BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1426—1430 (1970)

Reaction of Sulfoxides with Acylating Reagents. III. Mechanism of the Reactions of Phenyl Methyl Sulfoxide with Acetic Anhydride[1]

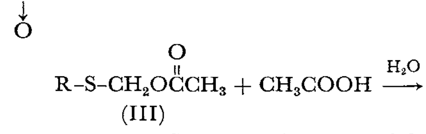
Masahiro Kise and Shigeru Oae

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sugimoto-cho, Sumiyoshi-ku, Osaka

(Received July 29, 1969)

The Pummerer reaction, *viz.*, the reaction of sulfoxides having at least one methyl or methylene group with carboxylic acid anhydride gives α-acyloxy derivatives of the corresponding sulfide. Earlier, 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. However, the Pummerer reaction is the main path when the reaction with acetic anhydride is performed at around 120°C. In the Pummerer reaction of aryl methyl sulfoxides, the substituent effect is large ($\rho = -1.6$) and the kinetic isotope effect (k_H/k_D) is also substantial, *i.e.*, 2.9. The reaction is assumed to involve the initial acetylation and the subsequent slow proton removal steps. Addition of sodium perchlorate or acetic acid accelerates the acetoxy exchange reaction rather than the Pummerer reaction.

The Pummerer Reaction[2] has been known for many years. When an alkyl (or aryl) methyl sulfoxide is treated with acetic anhydride, there is formed a rearranged ester (III) *i. e.* acetoxymethyl alkyl (or aryl) sulfide which upon hydrolysis results in the formation of alkyl (or aryl) mercaptan, formaldehyde and acetic acid. Among the mechanisms suggested for the Pummerer reaction[2-4] only the one by Bordwell and Pitt,[3] involving the



$$\begin{array}{l} R\text{-}\underset{\overset{\downarrow}{O}}{S}\text{-}CH_3 + (CH_3CO)_2O \rightleftarrows \\ \qquad R\text{-}S\text{-}CH_2O\overset{\overset{O}{\|}}{C}CH_3 + CH_3COOH \xrightarrow{H_2O} \\ \qquad\qquad (III) \\ \qquad\qquad\qquad R\text{-}SH + CH_2O + CH_3COOH \end{array}$$

---

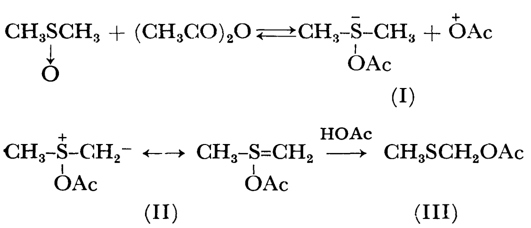
[1] Paper XXX on Sulfoxides.

[2] L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959), and references cited in this paper.

[3] F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

[4] W. J. Kenney, J. A. Walsh and D. A. Davenport, *ibid.*, **83**, 4019 (1961).

ylide-ylene intermediate (II), appears reasonable. 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 (II).[5]

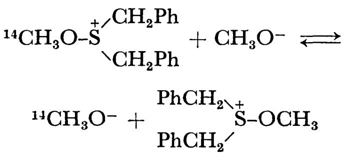


$$\underset{\underset{\displaystyle O}{\downarrow}}{CH_3SCH_3} + (CH_3CO)_2O \rightleftarrows \underset{\underset{\displaystyle OAc}{|}}{CH_3\text{-}\overset{-}{S}\text{-}CH_3} + \overset{+}{O}Ac \quad \text{(I)}$$

$$\underset{\underset{\displaystyle OAc}{|}}{CH_3\text{-}\overset{+}{S}\text{-}CH_2^-} \longleftrightarrow \underset{\underset{\displaystyle OAc}{|}}{CH_3\text{-}S\text{=}CH_2} \xrightarrow{HOAc} CH_3SCH_2OAc$$

$$\text{(II)} \qquad\qquad \text{(III)}$$

However, the fast interchange of alkoxy group in the following reactions found by Johnson and Phillips[6] made the significance of our ^{18}O tracer experiments doubtful,



$$^{14}CH_3O\text{-}\overset{+}{S}\begin{smallmatrix}\diagup CH_2Ph\\ \diagdown CH_2Ph\end{smallmatrix} + CH_3O^- \rightleftarrows {}^{14}CH_3O^- + \begin{smallmatrix}PhCH_2\diagdown\\ PhCH_2\diagup\end{smallmatrix}\overset{+}{S}\text{-}OCH_3$$

since a facile interchange could also take place within the salt (I) and the possible acetoxy interchange would also scramble the ^{18}O completely in the whole reaction system. We found that acetoxy interchange which causes both the oxygen exchange and the racemization does take place with diaryl sulfoxides in warm acetic anhydride. The rate of the racemization of *p*-tolyl phenyl sulfoxide was found to be twice that of the oxygen exchange suggesting that the reaction involves a Walden inversion at the rate-determining step.[7]

