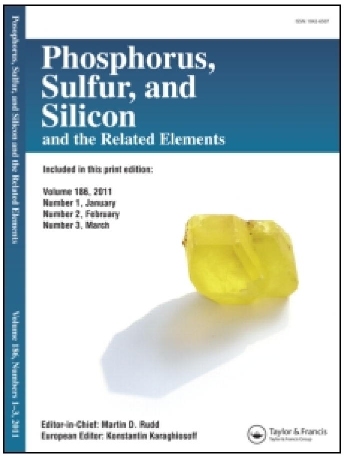

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CO-OXIDATIONS OF SQUALENE WITH DISULFIDES AND THIOSULFINATES

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Comparisons of the activities of alkyl and aryl disulfides in inhibiting the autoxidation of squalene show the greater efficiency of the alkyl derivatives. The effect of electron donating substituents in aryl derivatives, promoting efficiency in the order $CH_3O > CH_3 > H$, is reversed in the thiosulfinates when added directly, although they are considered to be inhibitors formed *in situ* from the disulfides. The anomaly is discussed in terms of rates of oxidation and stabilities of the oxidation products and leads to the concept of thiosulfinate/disulfide mixture as a more efficient antioxidant.

Key words: Antioxidants; disulfides; thiosulfinates; sulfinyl group; stability.

INTRODUCTION

It has long been recognized that the prior addition of organic sulfides and disulfides to olefins usually, but not always, results in retardation of autoxidation. However the efficiency of retardation is not uniform, varying considerably according to the structure of both olefin and sulfur additive. In extreme cases addition may result in accelerated oxygen uptake. Earlier studies of the role of sulfur compounds in olefin autoxidation used petroleum fuels and lubricating oils as substrates,[1] where the approach considered that sulfur compunds provided oxidizable substrates for reaction with hydroperoxides thereby removing the catalyst potential for chain-initiating free radicals otherwise resulting from their decomposition. Effectiveness in petroleum products has frequently been measured at temperatures about 140–150° which are related to conditions of use[2] but which make difficult, if not impossible, dissection of reaction sequences. Presently in the context of requiring an olefinic substrate related to the rubber molecule, the isoprenoid hydrocarbon, squalene, has been used to dissect the influences of disulfide structure and temperature on autoxidation.

RESULTS AND DISCUSSION

Uptake rates measured at 75° showed that in the presence of disulfides retardation occurred with squalene and other olefins after initial absorption of a small amount of oxygen, indicative of *in situ* formation of an inhibitor. The effect of concentration of an alkyl derivative, di-*n*-butyl disulfide is shown in Figure 1.†

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† Thanks are due to Dr. D. Barnard for permission to quote these results on alkyl disulfides.

