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REACTION OF *o*-CARBOXYPHENYL SULFOXIDES WITH ACETIC ANHYDRIDE

KINETIC STUDIES ON THE NEIGHBORING GROUP EFFECT OF *ORTHO*-CARBOXYL GROUP IN THE OXYGEN EXCHANGE AND PUMMERER REACTIONS

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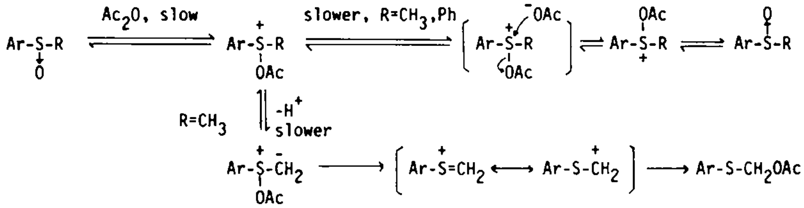
Abstract—Kinetic studies on the concurrent oxygen exchange and racemization reactions and Pummerer reaction of *o*-carboxyphenyl sulfoxides with acetic anhydride were carried out. In the reaction of *o*-carboxyphenyl phenyl sulfoxide, *ortho*-carboxyl group was found to enhance the rates of both oxygen exchange and racemization about 180 times, and the rate of racemization was nearly twice that of oxygen exchange. In the reaction of alkyl *o*-carboxyphenyl sulfoxides, an intramolecular Pummerer reaction took place to give 3,1-benzoxathian-4-one derivatives, and the Pummerer reaction was accelerated about 140 times that of the usual unassisted Pummerer reaction of aryl methyl sulfoxide. A very small deuterium kinetic isotope effect ($k_H/k_D = 1.07$ with trideuterated-methyl *o*-carboxyphenyl sulfoxide) and the rate-enhancing effect of α-alkyl group were also noticed. The markedly large rate-enhancement of both oxygen exchange and the Pummerer reactions is undoubtedly caused by the neighboring group participation of carboxyl group in the rate-determining intramolecular acylation of sulfinyl O atom.

There are usually concurrent oxygen exchange and racemization reactions and/or Pummerer rearrangement when alkyl sulfoxides are treated with acetic anhydride.[1,2] Diaryl sulfoxides undergo only oxygen exchange and racemization reactions, and the rate of racemization was found to be twice that of oxygen exchange, suggesting the reaction to involve a Walden inversion at the rate-determining nucleophilic substitution on S atom.[1] Meanwhile, aryl methyl sulfoxides undergo Pummerer reaction to afford acetoxymethyl aryl sulfides, accompanying the acetoxy interchange (oxygen exchange) as a minor pathway, and the rate-determining step of the Pummerer reaction is assumed to involve the initial acetylation and the subsequent slow proton removal steps in view of the substantial deuterium kinetic isotope effect ($k_H/k_D = 2.85$) and a large substituent effect on the benzene ring.[2]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Recently, we found that an intramolecular Pummerer reaction takes place in the reaction of alkyl *o*-carboxyphenyl sulfoxides with acetic anhydride and affords the corresponding cyclized products, i.e. 3,1-benzoxathian-4-one derivatives, nearly quantitatively (93–99% yields).[3]

Since the reaction appears to be quite novel, we have carried out kinetic studies on the reaction of *o*-carboxyphenyl alkyl sulfoxide with acetic anhydride in order to understand the mechanism of the reaction, especially focusing our attention on a possible neighboring group participation of the *ortho*-carboxyl group in the oxygen exchange and the Pummerer reaction of the sulfoxide, and found that the *o*-carboxyl group does display a large neighboring group effect to enhance the rates of both oxygen exchange and the Pummerer reactions.

RESULTS AND DISCUSSION

When optically active *o*-carboxyphenyl phenyl sulfoxide was treated with a large excess of acetic anhydride at 40–50°, the sulfoxide was found to lose its optical activity. The ^{18}O-labeled *o*-carboxyphenyl phenyl sulfoxide, in which ^{18}O was specifically labelled on the sulfinyl O atom, was found to undergo oxygen exchange with the solvent molecule, i.e. acetic anhydride, under the same condition, and no incorporation of ^{18}O into the *o*-carboxyl group of the recovered sulfoxide was observed.

