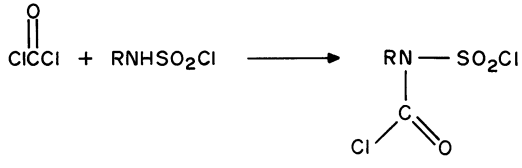
$$RNHSO_3H \xrightarrow[PCl_5]{\substack{SOCl_2 \text{ or} \\ COCl_2 \text{ or}}} RNHSO_2Cl \qquad (82)$$

and Leschinsky[275] have adapted the PCl_5 reagent for use in aromatic solvents and have reported for the first time the synthesis of monoarylsulphamoyl chlorides (**266**). The synthesis of sulphamoyl halides including alkyl, dialkyl, β-(haloalkyl) and *t*-butyl derivatives and their use in the synthesis of heterocyclic compounds has been reviewed by Hamprecht and coworkers[276]. The preparation of *O*-substituted *N*-hydroxysulphamoyl halides has been the subject of two patents[277,278]. The compounds were synthesized by the reaction of the corresponding alkoxysulphamic acids with PCl_5 using dichloroethane as solvent. The preparation of *N*,*N*-disubstituted sulphamoyl chlorides using phase transfer

methods, by substitution reactions on monoalkylsulphamoyl chlorides, has been reported (equations 83 and 84)[279]. Thus alkylsulphamoyl chlorides in dichloromethane and H_2O reacted with methoxy carbonyl chloride and $COCl_2$ respectively to give the *N,N*-disubstituted sulphamoyl halides (**267**) and (**268**).



(**265**) (**267**) (83)



(**265**) (**268**) (84)

The reaction of ureas with oleum followed by treatment with PCl_3 was used to prepare alkylsulphamoyl halides[280]. Zelcans has reported an increase in the yield of dimethylsulphamoyl chloride (**264**) by bubbling dimethylamine into sulphuryl chloride at a temperature of 55–56 °C while maintaining a two-fold excess of sulphuryl chloride[281].

The reaction of dimethylchloramine and sulphur dioxide leads to the synthesis of dimethylsulphamoyl chloride[282] (equation 85). The same reaction with chloramine (**270**), however, proved to be complex giving only low yields of sulphamoyl halide, which is inferred by its reaction with ammonia to give sulphamide to an extent of 2%. The *N*-chloramine decomposes to give ammonium chloride and a secondary reaction also occurs by ammonolysis of the initially formed sulphamoyl chloride to give sulphamide, which by oxidative coupling with chloramine yields the hydrazodisulphamide etherate $H_2NSO_2NHNHSO_2NH_2 \cdot (C_2H_5O)_2O$ (**271**) was also prepared independently by the reaction of sulphamide with chloramine (**270**) in diethylether (equation 86).

$$\underset{\textbf{(269)}}{(CH_3)_2NCl} + SO_2 \longrightarrow \underset{\textbf{(264)}}{(CH_3)_2NSO_2Cl} \tag{85}$$

$$\underset{\textbf{(270)}}{NH_2Cl} + SO_2 \longrightarrow [NH_2SO_2Cl] \longrightarrow NH_2SO_2NH_2$$

$$\xrightarrow{NH_2Cl} \underset{\textbf{(271)}}{H_2NSO_2NH\text{-}NHSO_2NH_2 \cdot (C_2H_5)_2O} + NH_4Cl \tag{86}$$

2. *Physical studies*

Semmoud and Vart[283] have recorded the IR spectra of sulphamoyl fluoride NH_2SO_2F (**272**) and its mercury salt (**273**) which was prepared according to equation 87. The IR spectra of the compounds have been compared to those for sulphamic acid and related

compounds. The presence of F and NH_2 cause bond contractions which depend on the number of electron pairs available on N and the electronegativity of the other ligands bonded to the sulphur atom. Two other spectroscopic studies, including pulse ^{35}Cl NQR studies[284] on the reorientation of the SO_2Cl groups in Cl_3PNSO_2Cl and $(CCl_3)_2ClPNSO_2Cl$ (**274**) and the mass spectra of some (triphenylphosphoranylidene) sulphamoyl chlorides (**275**), have been described[285].

$$\underset{\textbf{(272)}}{H_2NSO_2F} + Hg(NO_3)_2 \longrightarrow \underset{\textbf{(273)}}{HgNSO_2F} + 2HNO_3 \qquad (87)$$

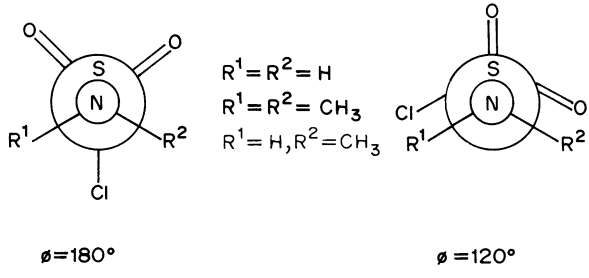
The reaction of triethylsilyl radicals, generated by the photolysis of di-*t*-butyl peroxide and triethylsilane, with dimethylsulphamoyl chloride led to the formation of dimethylaminosulphonyl radicals (**276**) by chlorine abstraction[286]. Kinetic measurements on the chlorine abstraction of a series of sulphonyl and sulphamoyl radicals show that the rate constants are high and approach the diffusion-controlled limit, indicating that there is very little interaction between the unpaired electron and the ligand attached to the sulphonyl group. The small differences in the rate constants are considered to be indicative of a polar contribution to the transition state for chlorine abstraction, since the rate constants increase with the electron ability of the ligand (equation 88).

$$Et_3Si^{\bullet +}ClSO_2N(CH_3)_2 \longleftrightarrow [Et_3Si^+\dot{C}l^-SO_2N(CH_3)_2] \qquad (88)$$

$$\swarrow$$

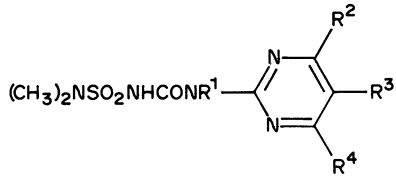
$$\underset{\textbf{(276)}}{[Et_3Si^+\ {}^-Cl^{\bullet}SO_2N(CH_3)_2]}$$

Semi-empirical MO calculations were performed by Lee[287] to investigate the configuration and conformation of a series of three sulphamoyl halides: H_2NSO_2Cl (**277**), CH_3NHSO_2Cl and $(CH_3)_2NSO_2Cl$. The preferred conformation of the three compounds is with $\phi = 180°$ in which the n–σ^* conjugative interaction is at a maximum and the least favoured conformation is the form with $\phi = 120°$ in which steric repulsion is large due to eclipsing of Cl and H or CH_3. The solvolysis of dimethylsulphamoyl chloride (**264**) has been investigated in methanol, ethanol, acetone and acetonitrile[288]. The results are indicative of a dissociative S_N2 mechanism.

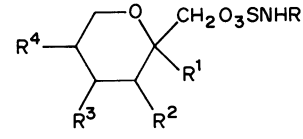


3. Reactions

A large number of papers have appeared describing the nucleophilic attack on the sulphur atom of sulphamoyl halides which has led to the preparation of a wide range of compounds including pyrimidinylaminocarbonyl sulphonamides (**278**)[289], fructopyranose sulphamates (**279**)[290], sulphamoylimidazoles (**280**)[291],2-sulphamoylbenzimida-



(278)



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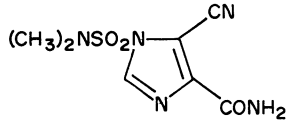

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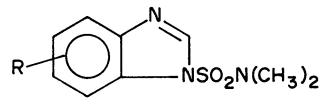

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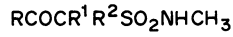
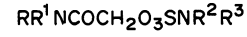


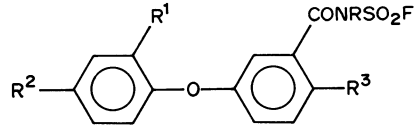
(282)



(283)

zoles (**281**)[292], 2-oxosulphonamides (**282**)[293] and *O*-(aminosulphonyl)glycolic acidamides (**283**)[294]. Sulphamoyl fluoride H_2NSO_2F has also been used in synthesis. Its reaction with diketene in acetone in the presence of K_2CO_3 yields the potassium salt of **284**, which is a precursor of the sweetening agent acesulfame K[295]. It has also been used in the synthesis of *N*-substituted-5-(substituted-phenoxy)-2-substituted benzoic acid sulphamoyl fluorides (**285**)[296]

(284)



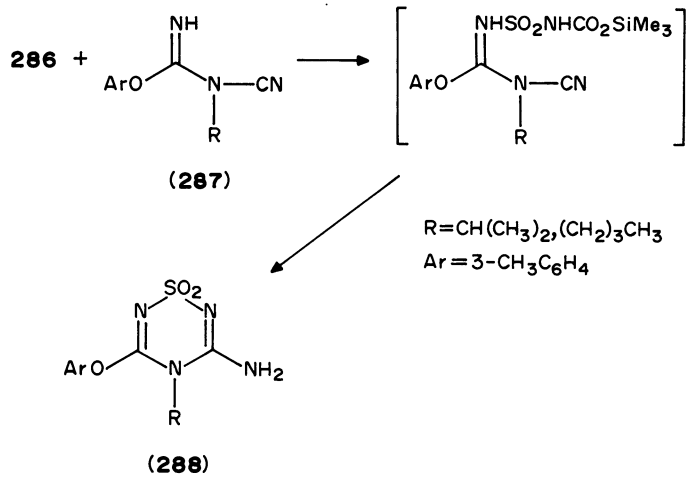
(285)

A new sulphamoylation agent, *N*-carbo(trimethylsilyloxy)sulphamoyl chloride (**286**), prepared by the reaction of (trimethylsilyl)ethanol with chlorosulphonyl isocyanate followed by the elimination of ethylene, has been reported[297] (equation 89). This reagent has been used successfully in the preparation of 3-amino-4-*N*-alkyl-5-aryloxy-1,2,4,6-thiatriazine-1,1-dioxide (**288**) (equation 90) by reaction of **286** with *N*-cyano-*N*-alkyl pseudoureas (**287**). The 2-*N*-alkyl isomer of **288** has also been synthesized.

$$ClSO_2NCO + HO(CH_2)_2SiMe_3 \longrightarrow ClSO_2NHCO_2(CH_2)_2SiMe_3 \quad (89)$$

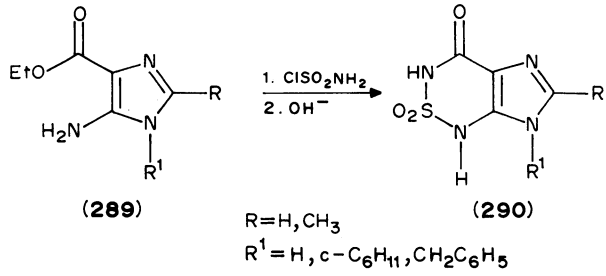
$$ClSO_2NHCO_2SiMe_3$$

(**286**)



(90)

Sulphamoyl chloride has been used in the cyclization of 5-amino-4-ethoxy carbonyl imidazoles (**289**) to give the corresponding imidazo[4,5-*C*]-1,2,6-thiadiazine derivatives **290** (equation 91)[298]. The attempted cyclization of **289** where R = 1-(tetra-*O*-acetyl-β-D-glucopyranose) using sulphamoyl chloride failed.

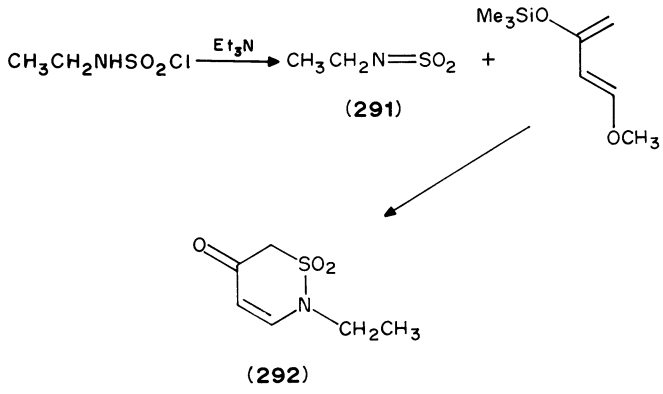


(91)

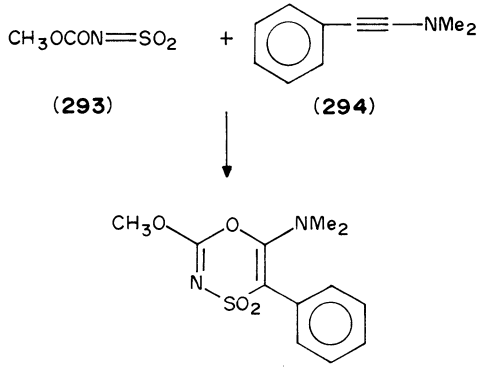
Kloek and Leschinsky[299] studied the reaction of sulphonylamines (**291**) generated from ethylsulphamoyl chloride and triethylamine at low temperatures. Reaction with activated dienes leads to the formation of the 2-ethyl-1,2-thiazin-5(6*H*)-one-1,1-dioxides (**292**) which, however, could only be isolated after acidic work-up of the mixture. The results from the studies of a range of activated dienes supports the conclusion that the reaction occurs in a stepwise fashion (equation 92).

