BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1090—1094 (1969)

Oxygen Exchange Reaction of Sulfoxides in Dinitrogen Tetroxide[1)]

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(Received August 17, 1968)

Sulfoxides are known to undergo concurrent oxygen exchange and racemization reactions with various reagents (*Bull. Chem. Soc. Japan*, **41**, 1025 (1968)). Especially well studied are the oxygen exchange reactions in acid media. We have found a similar concurrent oxygen exchange and racemization reaction of sulfoxides with liquid dinitrogen tetroxide. The pseudo first order reaction rates of both oxygen exchange and racemization reactions have been determined using both optically active and ^{18}O-labeled sulfoxides. The k_{ex}/k_{rac} value was found to be unity, and the polar effect of substituents on the rates of oxygen exchange of substituted diphenyl sulfoxides was found to be considerably large, and correlated with σ^+ values with $\rho = -1.30$. From these results a plausible mechanism for this reaction has been discussed.

Sulfoxides are of stable pyramidal structure and isoelectronic to carbanions, amines, phosphines, sulfonium ions, *etc.*[2)] Therefore, the optical isomerism can exist in sulfoxides, and the stereochemical stability of sulfoxides are known to be far exceeding those of similar sulfonium compounds. Furthermore, unlike those in sulfone group, the S–O linkage of sulfoxides is weak and readily cleaves. These are quite advantageoues for nucleophilic substitutions to occur on the sulfur atom. In fact, there are number of reactions which involve the facile cleavage of the S–O linkage.[3)] The concurrent oxygen exchange and racemization reactions of sulfoxides are interesting reactions in these connections, and have attracted considerable attentions in recent years. These oxygen exchange reactions are very convenient for studying the nature of nucleophilic substitution on the trivalent sulfur atom, since one can readily prepare both ^{18}O-labeled and optically active sulfoxides[4)] and follow both the loss of ^{18}O-content and the change of optical rotation simultaneously.

There are three types of mechanistic pathways in the nucleophilic substitution on the trivalent sulfur atom. The first type (Type-1) is like an S_N1-type reaction on sp^3 carbon atom, where, the cleavage of the S–O bond takes place in the initial slow step followed by fast recombination with solvent, resulting in the racemization. Among many examples of this type, there are concurrent oxygen exchange and racemization reactions of sulfoxides in concentrated sulfuric acid,[5)] in phosphoric acid[6)] and in chloroacetic acids.[7)] The second type (Type-2) is the mechanism involving an S_N2-like nucleophilic replacement at the sulfur atom forming a new S–O bond while cleaving the old S–O bond at the rate-determining step, resulting in the inversion of configuration of the original sulfoxide. However, unlike the S_N2 reaction on saturated carbon atom there are two possible steric arrangements of both entering and outgoing groups in the nucleophilic substitution involving steric inversion on the sulfur atom, since the intermediate or the incipient complex at the transition state is expected to assume a typical bipyramidal structure. Namely, in addition to the usual S_N2 type arrangement in which both entering and leaving groups assume axial positions, there is another arrangement in which both groups assume radical positions. Both steric arrangements will lead to the net inversion of configuration. Among the former examples are the oxygen exchange reactions of sulfoxides in acetic anhydride[8)] and in less concentrated sulfuric acid.[9)] The latter example may be found among the reactions of sulfoxides with cyclic oxy-compounds which is now under investigation. There is another type, *i. e.*, (Type-3); when leaving

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1) Paper XXVII on Sulfoxides.

2) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N.Y. (1965), p. 88.

3) For details see; C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y. (1962), Chapter 4.

4) a) K. K. Andersen, *Tetrahedron Letters*, **1962**, 93. b) N. Kunieda, K. Sakai and S. Oae, This Bulletin, **41**, 3015 (1968).

5) a) S. Oae, T. Kitao, Y. Kitaoka and S. Kawamura, This Bulletin, **38**, 546 (1965). b) S. Oae and N. Kunieda, *ibid.*, **41**, 696 (1968).

6) N. Kunieda and S. Oae, *ibid.*, **41**, 1025 (1968).

7) S. Oae, M. Yokoyama and M. Kise, *ibid.*, **41**, 1221 (1968).

8) S. Oae and M. Kise, *Tetrahedron Letters*, **1967**, 1409.

9) N. Kunieda and S. Oae, This Bulletin, in press.

