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REARRANGEMENT OF TERTIARY AMINE N-OXIDE—XVI[1]

THE MECHANISM OF THE REACTION OF ACRIDINE N-OXIDE WITH ACETIC ANHYDRIDE

S. OAE, S. KOZUKA and Y. SAKAGUCHI
Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshi Osaka, Japan

and

K. HIRAMATSU
Industrial Research Institute Osaka Prefecture, Enokojima Kamino-cho Nishi-ku Osaka, Japan

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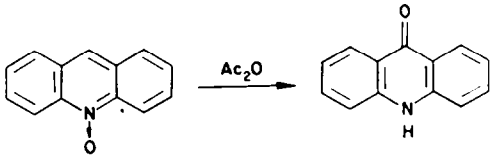
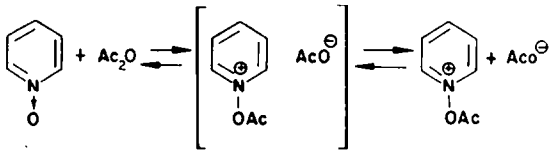
Abstract—The mechanism of the reaction of acridine N-oxide with acetic anhydride giving acridone was investigated using oxygen-18 as a tracer. Acridine N-oxide was allowed to react with ^{18}O-labelled acetic anhydride under various conditions and the amount of ^{18}O incorporation in the product was analysed. It was shown that the amount of ^{18}O incorporation in the product was affected not by the molarity of the acetic anhydride but mainly by the amount and the nature of the solvent used. These results clearly reject the intermolecular path, and seems to favor an intramolecular mechanism involving two competing processes, for this rearrangement.

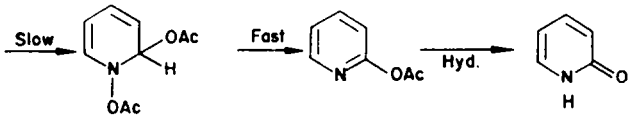
THE reaction of acridine N-oxide with acetic anhydride to give acridone has been known for many years,[2] and is considered quite analogous to that of pyridine N-oxide with acetic anhydride giving 2-pyridone. Here, however the rearrangement occurs at the trans-anular position since both the α-positions of pyridine skeleton are blocked by two fused benzene rings.



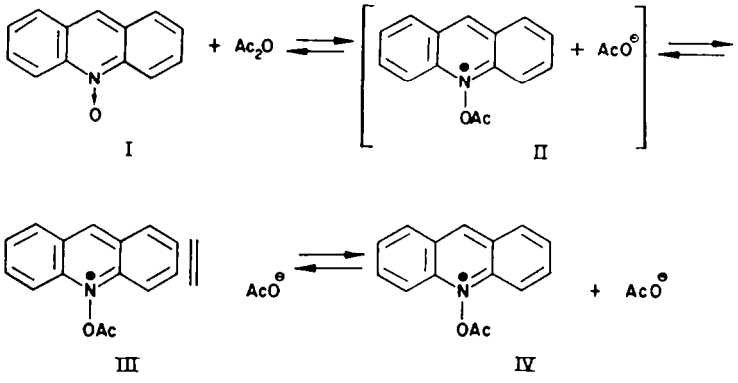
The mechanism of the rearrangement of pyridine N-oxide with acetic anhydride to give 2-pyridone has been investigated extensively by the kinetic study of Markgraf, Brown, Mohr and Peterson[3] together with our recent ^{18}O tracer study and the measurement of kinetic isotope effect,[4] and is considered to be the following:



[1] Paper XV, S. Oae and K. Ikura, *Bull. Chem. Soc. Japan* **39**, in press (1966); Paper XIV, S. Oae and S. Kozuka, *Tetrahedron* **21**, 1971 (1965).
[2] A. Kliegel and A. Fehrle, *Ber. Dtsch. Chem. Ges.* **47**, 1629 (1914).
[3] J. H. Markgraf, H. B. Brown Jr, S. C. Mohr and R. G. Peterson, *J. Amer. Chem. Soc.* **85**, 958 (1963).
[4] S. Oae and S. Kozuka, *Tetrahedron* **21**, 1971 (1965).



As for the rearrangement of acridine N-oxide, a kinetic investigation has been carried out by Markgraf and Ahn[5] in an excess acetic anhydride and the following equilibria was proposed for this reaction based on their observations that the reaction

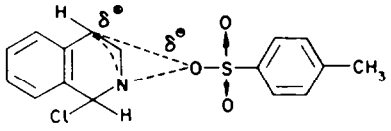


showed a pseudo first order kinetic behaviour in an excess acetic anhydride, while a little rate increasing effect (positive salt effect) was observed by the addition of salts such as sodium perchlorate or tetrabutyl ammonium acetate. Another important observation was that the cation III was unable to be trapped while the reaction was unaffected by the addition of perchlorate ion, giving the final product. Based on these observations they have suggested an intramolecular ionic rearrangement of N-acetoxy acridinium cation at the stage of the solvent separated ion pair III. They have rejected the radical mechanisms except one so securely caged, based on the fact that this reaction did not give any gaseous products.

