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Reaction of Sulfoxides with Acylating Reagents. IV.[1] The Catalytic Effect of Both the Brönsted and Lewis Acids in the Oxygen Exchange Reaction of Diaryl Sulfoxides with Acetic Anhydride

Masahiro Kise and Shigeru Oae

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshiku, Osaka

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Diaryl sulfoxides undergo oxygen exchange and racemization reaction with acetic anhydide. The rate of racemization of *p*-tolyl phenyl sulfoxide was found to be twice that of oxygen exchange. The remarkably small substituents effect is also in keeping with the S_N2 type mechanism. Addition of acetic acid increases the rate of both the racemization and oxygen exchange. Racemization of sulfoxides is also known to be catalyzed markedly by a small amount of Lewis acid. When the reaction was carried out in the presence of a small amount of both acetic acid and Lewis acid, the ratio of the rate constants, k_{ex}/k_{rac} becomes unity. This may mean that the presence of both Brönsted and Lewis acids facilitates the cleavage of S–O bond by easy protonation (or hydrogen-bonding) or coordination on the sulfoxide oxygen, and the assistance of the nucleophilic attack by acetate becomes less important in the reaction. The larger substituent effect is also in keeping with the S_N1 type mechanism.

In a previous paper,[2] dealing with the reaction of diaryl sulfoxides with acetic anhydride, we suggested on the basis of our kinetic investigations (such as the value of $k_{ex}/k_{rac}=1/2$, rather small substituent effect, *etc.*,) that the reaction proceeds through an S_N2 type Walden inversion process at the rate-determining step as shown below. (Fig. 1).

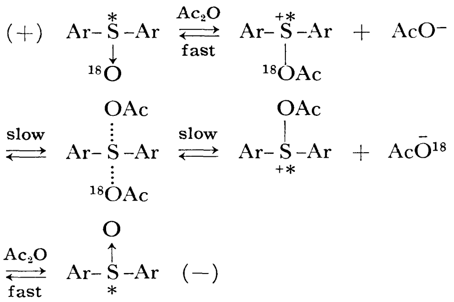
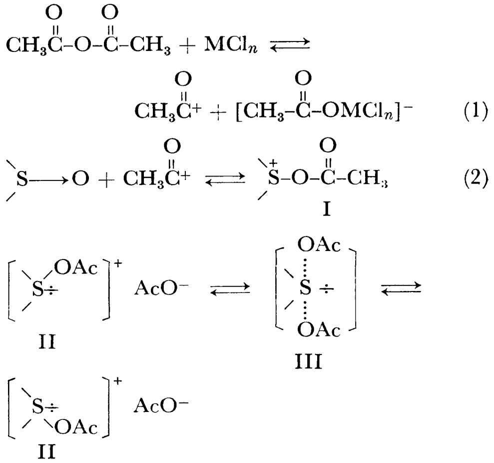


Fig. 1

The addition of acetic acid increases the rate of both the racemization[3] and oxygen exchange. Racemization of aryl benzyl sulfoxides in acetic anhydride is also known to be catalyzed markedly by a small amount of Lewis acid[4] such as mercuric chloride. In the racemization reaction of *p*-tolyl methyl sulfoxide with acetic anhydride, the large catalytic effect was reported by Jonsson[5] on the addition of metal halide such as mercuric chloride, zinc chloride or acetylating reagents. Jonsson proposed that in the racemization reaction of sulfoxide the acetylium ion formed reacts with the sulfoxide giving an acetoxysulfonium ion, and racemization was then brought about by exchange of acetate groups through a symmetrical transition state as proposed earlier.[2,3] The mechanism of the reaction is illustrated in Fig. 2.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 + MCl_n \rightleftarrows CH_3\overset{O}{\overset{\|}{C}}{}^+ + [CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}OMCl_n]^-} \quad (1)$$

$$\mathrm{{>}S\longrightarrow O + CH_3\overset{O}{\overset{\|}{C}}{}^+ \rightleftarrows {>}\overset{+}{S}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3} \quad (2)$$

Fig. 2

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[1] Paper XXXIII on Sulfoxides.

[2] S. Oae and M. Kise, *Tetrahedron Lett.*, **1967**, 1409.

[3] E. Jonsson, *Acta Chem. Scand.*, **21**, 1278 (1967).