TABLE 1. OXYGEN EXCHANGE REACTIONS OF ^{18}O-LABELED SULFOXIDES IN DINITROGEN TETROXIDE AT 0°C FOR 1 hr

Sulfoxide	Atom%-^{18}O of sulfoxide: Starting	Atom%-^{18}O of sulfoxide: Recovered	Ratio of ^{18}O-exchange(%)	Mole ratio of N_2O_4 to sulfoxide	Solvent
$C_6H_5SOC_6H_5$	0.98	0.24	97	10	None
	0.66	0.36	79	1.1	CCl_4
$C_6H_5SOCH_2C_6H_5$	1.05	0.40	95	1	$CHCl_3$
$(C_6H_5CH_2)_2SO$	1.68	0.33	91	1	$CHCl_3$
Dibenzothiophene oxide	0.43	0.24	88	10	CCl_4-$CHCl_3$
Phenoxathiin 5-oxide	0.86	0.26	93	10	CCl_4-$CHCl_3$

and entering groups assume axial and radial positions, the oxygen exchange will lead to the retention of configuration. The first example of this type may be the reaction of sulfoxides with DMSO.[10]

Dinitrogen tetroxide is known to be a unique reagent which can oxidize sulfides specifically to the corresponding sulfoxides.[11] Recently we have found that the oxygen exchange reaction of diphenyl sulfoxide readily takes place in liquid dinitrogen tetroxide[12] in similar conditions used for the oxidation of sulfides. Meanwhile Johnson and McCants have also reported that (+)- benzyl *p*-tolyl sulfoxide is rapidly racemized in this reagent.[13] Since dinitrogen tetroxide is a somewhat different oxygen exchange reagent from those used previously, one might expect an entirely different mechanistic route for the oxygen exchange reaction. However, a more careful kinetic study has been desired in order to elucidate a plausible mechanism for this reaction. We now have compiled substantial amounts of kinetic data on this reaction with several sulfoxides in liquid dinitrogen tetroxide and found that this reaction is one of a typical example of Type-1 proceeding through an S_N1-like S–O bond cleavage at the rate-determining step. This paper describes a detailed account of the kinetic study.

Results and Discussion

When a sulfoxide is dissolved in an excess of dinitrogen tetroxide at 0°C, the sulfoxide can be recovered almost quantitatively after an hour without undergoing further oxidation to the sulfone or any other side reaction with dinitrogen tetroxide, and its mp and IR spectrum are completely identical to those of the starting sulfoxide. A few representative results are shown in Table 1. The heteroaromatic sulfoxides, *i. e.*, dibenzothiophene oxide and phenoxathiin 5-oxide, also undergo the oxygen exchange with this reagent.

Earlier Johnson and McCants reported that (+)-benzyl *p*-tolyl sulfoxide is rapidly racemized by liquid dinitrogen tetroxide.[13] We have examined the oxygen exchange reaction of ^{18}O-labeled, optically active ethyl *p*-tolyl sulfoxide in this reagent,[12] and found, as shown in Table 2, that the racemization is not an independent reaction but accompanies concurrent oxygen exchange reaction in a fashion similar to that in acid media of our previous works.[14]

TABLE 2. CONCURRENT OXYGEN EXCHANGE AND RACEMIZATION OF (+)- ETHYL *p*-TOLYL SULFOXIDE-^{18}O IN DINITROGEN TETROXIDE[a)]

	^{18}O-concentration (atom%)	Rotation ($[\alpha]_D$ in acetone)
Starting sulfoxide	0.56	+183°
Recovered sulfoxide	0.25[b)]	0

a) Mole ratio of sulfoxide to $N_2O_4=1:10$, at 0°C for 1 hr.

b) Ratio of oxygen exhcange=91%.

In the oxidations of sulfides or disulfides with dinitrogen tetroxide, the reaction mixture usually develops a green or blue color, due to the formation of dinitrogen trioxide, and nitric oxide (NO) is evolved.[11]

$$R_2S + N_2O_4 \longrightarrow R_2S{\rightarrow}O + N_2O_3$$
$$N_2O_3 \rightleftharpoons NO + NO_2$$

However, when a sulfoxide is dissolved in dinitrogen tetroxide there is no color change or evolution of nitric oxide. Apparently the concurrent oxygen exchange and racemization reactions of sulfoxides proceed without consuming dinitrogen tetroxide. Actually, when 0.997 g of ^{18}O-labeled diphenyl sulfoxide (0.66 atom%-^{18}O) was dissolved in 2.386 g of dinitrogen tetroxide in a vessel connected to

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[10] S. Oae, M. Yokoyama and S. Oae, *Tetrahedron Letters*, **1968**, 4131.

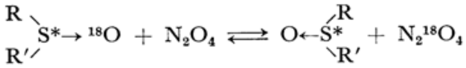
[11] L. Horner and F. Hübenett, *Ann*, **579**, 193 (1953); C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, **1956**, 2705.

