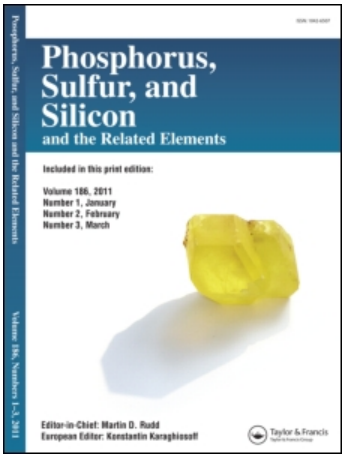

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INTERCHANGE REACTIONS OF AROMATIC THIOSULFINATES

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INTERCHANGE REACTIONS OF AROMATIC THIOSULFINATES

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Exchange reactions at ambient temperature in the dark between symmetrical aryl thiosulfinates Ar-S(O)-S-Ar are described. A polar mechanism involving a four-center transition state is proposed for the reaction, supported by the ease of fission of the S-S bond with the polarity introduced by the sulfinyl group. The thiosulfinate exchanges demonstrate a reaction common to a series of thioesters (disulfides/thiosulfinates) and their amides (sulfenamides/sulfinamides) differing in oxidation level of a sulfur atom but under conditions to be correlated with the type of functional group.

Keywords: Thiosulfinates; exchange reactions; sulfur-sulfur bond fission; electrospray mass spectrometry

INTRODUCTION

The instability of thiosulfinates compared to disulfides and thiosulfonates is well documented and has been explained by the weakening of the S-S bond with formation of the sulfinyl group [1]. The S-S bond energy of aryl thiosulfinates (36 kcal.mol^{-1} for the phenyl derivative [2]) is *ca* 20 kcal.mol^{-1} smaller than those for the corresponding disulfide and thiosulfonate. At ambient temperature and in the presence of light, thiosulfinates are known to disproportionate into the corresponding disulfides and thiosulfonates, both in the solid state on rigorous drying [3] and in solution [2, 4]. The optical stability of chiral thiosulfinates is also rather weak as they have been shown to racemize easily at 50°C in a number of protic and aprotic solvents [5]. The present results, reflecting the labile character of thiosulfinates, describe the interchange of aromatic derivatives, and suggest a bimolecular mechanism for the reaction.

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RESULTS AND DISCUSSION

Exchanges between symmetrical aryl thiosulfinates were carried out in the dark at both ambient temperature and 40°C. HPLC retention times for reactants and unsymmetrical products are reported in Table I for two chromatographic systems (normal and reverse phase).

TABLE I Exchange reaction of aryl thiosulfinates *p*-X-C_6H_4-S(O)-S-C_6H_4-Y-*p* at ambient temperature

Reactants		*Products*		*Chromatography (HPLC)*[ab]	
X	*Y*	*X*	*Y*	*Normal phase*	*Reverse phase*
H	H			10.9	11.8
		H	Cl	14.1	9.3
		Cl	H	14.1	9.3
Cl	Cl			18.3	7.7
H	H			10.9	11.8
		H	Br	15.3	9.15
		Br	H	15.3	9.15
Br	Br			22.1	7.4
CH_3	CH_3			17.5	11.9
		CH_3	Cl	18.0	8.8
		Cl	CH_3	18.0	8.8
Cl	Cl			18.3	7.7
CH_3	CH_3			17.5	11.9
		CH_3	Br	20.2	8.7
		Br	CH_3	20.2	8.7
Br	Br			22.1	7.4

a. Retention times are given in minutes. For the unsymmetrical derivatives, these are close to the average of the original components in both systems.
b. Details of HPLC conditions are given in the experimental section.

The temperature sensitivity of the reaction is illustrated by the reduction in time required for first detection of the mixed derivatives from 6 hours at

room temperature to 30 min at 40°C (at the concentration of 2×10^{-2} M). The time required for 25% of the symmetrical derivatives to exchange went from one week at room temperature to 30 hours at 40°C.

Products which built up to an equilibrium mixture with time were identified by electrospray-mass spectrometry (ES-MS) coupled to the HPLC system. Diaryl thiosulfinates have previously been studied by electron impact [6, 7] and chemical ionization [7] mass spectrometry.

Electrospray ionization (ESI) is particularly appropriate for the identification of such thermally unstable compounds as it allows analysis of sample ions at room temperature directly from solution [8]. The fragmentation patterns of both reactants and products are reported in Table II.