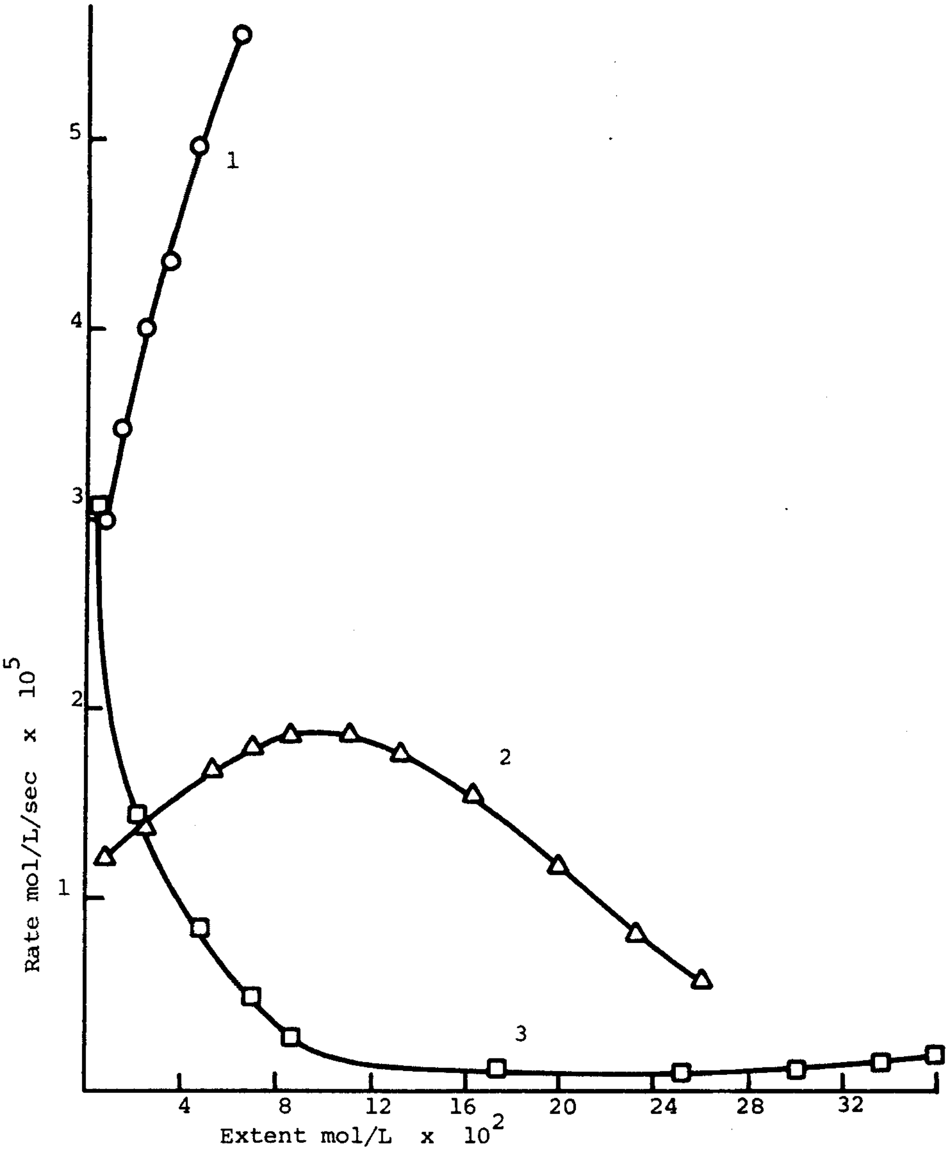


FIGURE 1 Rates of uptake of oxygen by squalene at 75° in the presence of di-*n*-butyl disulfide: 1, 0.057 M; 2, 0.105 M; 3, 0.25 M.

The concentration-dependent deflection of curves from the usual straight line of controls, ranging from the slight effect at the lowest concentration through the rather remarkable hump with the intermediate concentration, to the rapid decline and maintained low rate at the highest concentration, provides clear evidence of competing processes between oxygen uptake and *in situ* formation of inhibitor identified as thiosulfinate.[3]

Comparisons of the influences of alkyl and aryl disulfides are shown in Figure 2 where the superior performance of di-*n*-butyl disulfide requires its own time scale.

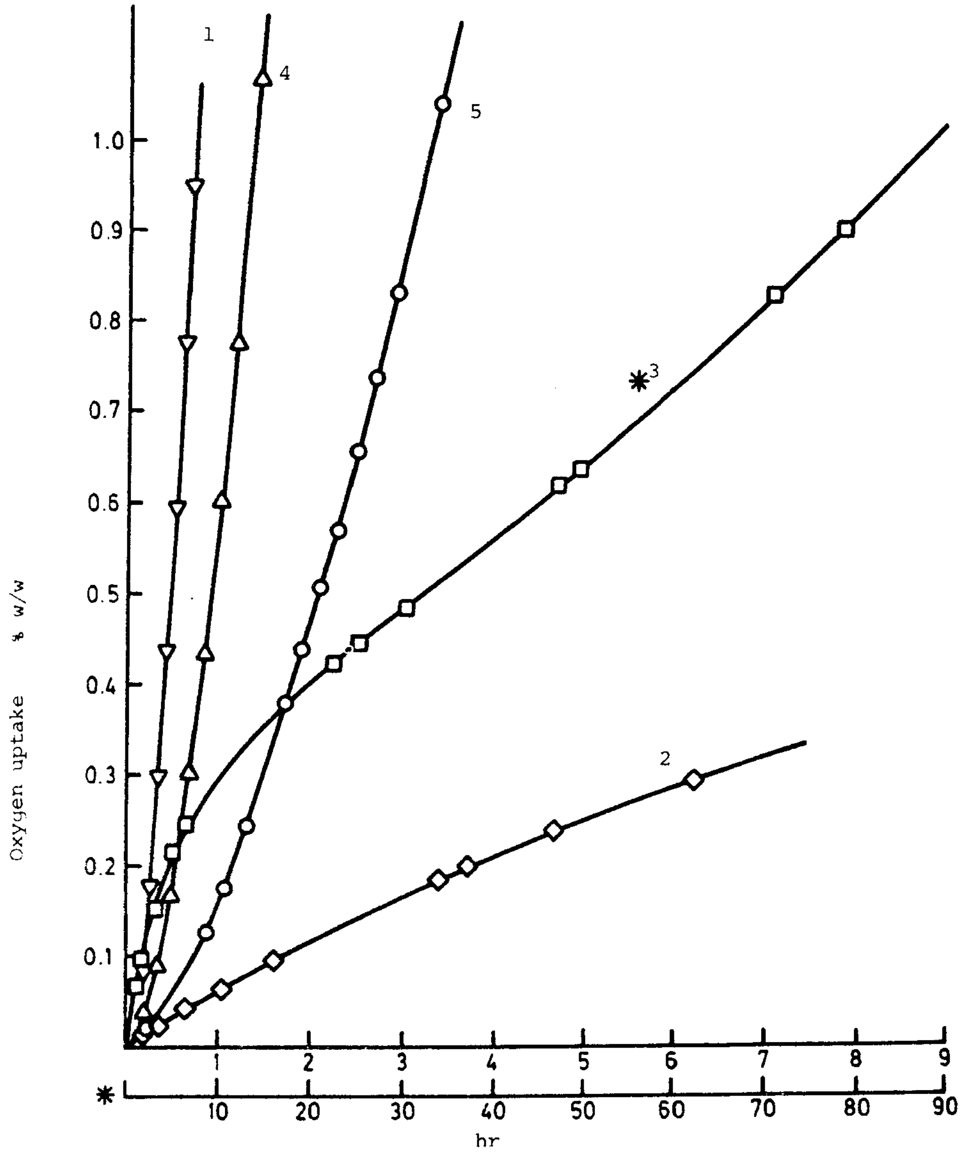


FIGURE 2 Oxygen uptake by squalene in the presence of disulfides (0.25 M): 1, control; 2, $(C_2H_5S)_2$; 3, $(n\text{-}C_4H_9S)_2$; 4, $(C_6H_5S)_2$; 5, $(pCH_3OC_6H_4S)_2$.

The importance of disulfide structure is evident. Results for alkyl and aryl derivatives fall into entirely different areas with the former giving markedly superior retardation.