[12] S. Oae, N. Kunieda and W. Tagaki, *Chem. & Ind.*, **1965**, 1790.

[13] C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, **86**, 2935 (1964).

[14] Summarized in; N. Kunieda and S. Oae, This Bulletin, **41**, 1025 (1968).

a vacuum line and the solution was kept for 30 min at 0°C, almost quantitative amount of dinitrogen tetroxide (2.379 g) (colorless crystals at the temperature of dry ice-acetone bath) was recovered together with 0.997 g of the oxygen-exchanged sulfoxide (0.25 atom%-^{18}O).



$$\mathrm{RR'S^{*}\rightarrow {}^{18}O + N_2O_4 \rightleftarrows O\leftarrow S^{*}RR' + N_2{}^{18}O_4}$$

Since the oxygen exchange reaction accompanies the racemization of sulfoxides, the mechanism of Type-3 is excluded, leaving two other possible mechanistic routes. If the cleavage of S–O bond takes place in the initial slow step followed by fast recombination with solvent according to the Type-1, each oxygen exchange will cause racemization, and then the rate of oxygen exchange becomes identical to that of racemization; $k_{ex}/k_{rac}=1$. The other is the Type-2 mechanism which involves an S_N2-like simultaneous bond forming and cleavage of S–O bond at the rate-determining step, and each oxygen exchange of sulfoxides will result in the inversion of configuration at the central sulfur atom and hence the ratio k_{ex}/k_{rac} becomes 0.5.

The rates of both oxygen exchange and racemization of ^{18}O-labeled and optically active *p*-tolyl phenyl sulfoxide in dinitrogen tetroxide - carbon tetrachloride solution were carefully measured. The results, shown in Table 3, clearly reveal that the rate of the oxygen exchange is identical to that of the racemization, suggesting that the reaction proceeds through the Type-1 mechanism. Furthermore, the rate of this reaction was found to be of first order dependence on the concentration of dinitrogen tetroxide as shown in Fig. 1. The rate constants obtained are of pseudo first order even under the condition when the mole ratio of sulfoxide to dinitrogen tetroxide is atmost 1 : 2—3.

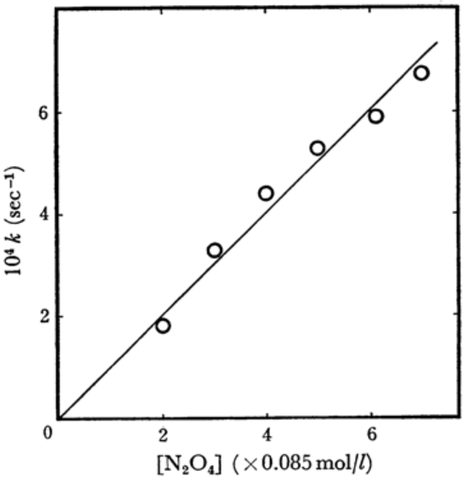


Fig. 1. Rate constants of racemization reaction of (+)- *p*-tolyl phenyl sulfoxide (0.1 mol/*l*) plotted against mole concentration of dignitrogen tetroxide in carbon tetrachloride at 0°C.
Slope = 1.01 (r=0.993)

It is known that alkyl sulfoxides form molecular addition compounds with dinitrogen tetroxide[15] and the formation of such addition compounds may inhibit further oxidation of sulfoxides to sulfones. The compound formation is considered to be resulted by the interation between electron-rich sulfoxide oxygen and the electron-deficient dinitrogen tetroxide molecule.

TABLE 3. RATE CONSTANTS OF ^{18}O-EXCHANGE AND RACEMIZATION OF *p*-TOLYL PHENYL SULFOXIDE[a] IN DINITROGEN TETROXIDE AT 0°C

Mole concentration of N_2O_4 (mol/*l*)	10^4k(sec^{-1}) k_{ex}	k_{rac}	k_{ex}/k_{rac}
0.530[b]	6.23±0.12	6.35±0.30	0.983±0.027
0.462[c]	10.4 ±0.1	10.4 ±0.6	1.00 ±0.05
0.281[c]	4.64±0.13	4.80±0.28	0.970±0.030

a) Sulfoxide=0.1 mol/*l*. b) and c) are media of different batch.