ESI mass spectra of diaryl thiosulfinates proved to be very simple to analyse, showing virtually only fragmentation at the unstable S-S bond. In most cases, the presence of the sodium-attached peak (M+23) was used as further diagnostic evidence of the molecular ion identity.

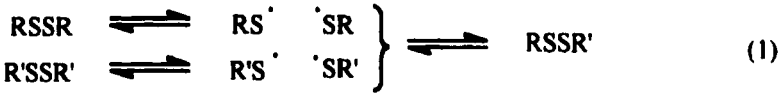
TABLE II Electrospray-mass spectrometry fragmentation patterns of aryl thiosulfinates *p*-X-C_6H_4-S(O)-S-C_6H_4-Y-*p*

Compound[a]		*Molecular ion*[b]	*Fragmentation pattern*[c] *m/z (%)*
X	*Y*		
H	H	234	125 (100), 235 (70), 257 (23)
CH_3	CH_3	262	139 (75), 263 (100), 285 (8)
Cl	Cl	302	159 (100), 161 (42), 303 (24), 305 (22), 307 (8), 325 (6)
Br	Br	390	203 (89), 205 (91), 391 (51), 393 (100), 395 (56), 415 (4)
H	Cl	268	125 (100), 159 (33), 269 (70), 271 (25), 291 (9)
Cl	H		
H	Br	312	125 (95), 203 (19), 205 (20), 313 (88), 315 (100), 335 (8)
Br	H		
CH_3	Cl	282	139 (68), 159 (36), 283 (100), 285 (47), 305 (15)
Cl	CH_3		
CH_3	Br	326	139 (85), 203 (16), 205 (17), 327 (88), 329 (100), 349 (2)
Br	CH_3		

a. Mixed derivatives were not resolved by HPLC.
b. Halogenated compounds molecular ions are given for ^{35}Cl and ^{79}Br.
c. Structural features from both reactants were taken in each asymmetrical derivative.

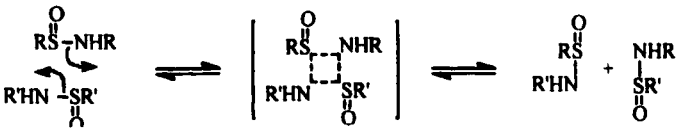
A feature of the reactivity of elemental sulfur, carried into many organic derivatives, is a capacity to react in a free radical or ionic manner in response to imposed conditions. This feature is shown in the changing pattern of conditions required for intermolecular exchanges of aromatic disulfides, sulfenamides and sulfinamides, ranging from a combination of higher temperature coupled with weak photo effect for disulfides [9], through a slight photo activation without need for higher temperature for sulfenamides [10], to ready exchanges between sulfinamides without either thermal or photo promotion [11].

This sequence has been discussed in terms of a change from a basically free radical process (1) for the formation of mixed disulfides to an extent expected from a statistical expectation to a four-center bimolecular reaction for the sulfenamides and sulfinamides (2), proceeding with greater ease with the latter group in response to the greater influence of the sulfinyl group on the S-N bond.



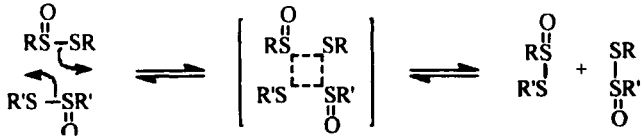
(1)

The material balance for (2) is confirmed [10] by the absence of secondary products such as thiosulfonates or (hydr)azobenzenes arising from alternative recombinations of a free radical process.



(2)

A similar four-center process is now proposed for aryl thiosulfinates exchange, initiated by the difference in polarity of the two sulfur atoms. The recognized electrophilicity of the sulfur of the sulfinyl group leaves it open to "attack" by the nucleophilic sulfenyl sulfur of an alternate molecule with its free electron pairs. The arrangement for a four-center transition state (3) is completed by involvement of the second pair of sulfur atoms in a similar manner. Material balance confirmed that exchanges occur without loss to secondary processes.



(3)

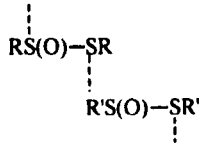
The specific polarity of the sulfinyl group is a necessary factor in thiosulfinates exchanges. The failures of disulfides and thiosulfonates to exchange with thiosulfinates is probably due to inability, for different reasons, to complete the four-center transition state. With the disulfides, the second sulfinyl group is missing and with the thiosulfonates the strength of the sulfone-sulfur conjugative interaction probably precludes this type of reaction.