Reaction of acetylsulphamoyl chloride with sodium hydride was used to generate the *N*-sulphonylurethane **293** which, when reacted with the ynamine **294**, yielded the 6-(dimethylamino)-2-methoxy-5-phenyl-1,4,3-oxathiazine-4,4-dioxide **295**[300] (equation 93).

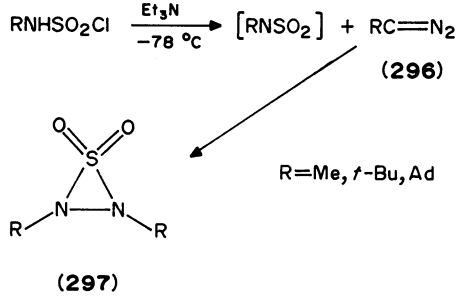
N-Sulphonylamines generated from sulphamoyl halides at −78 °C using triethylamine were also allowed to react with diazoalkanes **296**. Working the reaction mixture below −30 °C led to the isolation of 2,3-di-*tert*-alkylthiaziridine-1,1-dioxides **297**[301]. The compounds were characterised by the IR, UV, ^{1}H-NMR spectra as well as by their quantitative decomposition into sulphur dioxide and aldimines (equation 94).


CH3CH2NHSO2Cl
Et3N
CH3CH2N=SO2
(291)
Me3SiO
OCH3
O
SO2
N
CH2CH3
(292)

(92)


CH3OCON=SO2
(293)
NMe2
(294)
CH3O
O
NMe2
N
SO2
(295)

(93)


RNHSO2Cl
Et3N
−78 °C
[RNSO2]
RC=N2
(296)
R=Me, t-Bu, Ad
O
O
S
N
N
R
R
(297)

(94)

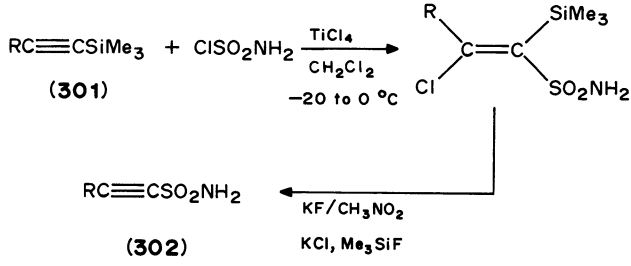
Gilmore and Morton[302] have described the first direct sulphamoylation of ester enolate anions (**298**). The reaction involved the addition of the *t*-butyl *N*-sulphonylamine generated at −78 °C from the sulphamoyl halide followed by addition of the carbanion, and the solution was worked up to room temperature to yield ethyl α-(*N*-*t*-butylsulphamoyl)phenyl acetate **299** (equation 95).

$$\underset{\textbf{(298)}}{CH_3CH_2OC(=O)CH^-(C_6H_5)} + SO_2{=}NBu\text{-}t \longrightarrow \underset{\textbf{(299)}}{CH_3CH_2OC(=O)CH(C_6H_5)SO_2NHBu\text{-}t} \qquad (95)$$

The reaction of disubstituted sulphamoyl chlorides R_2NSO_2Cl ($R = C_6H_5CH_2$, n-C_6H_{13} and $CH_2{=}CHCH_2$) with a slight excess of sodium nitrite gave the corresponding *N*-nitrosamines (**300**) in quantitative yields (equation 96)[303]. A discussion on the mechanism of the reaction does not favour a radical process but considers transnitrosation to proceed possibly by a four-membered ring mechanism.

$$R_2NSO_2Cl + NaNO_2 \xrightarrow[-SO_3]{CH_3CN} \underset{\textbf{(300)}}{R_2NNO} \qquad (96)$$

Babin has studied the sulphamoylation of organosilicon compounds (**301**) using unsubstituted sulphamoyl chloride. The reaction has led to the isolation of α,β-acetylenic sulphonamides (**302**) (equation 97)[304]. Most of the products are new compounds and constitute the first α,β-acetylenic sulphonamides bearing a saturated hydrocarbon group bonded to the triple bond.

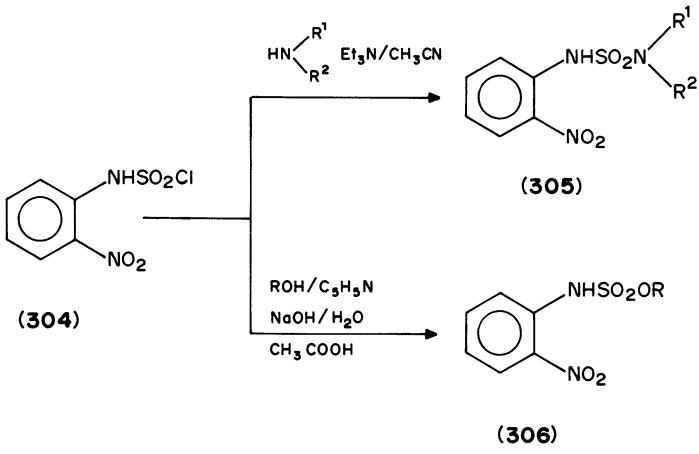


(97)

Sulphamoyl chloride when reacted with hydroperoxides in the presence of pyridine below −30 °C leads to the formation of the novel alkyl sulphamoyl peroxides $H_2NSO_2OOCH_2R$ ($R = CH_2CH_3$, $CH_2CH_2CH_3$) **303** (equation 98)[305]. Hydrolysis or ammonolysis of these compounds leads to formation of sulphamic acid or sulphamide respectively. 2-Nitrophenylsulphamoyl chloride (**304**), prepared from the corresponding sulphamic acid by reaction with PCl_5, has been used to prepare *N*-(2-nitrophenyl)-*N'*-substituted sulphamides (**305**) and aryl esters (**306**) (equation 99)[306].

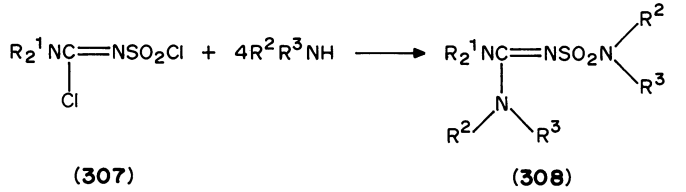
$$H_2NSO_2Cl + HOOCH_2R \xrightarrow[-30\,°C]{\text{Pyridine}} \underset{\textbf{(303)}}{H_2NSO_2OOCH_2R} \qquad (98)$$

A series of sulphamoyl guanidines (**308**) have been reported by the aminolysis of *N*,*N*-dialkyl-*N'*-chlorosulphonylchloroformamidines (**307**) with primary or secondary amines.



(99)

These were synthesized by the reaction of sulphuryl chloride with dialkylcyanoamides. The sulphamoyl guanidines (**308**) can also be prepared by the reaction of **307** with trimethylsilylamines[307] (equation 100).



(100)

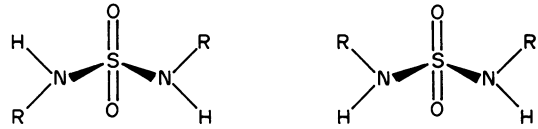
(307) (308)

IV. SULPHAMIDE

A. Physical Studies

1. X-ray

An X-ray crystal structure analysis of sulphamide has been carried out at 293 K and 100 K by an Austrian group[308]. At the former temperature the S–O and S–N distances of 1.429 and 1.620 Å respectively agree with IR data. The crystal and molecular structure of di-*t*-butylsulphamide, $Bu^tNHSO_2NHBu^t$ (**309**), has also been reported[309]. The steric demands of the *t*-butyl groups are evident from structural features. The geometry at nitrogen lies between trigonal planar and tetrahedral, but closer to trigonal planar. Di-*t*-butylsulphamide shows preference for C_2 rather than C_s confor-



C_2 C_s

mation. The structure of tetrasilver(I) sulphamide $Ag_4N_2SO_2$ (**310**) has been solved by a combination of direct methods and Fourier techniques[310]. One of the nitrogen atoms shows an unusual five coordination. The structure of trisilver(I) sulphamide–ammonia–water, $Ag_3HN_2O_2S)\cdot NH_3\cdot H_2O$ (**311**), consists of alternating layers of silver stoms and hydrogen bonded NH_3, H_2O and sulphamide molecules. The two nitrogen atoms of the sulphamide are covalently bonded to two and three atoms, respectively[311].

$H_2NSO_2NWCl_4$ (**312**) has been synthesized from WCl_6 and sulphamide and it forms adducts with pyridine and acetonitrile. The crystal structure of the acetonitrile adduct has a S–N–W angle of 169.3° and the nitrogen tungsten bond appears to be a double bond[312].

2. *Spectroscopic studies*

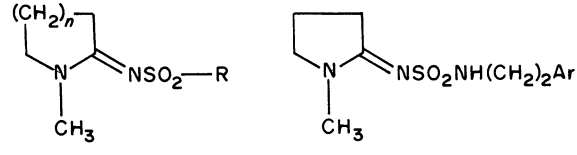
The IR (300 K) and Raman (300 and 90 K) spectra of single crystals of sulphamide (**313**) have been reported[313]. Four papers dealing with spectroscopic investigations of silver sulphamides have appeared from Popitsch's laboratory[314–317]. IR spectra of the three sulphamides $(AgNH)_2SO_2$ (**314**), $Ag_3(NH_2SO_2)\cdot NH_3\cdot H_2O$ (**315**) and $(Ag_2N)_2SO_2$ (**316**) have been determined in the 150–700 cm^{-1} region[314]. Diffuse reflectance spectra (d.r.s.) of **314** and **316** have been measured from 200 to 700 nm at 300 K and 77 K, respectively[315]. IR and Raman spectra of disilver sulphamide (**314**) and tetrasilver sulphamide (**310**) together with their ^{15}N and ^{2}H derivatives (at 300 K and 80 K) have been reported and interpreted[316]. IR, Raman and d.r.s. have been recorded from the copper and silver sulphamides, $Cu_3(N_2HSO_2)\cdot NH_3\cdot H_2O$ (**317**), $Ag_3(NH_2SO_2)\cdot NH_3\cdot H_2O$ (**315**) and $Ag_3(ND_2SO_2)\cdot ND_3\cdot D_2O$ (**318**)[317].

The variation of colour in silver compounds including sulphamides has been correlated with structure. The colour changes go from colourless to red, depending on the number of silver(I) atoms coordinating the donor atoms of the bases used[318]. Ag(I) sulphamides show different colours depending on the stoichiometry, disilver sulphamides are colourless, trisilver sulphamides are deep red.

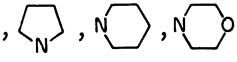
The polarized IR and Raman spectra of *N,N*-dimethylsulphamide, $(CH_3)_2NSO_2NH_2$ (**319**), $(CD_3)_2NSO_2ND_2$ (**320**) and $(CH_3)_2NSO_2ND_2$ (**321**) have been recorded and interpreted[319].

The ESCA spectra of a number of sulphamide nickel, copper, cobalt, zinc and chromium complexes have been determined[320]. The difference in the N_{1s} and S_{2p} binding energies is used to show if the sulphamide is coordinated via nitrogen in the complexes.

The ^{14}N nuclear quadrupole resonances (NQR) in sulphamide and methanesulphonamide $CH_3SO_2NH_2$ (**322**) have been studied by Japanese workers[321] using the pulse method.



(323) **(324)**

R = NH_2, 

Various sulphamides of general types **323** and **324** have been the subject of a mass spectral study and cleavages monitored[322].

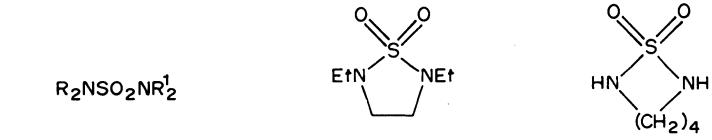
3. Protonation and miscellaneous

Two papers dealing with the ionization of di-[323] and tri-[323,324] substituted sulphamides have appeared. In the first study[323] potentiometric and UV methods were used to examine the equilibria (shown in equation 101) in 60% v/v ethanol–water. For equilibrium b neither H_- or H_{2-} are suitable for describing the ionization occurring and a number of other methods have been used, e.g. the modified Marziano–Cimino–Passerini method, to obtain thermodynamic pK_a values for the seven diarylsulphamides used in this study. The pK_a values for equilibrium b are ≈ 15. The effect of substituents on both equilibria is similar.

$$\mathrm{RNHSO_2NHR} \overset{a}{\rightleftharpoons} \mathrm{RN^-SO_2NHR} \overset{b}{\rightleftharpoons} \mathrm{RN^-SO_2N^-R}$$
$$\mathrm{RNHSO_2N(CH_3)_2} \overset{a}{\rightleftharpoons} \mathrm{RN^-SO_2N(CH_3)_2} \qquad (101)$$

In the second study[324] 27 trisubstituted sulphamides, mainly represented by the following series: $XC_6H_4NHSO_2NR^2R^1$ (**325**), where NR^2R^1 = piperidyl, morpholinyl and NPr^n_2 and $RNHSO_2NR^2R^1$ where R,R^1 and R^2 are c-C_6H_{11}, Ac and XC_6H_4 and XC_6H_4, Ac and XC_6H_4, have had equilibrium a examined in 60% v/v ethanol–water using the potentiometric method.

