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Reaction of Sulfoxides with Acylating Reagents. I. Mechanism of Oxygen Exchange Reaction of Diaryl Sulfoxides with Acetic Anhydride[1]

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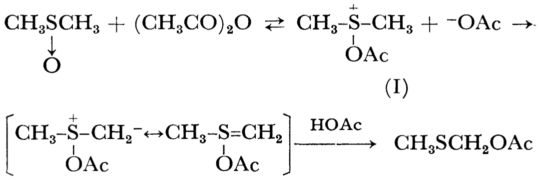
Racemization and oxygen exchange reactions were carried out by heating both optically active and ^{18}O-labeled diaryl sulfoxides in a large excess of acetic anhydride. The rate of racemization of *p*-tolyl phenyl sulfoxide was found to be twice the rate of oxygen exchange, suggesting the reaction to involve a Walden inversion at the rate-determining step. When the reaction was carried out in a mixture of acetic anhydride and chlorobenzene, the rate of racemization was found to be first order with respect to both the sulfoxide and acetic anhydride. The remarkably small substituent effect is also in keeping with the S_N2 type mechanism. The marked retardation of the rate of racemization by the addition of common salt is similar to well-known cases in the S_N2 reaction of alkyl halides, and the remarkably large acceleration of the rates of both racemization and oxygen exchange reactions by the addition of sodium perchlorate seems to be caused by a special salt effect.

The sulfur-oxygen linkage in sulfoxides has been considered to possess a semi-polar character,[2] and unlike those in sulfone groups, the sulfur-oxygen links in sulfoxides are weak and readily cleaved. Another important feature is that optical isomerism can exist in sulfoxide compounds,[3] and the stereochemical stability of sulfoxides is known greatly to exceed those of similar sulfonium compounds.[4] Thus sulfoxides are utilizable for studying the nature of nucleophilic substitutions on sulfur atom.

Sulfoxides have been known to undergo concurrent oxygen exchange and racemization reactions in various acidic media, such as concentrated sulfuric acid,[5,6] hydrochloric acid in aqueous dioxane,[7] hydrobromic acid in acetic acid,[8] dinitrogen tetraoxide[9] and acetic anhydride.[10] In a previous paper,[11] we showed that sulfoxides undergo concurrent oxygen exchange and racemization reactions through an acid catalyzed S_N1-type process in weak carboxylic acids. In this paper we would like to report a detailed account of another oxygen exchange reaction of aromatic sulfoxides in acetic anhydride, which appears to proceed through an S_N2-type route.

We suggested[12] 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 an acetate group on the methylene carbon of the ylide-ylene intermediate II.



$$CH_3\underset{\underset{O}{\downarrow}}{S}CH_3 + (CH_3CO)_2O \rightleftarrows CH_3\text{-}\underset{OAc}{\overset{+}{S}}\text{-}CH_3 + {}^{-}OAc \rightarrow$$

(I)

$$\left[CH_3\text{-}\underset{OAc}{\overset{+}{S}}\text{-}CH_2^{-} \leftrightarrow CH_3\text{-}\underset{OAc}{S}{=}CH_2\right] \xrightarrow{HOAc} CH_3SCH_2OAc$$

(II)

However, the rather fast interchange of alkoxy groups in the following reactions, found recently by Johnson and Phillips,[13] cast doubt on the

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[1] Paper XXVIII on Sulfoxides.

[2] C.C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York (1962), Chapter 4.

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

[4] a) D. Darwish and G. Tourigny, *J. Amer. Chem. Soc.*, **88**, 4303 (1966). *b*) R. Scartazzini and K. Mislow, *Tetrahedron Lett.*, **1967**, 2719.

[5] S. Oae and N. Kunieda, This Bulletin, **41**, 696 (1968) and references cited in this paper.

[6] H. J. Shine and D. R. Thompson, *Tetrahedron Lett.*, **1966**, 1591.

[7] K. Mislow, T. Simmons, J. T. Mellillo and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **86**, 1452 (1964).