Increase in chain length of the alkyl group, ethyl to *n*-butyl, gives an increase in efficiency of almost one order of magnitude. Despite their relatively poor performance structural influence on retardation is shown by aryl derivatives. An arbitrary end point, time to 1% w/w oxygen uptake, reached in 45 minutes in the control is doubled in the presence of diphenyl disulfide and then approximately

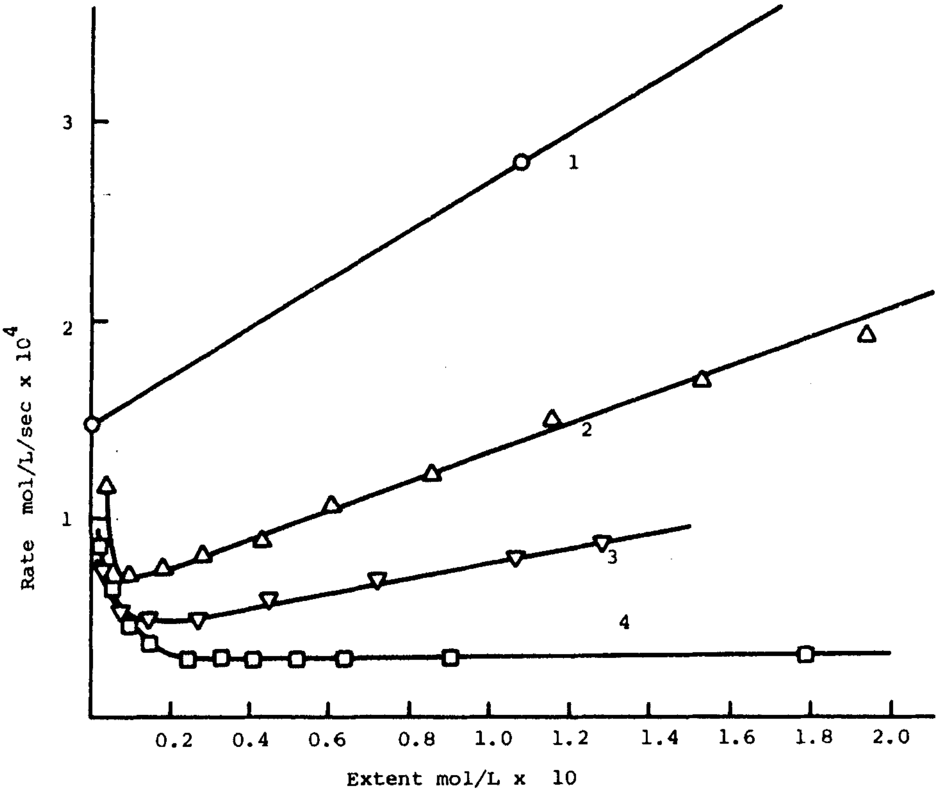


FIGURE 3 Oxygen uptake by squalene at 60° in the presence of aryl disulfides (0.25 M): 1, control; 2, $(C_6H_5S)_2$; 3, $(p\text{-}CH_3C_6H_4S)_2$; 4, $(p\text{-}CH_3OC_6H_4S)_2$.

redoubled in the presence of di-*p*-methoxyphenyl disulfide, but the point is re-emphasized that the most active aryl derivative is still very inferior to the alkyl derivatives as a source of retarder.

An expectation that substituent influence on the performance of aryl disulfides might be better resolved at lower temperature even at sacrifice to a lower control rate was realized by determinations at 60° (Figure 3).

Several important features of co-oxidations are now shown. The initial uptake of a small amount of oxygen prior to retardation not discernible at 75°, is now evident. Substituent influence is strong with retardation efficiency enhanced by electron donating groups but to different degrees. In the presence of 2 and 3 uptake of oxygen proceeds after reaching a minimum rate with the slope of the curves suggesting that inhibition is competing less successfully with uptake as time proceeds.

By contrast in the presence of 4 the rate drops to a much lower level at which it is maintained over the period during which uptake in the presence of 2 and 3 is increasing. It must be noted however that all curves show retardation rather than inhibition. Thus to the concept of oxygen uptake, inhibitor formation and retardation efficiency, must now be added inhibitor stability, all of which are subject to temperature control summarized in Table I.

TABLE I

Effect of temperature on disulfide inhibition of squalene autoxidation (c = 0.25 M)

Oxidizing system	Time to 1% w/w uptake[a]		Retardation ratio[b]	
	at 75°	at 60°	at 75°	at 60°
Squalene—control	0.75	2.5	—	—
+ di-*n*-butyl disulfide	85	—	113	—
+ diphenyl disulfide	1.5	5.5	2.0	2.2
+ di-*p*-methylphenyl disulfide	1.66	12	2.2	4.8
+ di-*p*-methoxyphenyl disulfide	3.33	24	4.4	9.6

[a] hr

[b] $\text{Retardation ratio} = \dfrac{\text{Time to 1\% uptake with additive}}{\text{Time to 1\% uptake in control}}$

The superior protection given by alkyl disulfides may reflect these contributing factors. First if it accepted that formation of thiosulfinate is a common initial reaction with oxidation regarded as an electrophilic process, then the inductive effects of alkyl groups contributing to a higher electron density at the reaction center as opposed to a withdrawing effect in the aryl derivatives, must result in faster oxidation. In this event alkyl derivatives will be providing a substrate for faster removal of hydroperoxide an important point in opposing the relatively greater catalytic efficiency of unimolecular free radical decomposition at lower concentrations.

Substituent effect on the reaction of aryl disulfides with excess *tert*-butyl hydroperoxide is shown in Figure 4.