Conductivity, photoconductivity and luminescence studies of the silver sulphamides $(AgNH)_2SO_2$ (**314**), $(Ag_2N)(AgNH)SO_2\cdot NH_3\cdot H_2O$ (**326**), $(Ag_2N)_2SO_2$ (**316**) and $(Ag_2N)_2SO_2\cdot 2NH_3$ (**327**) have been reported[325]. A number of sulphamides of types **328**, **329** and **330** have been found suitable as polar aprotic solvents[326].



R=R¹=C₂H₅; R=CH₃, R¹=C₂H₅

(**328**) (**329**) (**330**)

B. Inorganic and Industrial

An ESCA study of complexes of type $M(NH_2SO_3)\cdot(H_2O)_x$ (**331**), M = Ni, Co, Zn, Cu, Cr has been reported (see above)[320]. The preparation of a number of ethylenediamine(sulphamide) Ni(II) and Cu(II) complexes (**332**) in which the sulphamide is coordinated, partially coordinated and not coordinated has been reported[327].

A kinetic study in aqueous acid of the hydrolysis of the pentaaminecobalt(II) sulphamido complex, $(NH_3)_5CoNHSO_2NH_2^{+2}$ (**333**), has been reported[328]. The mechanism of hydrolysis involves protonation followed by Co—N bond breaking.

A Russian study of the distribution and extraction of sulphamides between organic solvents and water has been reported[329]. The sulphamide **334** has found application in the preservation of wood[330]. A recording material of type **335** has been made[331].

$(CH_3)_2NSO_2N(CFCl_2)C_6H_4CH_3$
(**334**)

$$R^1NHSO_2N=R^2R^3$$
(335)

($R^1 - R^3$ = alkyl, cycloalkyl, phenalkyl, phenyl, naphthyl, or R^2R^3N form a five or six membered heterocyclic groups).

Copolymers have been prepared by reaction of sulphamides of type **336** with $ClCH_2CH_2(OCH_2CH_2)_2Cl$[332].

$$((CH_3)_2NCH_2C(CH_3)_2CH_2NH)_2SO_2$$
(336)

C. Synthesis

The synthesis, physical and chemical properties of sulphamides have been the subject of various reviews down through the years[333–338]. Sowada[339] has summarized the three main synthetic routes in the preparation of sulphamides as follows: (a) reaction of primary amines (alkyl or aryl) with sulphuryl chloride; (b) reaction of primary amines with chlorosulphonic acid; (c) reaction of primary amines (alkyl, cycloalkyl and aryl) with sulphamide.

The synthesis of sulphamide $H_2NSO_2NH_2$ (**337**) was carried out by reaction of a solution of sulphuryl chloride SO_2Cl_2 in dichloromethane with ammonia at $-50\,^\circ C$; extraction of the product with acetonitrile yielded sulphamide of 97.8% purity[340]. Hydrolysis of *N,N'*-bis(trimethylsilyl)sulphamide prepared by the reaction of sulphuryl chloride and hexamethyldisilazane yielded sulphamide[341] also. Hydroxysulphamide (**338**) (*N*-amidosulphonyl hydroxylamine)[342], a colourless crystalline solid (m.p. 86–87 °C), is formed from the reaction of sulphamoyl fluoride with hydroxylamine (equation 102). *N,N'*-Dimethyl-*N'*-hydroxysulphamide[343] (**339**) was prepared in a similar manner by the reaction of dimethylsulphamoyl chloride with hydroxylamine. Trialkylsilyl halides have been used to prepare *N,N'*-dialkyl-substituted (**340**) and *N,N,N',N'*-tetrasubstituted (**341**) sulphamides[344,345]. The synthetic route involves reaction of the amines R^1R^2NH (where R^1 and R^2 are independently aliphatic, cycloaliphatic or aromatic) with trisubstituted silanes $R^3R^4R^5SiX$ (R^3,R^4 and R^5 are aliphatic or aromatic groups, X = halogen) to give the silylated amines **343** which, when reacted with sulphuryl chloride, give the sulphamides **340** and **341**. Thus when methylamine **342** is treated with trimethylchlorosilane at $-5\,^\circ C$ and heated to 82 °C, the trimethylsilylmethylamine **343** is formed. Addition of trimethylchlorosilane followed by SO_2Cl_2 at $-30\,^\circ C$ and allowing the reaction to proceed at 0 °C for 1 hour and 22 °C for 5 hours gives 73% yield of *N,N'*-dimethylsulphamide (**340**) (equation 103).

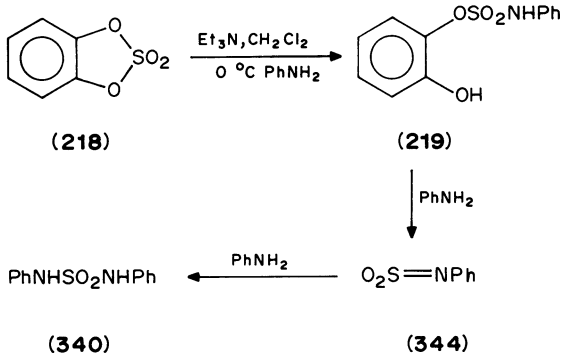
$$H_2NSO_2F + 2H_2NOH \longrightarrow \underset{\textbf{(338)}}{H_2NSO_2NHOH} + [H_3NOH]F \qquad (102)$$

$$\underset{\textbf{(342)}}{CH_3NH_2} + (CH_3)_3SiCl \longrightarrow \underset{\textbf{(343)}}{CH_3N{=}Si(CH_3)_3}$$

$$\xrightarrow[SO_2Cl_2]{(CH_3)_3SiCl,\ -35\,^\circ C} \underset{\textbf{(340)}}{CH_3NHSO_2NHCH_3} \qquad (103)$$

DuBois prepared 2-hydroxyphenyl esters of sulphamic acids by reaction of the appropriate amine with catechol sulphate (see Section III.A, equation 63). The reaction proved sluggish when the amine used was aniline, but work-up of the reaction yielded 28% of the *N,N'*-diphenylsulphamide **340**, R = Ph[346]. The formation of **340**, is considered to occur due to the low rate of attack by the poorly nucleophilic aniline on **218**.

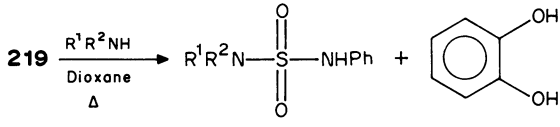
The unreacted aniline then promotes base-catalysed elimination of the ester **219** to give the transient *N*-sulphonylamine (**344**), which is quickly trapped by the aniline to give **340** (equation 104). Thus amination of 2-hydroxyphenyl esters of sulphamic acids using



(218) (219) (344) (340)

(104)

alkylamines proved to be very successful in the preparation of *N,N'*,-dialkylsubstituted sulphamides (**340**) and *N,N,N'*-trialkylsubstituted sulphamides (**345**) in high yield. Aromatic amines react slowly and the yield of the sulphamide is lower (equation 105).



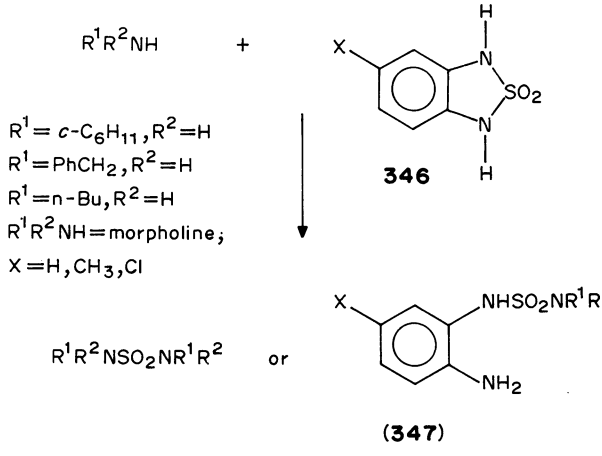
(340 or 345) (105)

Amination and amine exchange reactions of sulphamide and substituted sulphamides have been used to prepare a wide range of sulphamides[347–352] (equation 106).

$$R^1R^2NH + R^3R^4NSO_2NR^3R^4 \longrightarrow R^1R^2NSO_2NR^1R^2 \quad (106)$$

The transamination of 1,3-dihyro-2,1,3-benzothiadiazole-2,2-dioxides (cyclic sulphamides) (**346**) has successfully led to the formation of sulphamides[353]. Thus when cyclohexylamine, benzylamine and n-butylamine are used in a 1:1 ratio with **346**, the fully exchanged *N,N'*-dialkylsulphamides were obtained in 60 to 80% yield (equation 107).

Isolation of the half-exchanged sulphamides **347** should give compounds which would be the nitrogen analogues of 2-hydroxyphenyl-*N*-substituted sulphamate esters **219** (equation 104 and equation 63, Section III.A). When the amine morpholine was used, the 2-aminophenylsulphamide **347** or half-exchanged product was isolated. Monosulphamideamine transamination reactions as a route to unsymmetrical and symmetrical *N,N'*-disubstituted sulphamides has been reported by Spillane[354]. Using a 1:1 ratio of *N*-monoalkylsulphamide to amine and keeping the temperatures at 130 °C gives between 54 and 95% yields of *N,N'*-dialkylsulphamides (equation 108). Raising the temperature and changing the ratio of amine to *N*-monoalkylsulphamide (**348**) to 2:1 led to the formation of symmetrical *N,N'*-dialkylsulphamides (equation 109).



(107)

$$R^1NHSO_2NH_2 + R^2NH_2 \longrightarrow R^1NHSO_2NHR^2 \quad (108)$$

(348)

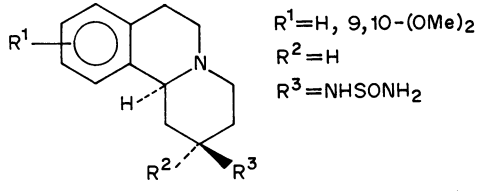
$R^1 = c\text{-}C_6H_{11}$, n-C_4H_9, $C_6H_5CH_2$, n-C_6H_{13}

$R^2 =$ n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, n-C_8H_{17}, i-C_5H_{11}, $C_6H_5CH_2$, c-C_6H_{11}, c-C_5H_9, c-C_7H_{13}

$$R^1NHSO_2NH_2 + 2R^2NH_2 \longrightarrow R^2NHSO_2NHR^2 \quad (109)$$

(348)

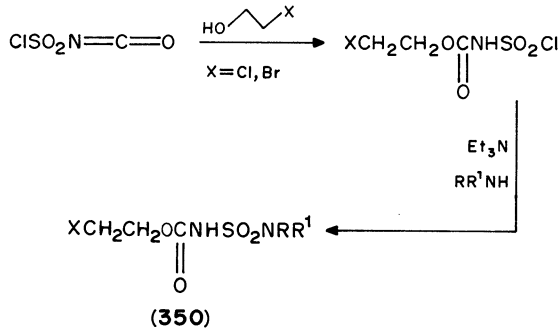
Reaction of sulphamide **337** with a series of amines has led to the synthesis of 2-sulphamido-1,3,4,6,7,11b-α-hexahydro-2H-benzo[a]-quinolizines (**349**), $R^3 = NHSO_2NH_2$, and the anti-hypertensive activity of the compounds in rats has been reported[355].



