Bull. Chem. Soc. Jpn., 56, 266—269 (1983) [Vol. 56, No. 1

Predominant Intramolecular Pummerer Reactions of Substituted Benzyl *p*-Tolyl Sulfoxides with Acetic Anhydride

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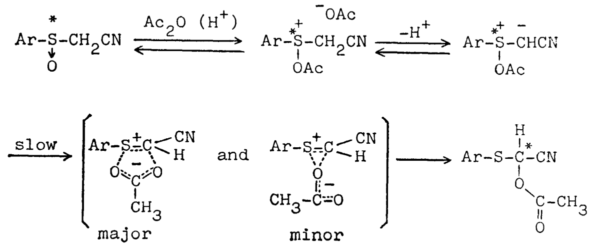
(Received June 7, 1982)

In the Pummerer reactions of ^{18}O-labeled benzyl, and 3,5-dichlorobenzyl *p*-tolyl sulfoxides with a large excess of unlabeled acetic anhydride in the presence of DCC as acid scavenger, the resulted Pummerer reaction products, the α-acetoxy sulfides, were found to have retained substantial amounts of ^{18}O-label of the original sulfoxides, *i.e.*, nearly a half or more. Meanwhile, when optically active benzyl, 3-chlorobenzyl, and 3,5-dichlorobenzyl *p*-tolyl sulfoxides were allowed to react with excess acetic anhydride in the presence of DCC, the α-acetoxy sulfides, the Pummerer reaction products obtained, were found to have no optical activity. These observations suggest that the acetoxyl migration from sulfur atom to α-carbon is predominantly intramolecular, however, the α-(*p*-tolylthio) carbenium acetate ion-pair formed during the reaction prior to racemization is less intimate than those which are formed in the reactions of cyanomethyl and (α-carbonyl-substituted methyl) *p*-tolyl sulfoxides which give the corresponding highly optically active α-acetoxy sulfides.

Most early examples of the Pummerer reaction in the mechanistic studies were found to be intermolecular rearrangements, based mainly on ^{18}O-tracer experiments.[1,2] Sulfoxides are usually dialkyl or aryl alkyl derivatives and the rate-determining setp is generally the α-proton-removal from the acyloxysulfonium salts after the initial acylation of the sulfoxides. Years later, we found a clear-cut case of intramolecular 1,2-rearrangement of acetoxyl group by the aid of ^{18}O-tracer experiments and stereochemistry; namely the Pummerer reaction of optically acetive aryl cyanomethyl sulfoxide with acetic anhydride was stereospecific, inducing a partial asymmetry at α-carbon and most of the ^{18}O-label in the original sulfoxide was retained in the resulted α-acetoxy sulfide.[3] Many more examples of intramolecular Pummerer reaction have been found ever since.[2,4] In these intramolecular rearrangements, the rate-determining step is generally the S–O bond cleavage after the reversible proton removal from the acetoxysulfonium intermediate, and the asymmetric induction from the chiral sulfur atom to the prochiral α-carbon is believed to be due to both the very tight nature of the α-thio carbenium acetate ion-pair, and the very rapid recombination, *i.e.*, ion-pair return.

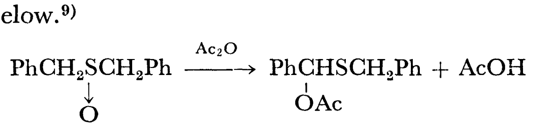


In the solvolytic S_N1 type reactions of optically active alkyl arenesulfonate-^{18}O, stereochemistry and the extent of oxygen scrambling are known to vary with the change of the alkyl derivatives and the reaction medium, and closely related to the tightness of the ion-pair formed by the initial cleavage of C–O bond of the sulfonate.[5] There are cases that the internal return is nearly quantitative with partial oxygen scrambling, however, with nearly complete racemization.[6]

We now have found the Pummerer reaction which proceeds predominantly intramolecularly, however, the original chirality of the sulfoxide is completely lost in the resulted α-acetoxy sulfide, namely, in the Pummerer reactions of benzyl, 3-chlorobenzyl, and 3,5-dichlorobenzyl *p*-tolyl sulfoxides (**1**, **3**, and **5**) with acetic anhydride in the presence of dicyclohexylcarbodiimide (DCC), scavenger of acetic acid. This paper deals with the mechanistic investigation with our usual ^{18}O-tracer and stereochemical experiments and their implication on the understanding of the mechanism.