Interchange between alkyl thiosulfinates MeSOSMe/EtSOSEt at 96°C yielding unsymmetrical derivatives has been suggested to proceed *via* scrambling reactions [12, 13], with sulfenic acids as key intermediates which attack alternative thiosulfinates in a propagation sequence (4).

$$\begin{aligned} &\text{MeS(O)SMe} \rightleftharpoons \text{MeSOH} + \text{CH}_2\text{=S} \\ &\text{MeSOH} + \text{EtS(O)SEt} \rightleftharpoons \text{MeS(O)SEt} + \text{EtSOH} \end{aligned} \qquad (4)$$

This process is not applicable to the aryl thiosulfinates since formation of sulfenic acid initiators by the reaction indicated is not possible.

The aryl interchanges may be considered as a chain reaction but such a process approaching a ternary character places greater demands for specific collisions of a multicenter process (5).



(5)

Rather the bimolecular thiosulfinate exchanges demonstrate a reaction established for a series of thioesters and their amides, differing in the oxidation level of a sulfur atom with varying degrees of reactivity (6).

$$\begin{array}{lll} \text{RSSR}^{(*)} & \text{———} & \text{RSNHR} \\ \text{disulfide} & & \text{sulfenamide} \\ & & \\ \text{RS(O)SR} & \text{———} & \text{RS(O)NHR} \\ \text{thiosulfinate} & & \text{sulfinamide} \end{array} \qquad (6)$$

$^{(*)}$ Ester of thiosulfenic acid

EXPERIMENTAL

Thiosulfinates preparation

Symmetrical aryl thiosulfinates were prepared in 85–95% yield by oxidation of the corresponding disulfides with one equivalent of freshly recrystallised *meta*-chloroperbenzoic acid in dry dichloromethane at –50°C [14]. They were purified from unreacted disulfide and small amounts of thiosulfonate by-product by preparative normal phase HPLC and recrystallised to satisfactory elemental analysis and melting points. HPLC separations were performed using a 250 × 22.5 mm, 10 µm Econosphere Sil® column (isocratic elution with hexane:ethyl acetate 96.5:3.5, flow rate 8 mL/min) purchased from Alltech (Deerfield, IL, USA).

Thiosulfinates interchange reactions

In a typical experiment, equimolar amounts of phenyl benzenethiosulfinate (47 mg) and *p*-chlorophenyl *p*-chlorobenzenethiosulfinate (57 mg) in benzene (10 mL) under nitrogen were allowed to stand at room temperature in the dark. Aliquots were withdrawn at intervals for HPLC/MS analysis. Authentic samples of pure symmetrical aryl thiosulfinates were also allowed to stand in similar conditions. Those preparations remained unchanged for up to one week at ambient temperature and 48h at 40°C. After this period, small amounts of disproportionation products started to appear.

Reverse phase thiosulfinates LC-MS analysis

ESI spectra were recorded using a Quattro II triple quadrupole mass spectrometer (Micromass, Altrincham, Cheshire, UK) fitted with an electro-

spray source. HPLC analysis were performed on a Hewlett-Packard (Palo Alto, CA, USA) 1090 liquid chromatograph equipped with a ABI Analytical Spectroflow 757 variable wavelength detector. The UV trace monitored at 260 nm was acquired by the MassLynx data system (Micromass) along with the MS data. A split of ~ 10:1 (UV detector:MS) was used with the LC-MS. Reverse phase separations were performed using a 250 mm × 4 mm, 5 μm Inertsil® ODS2 C18 column (isocratic elution with methanol:water 75:25, flow rate 0.6 mL/min) purchased from SGE (Ringwood, Vic, Australia). Two alternating mass spectrometer scan functions were used, one at a cone voltage of 35 V and the other at a cone voltage of 70 V to induce fragmentation. The fragment intensities reported are taken from the 35 eV scan. The mass spectrum was scanned from 120 to 600 mass units in 2 seconds.

Normal phase thiosulfinates HPLC analysis

Normal phase HPLC analysis were performed on the system described above. The UV trace monitored at 260 nm. Separations were performed using a 250 × 4.6 mm 5 μm Econosphere Sil® column (isocratic elution with hexane:ethyl acetate 96.5:3.5, flow rate 1.5 mL/min) purchased from Alltech.

Suitability of LC-MS for quantitative analysis of thiosulfinates interchange reactions

Authentic samples of pure symmetrical aryl thiosulfinates were analysed both by normal and reverse phase HPLC as described above. These chromatograms showed only one peak with retention time different from those of disproportionation products (disulfide and thiosulfonate) in both systems.

Acknowledgements

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