[8] W. Tagaki, K. Kikukawa, N. Kunieda and S. Oae, This Bulletin, **39**, 614 (1966).

[9] a) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965). b) S. Oae, N. Kunieda and W. Tagaki, *Chem. Ind.* (London), **1965**, 1790.

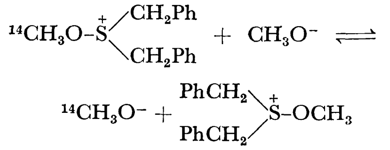
[10] a) S. Oae and M. Kise, *Tetrahedron Lett.*, **1967**, 1409.

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

[12] S. Oae, T. Kitao, S. Kawamura and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963).

[13] C. R. Johnson and W. G. Phillips, *Tetrahedron Lett.*, **1965**, 2101.

significance of our ^{18}O tracer experiments, since a facile acetoxy interchange could also take place within salt I.



$$^{14}CH_3O\text{-}\overset{+}{S}(CH_2Ph)_2 + CH_3O^- \rightleftharpoons {}^{14}CH_3O^- + (PhCH_2)_2\overset{+}{S}\text{-}OCH_3$$

In fact, when an optically active diaryl sulfoxide labeled with ^{18}O was heated in acetic anhydride and the sulfoxide was quantitatively recovered by quenching the reaction mixture with cold water, the recovered sulfoxide was found to have lost its optical activity as well as the excess of ^{18}O. Thus the acetoxy interchange appears to take place readily. We have investigated this oxygen exchange reaction of diaryl sulfoxides extensively in order to understand the nature of the reaction, focusing our attention only on the acetoxy interchange, since with these sulfoxides other competing reactions such as Pummerer rearrangement and the heterolysis of carbon-sulfur linkage which will be discussed in a succeeding paper[14] can be avoided.

Results and Discussion

The oxygen exchange reaction was carried out by heating both optically active and ^{18}O-labeled diaryl sulfoxides in a large excess of acetic anhydride. The sulfoxides employed in this study were *p*-tolyl phenyl, *p*-chlorophenyl phenyl and diphenyl sulfoxides.

When the reaction of *p*-tolyl phenyl sulfoxide with acetic anhydride was carried out in an inert solvent, chlorobenzene, the rate was found to be correlated nicely with a second order kinetic equation, *i. e.* $v=k_2[p\text{-}CH_3C_6H_4SOC_6H_5][Ac_2O]$. (Table 1, Fig. 1). The rate of the reaction of *p*-tolyl benzyl sulfoxide with acetic anhydride was found to be correlated similarly with a second order equation in the same solvent.[14] However, when the reaction was carried out in dioxane, the rate was found not to be correlated by a second order equation. A similar anomaly was observed in the case of *p*-substituted phenyl benzyl sulfoxides with acetic anhydride. The plot of the second order rate constants against the concentration does not give a straight line of slope one in Fig. 2. In fact, the rate is apparently correlated by a 3rd order kinetic equation, namely second order with respect to the concentration of acetic anhydride and first order with the sulfoxide ($v=k_3[{>}S{\rightarrow}O][Ac_2O]^2$).

Table 1. Determination of the kinetic order of racemization reaction in chlorobenzene[a]

Run No.	Ac_2O (g)	Relative concn. Ac_2O	Relative rate
1	3.7565	1.00	1.00
2	6.5447	1.74	2.04
3	10.451	2.78	3.05

a) The reaction was carried out at 120°C in a sealed tube, with sulfoxide, 10^{-3} mol, dissolved in 10 m*l* of the reaction mixture of chlorobenzene and acetic anhydride.

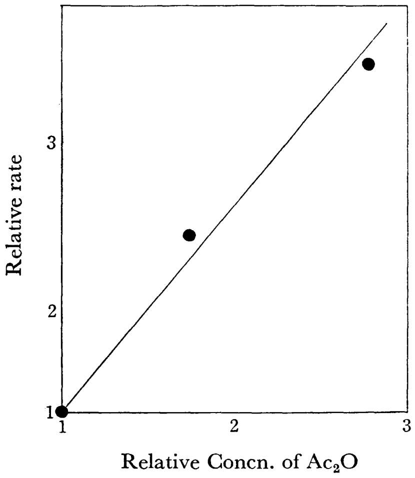


Fig. 1. Determination of the kinetic order of the racemization reaction in chlorobenzene. Plot of relative rate of racemization against concentration of acetic anhydride.