When an optically active sulfoxide was treated with a heated mixture of acetic anhydride in chlorobenzene, the rate of racemization was found to follow a linear correlation with the concentration of acetic anhydride, and hence the rate of racemization (k_{rac}) was found to depend on both the sulfoxide and acetic anhydride (first order each) as shown in Table 1.

The pseudo-first order rate constants of both the oxygen exchange and the racemization in a large excess of acetic anhydride, together with the relative ratio of the rates of the oxygen exchange and the racemization, are listed in Table 2.

Inspection of the data reveals that the rate of oxygen exchange and that of racemization are *ca.* 180 times higher than those of the *p*-carboxyl isomer, i.e. *p*-ben-

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

Ac_2O (gr)	10^5 k_{rac} (sec^{-1})	Rel. Concn. Ac_2O	Rel. Rate
4.220	5.88	1	1
5.713	6.97	1.35	1.19
6.898	7.31	1.63	1.24
8.477	8.55	2.01	1.45
9.698	9.54	2.30	1.62

[a] The reaction was carried out at 50.0 ± 0.05°C in a sealed tube, with sulfoxide (1 mmol) dissolved in 10 ml of the mixture of chlorobenzene and Ac_2O.

Table 2. Rate constants of oxygen exchange (k_{ex}) and racemization (k_{rac}) of Ph-S(O)-C_6H_4-X with acetic anhydride

R	Temp(°C)	10^5 k_{rac} (sec^{-1})	10^5 k_{ex} (sec^{-1})	k_{ex}/k_{rac}
o-COOH	49.9	9.52[a]	3.62[b]	0.38
	44.8	5.90[a]		
	40.1	3.84[a]	1.58[b]	0.41
	35.1	2.60[a]		
	120	1780[c]		
p-COOH	120	10.7[a]	4.80[b]	0.45
p-CH_3[d]	120	9.97	5.00	0.50

[a] Sulfoxide (1 mmol) was treated with 10 ml Ac_2O.
[b] Sulfoxide (2 mmol) was treated with 20 ml Ac_2O.
[c] Extrapolated value calculated from activation energy.
[d] Obtained from Ref. 1.

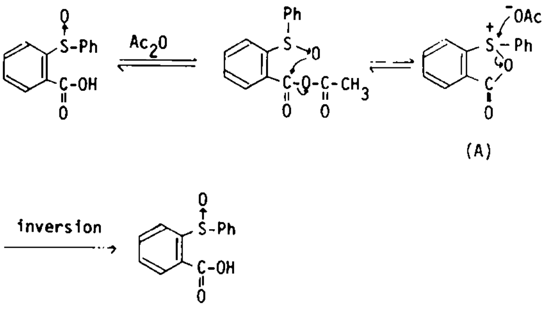
zenesulfinylbenzoic acid, and the *p*-methyl isomer, i.e. phenyl *p*-tolyl sulfoxide, and hence the reaction is assumed to involve the neighboring group participation of *o*-carboxyl group at the rate-determining step.

Meanwhile, the activation parameters for the racemizations of both the *o*-carboxyl and the *p*-methyl isomers are found to be 18.7 and 19.2 kcal/mole, −19.1 and −28.6 e.u., respectively. These values suggest that the concurrent oxygen exchange and racemization reactions of *o*-carboxyphenyl phenyl sulfoxide appear different from the unassisted reactions of the *p*-methyl isomer which proceed through a typical S_N2 on the sulfur atom as shown in eqn (1).

However, since the rate of racemization was a little more than twice that of oxygen exchange in the reaction of the *o*-carboxyl isomer and substantially higher than that of the *p*-methyl isomer, both the oxygen exchange and the racemization reactions of the *o*-carboxyl derivative are assisted anchimerically by the *o*-carboxyl group and apparently proceed through a somewhat different S_N2 type reaction path on the central trivalent S atom.

Thus the reaction should involve both an intramolecular assisted step and one inversion of configuration on the central S atom. The plausible reaction scheme is assumed to be as shown above.