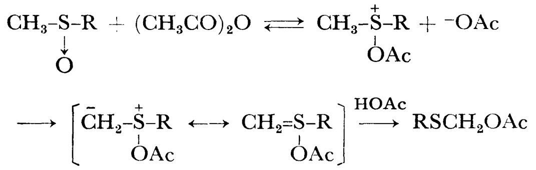
[4] M. Kise and S. Oae, This Bulletin, **43**, 1421 (1970).

[5] E. Jonsson, *Tetrahedron Lett.*, **1967**, 3675.

Since intermediate III is symmetrical the recovered sulfoxide should be racemized while the ratio of the rates, k_{ex}/k_{rac}, is expected to be 1/2.

We suggested,[2] on the basis of the ratio of the rate, $k_{ex}/k_{rac}=1$, in the oxygen exchange and racemization reaction of diaryl sulfoxide with acetic anhydride containing small amounts of acetic acid that the presence of Brönsted acid and acetic acid may facilitate the cleavage of S–O bond by the easy protonation or hydrogen bonding on the sulfoxide oxygen, and that the assistance of the nucleophilic attack by acetate becomes less important.

Sulfoxides bearing at least one methyl or methylene group directly attached to the sulfur atom undergo "Pummerer Rearrangement" in the reaction with acetic anhydrides as shown below[6] (Fig. 3).



$$\underset{\downarrow\atop \mathrm{O}}{\mathrm{CH_3\text{-}S\text{-}R}} + (\mathrm{CH_3CO})_2\mathrm{O} \rightleftarrows \mathrm{CH_3\text{-}}\underset{|\atop \mathrm{OAc}}{\overset{+}{\mathrm{S}}}\mathrm{\text{-}R} + {}^{-}\mathrm{OAc}$$

$$\longrightarrow \left[\bar{\mathrm{C}}\mathrm{H_2\text{-}}\underset{|\atop \mathrm{OAc}}{\overset{+}{\mathrm{S}}}\mathrm{\text{-}R} \longleftrightarrow \mathrm{CH_2{=}}\underset{|\atop \mathrm{OAc}}{\mathrm{S}}\mathrm{\text{-}R}\right] \xrightarrow{\mathrm{HOAc}} \mathrm{RSCH_2OAc}$$

Fig. 3

We suggested on the basis of ^{18}O tracer experiments with ^{18}O-labeled acetic anhydride that the Pummerer reaction of dimethyl sulfoxide with acetic anhydride proceeds through an intermolecular nucleophilic attack of acetoxy group on the methylene carbon of the ylide-ylene intermediate. Noticeable acetoxy interchange has been found to take place during a similar Pummerer reaction of aryl methyl sulfoxide. In the reaction of *p*-tolyl methyl sulfoxide with acetic anhydride, below 65°C, under which the Pummerer reaction is minor, only the oxygen exchange proceeds slowly. But the addition of Lewis acids accelerates both the reaction of acetoxy interchange and Pummerer rearrangement.[6] We have investigated this catalyzed oxygen exchange reaction of diaryl sulfoxides by Lewis acids extensively in order to understand the nature of the reaction. With diaryl sulfoxides, our attention is focused only on the acetoxy interchange, since the other competing reactions such as Pummerer rearrangement and the heterolysis of carbon-sulfur linkage do not take place with these sulfoxides. In fact, when an optically active diaryl sulfoxide labeled with ^{18}O- atom was reacted with acetic anhydride containing Lewis acid, the sulfoxide was recovered quantitatively by quenching the reaction mixture with an excess cold water.

Results and Discussion

When the reaction were carried out at 120°C with both optically active and ^{18}O-labeled diaryl sulfoxides in a large excess of acetic anhydride, the rate of racemization of *p*-tolyl phenyl sulfoxide was twice that of oxygen exchange. This suggests that the reaction involves a Walden inversion at the rate-determining step. Sulfoxides are known to undergo concurrent oxygen exchange and racemization reactions through an acid catalyzed S_N1 type process in weak carboxylic acids such as acetic, chloroacetic, dichloroacetic and trichloroacetic acids.[7]

TABLE 1. ACTIVATION PARAMETERS AND k_{ex}/k_{rac} VALUES OF (+) *p*-TOLYL PHENYL SULFOXIDES

Reagents	*Ea.* (kcal/mol)	$\Delta S^{\neq}$ (e.u.)	k_{ex}/k_{rac}	Temp. °C
Trichloroacetic acid[a]	18.6	−32.9	1.09	120
Acetic anhydride[b]	19.2	−28.6	0.50	120
Acetic anhydride-AcOH[c]	21.9	−17.0	1.11	90
Acetic anhydride-$HgCl_2$[d]	15.2	−23.1	1.02	10

a) Sulfoxide 0.001 mol, acid 0.25 mol in dioxane
b) Sulfoxide 0.005 mol, acetic anhydride 0.5 mol
c) Sulfoxide=0.05M $Ac_2O/AcOH=9$ AcOH 10% solution
d) Sulfoxide=0.05M $HgCl_2=0.018$M