The influence of the methoxyl group is so marked that the thiosulfonate, as a second stage oxidation product, appears in relatively large amount before the thiosulfinate from diphenyl disulfide is detectable as an initial product. It therefore becomes apparent that under these conditions there is a limit to the time which thiosulfinate remains in the solution.

Confirmation of the relative rates of oxidation comes when the two disulfides compete for a lesser amount of hydroperoxide (Figure 5).

The build-up of 1 from di-*p*-methoxyphenyl disulfide, starting almost immediately in the heating period, proceeded to an extent which fitted well with the results of separate oxidations. In this situation the level of products from diphenyl disulfide did not reach great heights.

In contrast with the separate oxidations, the level of thiosulfonate 2 does not rise despite the relative abundance of thiosulfinate available for the second stage oxidation. This seems to be associated with the most interesting feature of the oxidation *viz* appearance of a mixed thiosulfinate 4 for which the structure R.SO.S.R′ is suggested. Its appearance is accompanied by a decline in the symmetrical dimethoxylated derivative 1, without a rise in thiosulfonate 2 which could be expected from further oxidation or disproportionation. It is suggested that 4 may be the result of an intermolecular exchange with diphenyl disulfide, details of which remain to be determined. Formation of this derivative assists in explaining the low yield of products from diphenyl disulfide since in addition to the slower initial oxidation rate, its concentration is reduced in formation of the mixed thiosulfinate as struc-

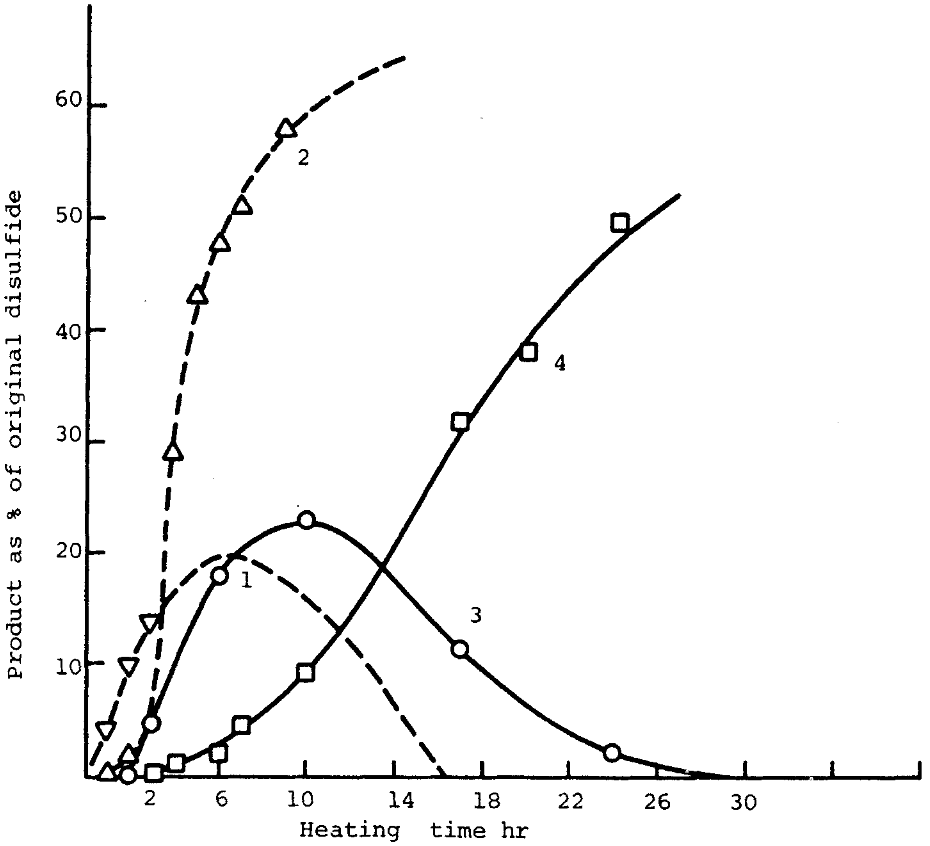


FIGURE 4 Products from the oxidation of aryl disulfides (1M) by *tert*-butyl hydroperoxide (5 M) in benzene at 60°: 1, R.SO.S.R; 2, $R.SO_2S.R$; 3, R'.SO.S.R'; 4, $R'.SO_2S.R'$; R = p-$CH_3OC_6H_4$; R' = C_6H_5.

tured. The importance of the oxidation with a lesser amount of oxidant lies in its replication of conditions existing at the beginning of an autoxidation when the concentration of hydroperoxide is relatively low.

The lack of build-up in thiosulfonate concentration is noteworthy since separate second step oxidations of thiosulfinate proceeded at a fast rate (Figure 6).

There has been much discussion on the oxidation of thiosulfinates to thiosulfonates in which attention has been focussed on attack at the sulfenyl sulfur as the more electron rich site leading to initial formation of an α-disulfoxide.[3] Recent low temperature oxidation confirms this view.[4] In the present context it could be envisaged that faster rates of oxidation of alkyl thiosulfinates would continue the disulfide comparison thereby sustaining a faster effect on hydroperoxide removal.

Differences in the kinetic behavior of phenolic and sulfur-containing antioxidants have been related to differences in mode of action.[5] On the one hand phenolics act as chain breakers by functioning as alternate hydrogen donors converting peroxy radicals to hydroperoxides, whereas sulfur derivatives based on their relative ineffectiveness in inhibiting azoisobutyronitrile initiated oxidations which would lead to peroxy radicals, function as peroxide destroyers. The formation of thiosulfinate from disulfide with potential for further oxidation fits this view.