In the case of aryl methyl sulfoxides both concurrent oxygen exchange with racemization reactions and Pummerer reaction take place. As in the case of diaryl sulfoxides[8] racemization of aryl methyl sulfoxides with acetic anhydride is also catalyzed markedly by a small amount of Lewis acid. In order to clarify the over-all feature of the reaction, the kinetic investigation of the reaction is desirable. This paper describes a detailed account of the kinetic study of the Pummerer reaction and the concurrent oxygen exchange and racemization reactions of *p*-substituted phenyl methyl sulfoxide with acetic anhydrides.

Results and Discussion

A few *p*-substituted phenyl methyl sulfoxides and two α-trideuterated derivatives were synthesized and subjected to both the Pummerer reaction and the concurrent oxygen exchange and racemization reactions. The rate of the Pummerer reaction can be readily followed spectrophotometrically, taking an advantage of the difference of UV spectra of the starting sulfoxide and the final compounds, *i. e.*, aryl mercaptan obtained by quenching the reaction mixture with water.

The rate of racemization reaction of optically active *p*-tolyl methyl sulfoxide was determined by the usual procedure, measuring the optical rotation of the reaction solution. In this case, the rate constant of the racemization consisted of two rate constants, the one due to the oxygen exchange and the other caused by the Pummerer reaction. When the reaction was carried out in dioxane, the rate of the Pummerer rearrangement of *p*-tolyl methyl sulfoxide with acetic anhydride was found to be correlated by the second order equation, *i. e.*,

$$v = k_2[p\text{-}CH_3C_6H_4SOCH_3][Ac_2O]$$

Similarly, the rate of the racemization reaction was also found to be correlated by the second order

TABLE 1. THE DETERMINATION OF KINETIC ORDER OF THE PUMMERER REACTION OF *p*-TOLYL METHYL SULFOXIDE WITH ACETIC ANHYDRIDE IN DIOXANE[a)]

Run No.	Ac_2O (g)	$k\times10^5$ (sec^{-1})	Relative concn. Ac_2O	Relative rate
1	2.139	2.72	1	1
2	5.311	6.42	2.483	2.360
3	7.450	8.73	3.483	3.210
4	10.451	17.6	4.886	6.471

a) This reaction was carried out at 120°C in sealed tubes, and sulfoxide (*ca.* 0.5×10^{-4} mol) was dissolved in 10 m*l* reaction mixture of dioxane and acetic anhydride.

TABLE 2. DETERMINATION OF KINETIC ORDER OF RACEMIZATION REACTION OF *p*-TOLYL METHYL SULFOXIDE WITH ACETIC ANHYDRIDE IN DIOXANE[a)]

Run No.	Ac_2O (g)	$k\times10^5$ (sec^{-1})	Relative concn. Ac_2O	Relative rate
5	2.1942	4.38	1	1
6	4.3416	9.08	1.98	2.07
7	6.1687	12.8	2.81	2.92
8	8.4894	19.8	3.87	4.52
9	10.4663	24.8	4.77	5.66

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

---

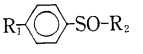
5) S. Oae, T. Kitao, S. Kawamura and Y. Kitaoka, *Tetrahedron*, **19**, 820 (1963).

6) a) N. J. Leonald and C. R. Johnson, *J. Amer. Chem. Soc.*, **84**, 3701 (1962). b) C. R. Jonhson and W. G. Phillips, *Tetrahedron Lett.*, **1965**, 2101.

7) a) S. Oae and M. Kise, *Tetrahedron Lett.*, **1967**, 1409. b) S. Oae and M. Kise, *ibid.*, **1968**, 2261.

8) E. Jonsson, *ibid.*, **1967**, 3675.