Activation parameters and k_{ex}/k_{rac} values of the reaction of (+) *p*-tolyl phenyl sulfoxide with trichloroacetic acid,[7] acetic anhydride,[2] acetic anhydride containing a small amount of acetic acid and mercuric chloride are summarized in Table 1.

The small value of entropy of activation in the reaction of *p*-tolyl phenyl sulfoxide with trichloroacetic acid was assumed to be due to the solvation by the acid in the transition state.[7] However, in the reaction with acetic anhydride, the addition of acetic acid or mercuric chloride resulted in the increase of the entropy of activation and also in a probable change from the S_N2 process to the S_N1 in the transition state.

TABLE 2. RATE CONSTANTS OF ^{18}O-EXCHANGE AND RACEMIZATION OF *p*-TOLYL PHENYL SULFOXIDE IN ACETIC ANHYDRIDE CONTAINING A SMALL AMOUNT OF ACETIC ACID AND RATIO OF THE RATE k_{ex}/k_{rac}

Temp. °C	k_{rac} (sec^{-1})	k_{ex} (sec^{-1})	k_{ex}/k_{rac}
90	$(9.08\pm0.22)\times10^{-5}$	$(10.05\pm0.30)\times10^{-5}$	1.11
100	$(2.18\pm0.20)\times10^{-4}$	$(2.32\pm0.30)\times10^{-4}$	1.06
110	$(4.74\pm0.20)\times10^{-4}$	$(4.52\pm0.19)\times10^{-4}$	0.95

$\Delta S^{\neq} = -17.0$ e.u. (90°C)
$E_a = 21.9$ kcal/mol.

The small change of the entropy is perhaps due

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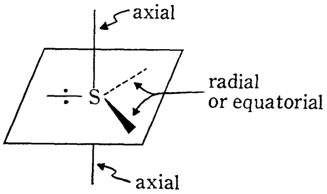
[6] a) S. Oae and M. Kise, *ibid.*, **1968**, 2261; b) M. Kise and S. Oae, This Bulletin, **43**, 1426 (1970).

[7] S. Oae and M. Yokoyama and M. Kise, This Bulletin, **41**, 1221 (1968).

TABLE 3. RATE OF ^{18}O-EXCHANGE AND RACEMIZATION OF *p*-TOLYL PHENYL SULFOXIDE IN ACETIC ANHYDRIDE CONTAINING A SMALL AMOUNT OF MERCURIC CHLORIDE AND RATIO OF THE RATE k_{ex}/k_{rac}

Temp. °C	k_{ex} (sec^{-1})	k_{rac} (sec^{-1})	k_{ex}/k_{rac}
10	$(10.3\pm0.31)\times10^{-5}$	$(10.1\pm0.23)\times10^{-5}$	1.02
15		$(1.65\pm0.05)\times10^{-4}$	
20	$(2.49\pm0.30)\times10^{-4}$	$(2.54\pm0.08)\times10^{-4}$	0.98
25		$(3.94\pm0.11)\times10^{-4}$	

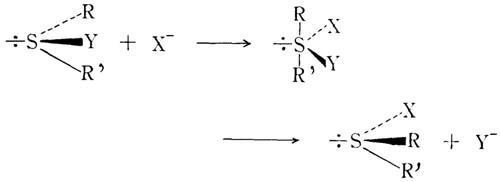
$\Delta S^{\ddagger} = -23.1$ e.u. (10°C)
$E_a = 15.2$ kcal/mol



to the solvation or participation of these acids in the transition state of the reaction with a weak acid such as trichloroacetic acid. Actually the ratios of the rate, k_{ex}/k_{rac}, became unity as shown in Tables 2 and 3 in the reactions of *p*-tolyl phenyl sulfoxide with acetic anhydride containing a small amount of Brönsted acid or Lewis acid. If the reaction proceeds through the path shown in Fig. 2, the ratio of the rate, k_{ex}/k_{rac}, would become 1/2. Thus the mechanism shown in Fig. 2 cannot account for the observation.