There are two possible structures, *i. e.*, molecular (I) and ionic complex (II), for the addition compounds of sulfoxides.

$$\underset{\text{(I)}}{[\mathrm{R_2SO\cdot N_2O_4}]} \quad \underset{\text{(II)}}{[\mathrm{R_2SO\cdots NO}]^{+}\mathrm{NO_3}^{-}}$$

Addison and Sheldon have shown that the molecular complex (I) is favorable in solid state.[15] But in liquid state the ionic structure (II) would be more favorable, since its equilibrium $N_2O_4 \rightleftarrows NO^+NO_3^-$ is also established in the liquid state and the NO^+ ion is also electron deficient, and, morevoer, the sulfoxides are considered to be the donors of medium strength.[16] Therefore, the sulfoxides would form the ionic complex (I) in liquid dinitrogen tetroxide at the initial step of the oxygen exchange and racemization reaction. On the basis of these informations, the following reaction scheme may be constructed, in which the second step of the cleavage of S–O bond is the slow rate-determining step. Path (a) is the heterolysis of the S–O bond to form the doubly positively charged "sulfidonium ion" intermediate. Path (b) is the homolysis to form the cation radical intermediate. If the reaction follows the path (a), the

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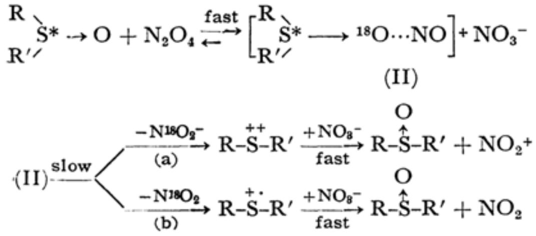
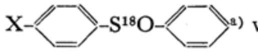
[15] C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, **1956**, 2705.

[16] The classification of structure of dinitrogen tetroxide addition compounds has been offered by Addison and Sheldon [Ref. 15, and H. H. Sisler, *J. Chem. Educ.*, **34**, 555 (1957)], which said a medium strength donors, *e. g.*, carbonyl compounds and sulfoxides, *etc.*, form together ionic and molecular complexes in liquid dinitrogen tetroxide.



rate would be substantially more effected by polar substituents like in the case of the S_N1-type reaction of carbon compounds than in the case of path (b). Recently, we have found that the most reasonable mechanism for the concurrent oxygen exchange and racemization reactions of diaryl sulfoxides in concentrated sulfuric acid is through the path involving the homolysis of the S–O bond forming the radical cation intermediate. In this case, the polar effects of substituents on the phenyl group are very small and *p*-methyl group accelerates the rate only less than twofold while the electron-withdrawing *p*-chloro group also give a small acceleration.[5b)] The rates of the oxygen exchange of several *p*-substituted diphenyl sulfoxides were measured in dinitrogen tetroxide - carbon tetrachloride solution. One finds in Table 4 that the polar effects of *p*-substituents on the rates are considerably large, and the rates are nicely correlated with Brown-Okamoto's σ^+ values and give a considerably large negative ρ value (for σ; $\rho = -1.58$, Correlation coefficient $r = 0.948$) (for σ^+; $\rho = -1.30$, $r = 0.990$).

TABLE 4. KINETICS OF OXYGEN EXCHANGE OF [a)] WITH DINITROGEN TETROXIDE[b)] IN CARBON TETRACHLORIDE AT 0°C

X	$10^4 k_{ex}$ (sec^{-1})
CH_3O	18.5 ± 0.7
CH_3	4.64 ± 0.13
H	2.50 ± 0.15
Cl	1.04 ± 0.04

a) Sulfoxide=0.1 mol/*l*. b) N_2O_4=0.281 mol/*l*.

TABLE 5. OXYGEN EXCHANGE OF ^{18}O-LABELED DIPHENYL SULFONE[a)] IN DINITROGEN TETROXIDE AT 0°C FOR 1 hr

	^{18}O-Concentration (atom%)	
	Starting sulfone	Recovered sulfone
Run 1	1.64	1.60
Run 2	1.76	1.71

a) Mole ratio of sulfone to N_2O_4 was 1 : 10.

These rather large polar effect seems to favor the heterolytic cleavage, *i. e.*, path (a) for the reaction.

Diphenyl sulfone was found not to undergo the oxygen exchange in this reagent even without the solvent, as shown in Table 5. This is undoubtedly due to the much strong nature of the S–O bond of sulfones for cleavage in comparison with that of sulfoxides.