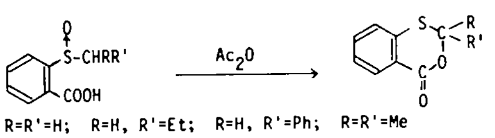
The reaction would proceed through the initial acetylation of *o*-carboxyl group, followed by the intramolecular assisted acylation of the sulfoxide to form a 5-membered cyclic sulfonium intermediate (A). The subsequent attack of acetate ion at the central S atom in the intermediate (A) to produce the starting sulfoxide will result in the inversion of configuration by the oxygen exchange.



Scheme 1.

This reaction scheme can be confirmed by a few more kinetic observations on the intramolecular Pummerer reaction of the alkyl *o*-carboxyphenyl sulfoxide (*vide infra*).

When the alkyl *o*-carboxyphenyl sulfoxide was allowed to react with a large excess of acetic anhydride at 100° for 1–2 hr, a cyclized compound, 2-substituted 3,1-benzoxathian-4-one, was obtained nearly quantitatively.[3]



The rate of this intramolecular Pummerer reaction (k_{pum}) can be readily measured spectrophotometrically, taking an advantage of the difference of UV spectra of the starting sulfoxide and the cyclized compound, and a good pseudo-first order rate constant was obtained up to 80% conversion.

The rate of racemization of optically active methyl *o*-carboxyphenyl sulfoxide was also determined by the usual procedure, by measuring the optical rotation of the mixture directly. In this case, the rate constant of racemization consists of two rate constants, the one for the oxygen exchange and the other for the Pummerer reaction.

The over-all rates of Pummerer and racemization reactions of a few alkyl *o*-carboxyphenyl sulfoxides were determined and the results are listed together with other pertinent data in Tables 3 and 4.

The data reveal clearly that the neighboring group participation of *o*-carboxyl group was also observed in the Pummerer reaction, which is accelerated about 140 times that of methyl *p*-tolyl sulfoxide. The activation

Table 3. Kinetic data of Pummerer and racemization reactions of R-S(O)-CH_3 in acetic anhydride[a]

R	Temp(°C)	$10^4\ k_{pum}$ (sec^{-1})	$10^4\ k_{rac}$ (sec^{-1})	$10^4\ k_{ex}$ (sec^{-1})	k_{pum}/k_{ex}
C_6H_4COOH-o	60.0	1.55	3.12 [b]	0.785 [c]	2.0
	70.1	4.24			
	80.1	10.1			
	120	245[d]			
p-$CH_3C_6H_4$[e]	120	1.77	2.35	0.305 [c]	5.8
C_6H_5 [e]	120	1.09			

[a] Sulfoxide (0.2 mmol) was treated with 10 ml Ac_2O.
[b] Sulfoxide (2 mmol) was treated with 20 ml Ac_2O.
[c] $k_{rac} = k_{pum} + 2k_{ex}$ is assumed. The rate of oxygen exchange was calculated from this equation.
[d] Extrapolated value calculated from activation energy.
[e] Obtained from Ref. 2.

Table 4. Kinetic data of Pummerer reaction of R-S(O)-C_6H_4COOH-*o* in acetic anhydride at 70.1°C[a]

R	$10^4\ k_{pum}$ (sec^{-1})	k_H/k_D	nm [b]
CH_2Ph	1.01		325
CH_3	4.24	1.07	322
CD_3	3.98		322
n-Pr	6.56		324
i-Pr	10.6		329

[a] Sulfoxide (0.2 mmol) was treated with 10 ml Ac_2O.
[b] Wavelengths in UV spectroscopy employed to determine the rate constants.

parameters for the Pummerer reactions of *o*-carboxyphenyl sulfoxide and methyl *p*-tolyl sulfoxide are found to be 21.6 and 21.2 kcal/mole, and −11.3 and −20.7 e.u., respectively. These values suggest that the rate-acceleration is due to the gain of activation enthropy, and apparently an intramolecularly assisted step should be involved in the transition state of the reaction of the *o*-carboxyphenyl sulfoxide, unlike the unassisted reaction of methyl *p*-tolyl sulfoxide which proceeds through a slow initial acetylation and a successive proton abstraction as shown in eqn (1).