Results and Discussion

Earlier, when ^{18}O-labeled and optically active aryl benzyl sulfoxides were treated with acetic anhydride at about 100 °C for 1—2 h in polar media, the main reaction was found to be the oxygen exchange which causes racemization and the Pummerer reaction was of rather minor.[7] However, dibenzyl sulfoxide has been known to undergo the Pummerer reaction with acetic anhydride,[8] and when the reaction was carried out at 76 °C, Wilson *et al.* actually obtained the Pummerer rearrangement product, the α-acetoxy sulfide which upon heating further with acetic acid decomposed to afford benzyl disulfide, benzyl sulfide, benzaldehyde and α,α-bis(benzylthio)toluene, as shown below.[9]



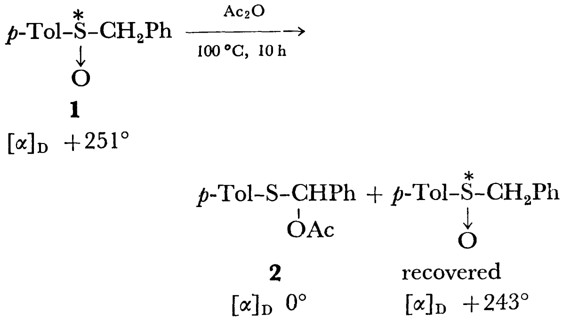
$$\underset{\downarrow \atop \mathrm{O}}{\mathrm{PhCH_2SCH_2Ph}} \xrightarrow{\mathrm{Ac_2O}} \underset{\mathrm{OAc}}{\mathrm{PhCHSCH_2Ph}} + \mathrm{AcOH}$$

$$+ \mathrm{(PhCH_2S)_2} + \mathrm{(PhCH_2)_2S}$$

$$+ \mathrm{PhCHO} + \mathrm{(PhCH_2S)_2CHPh}$$

When the reaction of ^{18}O-labeled benzyl *p*-tolyl sulfoxide (**1**) [1.246 ex. atm% of ^{18}O] was allowed to react again, however, this time with a large excess of acetic anhydride in the presence of an equimolar amount of DCC which scavenges acetic acid formed, at 100 °C for 10 h, the corresponding Pummerer reaction product, *i.e.*, α-acetoxy sulfide **2**, was obtained in *ca.* 10% yield while recovering much of the original sulfoxide. The recovered sulfoxide was found to retain 99.6% of original ^{18}O; namely, 1.241 ex. atom% of ^{18}O and the α-acetoxy sulfide was found to be incorporated with 46% of the original ^{18}O-label of the sulfoxide, namely 0.286 ex. atom% of ^{18}O, respectively.

This means, that the oxygen exchange of the sulfoxide with acetic anhydride is catalyzed markedly by acetic acid or any acid formed or present in the reaction mixture, while the overall rearrangement is predominantly intramolecular. However, when optically active benzyl *p*-tolyl sulfoxide (**1**) was allowed to react with excess acetic anhydride in the presence of DCC under the same conditions, the corresponding α-acetoxy sulfide (**2**) was found to have no optical activity while the sulfoxide recovered was found to have retained 90% of the original optical activity. Since α-acetoxybenzyl *p*-tolyl sulfide (**2**) formed in the reaction would be rather unstable, the chirality, once induced in the α-acetoxy sulfide **2** might have lost upon prolonged heating. However, in view of the high retention of