(349)

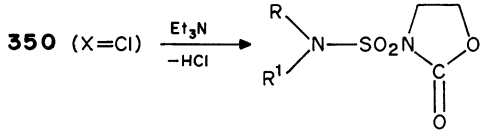
Chlorosulphonyl isocyanate is a useful reagent for the synthesis of sulphamides. Reaction of chlorosulphonyl isocyanate with 2-haloethanols (X = Cl, Br) followed by reaction with primary and secondary amines (R = C_6H_5, 3-$NO_2C_6H_4$, 2-NCC_6H_4,

4-$C_6H_5C_6H_4$, $C_6H_5CH_2$, furyl, cyclohexyl, picolyl, adamantyl, pentyl, $R^1 = C_6H_5$, CH_3, C_2H_5 and H) in a two-step reaction leads to the formation of a new series of 2-chloroethoxycarbonyl sulphamides, **350** (equation 110)[356,357]. Intramolecular cyclocon-



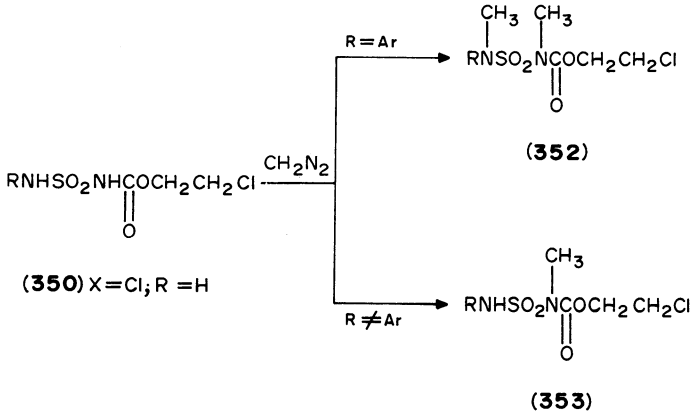
(110)

densation of **350** in the presence of triethylamine at ambient temperatures yielded the corresponding *N*-sulphamoyloxazolidines (sulphamides) **351** in 60–93% yields (equation 111). Methylation of **350** with diazomethane leads to the formation of the *N,N'*-



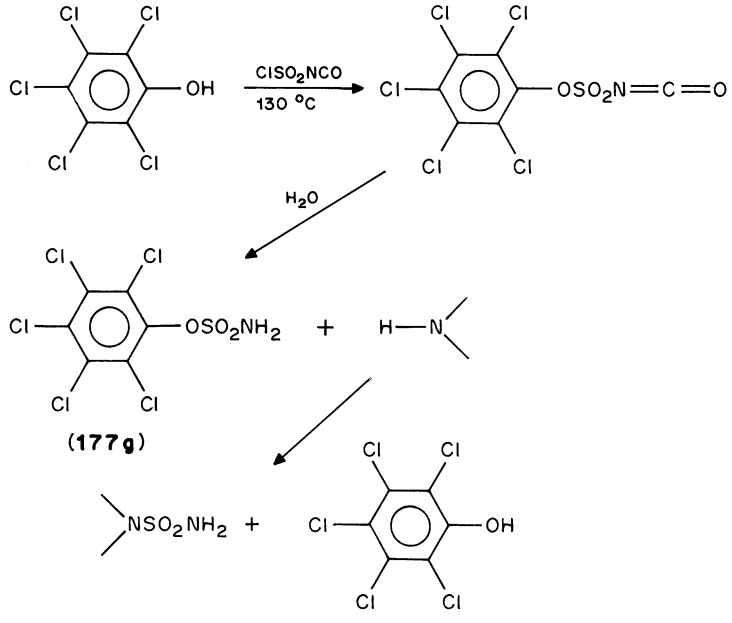
(111)

dimethylchloroethoxy carbonylsulphamides (**352**) where the R group is aromatic. If the R group in **351** is aliphatic, then monomethylation is achieved to yield the *N*-methylchloroethoxy carbonylsulphamides **353** (equation 112).

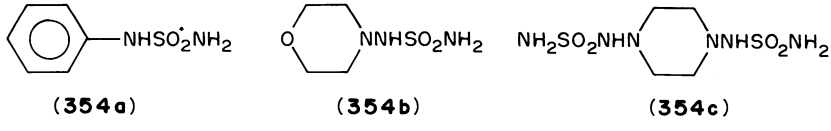


(112)

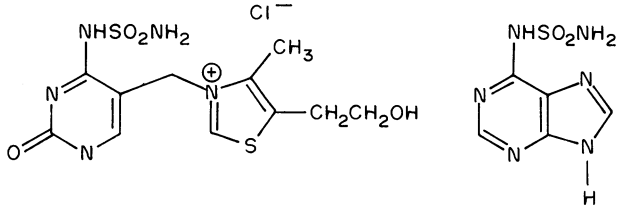
Hedayatullah and Hugueny[358] developed a useful synthesis for the preparation of *N,N'*-disubstituted sulphamides (**354**) using chlorosulphonylisocyanate. The reaction involves heating pentachlorophenol at 130 °C with chlorosulphonylisocyanate to yield the *N*-



(113)



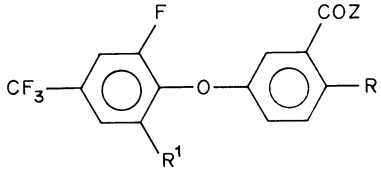
(354a) (354b) (354c)



(355 a,b,c,d)

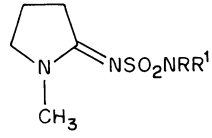
unsubstituted pentachlorophenyl sulphamide (**177g**). Refluxing of **177g** with aniline, morpholine and piperazine leads to the formation of the substituted sulphamides **354a,b,c** (equation 113). The reaction in equation 113 was extended to the bases cytosine, thiamine, adenine and guanine and the corresponding sulphamides (**355a–d**) were obtained in high yields.

Diphenyl ether sulphamides of the type **356** were prepared by the reaction of the alcohols **357** (R = H, halogen, alkyl, NO_2, CF_3; R^1 = F, Cl) with chlorosulphonyl isocyanate[359]. The intermediate sulphamoyl halide **358** was then reacted with amines to



(**356**) Z = $NHSO_2NHR$
(**357**) Z = H
(**358**) Z = $NHSO_2Cl$

yield **356**. A similar reaction of chlorosulphonyl isocyanate with 1-methyl-2-pyrrolidone (**359**) followed by reaction with amines leads to the synthesis of 1-methyl-2-pyrrolidinylidenesulphamides **360** (NRR^1 = sulphonamido, morpholine, pyrrolidine, NH_2



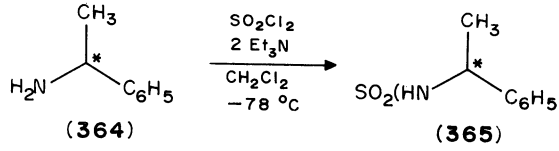
(**360**)

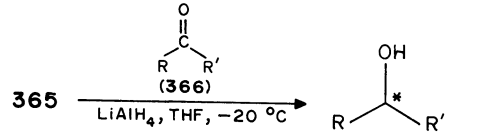
and R = alkyl, R^1 = phenyl)[360]. The reaction of amines with sulphuryl chloride in the presence of tertiary amine acid acceptors has been used extensively to synthesize substituted sulphamides. The reaction (equation 114) of substituted anilines 2,4-$R(NO_2)C_6H_3NH_2$ (R = F, Cl, Br and CF_3) (**361**) with sulphuryl chloride followed by the addition of dimethylamine yields *N,N,N'*-dialkylarylsulphamides (**362**)[361]. Primary aliphatic amines undergo similar reactions with sulphuryl chloride and, in the presence of triethylamine followed by the addition 2-aminomethylbenzoate, have been used to prepare *N*-alkyl-*N'*-aryl-disubstituted sulphamides 2-$(RCH_2NHSO_2NH)C_6H_4COOCH_3$ (**363**)[362].

$$\underset{\textbf{(361)}}{2,4\text{-}R(NO_2)C_6H_3NH_2} \longrightarrow \underset{\textbf{(362)}}{2,4\text{-}R(NO_2)C_6H_3NHSO_2N(CH_3)_2} \qquad (114)$$

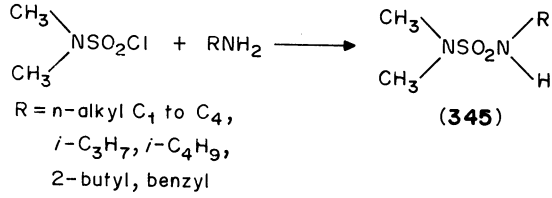
The reaction of either (*R*)- or (*S*)-α-methylbenzylamine (**364**) with sulphuryl chloride gives the (*R,R*) and (*S,S*) *N,N'*-bis(α-methylbenzyl) sulphamide **365**. When **365** is added to $LiAlH_4$ in the presence of *N*-benzylmethylamine in tetrahydrofuran, it leads to the asymmetric reduction of prochiral ketones **366** (equation 115)[363]. Optimization of the reaction was carried out with respect to enantioselectivity and reactivity of the reagents. The use of *N*-benzylmethylamine as an additive was found to be superior to ethanol. Reaction at −20 °C gave 87% selectivity with a one-hour reaction time. Both arylalkyl ketones and dialkyl ketones are asymmetrically reduced in the reaction.

The reaction of sulphamoyl halides with amines is a useful synthetic route to the preparation of sulphamides. Unterhalt and Seebach[364] have used this approach to prepare *N,N,N'*-trialkylsulphamides **345** (equation 116). The reaction was carried out at 50 °C in



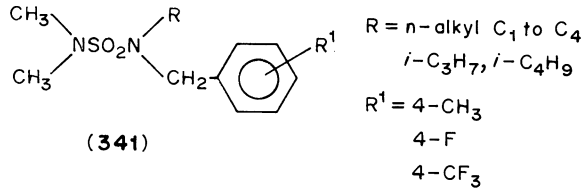


(115)



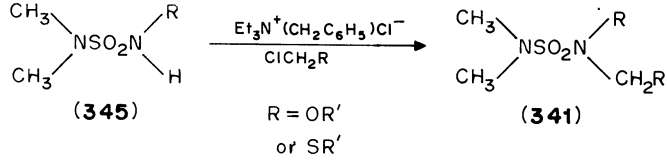
(116)

benzene and proved to be a general reaction with yields of **345** ranging from 54 to 89%. Deprotonation of the acidic nitrogen in **345** using sodium in ethanol and reaction of the conjugate base of **345** with benzyl and substituted benzyl chlorides leads to the formation of *N,N,N′N′*-tetrasubstituted sulphamides (**341**). The use of 4-nitrobenzyl chloride failed



to yield the corresponding sulphamide but yielded 4,4′-dinitrostilbene. However, reaction of **345** with 4-nitrobenzyl bromide in an atmosphere of N_2 using acetonitrile as solvent produced *N,N*-dimethyl-*N′*-methyl-*N′*-benzylsulphamide in 81% yield.

Phase transfer reaction of the conjugate base of the *N,N,N′*-trialkylsulphamides (**345**) in the presence of benzyl triethylammonium chloride with chloromethyl ethyl ether or chloromethyl alkylthioethers yields the *N,N*-dialkyl-*N′*-alkyl-*N′*-ether and thioether sulphamides (**341**)[365] (equation 117).



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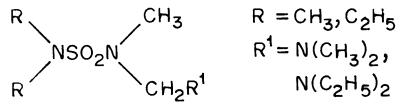
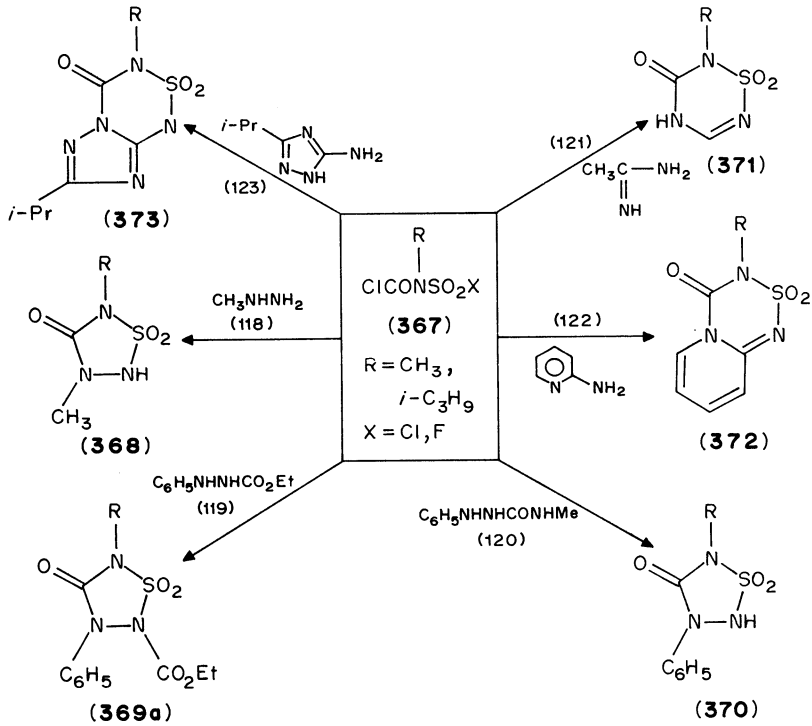


(341)

Aminomethylation of **345** with formaldehyde and secondary amines to give the *N,N,N'N'*-tetrasubstituted sulphamides (**341**) was achieved.