Another important observation for this reaction, made by Markgraf and Carson[6] was the measurement of kinetic isotope effect using acridine-9-*d*-N-oxide in which no significant isotope effect was found.

All these observations are similar to those of pyridine N-oxide. However, there is one noticeable difference; namely the rate deviation caused by the addition of salts appears to be in reverse order, which may mean that the rearrangement of acridine N-oxide is better explained by an intramolecular mechanism. However, these rate deviations are quite small as compared to the change of the conductance of the reacting solution. Even assuming the intramolecular path, the following two possible mechanisms can be considered for this reaction. The one, an intramolecular cyclic rearrangement of N-acetoxyacridinium cation, and the other, a sliding migration of the N-oxide oxygen of the cation without equilibrating the oxygen with that of the carbonyl, similar to the intimate ion pair process (V) suggested for the reaction of isoquinoline or pyridine N-oxide with tosyl chloride.[7]

[5] J. H. Markgraf and M-K. Ahn, *J. Amer. Chem. Soc.* **86**, 2699 (1964).
[6] J. H. Markgraf and C. C. Carson, *J. Org. Chem.* **29**, 2806 (1964).
[7] S. Oae, T. Kitao and Y. Kitaoka, *Tetrahedron* **19**, 827 (1963).



V

The apparently different two processes and also the intermolecular path are readily distinguished by the ^{18}O tracer experiment. Thus, we have extended our usual ^{18}O tracer experiments to this rearrangement.

In order to detect the oxygen exchange reaction between acridone and acetic anhydride or acetic acid, acridone containing no excess ^{18}O was heated with ^{18}O-labelled acetic anhydride or acetic acid–acetic anhydride mixture. Here again the recovered acridone revealed no noticeable incorporation of excess ^{18}O. Thus, it was found that there is no oxygen exchange reaction during the formation of the product. Acridine N-oxide was then treated with ^{18}O-labelled acetic anhydride in various molar ratio with or without solvent in various conditions and acridone was obtained. Oxygen-18 analyses were made only for the isolatable product, acridone, because there was no possibility to isolate the possible intermediate, 9-acetoxyacridine. These results are shown in Table 1 to 3.

The last data of Table 3 (Expt. 14) shows that the oxygen exchange reaction of acetic anhydride with acetic acid is much faster than the reaction of acetic anhydride with the N-oxide. This result strongly supports a rapid equilibration at the initial formation of N-acetoxyacridinium acetate (II) in the reaction between the N-oxide and acetic anhydride.

Table 1 contains the ^{18}O analytical results of the reaction of acridine N-oxide with acetic anhydride without using any additional solvent, while Table 2 shows the ^{18}O data obtained in that carried out in chloroform or sulfolane as a solvent. The results obtained by using acetic acid as the solvent, are shown in Table 3, in which ^{18}O atom per cent of both the labelled acetic anhydride and the product, acridone, are given.

If the reaction would proceed via an intermolecular ionic process involving a nucleophilic attack of acetate ion at the position 9 of acridine ring, similar to that of pyridine N-oxide with acetic anhydride, the product would contain an average concentration of ^{18}O of all the oxygens in the reaction system, like in the similar reactions

TABLE 1. THE REACTION OF ACRIDINE N-OXIDE WITH ^{18}O-LABELLED Ac_2O

Expt. No.	Mole ratio N-oxide : Ac_2O	^{18}O atom %		% incorporation			
					Theoretical value		
		Ac_2O (used)	Acridone (Obtained)	Obs.	intermol. ionic	cyclic process	sliding process
1	1:2·2	0·86	0·40	30	87	100	0
2	1:3·8	0·86	0·39	29	92	100	0
3	1:5	1·04	0·53	39	94	100	0
4	1:10	1·09	0·74	61	97	100	0

TABLE 2. THE REACTION OF ACRIDINE N-OXIDE WITH ^{18}O-LABELLED Ac_2O IN DIFFERENT SOLVENTS

Expt. No.	Mole ratio N-oxide : Ac_2O	Solvent	^{18}O atom % Ac_2O (used)	^{18}O atom % Acridone (obtained)	% incorporation Obs.	Theoretical value intermol. ionic	cyclic process	sliding process
5	1:1	$CHCl_3$[a]	1·06	0·74	63	75	100	0
6	1:1	$CHCl_3$[a]	1·04	0·77	68	75	100	0
7	1:3	$CHCl_3$[a]	1·06	0·75	64	90	100	0
8	1:10	$CHCl_3$[b]	1·09	0·93	82	97	100	0
9	1:10	$CHCl_3$[a]	1·04	0·90	83	97	100	0
10	1:1	Sulfolane[c]	1·09	0·47	30	75	100	0
11	1:3	Sulfolane[c]	1·09	0·61	46	90	100	0