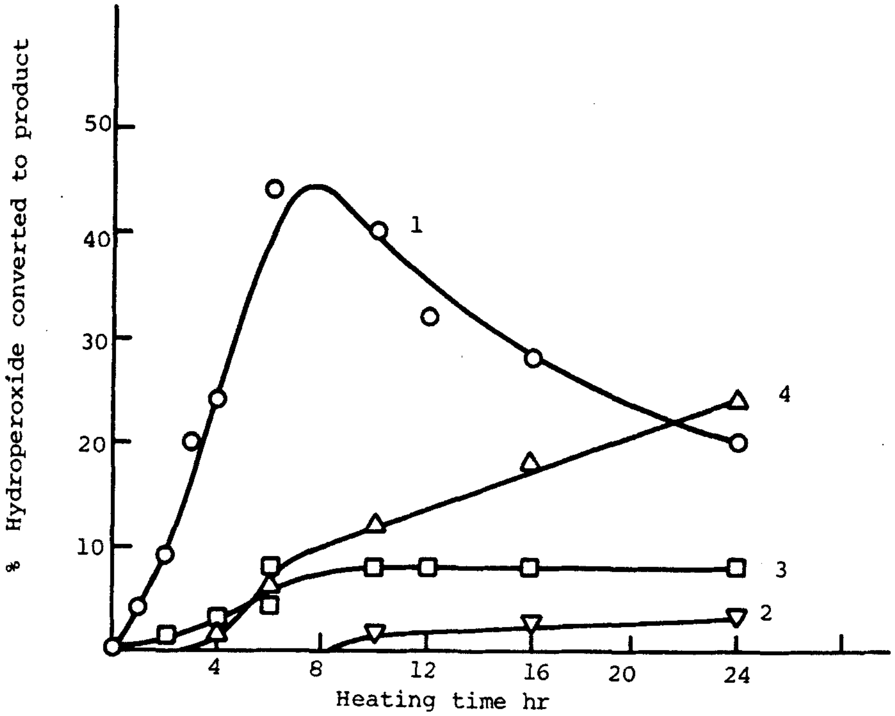


FIGURE 5 Products from competitive oxidation of disulfides by *tert*-butyl hydroperoxide in benzene at 60°: 1, R.SO.S.R; 2, $R.SO_2S.R$; 3, R'.SO.S.R'; 4, $R.SO_2S.R'$; R = p-$CH_3OC_6H_4$; R' = C_6H_5.

Thus it seems that in oxidations where there is excess disulfide it could be acting as a competitive protective agent for thiosulfinate. Evolving from the suggestion of a two step action of disulfides in providing substrates for hydroperoxide removal and at the same time giving thiosulfinate inhibitors, it appeared logical to test thiosulfinate activity by direct addition using a minimal amount to simulate formation at an early stage of the process. Results are shown in Figure 7.

Results are exactly the opposite to what might have been predicted from rates of formation in the oxidation of disulfides. Only the parent compound **1** displayed a reasonable retardation period, about 20 hr judged by the tangent extrapolation method. It is clear that the antioxidant action originating from disulfides is more complex than merely involving hydroperoxide destruction followed by thiosulfinate action, a situation which leads to consideration of thiosulfinate stability. In particular the question arises as to whether thiosulfinate instability means that antioxidant action requires replenishment from disulfide and/or whether entities formed in the decomposition offer competition between pro- and antioxidant action.

Differences in the stability of alkyl and aryl disulfides, which provide a basis for variations in the activities of derived thiosulfinates, may be partially explained by differences in the respective bond strengths. From kinetic evidence the S—S bond strength of diaryl disulfides is about 10 k cal/mol weaker than that of alkyl disulfides. The effect of oxidation is to lower the bond energy so that the S—S bond of thiosulfinates has been classified as unusually weak. Mass spectrometric appearance