The effect of alkyl group linked to sulfinyl sulfur was examined with a few alkyl phenyl sulfoxides, and the reactivity of the Pummerer reaction was found to decrease in the following order: i-Pr > n-Pr > CH_3 > CH_2Ph. One sees immediately that this reactivity order is identical to that of basicities of sulfinyl oxygens of these sulfoxides and not to that of the acidities of *alpha*-proton. This suggests strongly that the nucleophilic attack of sulfoxide O atom on the acid anhydride function is involved in the rate-determining step.

Since the deuterium kinetic isotope effect ($k_H/k_D = 1.07$) obtained with trideuterated-methyl *o*-carboxylphenyl sulfoxide was negligible, and both D-contents of the recovered starting sulfoxide and the cyclized compound produced did not change during the reaction, the proton abstraction and the following step would be very fast.

Although the acetylated product of carboxyl group of the *o*-carboxyphenyl sulfoxide, presumed to be formed at the initial step, was not successfully isolated, the acetylation of the carboxyl group with acetic anhydride is presumed to be more facile than that of sulfinyl function in view of the more nucleophilic nature of carboxyl group than sulfinyl group. Meanwhile, in a separate experiment what appeared to be the incipient formation of an acylated species of *o*-carboxyl group (a mixed acid anhydride) was observed in the spectral measurement of the reaction of the *o*-carboxyphenyl sulfoxide with a more reactive acylating agent, such as diphenyl ketene.

From these observations, the plausible mechanism of both oxygen exchange and the Pummerer reactions may be illustrated as shown by Scheme 2.

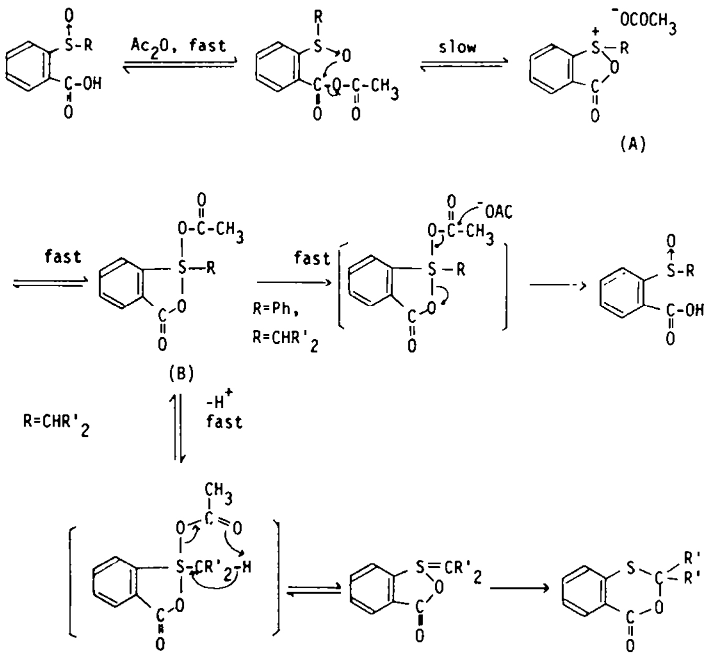
The reaction appears to proceed through the initial, fast and reversible acetylation of carboxyl group, followed by the rate-determining intramolecular nucleophilic attack of sulfinyl function to afford a five-membered cyclic sulfonium intermediate (**A**), which would easily be transformed to the sulfurane intermediate (**B**). The subsequent steps of either the S–O bond fission of the original sulfoxide or both the *alpha*-proton abstraction and the following 1,2-shift of acyloxyl group would be very fast.[18]

Moreover, since the rates of both oxygen exchange and the Pummerer reaction of alkyl *o*-carboxyphenyl sulfoxide, and the rate of oxygen exchange of phenyl *o*-carboxyphenyl sulfoxide are of nearly the same order, both reactions would proceed through the same reaction intermediate such as **A** or **B**, and the following reaction pathways would depend on the structures of the sulfoxides.

