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Abstract

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Mobility of RS Groups in Organic Thiosulfonates (Sulfonesulfides)

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For a number of years there has been discussion in the literature concerning the structure of “disulfoxides” :

$$\mathrm{R-SO-SO-R'} \quad (I) \quad \text{or} \quad \mathrm{R-SO_2-S-R'} \quad (II)$$

Relying chiefly on the reactions by which they are obtained, it was at first assumed that these compounds have the disulfoxide structure (I); under this name they entered the chemical literature. In recent years, in connection with the discovery ([1,2]) of antibacterial and antibiotic properties of these substances, interest in them has increased considerably; many new compounds of this class have been synthesized ([3]), and more and more evidence—both purely chemical and physicochemical—is being adduced in favor of the sulfonesulfide configuration (II).

Earlier ([4]) we measured the dipole moments and vibrational spectra of a large group of thiosulfo esters and also drew the conclusion that the “disulfoxides” have the sulfonesulfide (II) structure.

Table 1

System	Temp., °C	Time, hr	Activity, imp/min, before exchange: ester	Activity, imp/min, before exchange: disulf.	Activity, imp/min, after exchange: ester	Activity, imp/min., after exchange: disulf.	Activity, imp/min, at equilibrium (calc.): ester	Activity, imp/min., at equilibrium (calc.): disulf.	Percent exchange
$C_3H_5SO_2$ — *SC_3H_5 ++ C_3H_5S — SC_3H_5	20	2	4050	0	–	1834	1350	2700	67
$C_6H_5SO_2$ — SC_6H_5 ++ C_6H_5*S — *SC_6H_5	23	2	0	640	0	643	213	426	0
Same	61	0.5	0	120	40	84	40	80	100
Same	65	0.25	0	640	206	410	213	426	100
$C_2H_5SO_2$ — SC_2H_5 ++ C_2H_5*S — *SC_2H_5	25	5	0	1386	0	1380	462	924	0
Same	100	5	0	1386	0	1382	462	924	0
Same	162	1	0	2676	260	2150	892	1784	~30
Same	170	3	0	1386	469	915	462	924	100

In the present work, in order to study questions of structure and reactivity of these compounds, the tracer-atom method was applied, a method hitherto not used in the investigation of this interesting and important class of substances. We hoped, with the aid of this method, to obtain additional information on the structure of thiosulfoesters, as well as on their reactivity with other sulfur-containing substances. Study of the mechanism of interaction of thiosulfoesters with model compounds containing sulfhydryl and disulfide groups may not only provide information on the influence of structure on reactivity, which is of general theoretical interest, but also shed light on the mechanism of the antibacterial action of these compounds.

An attempt to carry out isotopic sulfur exchange between thiosulfoesters and elemental radioactive sulfur, as was to be expected, proved unsuccessful. None of the compounds studied—ethyl ester of toluenethiosulfonic acid, tolyl ester of toluenethiosulfonic acid, ethyl ester of ethanethiosulfonic acid, and phenyl ester of phenylthiosulfonic acid—exchanged with elemental radioactive sulfur on heating to 170°. In view of the results of studies (5) on the exchange of RS groups between organic polysulfides, and also between disulfides and mercaptans, it could be expected that if the compounds under study have the sulfonesulfide configuration (II), and not the disulfoxide configuration (I), then under certain conditions they may exchange RS groups with the corresponding disulfides.

The results of experiments on sulfur exchange between thiosulfoesters and disulfides are given in Table 1; in all cases the activity of benzidine sulfate precipitates was determined. As is seen from the data of Table 1, in all systems studied, under certain conditions, isotopic sulfur exchange is observed. To prove that the radioactive isotope of sulfur is transferred from one molecule to another as a result of exchange of RS groups, and not of sulfur atoms, experiments were carried out between a thiosulfoester and a disulfide with different *R*. Equimolar amounts of the tolyl ester of toluenethiosulfonic acid and labeled diethyl disulfide were kept for 3.5 hours at 162°. If exchange of the group takes place, labeled ethyl ester of toluenethiosulfonic acid should appear in the reaction mixture:

$$\mathrm{CH_3C_6H_4SO_2SC_6H_4CH_3 + C_2H_5S^* - S^*C_2H_5 \rightarrow CH_3C_6H_4SO_2 - S^*C_2H_5 + CH_3C_6H_4S - S^*C_2H_5}$$

By fractionation in vacuum, the ethyl ester of toluenethiosulfonic acid was isolated and identified: b.p. 115°/4 mm, $n_D^{20} = 1.5731$; sulfur found 29.3%, calculated sulfur 29.6%. The radioactivity of the sulfur of the thioester group corresponded to the activity of the original diethyl disulfide (3242 and 3260 counts/min, respectively). Consequently, the radioactive sulfur isotope is transferred from the disulfide molecule into the thioester molecule together with the ethyl radical, i.e., exchange of RS groups occurs. The occurrence of exchange of RS groups in the systems studied is very strong evidence in favor of the sulfonesulfide (II) configuration of thiosulfoesters.