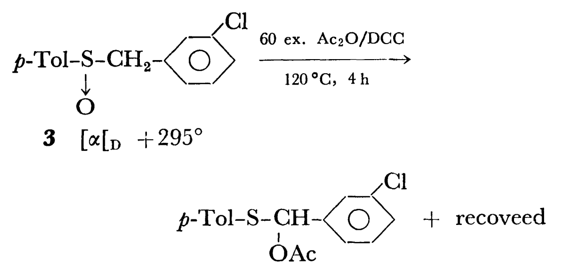


1 $[\alpha]_D$ +251°

2 $[\alpha]_D$ 0°

recovered $[\alpha]_D$ +243°

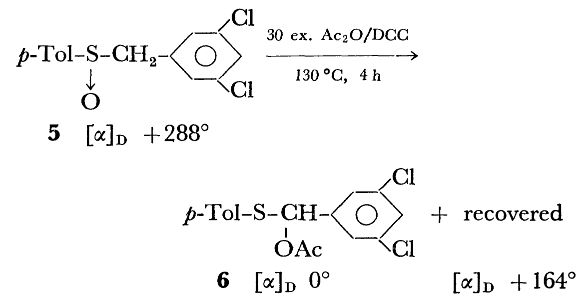
^{18}O in the resulting product **2**, the racemization of the α-acetoxy sulfide after its formation is rather inconceivable. Probably the ion-pair between the α-sulfur stabilized carbenium ion and acetate ion-pair is less intimate than those which are formed in the reactions of cyanomethyl aryl sulfoxide and (α-carbonyl-substituted methyl) aryl sulfoxides with acetic anhydride, though the ion-pair would be intimate enough to hold the original ^{18}O. Substitution of an electron-withdrawing group would increase the tightness of the ion-pair so that the corresponding resulting α-acetoxy sulfides can keep more of the original ^{18}O-label of the sulfoxide in the resulted α-acetoxy sulfide **2**, which might also be asymmetrically induced as in the Pummerer reaction of aryl cyanomethyl sulfoxide with acetic anhydride. Thus, the Pummerer reactions of optically active 3-chlorobenzyl *p*-tolyl and 3,5-dichlorobenzyl *p*-tolyl sulfoxides (**3** and **5**) were carried out. When these two optically active sulfoxides were allowed to react with excess acetic anhydride in the presence of 5 equivalent amounts of DCC for 4 h at 120 °C and 130 °C, respectively, the resulting both α-acetoxy sulfides **4** and **6** had no optical activity, while the recovered sulfoxides ($[\alpha]_D$ 290.3° for **3** and $[\alpha]_D$ 164° for **5**) retained the optical activities substantially.



3 [α[D +295°

4 $[\alpha]_D$ 0°

$[\alpha]_D$ +290.3°



5 $[\alpha]_D$ +288°

6 $[\alpha]_D$ 0°

$[\alpha]_D$ +164°

When ^{18}O-labeled 3,5-dichlorobenzyl *p*-tolyl sulfoxide (**5**) [0.790 ex. atom% of ^{18}O] was heated with a large excess acetic anhydride (60 equiv. amount) in the presence of 5 equiv. amount of DCC under the same conditions for the optically active sulfoxide **5**, the corresponding α-acetoxy sulfide **6** obtained in 9% yield, was found to retain 65% of ^{18}O [0.255 ex. atom% of ^{18}O] of the original ^{18}O-label in the starting sulfoxide **5**. The retention of 65% of ^{18}O in the ester **6** is substantially higher than that, *i.e.*, 46%, found in the ester **2** formed in the reaction of benzyl *p*-tolyl sulfoxide. This means that due to the destabilization of the carbenium ion formed from the acetoxysulfonium ylide derived from benzyl *p*-tolyl sulfoxide bearing two electron-withdrawing chlorines on the aromatic ring of the benzyl group, the ion-pair formed between 3,5-dichlorophenyl(*p*-tolylthio)methylium ion and acetate is considered to be more intimate than that derived from the reaction of unsubstituted benzyl *p*-tolyl sulfoxide and hence the intramolecularity of the migration of acetoxyl group increased. However, this intimate ion-pair is not enough to transfer the chirality on the sulfur atom to α-carbon. The lack of asymmetric induction into the benzylic α-carbon may be partly due to the highly resonance-stabilized nature of benzylic cation.

The Pummerer reaction of aryl benzyl sulfoxides would be at the threshold between a typical intramolecular and an intermolecular rearrangements in the mechanistic stectrum of the 1,2-acetoxyl migration which would reflect on the extent of tightness of the intimate ion-pair formed from the intermediary acetoxysulfonium ylide.

Experimental

General. All melting points were uncorrected. IR spectra were taken on a Hitachi 260-50 spectrometer. NMR spectra were recorded with a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were determined with a Hitachi RMU-6MG mass spectrometer. Acetic anhydride was purified by stirring with sodium metal for 7 d followed by refluxing under reduced pressure below 50 °C for 5 h under vacuum and then distillation under reduced pressure, bp 47—48 °C/20 mmHg.**

^{18}O-Analysis. ^{18}O-Analysis was carried out by the method developed by Rittenberg and Ponticorvo,[10] with a modification which involves the use of $Pb(OAc)_2$ to remove H_2S gas from the gas produced by the thermolysis of sample: About 20 mg of sample was pyrolyzed with

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** 1 mmHg≈133.3 Pa.