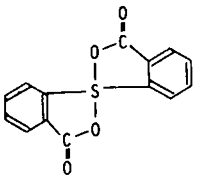
The intermediate (**A**) is considered to be stabilized by the fast transformation to the sulfurane intermediate (**B**) which would undergo either the subsequent facile *alpha*-proton abstraction or a rapid acyloxy interchange or both, since it is well known that the stable cyclic sulfurane compounds such as **C** and **D** were easily synthesized and their reactivities were studied in detail.[4,5]

This is a first example of the Pummerer reaction of sulfoxides in which the initial acylation step appears to be the rate-determining step, whereas the Pummerer reactions of sulfoxides and other trivalent sulfur compounds such as sulfilimine[6] and sulfonium ylide[7] which proceed via other various mechanistic routes have already been reported.[8-10]

Meanwhile, a few other examples involving the similar



Scheme 2.



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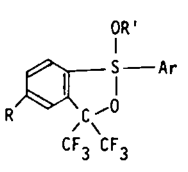

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intramolecular nucleophilic attack of sulfinyl O atom at reacting sites have already been reported.[11-14]

EXPERIMENTAL

Materials. Alkyl *o*-carboxyphenyl sulfoxides were synthesized, as reported,[3] by oxidation of the corresponding sulfides with bromine-pyridine complex, and purified by recrystallization. $R\text{-}S(O)\text{-}C_6H_4COOH\text{-}o$; (R, m.p. (°C)): $PhCH_2$, 170° (dec): CH_3, 175° (dec); n-Pr, 154 (dec); i-Pr, 144° (dec).

^{18}O-Labelled phenyl *o*-carboxyphenyl and phenyl *p*-carboxyphenyl sulfoxides were obtained by the reaction of the corresponding sulfides with bromine and H_2O^{18} (1.6 at%) in pyridine soln, according to the previously reported procedure.[15] *o*-Carboxyl isomer, m.p. 163.5–164° with 0.667 at%; *p*-carboxyl isomer, m.p. 197.5–198.5° with 0.659 at%.

Optically active methyl *o*-carboxyphenyl, phenyl *o*-carboxyphenyl and phenyl *p*-carboxyphenyl sulfoxides were obtained by the resolution of the corresponding racemic sulfoxides with brucine, brucine, and quinine, respectively. Methyl *o*-carboxyphenyl sulfoxide, m.p. 185° (dec) with $[\alpha]_D$ +220.7° (c = 0.67, EtOH); phenyl *o*-carboxyphenyl sulfoxide, m.p. 177.5°C with $[\alpha]_D$ −196.2° (c = 0.9, $CHCl_3$); phenyl *p*-carboxyphenyl sulfoxide, m.p. 198–199° with $[\alpha]_D$ −18.9° (c = 0.61, $CHCl_3$).

Trideuterated-methyl *o*-carboxyphenyl sulfoxide was synthesized by the H-D exchange reaction of the unlabelled sulfoxide in $NaOD\text{-}D_2O$ soln by heating under reflux for 2 hr. The sulfoxide recovered was nearly completely labelled with D atom (>95%), since no Me signal in NMR measurement was observed.

Diphenyl ketene was prepared by the thermolysis of phenyl benzoyl diazomethane according to the reported procedure,[16] b.p. 125°/3 mmHg (lit.,[16] 119–121°/3.5 mmHg).

Ac_2O, obtained commercially, was treated with anhyd NaOAc. After refluxing for several hr, it was distilled. b.p. 139.5–140°.

Test for the ^{18}O-distribution in o-carboxyphenyl phenyl sulfoxide. It was established that the sulfinyl oxygen was exclusively exchanged with solvent molecule, i.e. sulfuric acid[15] or perchloric acid,[17] in the reaction of ^{18}O-labeled *o*-carboxyphenyl phenyl sulfoxide, which was specifically labelled either on sulfinyl oxygen or on carboxyl oxygen.