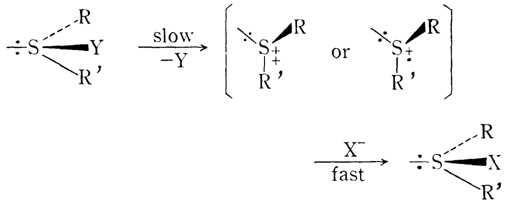
When an intermediate or an incipient activated complex at the transition state of the nucleophilic substitution reaction assumes a typical bipyramidal structure, two possible stereochemical consequences will arise depending upon the steric arrangement of both incoming and outgoing groups.[8]

When both the entering and leaving groups assume axial positions, the process is similar or identical to S_N2 reaction on carbon atom, and the net result is the inversion of configuration. A typical example of the reaction at the axial positions in trigonal bipyramidal might be the reaction of (+) *p*-tolyl phenyl sulfoxide with acetic anhydride.[2] Another example may be both the oxygen exchange and racemization reactions of (+) *p*-tolyl phenyl sulfoxide in less concentrated sulfuric acid (75.4%).[9] A similar net inversion would result also when both incoming and outgoing groups assume radial positions as shown below.



A possible example is the recent work of Day and Cram who showed that the formation of sulfilimine from the corresponding sulfoxide resulted in net inversion.[10] When the leaving and entering groups assume axial and radial arrangement with each other around the central sulfur atom of the trigonal bipyramidal structure, the displacement will lead to the retention of configuration at the sulfur atom. An example of this type was found for the first time in the oxygen exchange reaction between *p*-tolyl methyl sulfoxide and DMSO.[8]

Another reaction on the sulfur atom is similar to the S_N1 type reaction on sp^3 carbon atom, where the cleavage of S–O bond takes place in the initial slow step followed by a rapid recombination with solvent or a reagent, resulting in racemization. In this reaction, the ratio k_{ex}/k_{rac}, becomes unity.



Thus, in both the reactions in concentrated sulfuric acid (95.5%), the ratio of the rate k_{ex}/k_{rac} is unity.[11] This shift of mechanisn resulting from the change of the concentration of H_2SO_4 from 95% to 75%, is caused by the change of the nature of sulfuric acid solution, namely, the protonating ability of the solution diminishes steadily as acid concentration decreases while the activity of water increases. If the S_N1-like cleavage of the S–O bond of the sulfoxides takes place through the diprotonated species $>$S–OH$_2$ in the rate determining step, formation of this diprotonated species will decrease with the decrease of acid concentration. Other examples of this S_N1 type reaction are concurrent oxygen exchange and racemization reaction of sulfoxides in phosphoric acid[12] and dinitrogen tetroxide.[13]

Such a change in mechanism may be assumed to

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[8] a) S. Oae, M. Yokoyama and M. Kise, *Tetrahedron Lett.*, **1968**, 4131; b) K. Kimura and S. H. Bauer, *J. Chem. Phys.*, **39**, 3172 (1963).

[9] N. Kunieda and S. Oae, This Bulletin, **42**, 1324 (1969).

[10] a) J. Day and D. J. Cram, *J. Amer. Chem. Soc.*, **87**, 4398 (1965); b) D. R. Rayner, D. M. von Schriltz, J. Day and D. J. Cram, *ibid.*, **90**, 2721 (1968).

[11] S. Oae and N. Kunieda, This Bulletin, **41**, 696 (1968).

[12] N. Kunieda and S. Oae, *ibid.*, **41**, 1025 (1968).

[13] N. Kunieda, K. Sakai and S. Oae, *ibid.*, **42**, 1090 (1969).