Probably this is due mainly to a special interaction between dioxane and acetic anhydride. Since dioxane is a nucleophilic solvent, it would interact with acetic anhydride to form a loose complex and this interaction may compete with the acetylation of the sulfoxide oxygen of low basicity ($pK_a=-4.40$),[15] thus reducing the rate of the reaction. Incidentally, the reaction between more basic α- or γ-alkylpyridine- or alkylquinoline *N*-oxide with

Table 2. Determination of the kinetic order of racemization reaction[a] in dioxane

Run No.	Ac_2O (g)	Relative concn. Ac_2O	Relative rate
4	4.042	1.00	1.00
5	5.033	1.25	1.33
6	8.027	1.99	4.20
7	8.965	2.22	8.83
8	10.451	2.59	11.3

a) The reaction was carried out at 120°C in a sealed tube, with sulfoxide, 10^{-3} mol, dissolved in 10 m*l* of the reaction mixture of dioxane and acetic anhydride.

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[14] M. Kise and S. Oae, This Bulletin, **43**, 1421, 1426 (1970).

[15] a) K. K. Anderson, W. H. Edmonds, J. B. Biasotti and R. A. Strecker, *J. Org. Chem.*, **31**, 2859 (1966). b) K. Sakai, N. Kunieda and S. Oae, unpublished work in these laboratories.

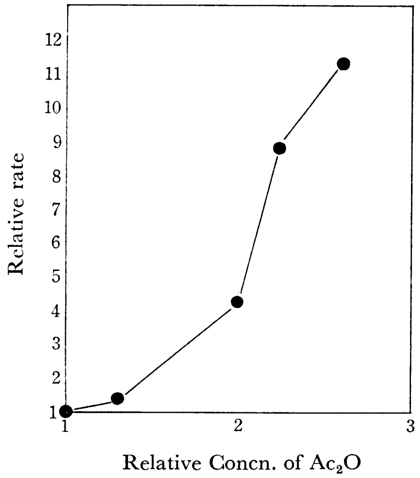
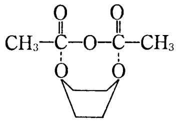


Fig. 2. Determination of the kinetic order of the racemization reaction in dioxane. Plot of relative rate of racemization against concentration of acetic anhydride.

acetic anhydride in dioxane is known to be correlated with the normal second order kinetic equation.[16] The oxygen exchange reaction is undoubtedly of ionic character and hence expected to be facilitated in a more polar solvent, acetic anhydride. A similar oxygen exchange reaction of aryl benzyl sulfoxides is accelerated markedly in a still more polar solvent, acetonitrile.[17]

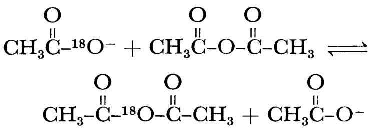


The rates of ^{18}O exchange and racemization in acetic anhydride, together with other pertinent data, are shown in Table 3.

Inspection of the kinetic data reveals that the rate of racemization, k(rac), of p-tolyl phenyl sulfoxides was twice that of oxygen exchange. This means that the reaction involves a Walden inversion at the rate determining step. The energy and the entropy (at 120°C) of activation for the reaction were found to be 19.2 kcal/mol and -28.6 e.u., respectively. The small value of the entropy of activation is also in keeping with the suggested mechanism. In the ^{18}O exchange reactions in both dinitrogen tetraoxide and highly concentrated sulfuric acid, k_{exch}/k_{rac} is unity, while the entropies of activation of both reactions are substantially large and positive. The oxygen exchange reaction in less concentraetd sulfuric acid (for example 75.4% H_2SO_4) is considered to be an S_N2-type process and gives a k_{exch}/k_{rac} value of roughly 1/2.[18] In this case the entropy of activation is quite small ($\Delta S^{\neq} = -18.9$ at 30°C).