Hence *o*-carboxyphenyl phenyl sulfoxide recovered from Ac_2O soln was dissolved in 74% H_2SO_4 and after 5 min the acid soln was quenched with ice-water, and then the sulfoxide precipitated was extracted with $CHCl_3$. The recovered sulfoxide was subjected to ^{18}O-analysis and no ^{18}O-content was observed in the molecule. Therefore, the incorporation of ^{18}O into *o*-carboxyl group from sulfinyl group, which was originally labelled with ^{18}O, did not occur under the kinetic condition.

Reaction of trideuterated-methyl o-carboxyphenyl sulfoxide

(i) The sulfoxide (200 mg) was heated at 100° for 1 hr with 10 ml Ac_2O containing 1 ml AcOH. After removing excess Ac_2O and any volatile product *in vacuo*, the remaining residue was purified by column chromatography, and then 2,2-dideuterated 3,1-benzoxathian-4-one (190 mg) obtained was found to retain the D-label nearly completely (D-label >95%) by the NMR measurement.

(ii) The sulfoxide (200 mg) was heated with 10 ml Ac_2O containing 1 ml AcOH at 70° for 0.5 hr (about the half-life period). After the work-up mentioned above, both D-contents of the starting sulfoxide recovered and the cyclized product obtained were found to retain completely (>95%).

Reaction of isopropyl o-carboxyphenyl sulfoxide with diphenyl ketene

(i) The sulfoxide (180 mg) and diphenyl ketene (400 mg) was dissolved in 2 ml $CDCl_3$, and the $CDCl_3$ soln was kept standing overnight. After evaporation of solvent, the oily residue was separated by column chromatography with benzene as an eluent, and then 2,2-dimethyl 3,1-benzoxathian-4-one (95 mg) was obtained.

(ii) When the above $CDCl_3$ soln was measured by NMR at several time intervals, unknown peak (s, δ = 5.32 ppm; $Ph_2C\underline{H}COOCOC_6H_4S(O)C_3H_7\text{-}o$) was found to increase gradually and then disappeared, except for the peaks of the sulfoxide, benzoxathiane derivative and diphenyl ketene. When the same $CDCl_3$ soln was monitored by the measurement of IR spectra at time intervals, an absorption band of $1820\,cm^{-1}$ was found to appear gradually and then disappeared. From these observations, the unknown compound is believed to be the mixed acid anhydride (diphenylacetic *o*-isopropylsulfinylbenzoic acid anhydride) formed by the acylation of *o*-carboxyphenyl sulfoxide with diphenyl ketene.

Kinetic procedure I (*The rate of Pummerer reaction*). The Pummerer reaction was carried out at 70.1 ± 0.05° in sealed tubes, in which alkyl *o*-carboxyphenyl sulfoxide (0.2 mmol) was dissolved in 10 ml Ac_2O without any solvent. A sealed tube containing 1 ml soln of the above mixture was recovered at time intervals and was cooled in an ice-bath to stop the reaction. The mixture was then diluted with EtOH to make up 50 ml soln, which was measured by UV spectrometer around 320–330 nm. Thus the rate of the Pummerer reaction was readily obtained by following the increase of the band of the product at *ca.* 320–330 nm, since the final cyclized compounds absorb light at about 320–330 nm (ϵ: 2500–3000) and the starting sulfoxides do not absorb light at the same range.

Kinetic procedure II (*Racemization*). The racemization reaction was carried out in sealed tubes in which optically active *o*-carboxyphenyl sulfoxide (1 mmol) was dissolved in 10 ml Ac_2O. A sealed tube containing 1 ml soln of the above mixture was removed at time intervals, and was cooled in an ice-bath. Then the Ac_2O soln was subjected to measurement of optical rotation up to *ca.* 30% conversion, and thus a good pseudo-first order rate contant was obtained.

Kinetic procedure III (*Oxygen exchange*). An ^{18}O-labelled sulfoxide (2 mmol) was dissolved in 20 ml Ac_2O. Five portions (4 ml) of the soln were removed at time intervals and were quenched with ice-water. The ppt formed was extracted with $CHCl_3$, and dried over $MgSO_4$. Finally $CHCl_3$ was distilled off, and then the sulfoxide recovered was recrystallized from $CHCl_3$-hexane. The sulfoxide thus obtained was subjected to the routine ^{18}O-analysis.

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