TABLE 3. KINETIC DATA OF THE PUMMERER REACTION IN ACETIC ANHYDRIDE$^{a)}$

Run No.	R_1R_2 in 		k_H(sec^{-1})	k_D(sec^{-1})	k_H/k_D
	R_1	R_2			
10	CH_3	CH_3	2.07×10^{-4}	(±0.10)	
11	H	CH_3	1.09×10^{-4}	(±0.22)	2.9
12	H	CD_3		3.67×10^{-5}	(±0.42)
13	Cl	CH_3	4.00×10^{-5}	(±0.08)	
14	NO_2	CH_3	6.12×10^{-6}	(±0.24)	2.8
15	NO_2	CD_3		2.15×10^{-6}	(±0.11)

a) Sulfoxide (0.4—0.6 × 10^{-4} mol) was allowed to react with acetic anhydride. No solvent was used. Each kinetic run was carried out at 120°C.

equation.

However, in dioxane solutions containing acetic anhydride in high concentration, the plots of relative rates of both the Pummerer rearrangement and the racemization against the concentration give convex upward curves probably due to the solvent effect.9) Tables 1 and 2, reveal that the rate of racemization was the sum of the rates of the Pummerer and twice that of the oxygen exchange reaction, *i. e.*, $k_{\mathrm{rac}}=k_{\mathrm{P}}+2k_{\mathrm{ex}}$

The over-all rates of the Pummerer reactions of a few *p*-substituted phenyl methyl sulfoxides were determined and the results are listed together with those of trideuterated compounds in Table 3.

The rates are in line with the Hammett equation, and a negative ρ value (for σ), −1.60, was obtained. When only the rate variation of *p*-substituted phenyl methyl sulfoxides is considered as if the first step of the reaction, *i e.*, acetylation, is the rate-determining step. A large positive ρ-value obtained10) in the reaction of dimethyl sulfoxide and *p*-substituted benzoic anhydride seems to support this.

However, the kinetic isotope effect, $k_H/k_D=2.85$ indicates that the rate-determining step is the succeeding step of the reaction, namely the proton removal by acetate anion. Recently Johnson reported that acetoxy group migrates to the least substituted α-carbon in the Pummerer reaction of a few unsymmetrical dialkyl sulfoxide with acetic anhydride. The result is also undoubtedly a reflection of the difference in the acidities of α-protons of the two alkyl groups of the intermediate acetoxysulfonium salts, and the removal of the proton is the rate-determining step of the reaction.11) The relatively small value of kinetic isotope effect is due mainly to the fact that the first step of the reaction requires also a substantial energy of activation, as in the reaction between quinaldine *N*-oxide and acetic anhydride.12) The addition of sodium perchlorate or acetic acid13) was found to accelerate the over-all rates by 3 or 4 fold. Apparently the

TABLE 4. THE INFLUENCE OF SODIUM PERCHLORATE ON THE PUMMERER REACTION$^{a)}$

Run No.	$NaClO_4$ (mg)	$k\times10^4$ (sec^{-1})	Relative rate
16	0	1.76	1
17	2.93	2.92	1.66
18	5.51	4.85	2.76
19	10.10	5.28	3.00

a) Each kinetic run was caried out at 120°C in sealed tubes and the sulfoxide (5 × 10^{-4} mol) was allowed to react with acetic anhydride. No solvent was used.

TABLE 5. INFLUENCE OF ACETIC ACID ON THE PUMMERERREACTION$^{a)}$ OF *p*-TOLYL METHYL SULFOXIDE

Run No.	AcOH (g)	$k\times10^{-4}$ (sec^{-1})	Relative rate
20	0	1.73	1
21	0.9561	4.97	2.87
22	1.9452	7.73	4.47
23	3.2010	7.73	4.47

a) Each kinetic run was carried out at 120°C in sealed tubes, and the sulfoxide (0.4—0.6 × 10^{-4}mol) was allowed to react with acetic anhydride. No solvent was used.

TABLE 6. INFLUENCE OF ACETIC ACID ON THE RATE OF RACEMIZATION REACTION$^{a)}$ OF *p*-TOLYL METHYL SULFOXIDE

Run No.	AcOH (g)	$k\times10^4$ (sec^{-1})	Relative rate
24	0	0.720	1
25	1.0257	3.53	4.90
26	2.0533	8.29	11.5
27	3.7261	15.4	21.4

a) Each kinetic run was carried out at 100°C in sealed tubes, and the sulfoxide (10^{-3} mol), allowed to react with acetic anhydride. No solvent was used.