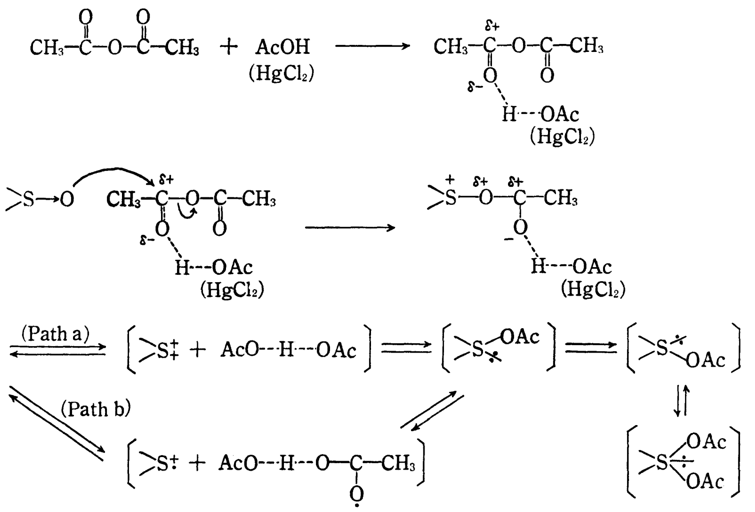


Fig. 4

take place also in the reaction of sulfoxides with acetic anhydride containing a small amount of acid. The transition state in these reactions may be assumed to be S_N1 type as in concentrated sulfuric acid. The change of transition state of this reaction may depend on the hydrogen bonding (protonating) or co-ordination on the oxygen atom of sulfoxide by these acids. The protonation or hydrogen bonding to the carbonyl oxygen of acetic anhydride of these acids can also enhance the initial acetylating step of these reaction (Fig. 4).

Table 4. Effect of aging at 10°C. Rate of ^{18}O-exchange and racemization of *p*-tolyl phenyl sulfoxide in acetic anhydride containing a small amount of mercuric chloride and ratio of the rate, k_{ex}/k_{rac}

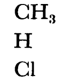
Period	k_{ex} (sec^{-1})	k_{rac} (sec^{-1})	k_{ex}/k_{rac}
0	$(1.06\pm0.07)\times10^{-4}$	$(1.34\pm0.02)\times10^{-4}$	1.19
3 days	$(2.56\pm0.35)\times10^{-4}$	$(2.91\pm0.09)\times10^{-4}$	0.90

Jonsson[5] suggested that the rate enhancement by the acids in this reaction depends only on the formation of acetylium ion in the initial step. According to this mechanism, formation of acetylium ion would bring about an increased conductivity of the acetic acid solution. However, a careful measurement of conductivity of the reaction solution revealed no increase of conductivity. Ion separation did not take place in these solutions as shown in Table 4.

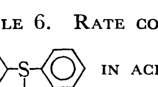
This effect may be due to the gradual formation of acylinium ion species which would react with sulfoxides so rapidly that measurement of conductivity becomes impossible.

The large enhancement of the rate, however, does not seem to be due to the discrete formation of a small amount of acetylium ion, but to the hydrogen bonding or participation of these acids in the initial acetylating step and also in the suc-

Table 5. Rate constants of ^{18}O-exchange of

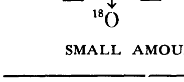


in acetic anhydride containing a small amount of mercuric chloride at 10°C[a)]

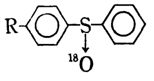
R in 	k_{ex} (sec^{-1})
CH_3	$(10.3\pm0.31)\times10^{-5}$
H	$(11.2\pm0.03)\times10^{-5}$
Cl	$(3.85\pm0.42)\times10^{-5}$
NO_2	very slow

a) Sulfoxide=0.05M $HgCl_2$=0.018M

Table 6. Rate constants of ^{18}O-exchange



in acetic anhydride containing small amounts of acetic acid at 90°C[a)]

R in 	k_{ex} (sec^{-1})
CH_3	$(10.05\pm0.30)\times10^{-5}$
H	$(10.3\ \pm0.02)\times10^{-5}$
Cl	$(\ 5.37\pm0.25)\times10^{-5}$
NO_2	$(\ 6.84\pm0.20)\times10^{-6}$

a) Sulfoxide=0.05M $Ac_2O/AcOH$=9 AcOH 10% solution ceeding fission of S–O bond. The over-all scheme of the oxygen exchange reaction of diaryl sulfoxides in acetic anhydride containing some acids may be formulated as in Fig. 4.

In order to confirm the S_N1-like character of this reaction, the oxygen exchage reaction of *p*-substituted diphenyl sulfoxides in acetic anhydride was carried out in the presence of a few acids. The results obtained with Lewis acids are shown in Table 5, while those with acetic acid are summarized in Table 6.

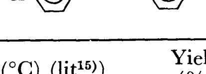
Kinetic data clearly reveal that the polar effect of substituents on the rate of oxygen exchange is markedly larger in this reaction than that in a typical S_N2 type reaction, such as reaction of sulfoxide with acetic anhydride[2] or with less concentrated sulfuric acid.[10] Two different mechanisms are conceivable, one in which the heterolysis of S–O bond involves the rate determining formation of the doubly charged "sulfidonium ion" intermediate (path a in Fig. 4), and the other in which the homolysis forms a radical cation intermediate (path b in Fig. 4). The relatively small polar effect ($\rho \doteqdot 1$) seems to favor the homolytic path for this reaction.