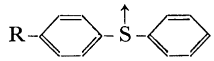
The small substituent effects are also in accordance with the S_N2-type mechanism, since the reaction is expected to pass through an ideal transition state in which both the entering and the leaving group are identical. The polar effect of substituents should be considerably cancelled and reduced in many typical S_N2 reactions at the saturated carbon atom.[19] Thus, the over-all process of the reaction can be illustrated as shown in Fig. 3.

It is known that the acetate ion, once formed, undergoes a rapid interconversion with acetic anhydride as represented by the following equation.[20]



$$CH_3\overset{O}{\overset{\|}{C}}{-}{}^{18}O^- + CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \rightleftharpoons CH_3{-}\overset{O}{\overset{\|}{C}}{-}{}^{18}O{-}\overset{O}{\overset{\|}{C}}{-}CH_3 + CH_3\overset{O}{\overset{\|}{C}}{-}O^-$$

Table 3. Kinetic data on oxygen exchange and racemization reactions in acetic anhydride[a] at 120°C

Run No.	R in 	Added salt	k(rac) × 10^5 (sec^{-1})	k(exch) × 10^5 (sec^{-1})
9	CH_3		9.97±0.35	5.00±0.20
10	CH_3	CH_3COONa[b]	2.29±0.10	
11	CH_3	$NaClO_4$[c]	497±22	275±45
12	Cl			3.97±0.55
13	H			4.68±0.42

a) Sulfoxide, 5×10^{-3} mol, was treated with 0.5 mol of acetic anhydride.
b) NaOAc, 0.001 mol, in 0.5 mol Ac_2O
c) $NaClO_4$, 0.001 mol, 0.5 mol Ac_2O

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[16] S. Tamagaki, S. Kozuka and S. Oae, unpublished work in these laboratories.

[17] M. Kise and S. Oae, This Bulletin, in press.

[18] N. Kunieda and S. Oae, *ibid.*, **42**, 1324 (1969).

[19] a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Chapter 5 and 7, Cornell Univ. Press, Ithaca and London (1953). b) K. Akagi, S. Oae and M. Murakami, *J. Amer. Chem. Soc.*, **78**, 4034 (1956).

[20] L. Ponticorvo and D. Rittenberg, *J. Amer. Chem. Soc.*, **76**, 1705 (1954).

Thus ^{18}O-containing acetate ion will be quickly diluted by rapid interchange with the bulk unlabeled acetic anhydride.

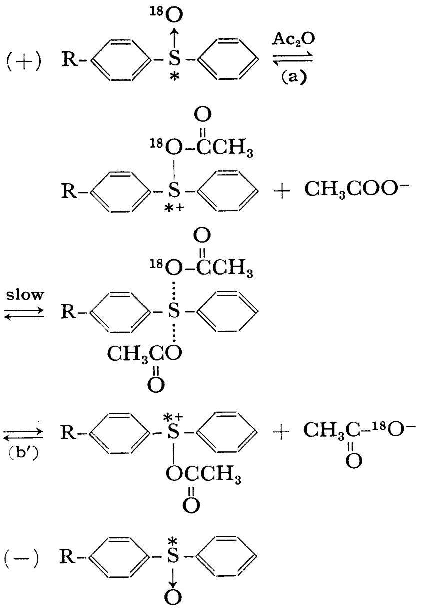


Fig. 3

The marked retardation of the rate of racemization by the addition of common salt is considered to be due to a similar retardation found in the S_N2 reactions of alkyl halides and related compounds.[21] A similar, though small, negative common salt effect was known in a few rearrangement reactions of heteroaromatic *N*-oxides and acetic anhydride.[22] The remarkably large acceleration of the rates of both racemization and oxygen exchange reactions by the addition of sodium perchlorate also seems to be caused by a special salt effect as in the well-known cases found by Winstein and his coworkers.[23] A similar rate acceleration by the addition of perchlorate ion was also observed in the reaction of quinaldine *N*-oxide and acetic anhydride.[24]