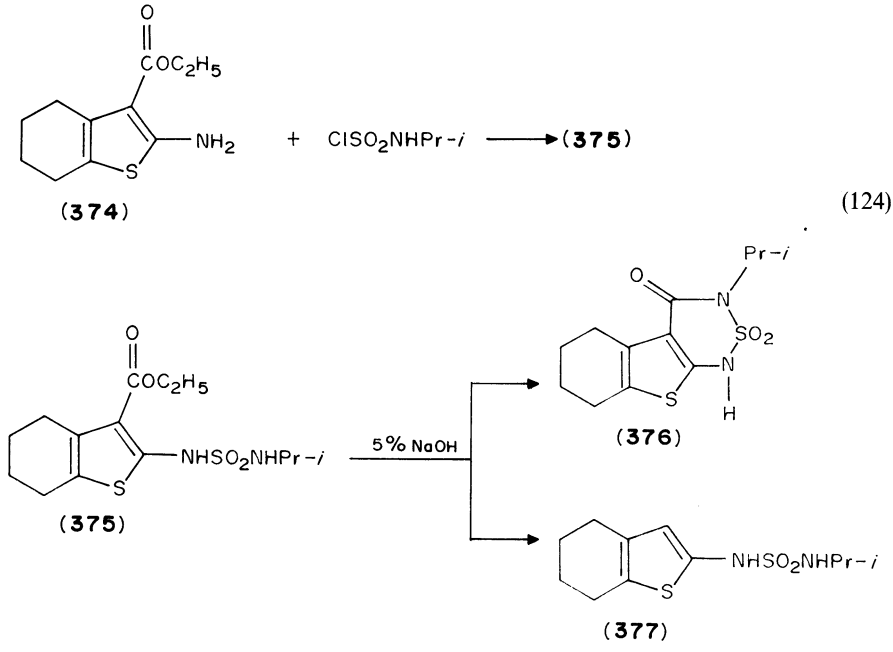
The sulphamide moiety has been incorporated into heterocyclic ring systems and has resulted in the synthesis of a wide range of cyclic sulphamides. Bartholomew and Kay[366–368] have studied the use of 1,3-dielectrophilic agents 2-alkyl-2-chloro and fluorosulphonylcarbamoyl chlorides (**367**) with primary and secondary amines followed by cyclization with sodium hydroxide, and have prepared a wide range of heterocyclic systems containing the sulphamide functional group (equations 118–123). Reaction of **367**



with methylhydrazine gave the 3-methyl-1,2,3,5-thiotriazolidin-4(2*H*)-one-1,1-dioxides **368** (equation 118). Cyclization of the intermediates, with bases other than sodium hydroxide such as pyridine or triethylamine, failed to occur. The use of phenylhydrazine in the reaction failed to give the cyclized product and yielded mainly phenylazocarboxamide $C_6H_5N = NCONHCH_3$. However, when the phenylcarbazate was used under cyclization

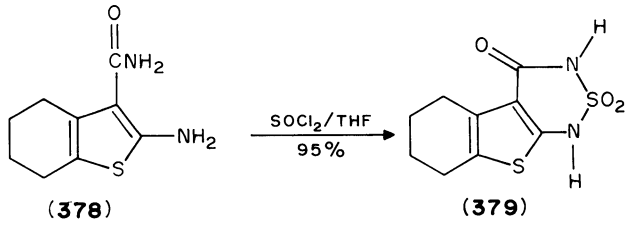
conditions the desired 3-phenyl 1,2,3-thiotriazolidinones (**369**) were obtained (equation 119). The parent 3-phenyl 1,2,3-thiotriazolidinones (**370**) were obtained by reacting **367** with the phenylcarbazide $C_6H_5NHNHCONHCH_3$ (equation 120).

The scope of the reaction was probed by extending the reaction to the synthesis of six-membered cyclic sulphamides. The reaction of **367** with acetamidine gave 1,2,4,6-thiatriazinone-1,1-dioxides **371** (equation 121) in yields of 20%. Fragmentation of the intermediates prior to cyclization is considered to account for the low yields. Modest yields of the pyridothiatriazinone **372** were obtained by condensation of aminopyridine with **367** (equation 122). Aminotriazoles when reacted with **367** yielded the triazolothiatriazinones **373** (equation 123). The reaction of 2-amino-3-ethoxycarbonyl 4,5,6,7-tetrahydro-1-benzothiophen (**374**) with isopropyl sulphamoyl chloride gives the *N*-(isopropyl)-*N'*-(3-ethoxycarbonyl-4,5,6,7-tetrahydro-1-benzothiophene)sulphamide (**375**)[369]. Cyclization of **375** with 5% sodium hydroxide leads to the formation of the cyclic sulphamide 3-isopropyl-4-oxo-3,4,5,6,7,8-hexahydro-1*H*[1]-benzothieno[2,3-*d*]-2,1,3-thiadiazin-2,2-dioxide (**376**) in 42% yield. Decarboxylation of **375** also occurs in the reaction with the formation of *N*-(isopropyl)-*N'*-(4,5,6,7-tetrahydro-1-benzothiophene)sulphamide **377**



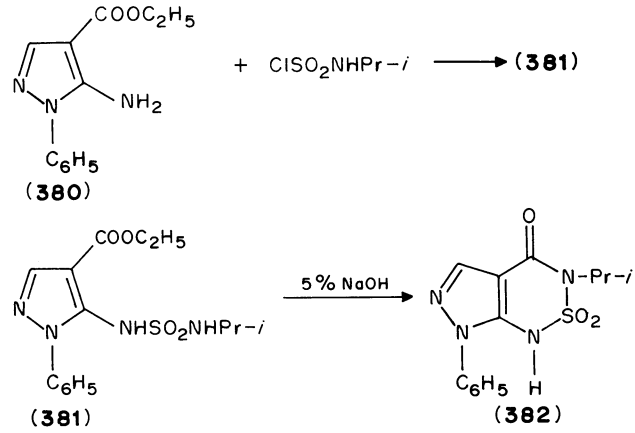
(equation 124). The parent cyclized sulphamide **379**, namely 2-oxo-3,4,5,6,7,8-hexahydro-1*H*-[1]-benzo-thieno[2,3-*d*]-2,1,3-thiadiazin-2-oxide, is prepared by the direct condensation of 2-amino-3-carbamoyl-4,5,6,7-tetrahydro-1-benzothiophene (**378**) with thionyl chloride (equation 125).

A similar reaction is observed for 4-ethoxycarbonyl-5-amino-1-phenylpyrazole (**380**) with isopropylsulphamoyl chloride and leads to the formation of *N*-(isopropyl)-*N'*-4-ethoxycarbonyl-1-phenylpyrazole sulphamide (**381**), which undergoes cyclization in base



(378) (379) (125)

to give the cyclic sulphamide 3-isopropyl-4-oxo-7-phenyl-11,3,4,7-tetrahydropyrazolo-[3,4-d]-2,1,3-thiadiazine (**382**) (equation 126).



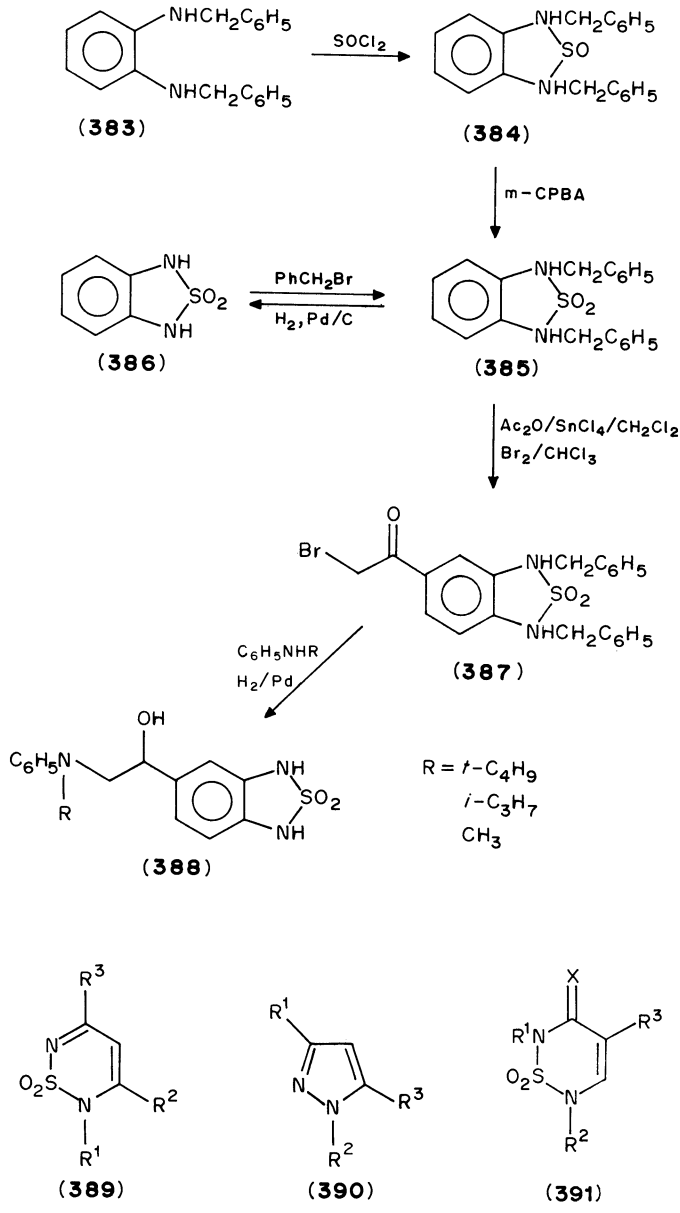
(126)

A new synthesis of 1*H*,3*H*-2,1,3-benzothiadiazole-2,2-dioxide has been reported by Acheson and collaborators[370]. The reaction of *N*,*N*′-dibenzyl-1,2-diaminobenzene (**383**) with thionyl chloride (equation 127) gives the 1,3-dibenzyl-1*H*,3*H*-2,1,3-benzothiadiazole-2-oxide (**384**) which, on oxidation with *m*-chloroperbenzoic acid, yields the *N*,*N*′-dibenzylated thiadiazole-2,2-dioxide (**385**). Debenzylation of **385** leads to the parent thiadiazole-2,2-dioxide (**386**), which heretofore was not readily synthesized.

Friedel–Craft acetylation of **385** followed by bromination yields 5-(2-bromoacetyl)-1,3-dibenzyl-1*H*, 3*H*-2,1,3,-benzothiadiazole-2,2-dioxide (**387**). Reaction of **387** with *N*-benzylated amines followed by reduction with hydrogen produces (**388**). No significant increase in heart rate, blood pressure, left ventricular pressure and bronchodilator activity was observed when the thiadiazoles **388** were tested in dogs.

1,2,6-Thiadiazine 1,1-dioxides (**389**) have been synthesized by Ochoa's group and a comparative study of their physiochemical properties with that of pyrazoles **390** has been made[371,372]. Rough parallels are observed in the tautomeric equilibria of (**389**) and (**390**) with ^{13}C chemical shifts and the reactivity of the 4-position while differences in their aromaticity have been observed. The 1,2,6-thiadiazine-1,1-dioxides **389** are prepared either by reaction of sulphamide or substituted sulphamides with 1,3-dicarbonyl compounds or their acetal derivatives or by *N*-alkylation of the unsubstituted derivatives.

Glycosidation reactions were also carried out on the unsubstituted cyclic sulphamides to yield nucleosides of 1,2,6-thiadiazine-1,1-dioxides (**391**)[373]. The thiadiazines were reacted with suitable sugar halides using mercuric cyanide and nitromethane. The site

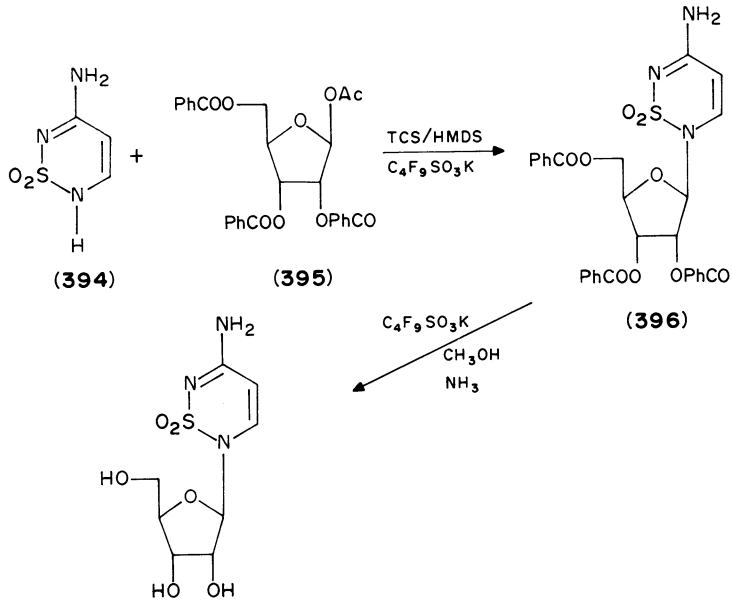


(127)

X = O, NH
R^1 = H, CH_3, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl
R^2 = H, CH_3, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl, 2,3,5-tri-*O*-benzoyl β-ribofuranosyl
R^3 = NO_2, $CO_2C_2H_5$, CN

of glycosidation was established by comparing the UV spectra of the nucleosides with those of the corresponding methyl derivatives and other substituted thiadizines. The β configuration was established on the basis of mechanistic considerations and NMR coupling constants.