Experimental

Materials. *^{18}O-Labeled sulfoxides* were prepared by the oxidation of corresponding sulfides with bromine complex of pyridine and ^{18}O-enriched water in acetic acid by the same procedure as described in our previous paper.[17)] Diphenyl sulfoxide; mp 70—71°C (71°C),[18)] 0.86_3atom%-^{18}O. Phenyl *p*-tolyl sulfoxide; mp 71—72°C (71—72°C),[18)] 1.0_7atom%-^{18}O. Phenyl *p*-chlorophenyl sulfoxide; mp 45—46°C (45—46°C),[18)] 1.1_8atom-^{18}O. Phenyl *p*-methoxyphenyl sulfoxide; mp 60°C (55—57°C),[18)] 0.57_0atom%-^{18}O. Benzyl phenyl sulfoxide; mp 121—122°C (123°C),[19)] 1.0_5atom%-^{18}O. Dibenzyl sulfoxide; mp 136—137°C (133°C),[19)] 1.6_8-atom%-^{18}O. Dibenzothiophene oxide; mp 62—67°C, 0.43atom%-^{18}O. Phenoxathiin 5-oxide; mp 151°C (153—154°C),[20)] 0.86atom%-^{18}O.

Optically active p-tolyl phenyl sulfoxide was prepared from (−)-menthyl (−)-*p*-toluenesulfinate and phenyl magnesium bromide according to the method developed by Andersen.[4a)] Mp 91.5—92°C, $[\alpha]_D = +31.8°$ in CCl_4 ($l=0.5$, $c=1.68$), $[\alpha]_D = +27.8°$ in 96% EtOH ($l=0.5$, $c=1.63$) (lit.[21)]; mp 92—93°C, $[\alpha]_D = +27°$ in 95% EtOH).

^{18}O-Labeled optically active ethyl p-tolyl sulfoxide was prepared by Andersen's method[4a)] using ^{18}O-labeled (−)-menthyl (−)-*p*-toluenesulfinate which was prepared from ^{18}O-labeled sulfinic acid.[4b)] Bp 95—97°C/0.5 mmHg, $[\alpha]_D = +183°$ in acetone ($l=1$, $c=2.1$) (lit[4a)]; bp 123—126°C/1.5 mmHg, $[\alpha]_D^{25} = +186°$ in acetone).

^{18}O-Labeled diphenyl sulfone was prepared by the oxidation of diphenyl sulfide with *t*-butyl hypochlorite in the presence of ^{18}O-enriched water by the same procedure as described in our previous paper.[22)] Mp 125—126°C (lit.[23)]; 124°C), yield 98%.

Dinitrogen tetroxide was prepared by the pyrolysis of dinitrogen pentoxide.[24)] The crude oxide was twice distilled over phosphorus pentoxide under faint stream

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17) S. Oae, Y. Ohnishi, S. Kozuka and W. Tagaki, This Bulletin, **39**, 364 (1966).

18) C. Modena, *Gazz. Chim. Ital.*, **89**, 834 (1959).

19) R. L. Shriner, H. C. Struck and W. J. Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930).

20) H. J. Shine and R. J. Small, *J. Org. Chem.*, **30**, 2140 (1965).

21) K. Mislow, M. M. Green, P. Laur, J. Melillo, T. Simmons and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965).

22) K. Kikukawa, W. Tagaki, N. Kunieda and S. Oae, This Bulletin, **42**, 831 (1969).

23) C. A. Buehler and J. E. Masters, *J. Org. Chem.*, **4**, 262 (1939).

24) A. Pedler and F. H. Pollard, "Inorganic Syntheses," Vol. V, ed. by T. Moeller, McGraw-Hill Book Company, Inc., New York, N. Y. (1957), p. 87—90.

of dry oxygen, and then dissolved in pure carbon tetrachloride. The solution was stored in glass vessel with a secured stopper. Concentrations of dinitrogen tetroxide in carbon tetrachloride were determined by titration with a standard alkali solution.

Kinetic Procedure of the Oxygen Exchange and Racemization Reactions of Sulfoxides. An ^{18}O-labeled or an optically active sulfoxide was dissolved in the dinitrogen tetroxide - carbon tetrachloride solution of a predetermined concentration, in such a way as to maintain the concentration of the sulfoxide just about 0.1 mol/*l*, at a preset temperature (0°C). An aliquot portion (7.0 m*l*) of the solution was taken up from time to time for 6—7 times and was quenched witha cold alkaline solution (10% aqueous solution of K_2CO_3). The recovered sulfoxide was extracted with carbon tetrachloride, and the solution was washed with water, and dried over anhydrous sodium sulfate. Finally, carbon tetrachloride was distilled *in vacuo* and then the sulfoxide recovered was subjected to the ^{18}O-analysis or the measurement of optical activity according to the same procedures described in our previous paper[5] using Yanagimoto OR-10 Type polarimater and Hitachi RMU-6E Type mass-spectrometer.