---

9) M. Kise and S. Oae, following paper in these series.

10) S. Arita, private communication.

11) a) C. R. Johnson, J. C. Sharp and W. G. Phillips, *Tetrahedron Lett.*, **1967**, 5299. b) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969).

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

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

Table 7. Kinetic data of the Pummerer and racemization reactions in acetic anhydride[a]

Temp. (°C)	k_{obs} $\times 10^4$ $k_{racemization}$[b] (sec^{-1})	$\times 10^4$ $k_{Pummerer}$ (sec^{-1})	$\times 10^4$ $2\,k_{exchange}$ (sec^{-1})	$k_{Pummerer}/k_{exchange}$
100	0.720±0.04			
110	1.25 ±0.19	0.853±0.12	0.397	4.3
120	2.53 ±0.06	1.77 ±0.12	0.610	5.8
130	4.48 ±0.09	3.53 ±0.05	0.905	7.4

a) Sulfoxide ($0.4-0.6 \times 10^{-4}$ moll^{-1}) was allowed to react with acetic anhydride. No solvent was used. This reaction was carried out at 120° C in a sealed tube.

b) The relation, $k_{racemization} = k_{pummerer} + 2\,k_{exchange}$ is assumed. The rates of the oxygen exchange reaction were calculated from this equation.

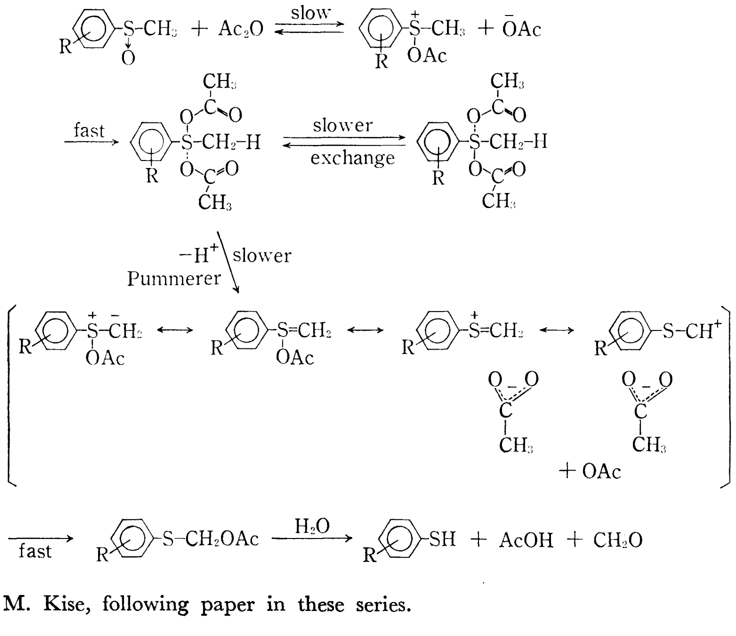
addition of perchlorate tends to shift the equilibrium to the right to increase the concentration of the acetoxysulfonium salts, increasing the rate of the Pummerer reaction. The addition of both sodium perchlorate and acetic acid was found to increase the rate of the reaction of the acyloxy exchange markedly.

Racemization of sulfoxides in acetic anhydride is known to be catalyzed markedly by a small amount of Lewis acid.[8)]

In the oxygen exchange and racemization reactions, both Brönsted and Lewis acids will catalyze the first acetylation step and also the second slow step of S_N2 type process because the leaving of acetate group will be facilitated by either protonation or coordination of Lewis acids.[14)] But in the Pummerer reaction, the effect of the rate acceleration by the addition of acetic acid or sodium perchlorate was considerably smaller than that in oxygen exchange and racemization reaction. The over-all picture of the reaction can be depicted as follows. A mechanism similar to that of this reaction was recently suggested by Johnson.[11)] We have measured the rate of racemization of an optically active *p*-tolyl methyl sulfoxide in acetic anhydride in order to estimate the rate of concurrent oxygen exchange during the reaction. The results are listed together with the rates of the Pummerer reaction in Table 7.

Apparently, the rate of the Pummerer reaction increases markedly with the rise of reaction temperature. This can be seen from a comparison of the enthalpies and entropies of activation of the two reactions, *i. e.*, for O-exchange: E_a, 13.1 kcal/mol; $\Delta S^{\neq}$, −45.1 e. u., for the Pummerer reaction: E_a 21.2 kcal/mol; $\Delta S^{\neq}$, −20.7 e.u., respectively. Below 65°C, under which the Pummerer reaction is negligible, only the oxygen exchange proceeds slowly.

