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REARRANGEMENT OF TERTIARY AMINE OXIDES—XI

SOLVENT EFFECTS ON THE REACTIONS OF 2- AND 4-PICOLINE N-OXIDES WITH ACETIC ANHYDRIDE

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Abstract—The reactions of 2- and 4-picoline N-oxides with acetic anhydride uniformly labelled with ^{18}O have been studied in three different solvents and the products subjected to ^{18}O analyses.

With 2-picoline N-oxide, the change of solvent did not effect the ^{18}O distribution of the resulting main product, 2-acetoxymethylpyridine. The reaction proceeds *via* "radical cage process", similar to the previous experiment with no solvent. In the case of 4-picoline N-oxide, the reaction in the solvents appears to be different, the concentration of ^{18}O in the resulting ester mixture, i.e., 3-acetoxy-4-methylpyridine and 4-acetoxymethylpyridine approaching the value that is expected from the radical pair process. The effect of solvent and the nature of these rearrangements are briefly discussed.

THE rearrangements of tertiary amine N-oxides with acetic anhydride have been studied by several workers. When pyridine N-oxide[1] or 3-picoline N-oxide[2] react with acetic anhydride, the acetoxy group is introduced into the 2-position of the pyridine ring. But when 2- or 4-picoline N-oxide are treated with acetic anhydride, 2- or 4-acetoxymethylpyridine is the main product. While the reaction of pyridine or 3-picoline N-oxide with acetic anhydride has only recently been studied,[3] the rearrangements of 2- and 4-picoline N-oxides with acetic anhydride have been investigated by several workers[2,4–9] and the initial formation of anhydrobases (I–II) has been suggested in these reactions.

Further supporting evidence for the initial formation of the anhydrobase I was shown by Traynelis *et al.* in their work dealing with the reaction of 2-picoline N-oxide with substituted phenylacetates in which 2-acetoxymethylpyridine was obtained and no aryloxymethylpyridine was formed.[8]

In our previous work[10–12] on the reactions of tertiary amine N-oxides with acetic

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anhydride, the reaction of acetic anhydride with 2- or 4-picoline N-oxides was carefully studied using O^{18} labelled acetic anhydride in tracer experiments. Based mainly on the results of ^{18}O distributions of the products, it was suggested that the reaction of 4-picoline N-oxide proceeds through an intermolecular pathway which involves a nucleophilic attack on the methylene group or the C-3 position of the pyridine ring by acetoxy anions together with the heterolytic cleavage of the nitrogen-oxygen bond of the anhydrobase, giving 4-acetoxymethylpyridine or 3-acetoxy-4-methylpyridine as shown below (Fig. 1)

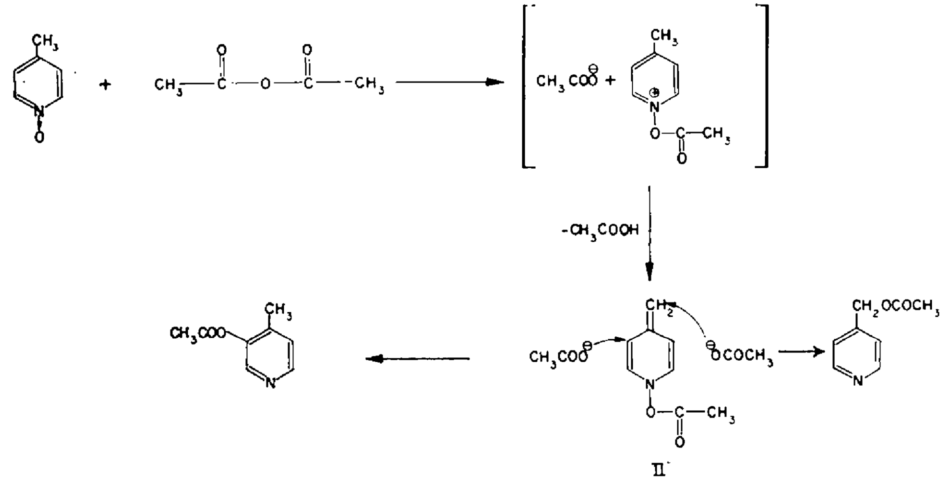

Fig. 1

It has been suggested that, the reaction with 2-picoline N-oxide proceeds *via* an intramolecular pathway which involves homolytic cleavage of the N–O bond of the anhydrobase in a solvent cage, followed by rapid recombination to give 2-acetoxymethylpyridine as follows:

