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Intermolecular Pummerer Rearrangement Reactions of Alkyl Phenyl and Dialkyl Sulfoxides with Acetic Anhydride

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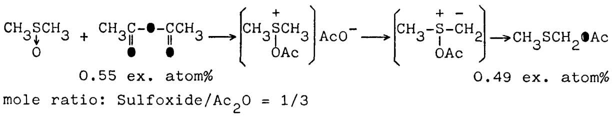
Synopsis. The Pummerer reactions of alkyl phenyl sulfoxides, PhS(O)R (R: methyl and isobutyl), and benzyl methyl sulfoxide with acetic anhydride were found to proceed through the intermolecular acetoxyl migration, based on the ^{18}O-tracer experiments with ^{18}O-labeled sulfoxides and unlabeled acetic anhydride.

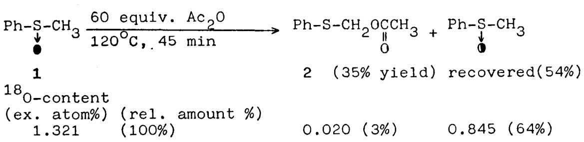
In our earliest ^{18}O-tracer experiment on the Pummerer reaction of dimethyl sulfoxide with 3 equiv. molar amount of uniformly ^{18}O-labeled acetic anhydride in ether solution, the amount of ^{18}O-label in the resulting ester was 9/10 of that of the acetic anhydride used.[1)] Namely, all the oxygen atoms of the starting materials were found to be completely scrambled in the resulting ester as shown below. Thus, the intermolecular migration of acetate from the acetoxysulfonium ion to the α-carbon was postulated for this Pummerer reaction.



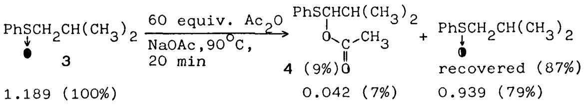
Years later, we found that sulfoxides undergo oxygen exchange with acetic anhydride[2)] and various other acids.[3,4)] However, the rate of oxygen exchange of methyl *p*-tolyl sulfoxide with acetic anhydride at 120 °C was found by us to be only 1/6 of that of the Pummerer reaction, revealing clearly that the earlier postulate of the predominant intermolecular nucleophilic attack of acetoxyl group at the α-carbon terminal is still valid.[5,6)] However, our recent findings of several intramolecular Pummerer reactions with the aid of ^{18}O-tracer experiments[7—9)] and others[7d,8d)] have led us to reinvestigate the Pummerer reactions of a few other alkyl aryl sulfoxides and dialkyl sulfoxides, using this time ^{18}O-labeled sulfoxides so that the ^{18}O-distribution in the resulting ester can be determined in order to estimate the extent of the intermolecular acetoxyl migration and also the extent of ^{18}O-exchange in the recovered sulfoxides. As the results of this new investigation, our earlier observation and conclusion have been found to be quite acceptable.

Results and Discussion

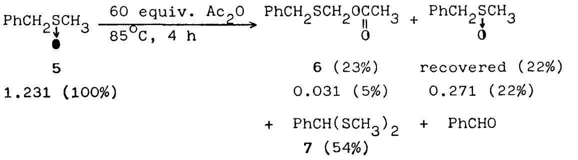
The Pummerer reactions of two alkyl aryl sulfoxides with a large excess of unlabeled acetic anhydride have been carried out using ^{18}O-labeled methyl phenyl sulfoxide (**1**) and isobutyl phenyl sulfoxide (**3**) to examine the fate of ^{18}O-label in the resulting ester, **2** and **4**, along with the sulfoxide recovered at partial completion of the reaction. ^{18}O-Labeled benzyl methyl sulfoxide **5** was treated similarly. These ^{18}O-tracer experimental results are illustrated in the following equations.



(1)



(2)



(3)