The addition of acetic acid also increases the rate of both the racemization[25] and the oxygen exchange. Racemization of sulfoxides in acetic anhydride is also known to be catalyzed markedly by a small amount of Lewis acid.[26]

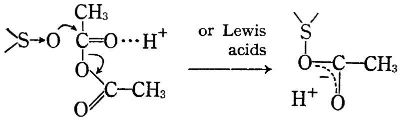
TABLE 4. INFLUENCE OF ACETIC ACID ON THE RACEMIZATION REACTION OF SULFOXIDES IN ACETIC ANHYDRIDE[a)]

Run No.	AcOH	$k_{rac}\times 10^5$ (sec^{-1})	Rel rate
14	0	4.45	1
15	0.0663	6.25	1.40
16	0.1230	10.1	2.28
17	0.2492	16.7	3.75
18	1.0254	102.7	23.1
19	2.0484	231.7	52.1

a) The reaction was carried out at 120°C in a sealed tube. Sulfoxide, 10^{-3} mol, was treated with acetic anhydride. No solvent was used.

A question arises whether the acid catalyzed reactions would proceed through an S_N1-like path involving rate-determining S–O bond cleavage, as in the oxygen exchange reactions in carboxylic acids and concentrated sulfuric acid. When the reaction was carried out in the presence of a small amount of acetic acid, the ratio of the rate constants, k_{exch}/k_{rac} became unity. This may mean than the presence of Brönsted acid facilitates the cleavage of S–O bond by the easy protonation on the sulfoxide oxygen and the assistance of the nucleophilic attack by acetate becomes less important in the reaction.

The catalytic effect of both the Brönsted and Lewis acid is considered to be due to the acceleration of both the first acetylation step (a) and also the second slow step of S_N2 type process, since in both steps the leaving of acetate group will be facilitated by either protonation or co-ordination with a Lewis acid as shown below.



Phenol, albeit a weak Brönsted acid, was found to accelerate the rate of racemization of sulfoxides.

Experimental

Materials. *Optically Active p-Tolyl Phenyl Sulfoxide.* This sulfoxide was prepared by the method of Anderson[3] whereby (—)- menthyl (—)-*p*-toluenesulfinate was allowed to react with phenylmagnesium bromide in ether (mp 91—93°C $[\alpha]_D=+26.9°$ in ethanol).

^{18}O-Labeled p-Substituted Aryl Phenyl Sulfoxide. The corresponding sulfide was oxidized with bromine in the presence of pyridine in acetic acid and $H_2{}^{18}O$, according to the usual procedure.[27] All the sulfoxides had $\rangle$S→O stretching bands in their infrared spectra at about 1050 cm^{-1}. Their melting points and ^{18}O-contents are shown below.

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21) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. S. Robinson, *ibid.*, **78**, 328 (1956).

22) J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr and R. G. Teterson, *ibid.*, **85**, 958 (1963).

23) C. A. Bunton, "Nucleophilic Substitution at Saturated Carbon Atom," Chapter, 5 Elsevier, Amsterdam (1963).

24) S. Oae, S. Tamagaki, T. Negoro, K. Ogino and S. Kozuka, *Tetrahedron Lett.*, **1968**, 917.

25) E. Jonsson, *Acta Chem. Scand.*, **21**, 1278 (1967).

26) E. Jonsson, *Tetrahedron Lett.*, **1967**, 3675.

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

28) G. Modena, *Gazz. Chim. Ital.*, **89**, 834 (1959).

p-CH_3;	69.8—71°C	lit,[28] 71—72°C	(1.09 atom%)
p-Cl;	45—46°C	lit,[28] 45—46°C	(1.05 atom%)
p-H;	71°C	lit,[28] 71°C	(0.89 atom%)

Dioxane, obtained commercially, was purified according to the usual procedure, thoroughly dried with sodium and distilled (bp 101.5°C).