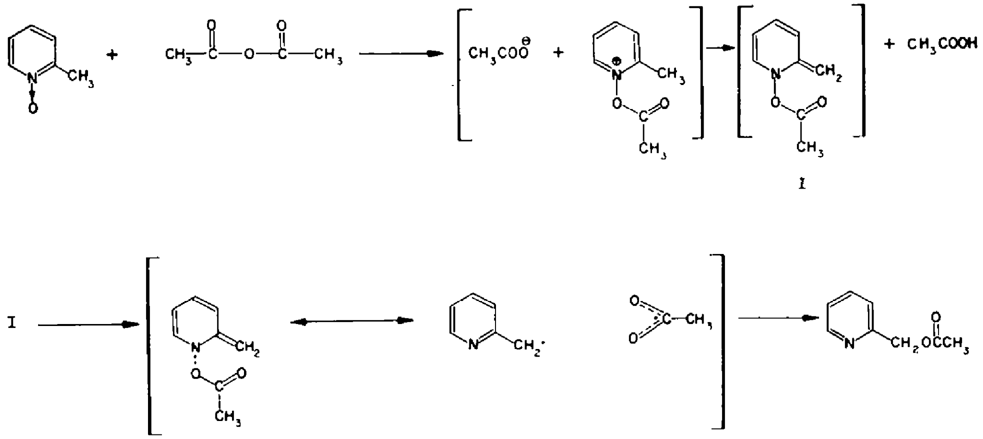

Fig. 2

The difference between the two reactions is assumed due to the difference in the strength of the two O–N linkages in the anhydrobases and also to the rearranged position of the acetoxy group.

Although it appears that the N–O bond tends to cleave homolytically while the reaction becomes more vigorous when it becomes weaker, steric factors must also be considered.

In preliminary experiments and also previous work with n-butyric anhydride, it was found that the nature of the pathway varies with different solvents, especially in the case of 4-picoline N-oxide.

In this paper, we wish to report observations of the solvent effects on the reactions mainly through the determination of the ^{18}O incorporation in the reaction products. Oxygen-18 labelled acetic anhydride was reacted with an equimolar amount of 2-picoline N-oxide, but in ten fold molar amounts of solvent. All the solvents used were chosen to have boiling points higher than 130°. Among many solvents tried, some were not suitable for the isolation of the products or because of poor solubility of reagents, and only three solvents, i.e., xylene, chlorobenzene and nitrobenzene proved satisfactory.

The products were isolated and the ^{18}O-analyses of the resulting products performed as usual. In the case of 4-picoline N-oxide, no attempt was made to separate the acetylated ester into two components, i.e., 3-acetoxy-4-methylpyridine and 4-acetoxymethylpyridine and the mixture was subjected to ^{18}O-analyses. The analytical results of ^{18}O in the 2-acetoxymethylpyridine are shown in Table 1, while the results of ^{18}O-analyses in the reactions of 4-picoline N-oxide with acetic anhydride are given in Table 2.

TABLE 1. THE ANALYTICAL RESULTS OF ^{18}O OF 2-ACETOXYMETHYLPYRIDINE OBTAINED IN DIFFERENT SOLVENTS

Solvent	2-Acetoxymethylpyridine atom % ^{18}O
Xylene	0·44
Chlorobenzene	0·44
Nitrobenzene	0·44

TABLE 2. THE ANALYTICAL RESULTS OF ^{18}O IN THE MIXTURE OF 4-ACETOXYMETHYLPYRIDINE AND 3-ACETOXY-4-METHYLPYRIDINE OBTAINED IN DIFFERENT SOLVENTS

Solvent	Mixture of 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine atom % ^{18}O
Xylene	0·51
Chlorobenzene	0·53
Nitrobenzene	0·49

Acetic anhydride used was 0·765 atom % ^{18}O.
Natural abundance of oxygen-18 was 0·206 atom % ^{18}O.

In the reaction of 2-picoline N-oxide with acetic anhydride, three different solvents gave the same ^{18}O values within experimental error. The value of ^{18}O in the 2-acetoxymethylpyridine is somewhat lower than the mean average value (0·48 atom % ^{18}O) of one natural and one enriched oxygen. Namely, the ^{18}O value, 0·44, is lower than that (0·48) expected from the intramolecular radical pair process. This, however, is not particularly surprising in view of our previous experiment with N,N-dimethylaniline N-oxide in which a similar loss of ^{18}O was observed but the reaction was definitely a radical pair process in solvent cage.[12] The change of solvent does not effect any variation of ^{18}O distribution in the product. This again indicates that the reaction of 2-picoline N-oxide with acetic anhydride proceeds *via* radical pair process as illustrated in Fig. 2.