Two new nucleosides of cyclic sulphamides (**392** and **393**) have been reported by Vorbruggen and coworkers[374]. The synthesis involves reaction (equation 128) of the 1,2,6-thiadiazine-1,1-dioxide (**394**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**395**); the intermediate nucleoside (**396**) is debenzylated to give 3-amino-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,6-thiadiazine-1,1-dioxide (**392**). 3,6-Dihydro-3-oxo-6-(β-D-ribofuranosyl)-2*H*-1,2,6-thiadiazine-1,1-dioxide (**393**) is prepared in a similar manner.



(**394**) (**395**) (**396**) (128)

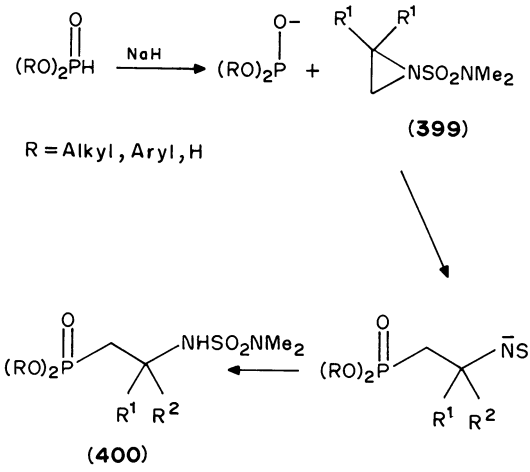
(**392**)

Sulphamides containing the element phosphorous have been reported by Arrington[375], who prepared a series of triphenylphosphoranylidene sulphamides (**398**) by reaction of the novel compound (triphenylphosphoranylidene)sulphamoyl chloride (**397**) with amines (equation 129).

$$\underset{\textbf{(397)}}{(C_6H_5)_3PNSO_2Cl} \longrightarrow \underset{\textbf{(398)}}{(C_6H_5)_3PNSO_2NHR} \qquad (129)$$

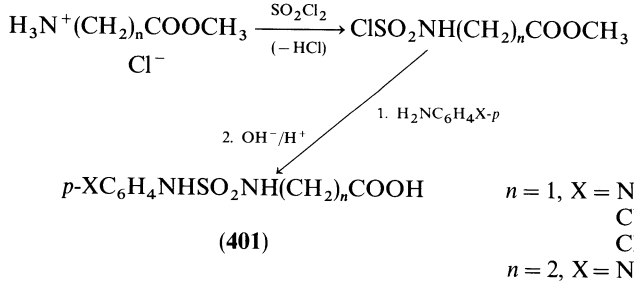
$$R = CH_3,\ C_2H_5,\ \text{and } o\text{-},\ m\text{-},\ p\text{-}BrC_6H_4$$

Sulphamides containing the dialkyl ester of the phosphoric acid functional group are prepared by reacting the sodium salt of the phosphoric acid with *N*-sulphonylaziridines (**399**) at room temperature (equation 130). Acidification gives the *N*,*N*-dialkyl-*N'*-alkyl phosphonate) sulphamides (**400**) in good yields[376].



(130)

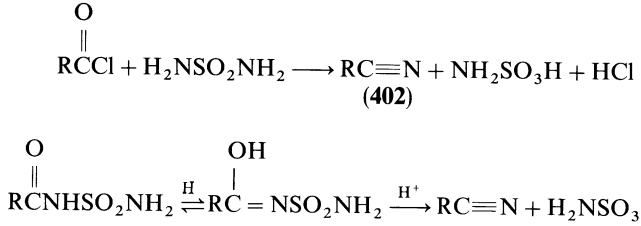
Unterhalt and Hanemacker have recently reported the synthesis of sweet-tasting *N*-(phenyl)-*N'*-carboxymethyl sulphamides (**401**)[377]. The compounds were prepared by the reaction (equation 131) of amino carboxylic acids with sulphuryl chloride and subsequent condensation with 4-substituted anilines followed by hydrolysis in base.



(131)

D. Reactions

Unsubstituted sulphamide $NH_2SO_2NH_2$ has recently been reported to be useful in functional group synthesis. Reaction of sulphamide with acid chlorides leads to a one-pot synthesis of nitriles **402**[378] (equation 132). The reaction is successful for a large variety of aliphatic and aromatic acid chlorides with electron-withdrawing and electron-donating substituents. Sterically hindered as well as heterocyclic nitriles are also obtained in high yields. The reaction is considered to proceed via the *N*-acylsulphamide, which is further enolized and cleaved to yield the nitrile **402** and sulphamic acid.



(132)

The reaction of diarylidenesulphamides (**403**), prepared by the reaction of sulphamide with benzaldehyde, with Grignard reagents followed by hydrolysis in pyridine and treatment with sodium hydroxide solution leads to the formation of substituted primary amines (**406**)[379] (equation 133). The reaction works equally well for both alkyl and aryl Grignard reagents and gives high yields in both cases. The hydrolysis of the sulphamides **404** with pyridine is considered to occur via an intermediate *N*-sulphonylamine ($C_6H_5CH(R)—N{=}SO_2$) which adds water to give the sulphamic acid ($C_6H_5CH(R)$-$NHSO_3H$), which is further hydrolysed to the sulphate **405**.

$$2C_6H_5CHO + NH_2SO_2NH_2 \xrightarrow[\text{toluene}]{H^+} (C_6H_5CH{=}N)_2SO_2 \xrightarrow{RMgX} \underset{\textbf{(403)}}{} \tag{133}$$

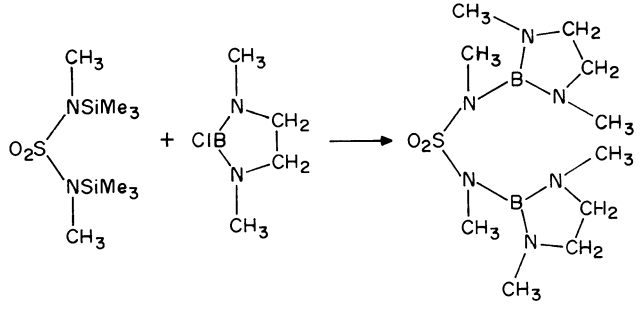
$$\underset{\textbf{(404)}}{(C_6H_5\overset{R}{\overset{|}{C}}HNH)_2SO_2} \xrightarrow[\text{Pyridine}]{H_2O} \underset{\textbf{(405)}}{(C_6H_5\overset{R}{\overset{|}{C}}HN)_2SO_4} \xrightarrow{NaOH} \underset{\textbf{(406)}}{C_6H_5\overset{R}{\overset{|}{C}}HNH_2}$$

The formation of adducts by sulphamide has been reported. Sulphamide reacted with water-free SO_2 and SeO_2 in nitromethane in a 1:1 and 1:2 ratio between 0 °C and 25 °C to give colourless crystals[380]. Aqueous solutions of these compounds showed them to be the 1:1 adducts $H_2NSO_2NH_2 \cdot H_2SO_4$ (**407**) and $H_2NSO_2NH_2 \cdot H_2SeO_4$ (**408**). The adducts were also obtained by reaction of sulphamide with H_2SO_4 and H_2SeO_4 without solvent. At higher temperatures disproportionation occurs (equation 134). IR spectra confirm the formation of the 1:1 adduct which is stabilized by proton exchange[381].

$$\underset{\textbf{(407)}}{H_2NSO_2NH_2 \cdot H_2SO_4} \longrightarrow 2NH_2SO_3H$$

$$\underset{\textbf{(408)}}{H_2NSO_2NH_2 \cdot H_2SeO_4} \longrightarrow NH_2SO_3H + NH_2SeOH \tag{134}$$

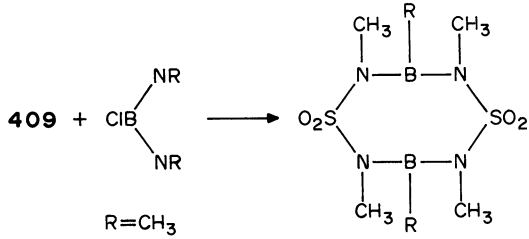
Sulphamides containing boron have been prepared by Einholz[382]. Reaction (equation 135) of the silylated sulphamide **409** with 2-chloro-1,3-dimethyl-1,3,2-diazaborolidine (**410**) gives the diborylated sulphamide *N,N'*-bis(1,3-dimethyl-1,3,2-diazaborolidine-2-yl)-*N,N'*-dimethylsulphamide (**411**). Reaction of the sulphamide **409** with $((CH_3)_2N)_2BCl$ yields the cyclic disulphamide, 1,1,5,5-tetroxo-2,4,6,8-tetramethyl-3,7,-bis(dimethylamino)-1λ^6,5λ^6,2,4,6,8,3,7-dithiatetrazadiboracin (**412**) (equation 136). The reaction of the sodium



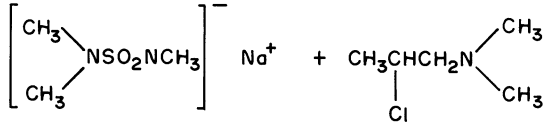
(135)

(409) **(410)** **(411)**

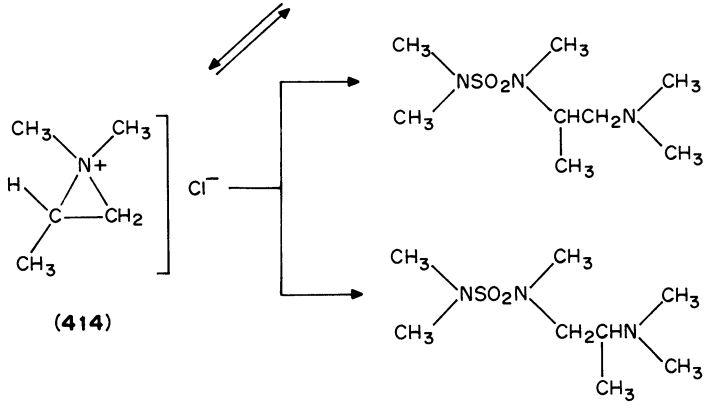
salt of *N,N,N'*-trimethylsulphamide (**345**) with 2-chloro-1-dimethylaminopropane (**413**) yields two *N,N,N',N'*-tetra-substituted sulphamide isomers (equation 137) which were separated by column chromatography[383]. The two isomers arise due to the fact that **413** is considered to initially form the three membered ring **414**, which can subsequently undergo (CH_2—N^+) cleavage or (CH_3)(H)C—N^+ cleavage and hence can give rise to both isomers.



(412) (136)



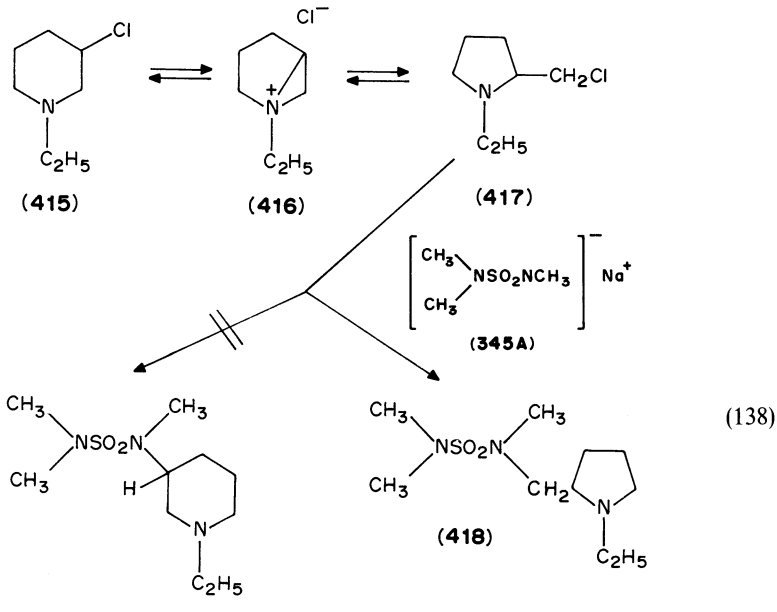
(345) (413)



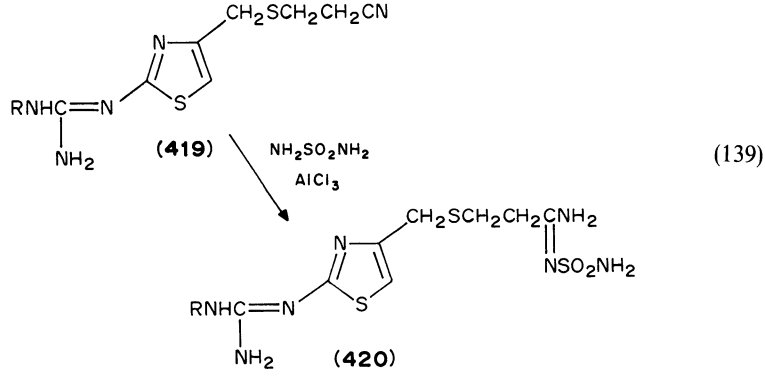
(414) (137)

In a similar reaction with 3-chloro-1-ethylpiperidene (**415**), *N,N,N'*-trimethyl-*N'*-(2-methylenepyrrolidine)sulphamide (**418**) is formed. The intermediate **416** undergoes ring contraction to yield 2-(chloromethyl)-1-ethylpyrrolidine (**417**), which then reacts with **345A** to give the tetra-substituted sulphamide **418** only (equation 138).