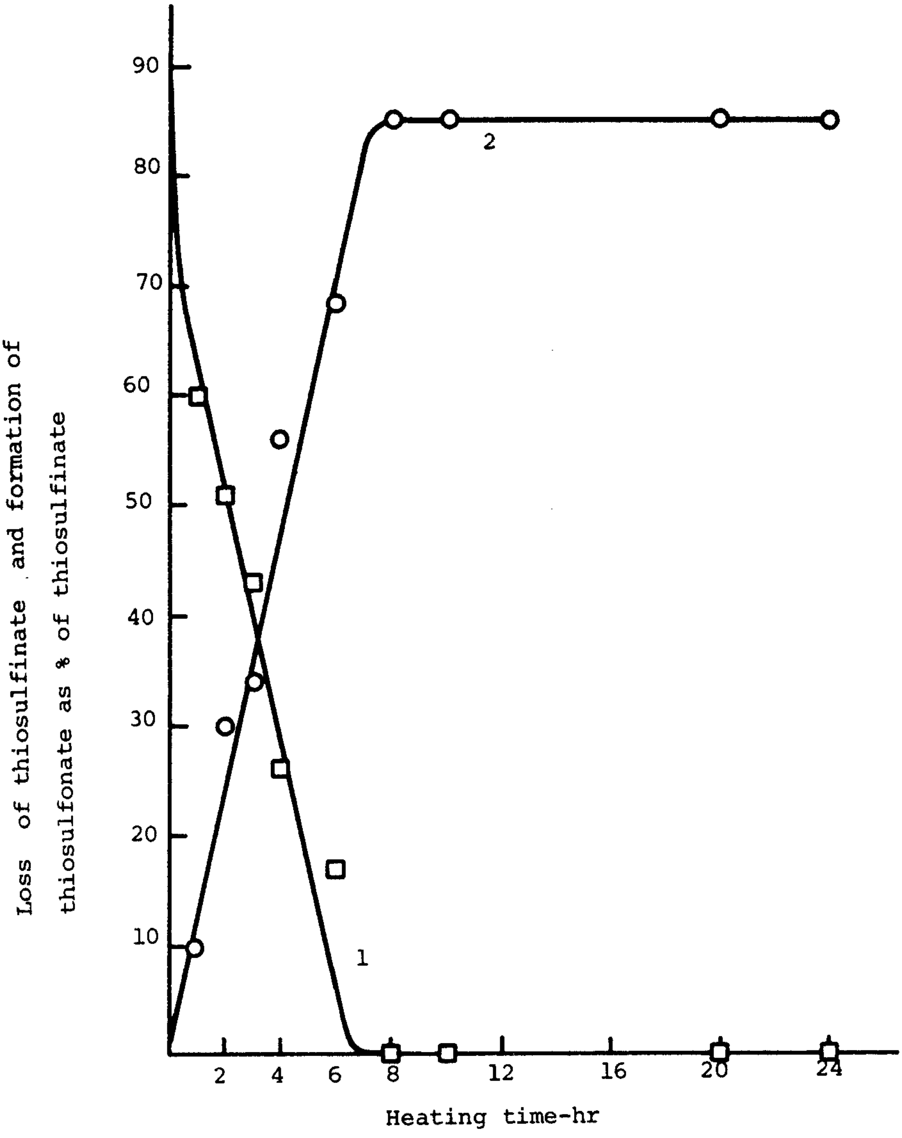


FIGURE 6 Oxidation of phenyl benzenethiosulfinate by *tert*-butyl hydroperoxide in benzene at 60°: 1, R.SO.S.R; 2, $R.SO_2S.R$.

potential measurements place the bond strength of methyl methanethiosulfinate at 45 k cal/mol compared to the similarly determined value for dimethyl disulfide at 70 k cal/mol. Other reports give 46 ± 4.6 k cal/mol and 75 k cal/mol respectively which means that the bond energy is lowered by about 29 k cal/mol in the thiosulfinate.

Since the relative difference in the bond strengths of the disulfides is maintained in the thiosulfinates it follows that the bond energy of aryl thiosulfinates reported at 34.5 k cal/mol is about 10–12 k cal/mol lower than that of the alkyl derivatives.[9]

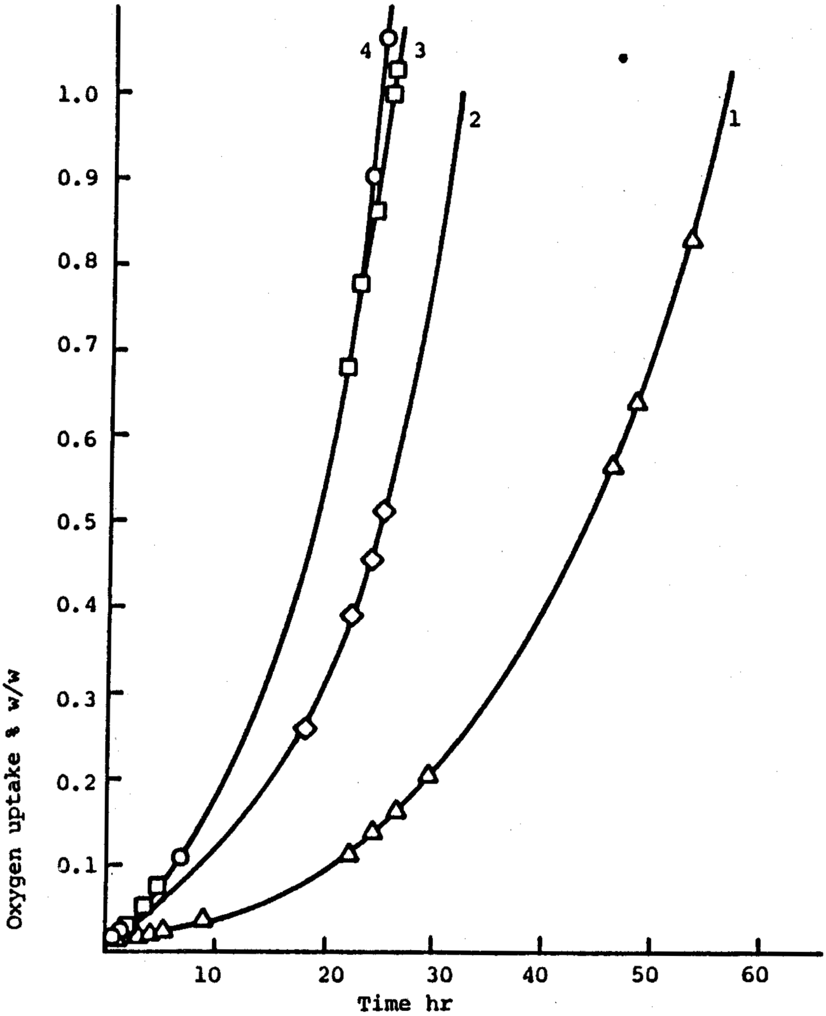
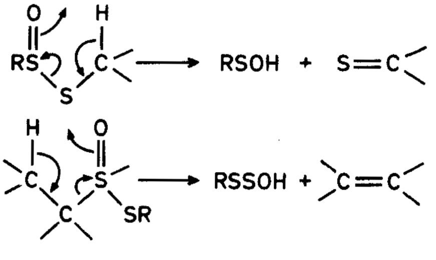


FIGURE 7 Autoxidation of squalene at 60° in the presence of thiosulfinates R.SO.S.R′ (0.005 M): 1, R = R′ = C_6H_5; 2, R = p-$CH_3OC_6H_4$, R = C_6H_5; 3, R = C_6H_5, R′ = p-$CH_3OC_6H_4$; 4, R = R′ = p-$CH_3OC_6H_4$.