250 mg each of purified $HgCl_2$ and $Hg(CN)_2$, respectively, in an evacuated sealed Pyrex tube at *ca.* 500 °C for 12 h. Then the tube was broken in a vacuum line and CO_2 gas formed was purified by distillation and the mass peaks of *m/e* 44 and 46 which correspond to $C^{16}O_2$ and $C^{16}O^{18}O$, respectively, were recorded on a mass spectrometer.

Materials. *Optically Active Benzyl* p-*Tolyl Sulfoxide (**1**)*:[11] The optically active **1** was prepared by known method[11] from menthyl *p*-toluenesulfinate and benzyl Grignard reagent. $[\alpha]_D$ +251° (acetone).

^{18}O-*Labeled Benzyl* p-*Tolyl Sulfoxide (**1**)*: The corresponding sulfide (2.16 g, 10 mmol) prepared from benzyl chloride and *p*-toluenethiol was dissolved in a mixture of acetic acid (40 ml), pyridine (2.4 g) and ^{18}O-enriched water (4 ml, 1.5 atom%). To the cooled solution was added bromine (1.60 g, 10 mmol) at 0 °C.[12] When reaction was complete, 100 ml of water was added and extracted with 100 ml portions of chloroform. The chloroform solution was washed with aqueous $Na_2S_2O_3$ solution, diluted aqueous HCl solution and water, and then dried ($MgSO_4$). The solvent was removed and the residue was recrystallized from ethyl acetate–hexane to give the ^{18}O-labeled **1** in 70% yield (1.629 g). The title sulfoxide was found to contain 1.246 ex. atom% of ^{18}O.

Optically Active 3-Chlorobenzyl p-*Tolyl Sulfoxide (**3**)*: To a stirred solution of 3-chlorobenzylmagnesium chloride prepared from 3-chlorobenzyl chloride (1.23 g, 8 mmol) and magnesium (194 mg, 8 mmol) in 100 ml of dry ether at −15 °C under argon was added diastereomerically pure (−)-menthyl *p*-toluenesulfinate (1.176 g, 4 mmol) at −78 °C. The work-up mentioned above gave the title sulfoxide **3** (972 mg, 92% yield) with $[\alpha]_D$ +295° (acetone). Mp 88—88.5 °C; IR (KBr) 1045 and 820 cm^{-1}; NMR ($CDCl_3$) δ=7.18—6.73 (8H, m), 3.83 (2H, s), 2.37 (3H, s); Found: C, 63.52; H, 4.90%. Calcd for $C_{14}H_{13}ClOS$: C, 63.50; H, 4.94%.

^{18}O-*Labeled Optically Active 3,5-Dichlorobenzyl* p-*Tolyl Sulfoxide (**5**)*: To a stirred solution of 3,5-dichlorobenzylmagnesium chloride prepared from 3.128 g (16 mmol) of 3,5-dichlorobenzyl chloride in dry ether at −15 °C under argon was added at −78 °C ^{18}O-labeled diastereomerically pure (−)-menthyl *p*-toluenesulfinate (2.35 g, 8 mmol, $[\alpha]_D$ −199° in acetone) synthesized from the reaction between ^{18}O-labeled *p*-toluenesulfinyl chloride and *l*-methol. The usual work-up gave the title sulfoxide **5** (1.568 g) which have an optical activity $[\alpha]_D$ +288° and ^{18}O-content was found to be 0.790 ex. atom%. Mp 106.5—107 °C; IR (KBr) 1560, 1040, and 800 cm^{-1}; NMR ($CDCl_3$) δ=7.17—6.73 (7H, m), 3.87 (2H, s), and 2.35 (3H, s); Found: C, 56.40; H, 4.04%. Calcd for $C_{14}H_{12}OSCl_2$: C, 56.19; H, 4.40%. Racemic **5** was also prepared by oxidation of the corresponding sulfide with H_2O_2 in acetic acid. Mp 130—130.5 °C.

Reaction of ^{18}O-*Labeled Benzyl* p-*Tolyl Sulfoxide (**1**) with Acetic Anhydride.* After the ^{18}O-labeled sulfoxide **1** (1.2 g) was heated with 60 equiv. molar amount of acetic anhydride to the sulfoxide in the presence of 5 equiv. DCC at 100 °C for 10 h, a large excess acetic anhydride and any volatile substance were removed under vacuum to afford the residue which was separated through silica gel column chromatography with hexane–ethyl acetate (4:1) and then with chloroform as eluents. The Pummerer product **2** (92 mg) and the sulfoxide (840 mg) which were found to contain 0.288 and 1.241 ex. atom% of ^{18}O, respectively. **2**: mp 66—67 °C; IR (KBr) 1740 and 1220 cm^{-1}; NMR ($CDCl_3$) δ=7.25 (1H, broad s), 7.08 (1H, s) and 1.99 (3H, s). Since **2** is unstable, it was converted to the corresponding sulfone: mp 153—154 °C; IR (KBr) 1755, 1320, 1220, and 1160 cm^{-1}; Found: C, 63.22; H, 5.30%. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.29%.