Experimental

Materials. *^{18}O-Labeled Diaryl Sulfoxides* were prepared by the bromine oxidation of the corresponding sulfides using ^{18}O-enriched water.[14]

An aryl sulfide (0.1 mol) was dissolved (0.2—0.5 mol) in a mixture of ^{18}O-enriched water (1.63 atom%), pyridine (0.12 mol) and small amount of acetic acid, and the solution was cooled down to 0°C, and an acetic acid solution of bromine (0.1 mol) was then added dropwise over a period of 1 hour. After one hour of stirring, the reaction mixture was poured into a large excess of ice-water, and the aqueous solution was neutralized with sodium bicarbonate. The precipitate formed was extracted with ether and the ether solution was washed with 10% sodium thiosulfate to remove both bromine and water, respectively, and dried over anhydrous sodium sulfate. After the solvent was distilled off thoroughly, the ^{18}O-labeled sulfoxide obtained was recrystallized three times from *n*-hexane - ether solution. The yields, melting points and ^{18}O-concentrations of the sulfoxides obtained are listed in Table 7.

Table 7. ^{18}O-labeled aryl sulfoxides



X	Mp (°C) (lit[15])	Yield (%)	^{18}O-concn. (atom %)
H	71 (71)	85	0.89
CH_3	69.8—71 (71—72)	80	1.09
Cl	45—46 (45—46)	70	1.05
NO_2	107 (106—107)	70	0.996*

* Prepared from 3.50 atom %-H_2O^{18}

Optically Active p-Tolyl Phenyl Sulfoxide. This sulfoxide was prepared by the method of Anderson[16] in which (−)-menthyl (−)-*p*-toluenesulfinate was allowed to react with phenylmagnesium bromide in ether (mp 91—93°C $[\alpha]_D = +27°$ in EtOH).

Acetic Acid obtained commercially was treated with chromic anhydride and after refluxing for several hours, it was distilled (bp 117.5—118°C).

Acetic Anhydride obtained commercially was treated with anhydrous sodium acetate and then distilled (bp 139.5—140°C).

Kinetic Procedure I (Oxygen Exchange Reaction). The oxygen exchange reaction was carried out in sealed tubes at a set temperature, ranging from 90 to 110°C in acetic anhydride containing a small amount of acetic acid, or from 10 to 20°C in acetic anhydride containing a small amount of mercuric chloride. In the sealed tubes were placed aliquots of the reaction mixture containing optically active *p*-tolyl phenyl sulfoxide (1.25×10^{-3} mol) in 25 m*l* acetic anhydride - acetic acid solution ($Ac_2O/AcOH$ 9/1 (v/v)) or in the same acetic anhydride solution containg $HgCl_2$ (2.4353 g $HgCl_2$/500 m*l* Ac_2O) without other solvents. From time to time a sealed tube containing 4 m*l* of the reaction mixture was drawn out from the bath and quenched with ice water. The sulfoxide separated out was extracted with carbon tetrachloride, carbon tetrachloride was then distilled off and the resulting sulfoxide was recovered. The recovered sulfoxide was dried thoroughly and subjected to ^{18}O-analysis.[11]

Kinetic Procedure II (Racemization Reaction). The racemization reaction was carried out under the same conditions as for the oxygen exchange reaction. From time to time a sealed tube containing 4 m*l* of reaction mixture was drawn out from the paraffin bath and poured into an ice bath to stop the reaction of *p*-tolyl phenyl sulfoxide with acetic anhydride - acetic acid. In the reaction of *p*-tolylphenyl sulfoxide with acetic anhydride-mercuric chloride, the rates were measured directly by checking the polarimeter which was set at a desired temperature by connecting it with a constant temperature bath. The rate constants obtained by these methods are usually in good agreement with those obtained by isolating the product under kinetic procedure I.

Measurement of Conductivity. The electric conductivity of the solutions was measured by a universal bridge. At first the conductivity of acetic anhydride solution was measured by using a regular cell with platinum plates, and the value 40 MΩ was obtained. The conductivity of 25 m*l* acetic anhydride containing 136 mg mercuric chloride was found to be also 40 MΩ. The same value was obtained after 3 days and also after a week.

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

[15] G. Modena, *Gazz. Chim. Ital.*, **89**, 834 (1959).

[16] K. K. Anderson, *Tetrahedron Lett.*, **1962**, 93.