Reports on the use of *N*-sulphamoyl amidine derivatives as histamine H_2 receptor antagonists has prompted interest in the synthesis of these compounds. Thus the Lewis acid catalysed reaction of propionitriles **419** (R = H, alkyl) with sulphamide gives the 3-(4-thiazolemethylthio)propionamidine **420** (equation 139)[384]. The compounds were found useful as gastric secretion inhibitors.

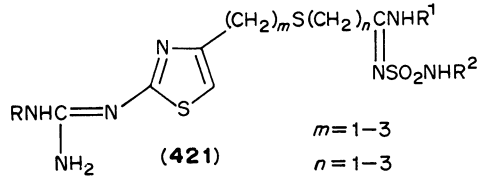


(138)



(139)

An analogues series of *N*-sulphamoyl amidine derivatives (**421**), in which the chain length between the thiazole and amidine is varied, have been prepared. The compounds also exhibited inhibition of gastric juice secretion[385].



$m = 1-3$

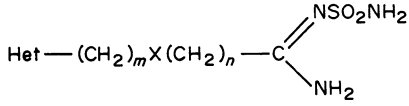
$n = 1-3$

R = H, alkyl, OH

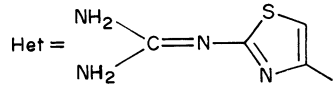
R^1 = alkyl, haloalkyl, NH_2

R^2 = alkyl, haloalkyl, alkenyl

Yanagisawa and collaborators[386] have reported a wide range of *N*-sulphamoyl- and *N*-sulphonylamidines and their pharmacological activities. The *N*-sulphamoylamidines were more potent in the inhibition of gastric acid secretion induced by histamine in anesthetised dogs than the *N*-sulphonylamidines. Two groups of *N*-sulphamoyl compounds were prepared and evaluated by reaction of sulphamide with the corresponding imidates. One series (**422**), in which the aromatic nucleus was varied and the terminal nitrogen atom of the sulphamoyl moiety was unsubstituted, showed that when the heterocyclic moiety was 2-[(diaminomethylene)amino]thiazole (famotidine) very high potencies were observed in the assays. Replacement of the sulphur atom X in **422** by a methylene group resulted in a compound with similar potency, while changing the S to sulphoxide resulted in markedly reduced potency. Incorporation of a methyl group at the guanidine nitrogen also led to a decrease in gastric inhibition. The effects of substituents on the nitrogen sulphamoyl function were also studied; the monomethyl compound was about one third as active as **422**. The *N,N*-disubstituted compound was significantly less active than the monosubstituted compound. Introduction of more lipophilic groups such as propyl, cyclohexyl and benzyl also resulted in decreased potency. These results showed that a free NH_2 is the most desirable for affinity to the H_2 receptor.



(422)



X=S

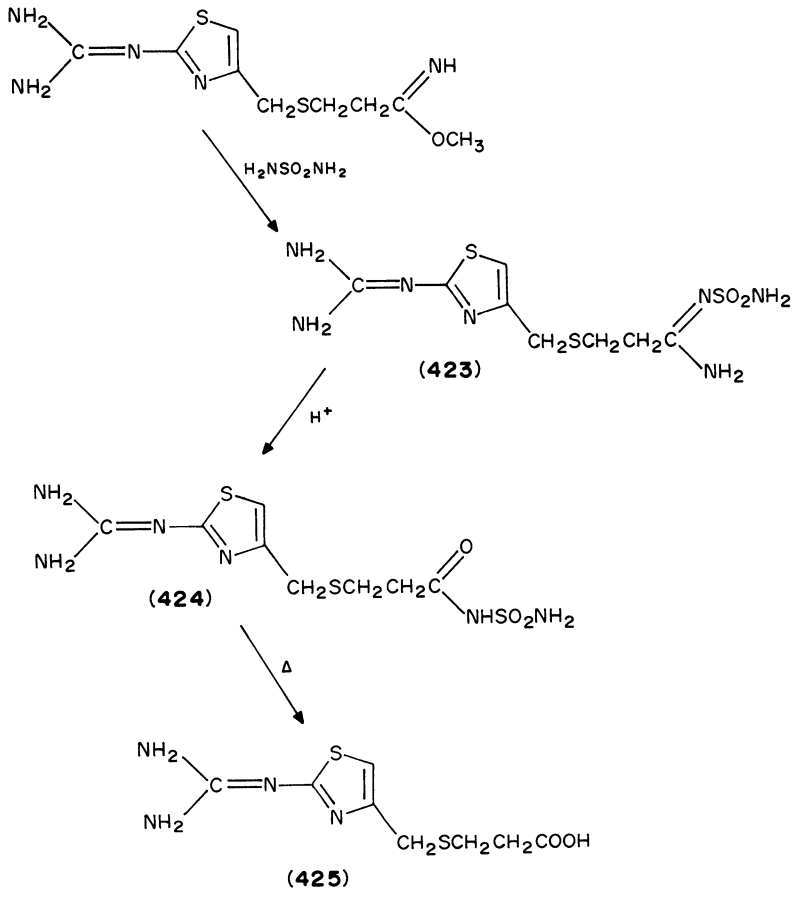
m=1

n=2

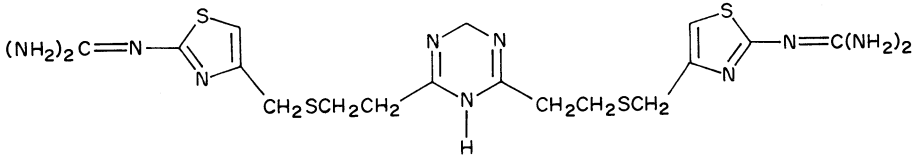
Yanagisawa[386] studied the chemistry of famotidine (**423**) 3-[[[2-[(diamonomethylene)-amino]-4-thiazolyl]methyl]thiol]-N^2-sulphamoylpropionamidine. The compound is prepared by reaction of sulphamide with the appropriate imidate (equation 140). Famotidine is relatively susceptible to acid-catalysed hydrolysis in the presence of excess hydrochloric acid to give the sulphamoyl amide **424** which, at elevated temperatures, is converted to the carboxylic acid **425**. A small amount of the compound **426** is also produced as a by-product. Compounds **423, 424, 425** and **426** have only weak antagonist potency and neither of the acid decomposition products is found to a significant extent in the metabolites of famotidine. Famotidine is excreted largely in the unchanged form, together with small amounts of the sulphoxide form.

Single-crystal X-ray determination of famotidine showed it to be in a strongly folded conformation with intramolecular hydrogen bonding between the guanidino nitrogen and sulphamoyl nitrogen and between the guanidino nitrogen and the thiazole nitrogen. This folded conformation has been observed in other H_2 receptor antagonists, e.g. cimetidine[387] and ranitidine[388], although this geometry may not represent the actual conformation bound at the H_2 receptor[389]. The ^{15}N NMR spectrum of famotidine is also reported. *N*-(trimethylsilyl)sulphamide, prepared by the reaction of sulphamide with Me_3SiX, has been used to prepare famotidine[390]. Sulphamide has also been condensed with a variety of imidates $R^3SCH_2CH_2C(:NR^2)OR^4$ oxidation with perbenzoic acid to the sulphoxide and reaction with triethylamine, and coupling with various heterocyclic thiols has yielded a variety of sulphamoylamidine antisecretory agents[391].

N-Sulphamoyldiphenylimidocarbonate (**427**), prepared by the reaction of sulphamide with diphenoxydichloromethane or dichloromethane, has been used as an intermediate for the synthesis of histamine H_2 antagonists. Thus the reaction of **427** with 3-[3-(1-piperidinylmethyl)phenoxy]propylamine (**428**) gave *N*-sulphamoyl-*N'*-3-[3-(1-piperidinylmethyl)phenoxy]propyl-*N'*-methylguanidine (**429**)[392].



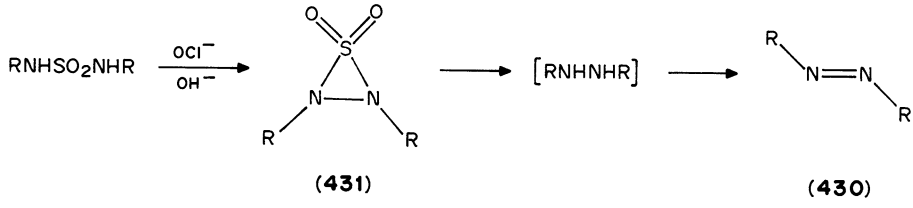
(140)



(426)

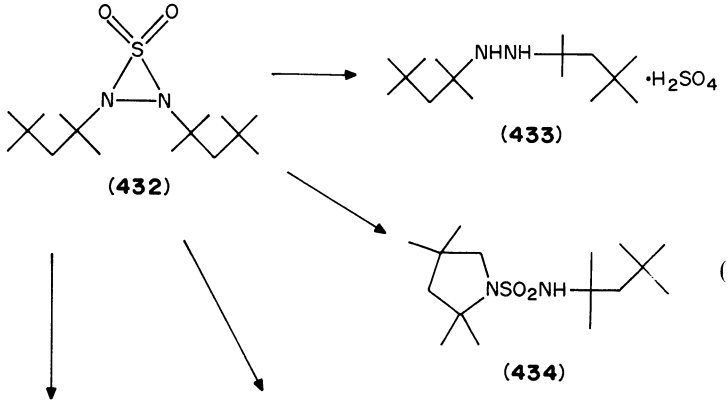
The alkali hypochlorite reaction of *N,N'*-dialkylsulphamides leads to the formation of dialkyldiazenes **430**. Ohme's group[393,394] has postulated thiadiaziridine-1,1-dioxides (**431**) as intermediates in the reaction (equation 141).

Timberlake's group[395–397], by using nonaqueous media for the hypochlorite reaction with sulphamides, isolated thiadiaziridine 1,1-dioxides (**431**) where both R groups are tertiary alkyl groups. Since then, a wide range of other thiadiaziridine-1,1-dioxides have been prepared[398,399].



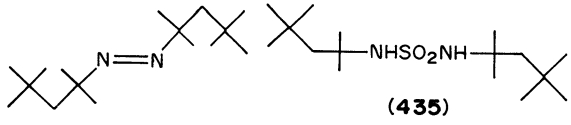
(431) (430)

(141)



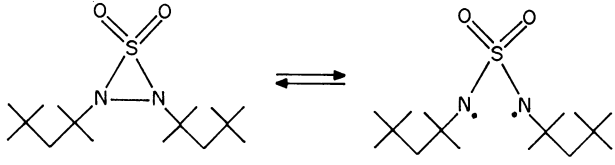
(432) (433) (434)

(142)



(436) (435)

The same group has subsequently prepared and studied the chemistry of a wide variety of these compounds. The reactions of *N*,*N*-bis(1,1,3,3,-tetramethylbutylthiadiaziridine-1,1-dioxide (**432**) is shown in equation 142[400]. Reaction of (**432**) with a wide range of reagents including NaOH, Cl_2, HCl, *t*-BuOCl and C_6H_5Cl at moderate temperatures for short periods leads to the formation of *N*,*N*′-bis(1,1,3,3-tetramethylbutyldiazenes) (**436**). **432** heated in benzene with thiophenol or tri-n-butyltin hydride leads to the formation of the symmetrical di-*tert*-octylsulphamide (**435**). Prolonged heating of **432** in benzene, toluene or cumene gives the rearranged sulphamide **434** (equation 142). The results are consistent with either direct reaction of the thiadiaziridine with the reagents or with initial reversible formation of the diradical **437** (equation 143); this mechanism was preferred

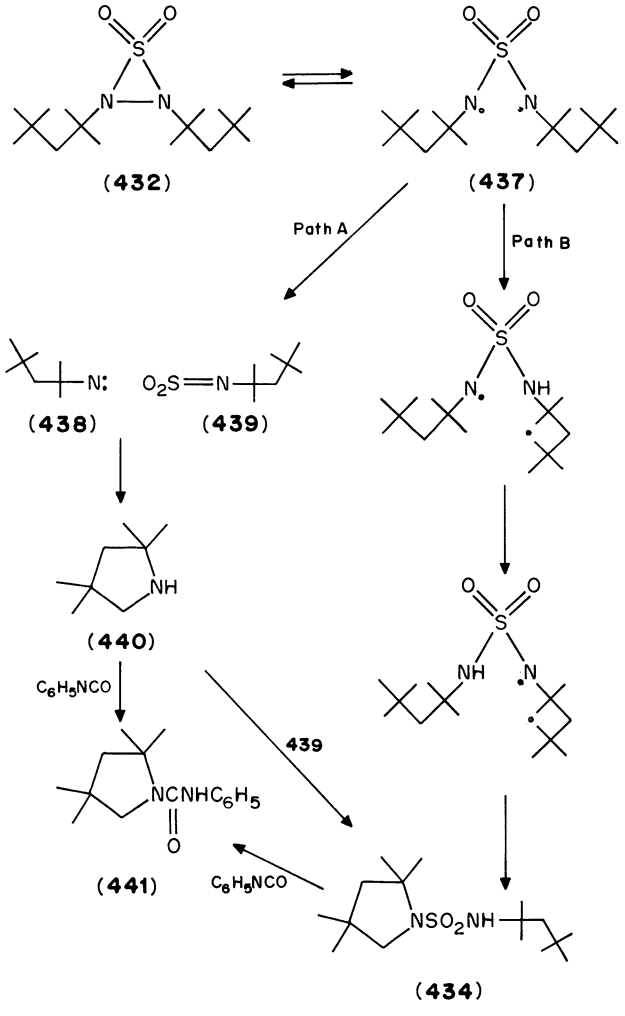


(432) (437)

(143)

even though no direct evidence of diradical existence using trapping reagents was observed.