Reaction of Optically Active Benzyl p-*Tolyl Sulfoxide (**1**) with Acetic Anhydride in the Presence of DCC.* When the optically active sulfoxide **1** (220 mg, $[\alpha]_D$ +251° was heated with 5 ml of acetic anhydride at 100 °C for 10 h in the presence of 5 equiv. DCC to the sulfoxide, the resulting semioily residue obtained, after evaporation of excess acetic anhydride and any volatile product *in vacuo*, was separated through silica gel column chromatography with hexane–ethyl acetate (4:1) and then with benzene–ethyl acetate (4:1) as eluents at 0—4 °C in a low-temperature room. The Pummerer product (**2**, $[\alpha]_D$ 0°) was obtained in 10% yield and the sulfoxide recovered was purified through alumina column chromatography with hexane–ethyl acetate (3:1) and then silica-gel column chromatography with chloroform to afford the sulfoxide (158 mg, $[\alpha]_D$ +243°) which retained 97% of optical activity based on the starting sulfoxide.

Reaction of Optically Active 3-Chlorobenzyl p-*Tolyl Sulfoxide (**3**) with Acetic Anhydride in the Presence of DCC.* After the optically active sulfoxide **3** (397 mg, $[\alpha]_D$ +295°) was heated at 120 °C for 4 h with 7 ml of acetic anhydride in the presence of 5 equiv. DCC, the usual work-up and silica-gel column chromatography with hexane–ethyl acetate (4:1) in a low-temperature room gave the Pummerer product **4** (43.3 mg, 9.4% yield, $[\alpha]_D$ 0°) while the chromatography with benzene–ethyl acetate (4:1) as eluents at room temperature afforded the sulfoxide recovered which was further purified through alumina and then silica-gel column chromatography using hexane–ethyl acetate (3:1) and chloroform, respectively, giving the pure sulfoxide **3** (359 mg, $[\alpha]_D$ +290.3°). **4**: Oil; IR (neat) 1745 and 1217 cm^{-1}; NMR ($CDCl_3$) δ=6.80—7.23 (9H, m), 2.27 (3H, s), 2.00 (3H, s). Sulfone derivative of **4**: mp 113—114 °C; IR (KBr) 1760, 1320, 1205, and 1155 cm^{-1}; NMR ($CDCl_3$ δ=7.08—7.55) (8H, m), 6.55 (1H, s), 2.38 (3H, s); Found: C, 56.81; H, 4.46%. Calcd for $C_{16}H_{15}ClO_4S$: C, 56.72; H, 4.46%.

Reaction of ^{18}O-*Labeled Optically Active 3,5-Dichlorobenzyl* p-*Tolyl Sulfoxide (**5**) with Acetic Anhydride in the Presence of DCC.* When the title sulfoxide **5** (800 mg) was heated with 60 equiv. acetic anhydride in the presence of 5 equiv. DCC at 130 °C for 4 h, after the usual work-up and chromatography through silica gel with benzene and chloroform as eluents the Pummerer product **6** (64 mg, 7% yield) and the sulfoxide recovered which was purified through alumina column chromatography with hexane–ethyl acetate (4:1) as an eluent giving the pure sulfoxide in 93% yield (716 mg). The Pummerer product had practically no optical rotation but the ^{18}O-content was found to be 0.255 ex. atom% of ^{18}O. No enathiomeric excess of the Pummerer product was observed from a measurement of NMR contact shift using chiral lanthanoids shift reagent, Eu(hfc)$_3$. **6**: Mp 63.5—64 °C; IR (KBr) 1740, 1230, and 800 cm^{-1}; NMR ($CDCl_3$) δ=7.20—6.85 (7H, m), 6.78 (1H, s), 2.30 (3H, s), 2.10 (3H, s); Found: C, 56.43; H, 4.12%. Calcd for $C_{16}H_{14}Cl_2O_2S$: C, 56.31; H, 4.13%.

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