As compared with the previous experiment of 4-picoline N-oxide without solvent, the present results obtained in the solvents are different. The ^{18}O values are decidedly lower (0·49–0·53 atom% ^{18}O) than what one would expect from an intermolecular process, 0·62 atom% ^{18}O. Even admitting that the experimental error is ± 0·03 atom% ^{18}O, the intermolecular mechanism demands the ^{18}O value in the esters to be 0·59 atom% ^{18}O; while even if we consider the unexplained loss of ^{18}O by using solvent to be 0·04 atom% ^{18}O, the incorporation of ^{18}O in the esters is too low. On the other hand, the intramolecular process requires the theoretical value to be 0·48 atom% ^{18}O. The actual value (0·49 atom% ^{18}O) is within the range of experimental error; but in the ^{18}O tracer experiment, it is not usual to find a value larger than the theoretical. Thus, the value (0·49 atom% ^{18}O) cannot have only originated by the intramolecular process when one considers the unexplained loss of ^{18}O by the use of solvent. Therefore, the main reaction is the intramolecular radical pair process which is partially combined with the intermolecular rearrangement. In the absence of solvent, the reaction of 4-picoline N-oxide with acetic anhydride proceeds through the intermolecular pathway while in solvents the intermolecular process is substantially suppressed and the intramolecular process becomes dominant. The predominance of the intramolecular radical pair process over the intermolecular ionic path may be ascribed to diminished nucleophilic attack on the anhydrobase by acetic acid or acetate due to dilution by the solvent used. In an extreme case where there is no nucleophilic attack by acetate, the cleavage of the anhydrobase would be only homolytic; whereas if acetate acid is present in excess, a facile nucleophilic attack on the anhydrobase by acetate becomes predominant, as previously found.

It is interesting to note here that the ratio of the intermolecular to the intramolecular processes varies according to the solvent, but, no reasonable explanation for this variation of ^{18}O value with these solvents can be offered. If the intermolecular-heterolytic process increases with the increasing dielectric constant, the amount of ^{18}O incorporation will increase in the order of xylene, chlorobenzene and nitrobenzene but this tendency was not observed. In general, it is known that the cage process is favoured in solvents with decreasing dielectric constant and with increasing molecular weight. However, the ^{18}O values cannot be correlated with any of these relationships.

The reaction of 2-picoline N-oxide with acetic anhydride is not influenced by the nature of the solvent[10] and proceeds *via* radical pair process while that of 4-picoline N-oxide is substantially affected by solvent, but proceeds by the intermolecular rearrangement when there is no solvent or in the presence of acetic acid.

The fact that the rearrangement to the far position is mainly intermolecular and that to the neighboring position is intramolecular was also found in the Wallach rearrangement of azoxybenzene to for 2- or 4-hydroxyazobenzene.[14]

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EXPERIMENTAL

Materials. Extra pure reagent of liquid paraffin purchased from K and K Laboratories, Inc. (Sp. Gr. above 0·855, b.p. above 300°) was used without further purification.

Special grade of nitrobenzene purchased from K and K Laboratory Inc. was used after usual purification. Trichloroethylene, xylene, ethylene–glycol, monochlorobenzene were used after redistillation.

2- or 4-picoline N-oxide was prepared by the method reported by Ochiai.[15] ^{18}O labelled acetic anhydride was prepared by a similar method reported in the previous papers.[10–12]

Reaction of 2- or 4-picoline N*-oxide with ^{18}O labelled acetic anhydride*

2-Picoline N-oxide (10·9 g 0·10 mole) and ^{18}O labelled acetic anhydride (10·2 g 0·10 mole; 0·76 atom % ^{18}O) were dissolved in the solvents (1·0 mole). The solvent selected had a b.p. higher than 130°, e.g. xylene, monochlorobenzene, nitrobenzene, trichloroethylene, ethyleneglycol and liquid paraffin, but the latter 3 solvents were not suitable for this reaction because of the difficulty in isolating products or due to poor solubility of reagents.

Using the same quantities of reagents and conditions similar to those for 2-picoline N-oxide, the reactions of 4-picoline N-oxide with ^{18}O labelled acetic anhydride were carried out. The proper solvents for this reaction are xylene, nitrobenzene and monochlorobenzene.

Both reactions were initiated by a free flame and after the initial exothermic reaction, the mixture was refluxed 2 hr. After removal of solvents, the products were distilled under red. press. The analytical sample was further distilled until the refractive index was in agreement with that given in the literature. The middle fraction of the distillate was taken and subjected to the usual ^{18}O analysis.

Identification of the products was made by a b.p., refractive index and IR spectrum.

Solvent	2-Acetoxymethylpyridine		A mixture of 4-acetoxymethyl pyridine and 4-methyl-3-acetoxy pyridine	
	b.p.	N_D	b.p.	N_D
Xylene	3, 80°	N_D 29·5° 1·4956	5, 100°	N_D 26·2° 1·5032
Monochlorobenzene	2, 73°	N_D 30·5° 1·4964	2·5, 78°	N_D 27·7° 1·5001
Nitrobenzene	5, 95°	N_D 27·5° 1·4960	3, 85°	N_D 25·5° 1·5037

Isotope analyses. Experimental procedures and calculations were similar to those used in previous papers. A Hitachi model RMU-5G mass spectrometer was for the spectra.

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