Two main pathways for the formation of the rearranged sulphamide **434** can be considered (equation 144). Path B involves an intramolecular path for the formation of the sulphamide **434**. However, when the reaction was carried out in the presence of phenyl isocyanate, the urea (**441**) was isolated from the reaction mixture. This provided evidence for the existence of free 2,2,4,4-tetramethylpyrrolidine (**440**), which was considered to arise from the *tert*-octyl nitrene (**438**) by γ-hydrogen insertion. Later work[401], however, showed that when the rearranged sulphamide is heated in the presence of phenylisocyanate under identical conditions to those for its formation, pyrrolidinylurea (**441**) is formed in 60% yield. Thus the formation of **441** is not evidence of the existence of free **440**, because **434** once formed is capable of dissociation and reaction with phenylisocyanate to give **441**. In addition, attempts to independently generate *tert*-octyl nitrene failed to produce any



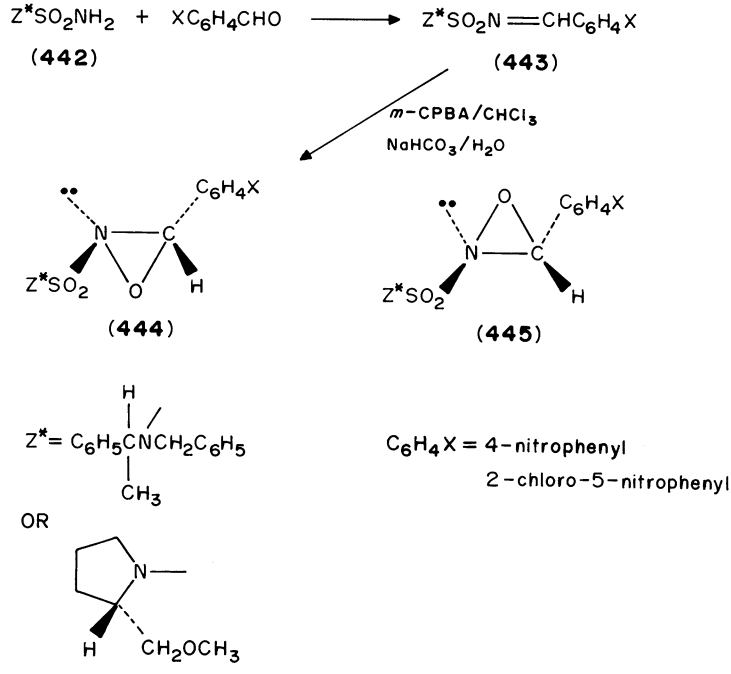
(144)

tetramethylpyrrolidine (**441**). Diazoalkanes, prepared by the hypochlorite oxidation of a wide range of *N,N'*-dialkylsulphamides, have found use as both polymerization and crosslinking catalysts[402,403].

Chiral sulphamides (**442**) have been prepared by Davis and coworkers[404,405]. The compounds are prepared by heating equivalent amounts of the amine with sulphamide (equation 145). **442a** was formed in 78% yield while **442b** was formed in 51% yield only after 5 days; however, the yield was improved to 66% when the two reagents were heated in the absence of the solvent for 24 hours at 90 °C. The chiral sulphamides were used to prepare a new class of chiral 2-sulphamyloxaziridines in a two-step process (equation 146). Reaction of the chiral sulphamides with aldehydes leads to the formation of sulphamylimines **443** in 95% yields. Biphasic oxidation (*m*-CPBA-$CHCl_3$/$NaHCO_3$/H_2O) yields the diastereomeric (*E*)-2-sulphamyloxaziridines **444** and **445**, which were separated by crystallization and chromatographic techniques.

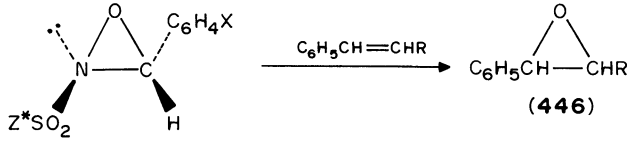
$$R^*RNH + NH_2SO_2NH_2 \longrightarrow \underset{\textbf{(442)}}{RR^*NSO_2NH_2} \qquad (145)$$

R*RNH = (a)(−)-(*S*)-*N*-(α-methylbenzyl)-*N*-benzylamine
(b)(+)-(*S*)-2-(methoxymethyl)pyrrolidine

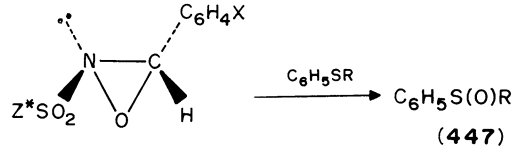


The chiral sulphamyloxaziridines are extremely useful in the asymmetric epoxidation of non-functionalized alkenes to **446**[406] (equation 147) and the oxidation of non-functionalized sulphides to sulphoxides **447**[407] (equation 148). High enantioselectivity for both types of reactions was observed with asymmetric bias increasing as the temperature of the reaction is decreased. The fact that oxaziridine (+)(*R,R*) (**444**) gives products with the *R,*(*R,R*) configuration while (−)(*S,S*) (**445**) gives products with the *S,*(*S,S*) configuration is

consistent with a planar transition state geometry, where lone pairs share a common plane with the oxaziridine ring.

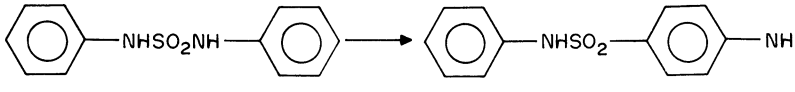


(+)(*R*,*R*)-1 (446) (147)

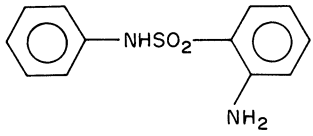


(−)(*S*,*S*)-2 (447) (148)

The rearrangement of *N*,*N*′-diphenylsulphamide **448** (equation 149) was first reported in 1961[408].



(448) (449) (149)



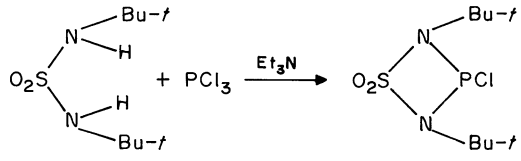
(450)

Recently, a new study of the rearrangement[409] showed that when **448** was heated in neat aniline, a second material isomeric with **449** and **448** was formed. X-ray crystal structure showed that the compound was 2-aminobenzenesulphonanilide (**450**). Using ^{14}C-labelled aniline and ^{14}C-labelled **448** it is reported that amine exchange occurs more rapidly than the rearrangement of **448** to **449** and **450**.

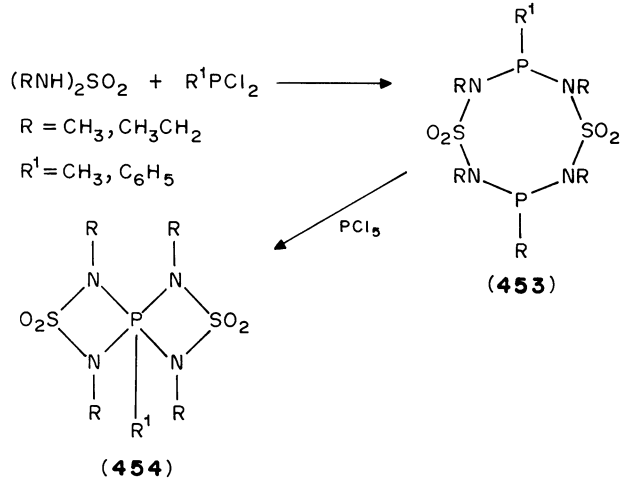
In an attempt to prepare four-membered heterocyclic ring systems containing nitrogen, sulphur and tricoordinate phosphorus, *N*,*N*′-dimethyl- and *N*,*N*′-diethylsulphamide were reacted with phosphorous trichloride in the presence of tertiary amines[410,411]. The products isolated from the reaction had the composition $[O_2S(NCH_3)_2PCl]_n$. The use of sterically bulky substituents on the nitrogen atoms was considered in an attempt to stabilize the four-membered ring. Thus the action of PCl_3 on *N*,*N*′-di-*tert*-butylsulphamide (**451**) in the presence of triethylamine led to the formation of 2,4-di-*tert*-butyl-3-chloro-1λ^6-thia-2,4-diaza-3-phosphetidine-1,1-dioxide (**452**) (equation 150), which represents the first example of a four-membered nitrogen–sulphur–phosphorus(III) ring. The monomeric nature of **452** is seen from its mass spectrum with a parent peak at *m*/*e* 273 and the structure is considered to have a slightly puckered four-membered ring with both nitrogens possessing trigonal-planar geometries.

When the reaction of *N*,*N*′-di-*tert*-butylsulphamide (**451**) was carried out using phosphinous chloride CH_3PCl_2 instead of PCl_3, the eight-membered heterocyclic com-

pounds **453** formed and when further reacted with PCl_5 gave the four-membered nitrogen–sulphur–phosphorus(V) ring system **454** (equation 151).

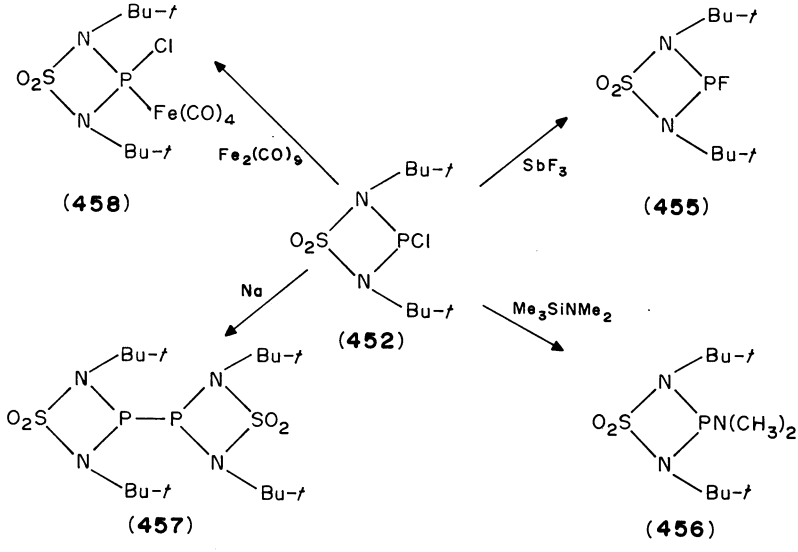


(150)



(151)

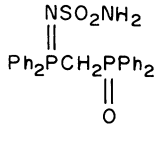
The chemical reactivity of the phoshetidine **452** is shown in equation 152 and shows that the ring remains intact during the reaction with SbF_3 in the presence of a catalytic amount of SbF_5 yields the 3-fluorophoshetidine (**455**). The metathetical reaction of **452** with



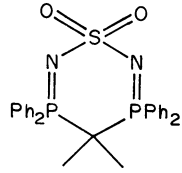
(152)

Me_3SiNMe_2 yields the *N*-dimethyl derivative **456**. Spectroscopic identification or attempted isolation of the P radical of **452** by reaction of **452** with sodium in octane failed, but the dimer phosphine **457** was isolated. **458** is obtained in quantitative yield by reaction of **452** with $Fe_2(CO)_9$.

Sulphamide reacts with bis(diphenylphosphino)methane (**459**) in the presence of diethylazodicarboxylate to give 69% yield of [(sulphamidodiphenylphospha-λ^5-azeno)methyl]diphenylphosphine oxide (**460**)[412] and 6% of the cyclic compound 3,3,5,5-tetraphenyl-4*H*-1,2,6,3,λ^5,5λ^5-thiadiazadiphosphorin-1,1-dioxide (**461**).



(460)



(461)

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