The stability of alkyl thiosulfinates is increased by increase in the chain length of the alkyl substituents.[9]

Alternatively decomposition of alkyl thiosulfinates may proceed *via* intramolecular reactions involving α-sulfenyl or β-sulfinyl protons in elimination processes.[10]



The decomposition of methyl ethanethiosulfinate has been discussed from this point of view so that inhibitor activities of alkyl thiosulfinates have been ascribed to sulfenic and sulfinic acids and ultimately sulfur dioxide acting as catalysts for decomposition of hydroperoxides by non-radical processes.[10–12] However, it is also necessary to be aware of built-in pro-oxidant functions as from dithiopropionate esters[13] and the alternative radical producing sulfinic acid-hydroperoxide reaction.[14]

$$R.SO_2H + R'OOH \rightarrow R.SO_2^{\cdot} + H_2O + R'O^{\cdot}$$

Decompositions involving α-sulfenyl and β-sulfinyl protons are not available to aryl thiosulfinates but following upon the earlier discussion on its stability the

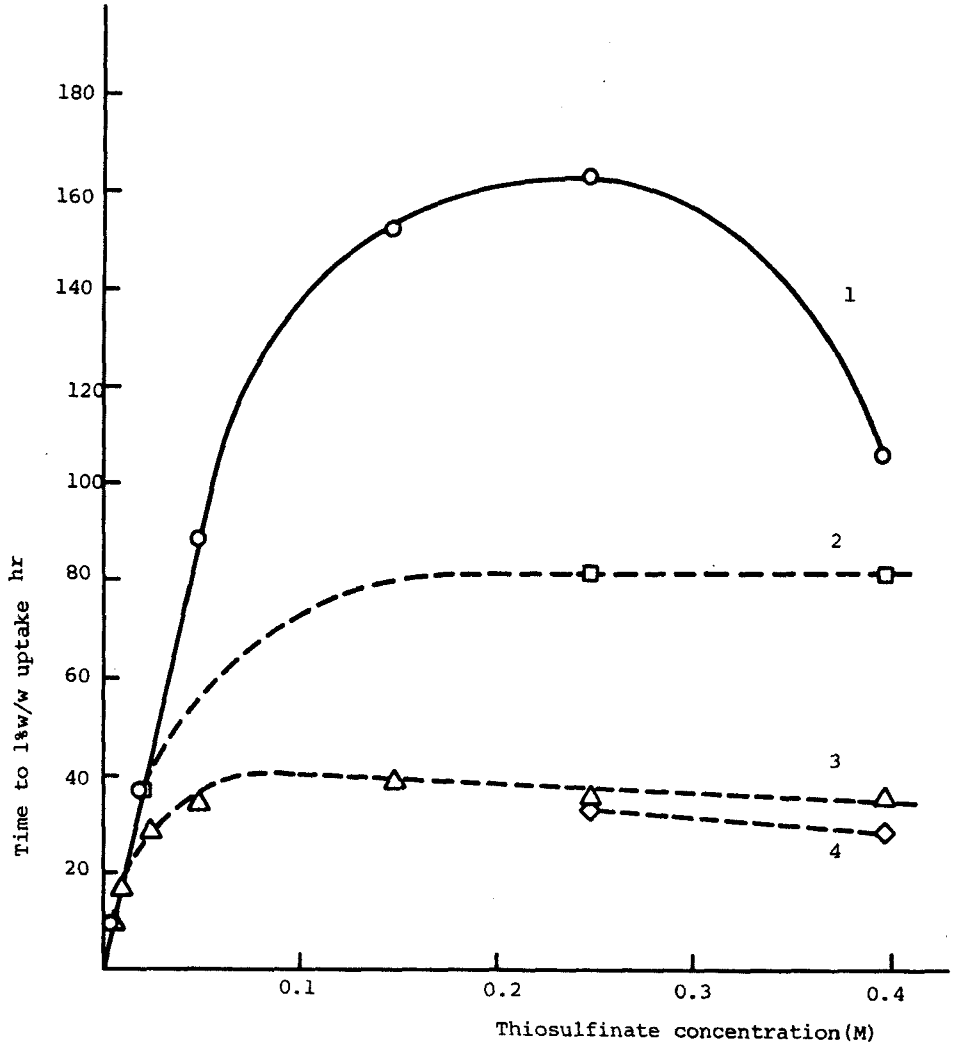


FIGURE 8 Effect of thiosulfinate concentration on the autoxidation of squalene at 75°: 1, R = R = C_6H_5; 2, R = p-$CH_3OC_6H_4$, R = C_6H_5; 3, R = C_6H_5, R = p-$CH_3OC_6H_4$; 4, R = R′ = p-$CH_3OC_6H_4$.

possibility of chain initiation resulting from attack on the olefin by sulfenyl radicals from S—S bond homolysis.

$$\mathrm{R.SO.S.R} \rightarrow \mathrm{R.SO^{\cdot}} + \mathrm{R.S^{\cdot}}$$

$$\mathrm{R.S^{\cdot}} + \mathrm{CH{=}CH} \rightarrow \mathrm{R.S.CH{-}\dot{C}H}$$

Trapping of both ArS˙ and ArSO˙ radicals has been discussed to account for product distribution from the thermal decomposition of aryl thiosulfinates in olefins.