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

Acetic Anhydride, obtained commercially, was treated with anhydrous sodium acetate. After refluxing for several hours, it was distilled (bp 139.5—140°C).

Kinetic Procedure (I). Concurrent oxygen exchange and racemization reactions were carried out at 120 ± 0.05°C (paraffin bath) while the molar ratio of sulfoxide to acid anhydride was kept at 1 : 100. Thus, a mixture of sulfoxide (5×10^{-3}) and acetic anhydride (5×10^{-1} mol) was allowed to react. From time to time, 5 m*l* of the reaction mixture was pippetted out and poured into an excess of water. The sulfoxide separated out, was then extracted with carbon tetrachloride, and dried with anhydrous magnesium sulfate. Carbon tetrachloride was distilled off and the resulting sulfoxide was recovered. The recovered sulfoxide was dried thoroughly and subjected to measurements of both specific rotation and ^{18}O-analysis. The specific rotation was measured in ethanol at *c* : 3.00, and ^{18}O-analysis of sulfoxide-oxygen was carried out as usual according to the modified Rittenberg-Porticorvo method.[5] The *k* values in Table 3 and the activation parameters were determined by this procedure. All the rate constants quoted were determined from the equations for racemization.

$$\log\,[\alpha]_{D0} - \log\,[\alpha]_{Dt} = \frac{kt}{2.303},$$

where $[\alpha]_{D0}$ and $[\alpha]_{Dt}$ are the rotatory powers at times 0 and *t*, respectively, and for oxygen exchange,

$$\log\,[\beta_0 - \beta] - \log\,[\beta_t - \beta] = \frac{kt}{2.303},$$

where β_0 and β_t are the atom % ^{18}O at times 0 and *t*, respectively, and β is the atom % ^{18}O of natural CO_2. A typical kinetic run is shown below.

Polarimetric Run

No. 10 *p*-Tolyl phenyl sulfoxide, 10^{-3} mol, in 10^{-1} mol of Ac_2O

Time (min)	0	30	60	90	120	150	180
$[\alpha]_D$	23.7°	19.7°	16.9°	13.7°	12.2°	9.7°	7.5°

10^5k (sec^{-1}) = 9.98 ± 0.35

No. 11 *p*-Tolyl phenyl sulfoxide, 10^{-3} mol, in 10^{-1} mole of acetic anhydride contg. 2×10^{-4} mol NaOAc

Time (min)	0	25	55	85	115
$[\alpha]_D$	24.8	23.9	23.0	22.2	21.3

10^5k (sec^{-1}) = 2.29 ± 0.10

Exchange Run

No. 10 *p*-Tolyl phenyl sulfoxide, 10^{-3} mol, in 10^{-1} mol of Ac_2O

Time (min)	0	30	90	120	150	210
β_t	0.818	0.753	0.630	0.571	0.504	0.428

10^5k (sec^{-1}) = 5.00 ± 0.20

Kinetic Procedure II. The racemization reaction was carried out at 120 ± 0.05°C in sealed tubes in which *p*-tolyl phenyl sulfoxide (10^{-3} mol) was dissolved in 10 m*l* of acetic anhydride containing no other solvent or solute. From time to time a sealed tube was taken out from the paraffin bath and placed in an ice bath in order to stop the reaction. Then the acetic anhydride solution containing the sulfoxide was immediately subjected to the measurement of specific rotation.

Determination of the Kinetic Order of Racemization Reaction in Dioxane. The reaction was carried out at 120°C in sealed tubes, each containing 10 m*l* of the reaction mixture, which was prepared from dioxane and acetic anhydride containing optically active *p*-tolyl phenyl sulfoxide (10^{-3} mol). From time to time, a sealed tube was taken out from the paraffin bath. Each kinetic run was carried out as in the above procedure.

Influence of Acetic Acid on Racemization. The reaction was carrried out at 120°C in sealed tubes. A mixture af acetic anhydride and acetic acid containing an optically active sulfoxide (10^{-3} mol) was prepared and 10 m*l* of the reaction mixture was sealed in each tube and subjected to the usual kinetic measurements.