When the Pummerer reaction product (**2**-^{18}O) [0.760 ex. atom% of ^{18}O] was allowed to react with 60 equiv. amount of acetic anhydride in the presence of ether 0.4 or 2 equiv. amount of acetic acid at 120 °C for 45 min, the ^{18}O-content of the α-acetoxy sulfide, the Pummerer reaction product (**2**-^{18}O) recovered were found to retain 0.755 or 0.708 ex. atom% of ^{18}O, respectively. This implies explicitly that acetoxymethyl phenyl sulfide (**2**) once formed does not seem to exchange acetoxyl group readily with acetic acid present under the Pummerer reaction conditions. The sulfoxides recovered, **1** and **3** after 40 and 10% conversions respectively were found to have retained the ^{18}O-label of the original sulfoxides in 64 and 79%, respectively. Thus the large loss of ^{18}O-label in the Pummerer reaction products is not due to the concurrent oxygen exchange of the ^{18}O-labeled sulfoxides with acetic anhydride.[5)] All these observations suggest clearly that the Pummerer reaction of these sulfoxides proceeds through the intermolecular acetoxyl migration, after the rate-determining α-proton-removal.[3)] Earlier, acetoxyl group was reported to migrate preferentially to the benzylic carbon in the reaction of sulfoxide **5** with acetic anhydride.[10)] However, we found that the migration of acetoxyl group occurs to both benzylic and methyl carbon in the ratio of 2:1. α,α-Bis(methylthio)toluene (**7**) is the secondary product formed by the migration of acetoxyl group to the benzylic carbon. The Pummerer reactions of dibenzyl and benzyl phenyl sulfoxides are not facile and require relatively higher temperatures than would be expected from the acidity of benzylic protons.[11—14)] The relatively low basicity of the sulfinyl oxygen in **5** and steric shielding by phenyl group may be partly responsible for the somewhat low reactivity of the Pummerer reaction, however, the oxygen exchange reaction of this sulfoxide **5** with acetic anhydride is as facile as that of benzyl phenyl sulfoxide with acetic anhydride.[13)]

The large kinetic isotope effect $k_H/k_D=5—9$ in the

Pummerer reaction of dibenzyl sulfoxide with acetic anhydride,[11,12] seems to indicate that the rate-determining step of this intermolecular rearrangement of benzyl methyl sulfoxide is the α-proton removal.

Experimental

^{18}O-*Analysis.* ^{18}*O*-Analysis was carried out by the method developed by Rittenberg and Ponticorvo.[15]

^{18}O-*Labeled Sulfoxides.* ^{18}*O*-Labeled methyl phenyl sulfoxide (**1**), isobutyl phenyl sulfoxide (**3**), and benzyl methyl sulfoxide (**5**) were synthesized according to our usual method by oxidation of the corresponding sulfides with bromine in the presence of ^{18}*O*-enriched water.[16] Thus methyl phenyl sulfoxide, isobutyl phenyl sulfoxide, and benzyl methyl sulfoxide containing 1.321, 1.189, and 1.231 ex. atom% of ^{18}*O*, respectively, were obtained in 65, 61, and 57% yields.

Reaction of ^{18}O-*Labeled Methyl Phenyl Sulfoxide (1), Isobutyl Phenyl Sulfoxide (3), and Benzyl Methyl Sulfoxide (5) with Acetic Anhydride.* When the ^{18}*O*-labeled title sulfoxides **1**, **3**, and **5** (a few hundred mg) were heated separately with a large excess (*ca.* 60 fold) of acetic anhydride at a set temperature for some length of time, the oily residue, obtained after evaporation of excess acetic anhydride and any volatile product in vacuo, was separated through column chromatography with benzene and then $CHCl_3$ as eluents or Kugelrohr distillation. The Pummerer product **2** (120 °C/20 mmHg** (Kugelrohr)), **4** (130 °C/20 mmHg (Kugelrohr)), and **6** (126 °C/20 mmHg (Kugelrohr)) and the recovered sulfoxides were obtained along with some minor by-products as shown in Eqs. 1, 2, and 3.

Preparation of ^{18}O-*Labeled Acetoxymethyl Phenyl Sulfide (2-*^{18}O*).* When methyl phenyl sulfoxide (**1**) (500 mg) was allowed to react with 2 equiv. molar amount of ^{18}*O*-labeled acetic anhydride at 120 °C for 3 h. The ^{18}*O*-labeled Pummerer product **2** (0.760 ex. atm% of ^{18}*O*) was obtained in 90% yield (585 mg), upon distillation with Kugelrohr (120 °C/20 mmHg).

Acetate Exchange Reaction of ^{18}O-*Labeled Acetoxymethyl Phenyl Sulfide (2-*^{18}O*) with Acetic Anhydride in the Presence of Acetic Acid.* After the ^{18}*O*-labeled title compound **2**-^{18}*O* [0.760 ex. atom% of ^{18}*O*] was heated with 60 equiv. acetic anhydride in the presence of ether 0.4 or 2 equiv. amount of acetic acid to the ester (**2**-^{18}*O*) at 120 °C for 45 min. Upon removal of the solvent *in vacuo*, chromatography and final distillation, the pure acetoxymethyl phenyl sulfide recovered was found to remain either 0.755 or 0 708 ex. atom% of ^{18}*O*, respectively.

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** 1 mmHg≈133.3 Pa.