In these circumstances a net outcome should be that increase in concentration beyond a point of maximum efficiency representing the compromise between inhibition and promotion, should lead to a decline in protection. This point was tested by raising the temperature to 75° to enhance the decomposition factor. Figure 8 shows that a negative factor becomes apparent at the higher concentrations.

The steep rise in efficiency up to about 0.075 M begins to taper off at 0.1 M so that the curve is almost flattened about 0.2 M. Further increase leads to a marked decline in performance so that 0.4 M gives the same result as less that 0.1 M. Thiosulfinate efficiency is subject to substituent influence decreasing with introduction of electron donating groups. Attack of sulfenyl radicals on an olefin has recently been shown to occur during the photolysis of aryl sulfenamides in cyclohexene,[14] where a multiplicity of products were primarily associated with sulfenyl radical activity. These results lead to the concept of 'limiting concentration' for aryl thiosulfinate addition (Table II).

The limiting concentration of a thiosulfinate is temperature dependent so that higher initial concentrations should be possible at lower temperatures.

To this point the discussion has mainly concerned the balance of competing reactions with respect to separate additions of disulfides and thiosulfinates. On balance it seemed likely that useful results would be achieved with mixtures consisting of a smaller amount of thiosulfinate with a larger quantity of disulfide. At 75° the time to 1% uptake with 0.25 M diphenyl disulfide, 1.5 hr (Table I), was extended to 30 hr by the inclusion of phenyl benzenethiosulfinate 0.005 M, which alone extended the time to 9 hr. The benefit of slowing the early stages of the oxidation allows inhibitor to be replaced from the reservoir of disulfide so that pro-oxidative effects from larger quantities of thiosulfinate are minimized.

TABLE II

"Limiting concentrations" of aryl thiosulfinates for the autoxidation of squalene at 75°

Thiosulfinate R.SO.S.R′		Time to 1% w/w oxygen uptake	Limiting concentration
R	R′	hr	M
C_6H_5	C_6H_5	160	0.25
$CH_3OC_6H_4$	C_6H_5	80	0.15
C_6H_5	$C_6H_4OCH_3$	40	0.1
$CH_3OC_6H_4$	$C_6H_4OCH_3$		

EXPERIMENTAL

Materials were prepared by standard methods—disulfides by oxidation of thiols with iodine, thiosulfinates by condensation of sulfinyl chlorides with thiols,[15] and thiosulfonates by decomposition of sulfinic acids[16]—to satisfactory purity shown by only one spot on chromatograms,[17] elemental analysis and melting point.

Oxygen uptake rates, at 400 mm pressure were determined using apparatus previously described[18] with essential features—capacity to maintain constant pressure and provision for fine adjustment manually before each reading. Squalene, purified by molecular distillation, was passed down a column of alumina as a final treatment. Small batches were stored *in vacuo*. During a series of tests the autoxidation rate of the olefin itself was checked. A cathetometer was used to measure changes in absorption burette levels. Results have been expressed as % oxygen absorbed or on a rate basis as mol/L/sec according to the aim of the experiment. Time to 1% w/w uptake has been adopted as an arbitrary standard for comparisons of inhibitor efficiency.

tert-Butyl hydroperoxide was purified by the sodium salt method[19] to 98% purity by iodometric estimation. Separation and analysis of products was performed by paper chromatography at room temperature, matching against standards.[17] The technique allowed rapid estimation and avoided the possibility of decomposition and exchange at higher temperatures of other methods.

Oxidations by tert-butyl hydroperoxide.

1. Diphenyl disulfide. Aliquots (0.5-1.0 ml) of a solution of diphenyl disulfide (0.545 g, 0.1 M) and *tert*-butyl hydroperoxide (1.125 g, 0.5 M) benzene (sodium dry, 25 ml) were placed in a series of small glass ampoules. After degassing by the freezing/thawing process and sealing *in vacuo* ampoules were heated at 60° in a bath, avoiding exposure to light. Ampoules, in duplicate, withdrawn after heating period of 1, 2, 4, 6, 8, 11, 17, 18 and 20 hr were cooled and kept as required in liquid nitrogen before analysis.

Samples, 0.01 ml and 0.02 ml were used for estimations of thiosulfinate and thiosulfonate respectively comparing against ranges 0–50 μg in 5 μg intervals on chromatograms developed at the same time.

2. Di-p-methoxyphenyl disulfide. A solution of the disulfide (0.695 g, 0.1 M) and *tert*-butyl hydroperoxide (1.125 g, 0.5 M) in benzene (25 ml) was treated similarly with estimations of thiosulfinate and thiosulfonate also carried out from duplicate samples.

*3. Competitive oxidation of a mixture of diphenyl and di-p-*methoxyphenyl disulfides. A solution of diphenyl disulfide (0.436 g, 0.08 M) and di-*p*-methoxyphenyl disulfide (0.556 g, 0.08 M) with *tert*-butyl hydroperoxide (0.36 g, 0.16 M) in benzene (25 ml) was treated similarly.

4. Phenyl benzenethiosulfinate. A solution of the thiosulfinate (0.293 g, 0.125 M) and *tert*-butyl hydroperoxide (0.45 g, 0.5 M) in benzene (10 ml) was treated similarly. Estimations of residual thiosulfinate and of thiosulfonate formed were performed from duplicate ampoules for each heating period.

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