We believe that at present, as a result of the whole body of investigations, the thiosulfonate or sulfonesulfide (II) structure of the "disulfoxides" may be considered proven.

From the data of Table 1 it is evident that the ability of RS groups to exchange between thiosulfoesters and disulfides depends to a considerable extent on the nature of the radicals *R*. The allyl ester of allylthiosulfonic acid (pseudoallicin) exchanges C_3H_5S groups with allyl disulfide already at room temperature; analogous compounds with phenyl radicals exchange C_6H_5S groups on gentle heating (50–60°), while derivatives with ethyl radicals exchange only at $\sim 160°$.

To clarify the extent of the influence of R and R' on the exchangeability of RS groups in the systems studied, the rate of isotopic sulfur exchange was measured between ethyl esters of several thiosulfonic acids, on the one hand, and labeled diethyl disulfide, on the other. The rate constants of isotopic exchange K at a temperature of 162° are given below:

Ethyl ester	$K \cdot 10^3$, sec^{-1}
Ethanethiosulfonic acid $C_2H_5SO_2—SC_2H_5$	0.25
Benzenethiosulfonic acid $C_6H_5—SO_2—SC_2H_5$	0.14
β-Naphthalenethiosulfonic acid $C_{10}H_7SO_2—SC_2H_5$	0.41
p-Bromobenzenethiosulfonic acid $BrC_6H_4SO_2—SC_2H_5$	0.32
p-Toluenethiosulfonic acid $CH_3C_6H_4SO_2—SC_2H_5$	0.44
p-Nitrobenzenethiosulfonic acid $NO_2C_6H_4SO_2—SC_2H_5$	1.05

Ethyl esters of various thiosulfonic acids exchange C_2H_5S groups with labeled diethyl disulfide under approximately identical conditions: the exchange proceeds at a measurable rate at 162°. All the observed changes in the rate constants of isotopic exchange fall approximately within one order of magnitude.

From a comparison of the data given and those presented in Table 1, one may conclude that the composition and structure of the radical R', which is part of the thiyl $R'S$ group, has a considerably greater effect on the reactivity of the systems $RSO_2—SR' + R'S—SR'$ than does the radical R attached to the sulfone group. It should be noted that this result, obtained by us through a study of the mobility of RS groups in model systems, is in agreement with the data of Belous (^{6}) and Boldyrev (^{7}) from the study of the antibacterial properties of various esters of thiosulfonic acids. It was shown, for example (^{6}), that replacement of an allyl radical by a phenyl one adjacent to the sulfonyl group –allyl–SO_2—S–allyl and phenyl–SO_2—S–allyl–causes practically no change in antibacterial activity, whereas a similar replacement of the allyl radical by phenyl in the $R'S$ group makes the compound only slightly active. However, data on the influence of radicals on the reactivity of thiosulfo esters are still far from sufficient for more far-reaching conclusions.

The phenomenon found in the present work–exchange of RS groups between thiosulfo esters and disulfides–appears to be of considerable interest, especially in connection with the antibacterial activity of thiosulfo esters.

The question of the mechanism of the antibacterial action of these compounds has been raised in the literature, but it remains far from clarified. Some authors (^{1,2}), on the basis of the reaction of thiosulfo esters with mercaptans and compounds containing sulfhydryl groups (cysteine, glutathione), suggested that the mechanism of antibacterial action consists in the blocking of sulfhydryl groups of the metabolite according to the reaction:

$$R—SO_2—SR' + R''SH \to RSO_2H + R''S—SR'$$

The consequence of this is a disturbance of the metabolic processes of the bacterial cell.

The results of the present work indicate that thiosulfo esters can react not only with sulfhydryl groups, but also with disulfide groups of compounds and, apparently, with disulfide bonds of protein molecules. Therefore the mechanism of antibacterial action of thiosulfo esters may be different from what was previously assumed.

We believe that, in investigating the antibacterial and antibiotic activity of thiosulfo esters, possible reactions with disulfide groups of protein must be taken into account.

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Note: Figure translations are in progress. See original paper for figures.