The Pummerer reaction involves the rate-determining proton removal and is accelerated slightly. However, the oxygen-exchange and racemization reactions are markedly accelerated by the addition of acid or sodium perchlorate as in the case of



---

14) S. Oae and M. Kise, following paper in these series.

diaryl and aryl benzyl sulfoxides. The Pummerer reaction becomes significant and takes place faster than the possible oxygen exchange reaction at a high temperature. Our ^{18}O experiments may be still valid in the interpretation of the mechanism especially in connection with the rearrangement steps of the reaction. However, both the S–O bond cleavage and the succeeding formation of the ester are considered to be so fast that these steps cannot be significant in the energy profile of the over-all reaction.

Experimental

Materials. *Optically Active p-Tolyl Methyl Sulfoxide.* The sulfoxide was prepared by the method of Mislow[15] in which(−)-menthyl(−)-*p*-toluenesulfinate was allowed to react with methylmagnesium iodide in ether, (mp 75°C $[\alpha]_D$ +151° in ethanol), lit,[15] mp 73—74°C $[\alpha]_D$ +145.5° (*c* 2.0, acetone).

p-Substituted Phenyl Methyl Sulfoxides. The corresponding sulfide was oxidized with bromine in the presence of pyridine in acetic acid and water, according to the usual procedure.[16] All the sulfoxides has S–O stretching bands in the infrared region at about 1050 cm^{-1}. Thier melting points (boiling points where pressures are given) were *p*-CH_3: 42—43°C, lit,[16] 42—43°C. H: 110°C (1—2 mmHg), lit,[16] 84°C (0.25 mmHg). *p*-Cl: 46—47°C, lit,[16] 47—48°C. *p*-NO_2: 148—149°C, lit,[16] 148—147°C.

p-Substituted Phenyl Tridueterated Methyl Sulfoxide. Phenyl methyl sulfoxide (10^{-2} mol) was heated with deuterium oxide (5×10^{-1} mol) containing triethylamine (10^{-1} mol) for 20 hr at 100°C. After heating, triethylamine and deuterium oxide were distilled off and the residue was distilled *in vacuo* (105°C/1.5 mmHg, lit[16] 84°C/0.25 mmHg). From NMR spectrum the resulting phenyl methyl sulfoxide was found to contain only 85% deuterium at the methyl group. The above procedure was repeated until the resulting sulfoxide showed no methyl proton signal in the NMR spectrum. *p*-Nitro compound was also synthesized by the same procedure. (mp 149°C, lit,[17] 148—149°C).

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

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

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

Kinetic Procedure I (The Rate of the Pummerer Reaction). The Pummerer reaction was carried out at 120±0.5°C in sealed tubes in which *p*-substituted phenyl methyl sulfoxide (5×10^{-5} mol) was dissolved without solvent in 10 m*l* of acetic anhydride. From time to time a sealed tube containing 1 m*l* solution of the above mixture was drawn out form the paraffin bath and cooled in an ice-bath to stop the reaction. The mixture was then hydrolyzed with 50 m*l* of alkaline solution (3%). The rates of the Pummerer reaction were readily followed spectrophotometrically, taking advantage of the difference of UV spectra of the starting and the final hydrolyzed compounds (*p*-substituted phenyl mercaptans). All the rate constants quoted in Table 2 were determined from the equation for the Pummerer reaction.

$$\log\frac{a-a_0}{a-a_t}=\frac{k\cdot t}{2.303},$$

where a = the intensity of the absorption due to resulting mercaptide.

Kinetic Procedure II (Racemization Reaction). Recemization reaction was carried out at 120±0.5°C in sealed tubes in which optically active *p*-tolyl phenyl sulfoxide (10^{-3} mol) was dissolved without any solvent in 20 m*l* acetic anhydride. From time to time a sealed tube containing 3 m*l* of the reaction mixture was drawn out from the paraffin bath and cooled in an ice bath to stop the reaction. After the reaction, 3 m*l* of dioxane was added into the sealed tube, and the acetic anhydride solution was subjected to measurement of specific rotation.

---

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

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

17) K. K. Anderson, W. H. Edmonds, J. B. Biasotti and R. A. Strecker, *J. Org. Chem.*, **31**, 2859 (1966).