[a] N-oxide 0·2 g in 10 ml chloroform, reflux 3 hr
[b] N-oxide 0·2 g in 20 ml chloroform, reflux 3 hr
[c] N-oxide 0·2 g in 3 ml sulfolane, reflux 3 hr

TABLE 3. THE REACTION OF ACRIDINE N-OXIDE WITH ^{18}O-LABELLED Ac_2O IN AcOH

Expt. No.	method	Mole ratio N-oxide : Ac_2O	^{18}O atom % Material	Acridone	Average value of the reaction system
12	A	1:3·6	$Ac^{18}OH$–$Ac_2{}^{18}O$ 1·10	0·79	1·05
13	A	1:11	$Ac^{18}OH$–$Ac_2{}^{18}O$ 1·10	0·79	1·08
14	B	1:2·6	$Ac_2{}^{18}O$ 1·04	0·22	0·21

A; The reaction using $Ac^{18}OH$–$Ac_2{}^{18}O$ (mole ratio: 6:7) mixture.
B; To a solution of acridine N-oxide (0·2 g) in AcOH (20 ml), $Ac_2{}^{18}O$ was added.

of pyridine N-oxide[4] and 3-picoline N-oxide,[8] to give eventually the corresponding 2-pyridones, in which the oxygen contains an averaged concentration of ^{18}O of all the oxygens in the reaction system.

The present data clearly reject the intermolecular ionic mechanism for this reaction and support the early prediction made by Markgraf *et al.* from their kinetic study, since the incorporation of ^{18}O in the product is too small as compared to the theoretical value expected from the mechanism while there was no increasing amount of ^{18}O in the product where an increasing amount of acetic anhydride was used except in the case where acetic anhydride was used in a large excess.

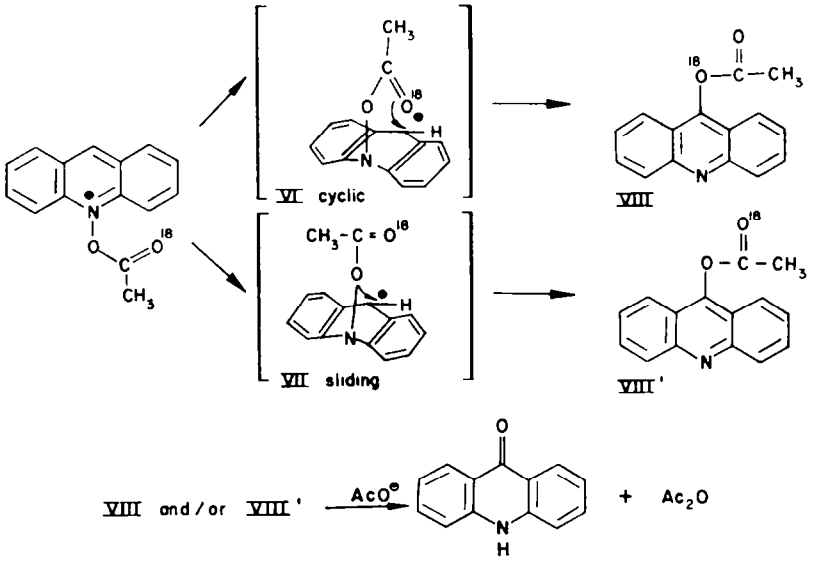
Meanwhile, the two possible intramolecular pathways will reveal quite different outcome of ^{18}O incorporations in the product. The product, formed by the cyclic process, should contain the same ^{18}O concentration as that of the acetic anhydride used, while the sliding migration of N-oxide oxygen will give the product in which the oxygen should remain to be natural.

The percentage incorporation of ^{18}O in the product and the theoretical amount of ^{18}O for these mechanisms are also given in the same tables.

[8] S. Oae and S. Konzuka, *Tetrahedron* **20**, 2691 (1964).

The solvent caged radical pair process similar to that suggested for the reaction between 2-picoline N-oxide and acetic anhydride[9] or quinaldine N-oxide with benzoyl chloride[10] has not been favoured for this reaction from the careful product analysis of Markgraf and Ahn.[5] The present ^{18}O tracer study also clearly disfavours the mechanism because acetoxy radical, if formed, would equilibrate its two oxygens in a solvent cage and the product would contain nearly 50% of excess ^{18}O originally incorporated in the labelled acetic anhydride. The lack of any free radical fragment, such as methane, carbon dioxide or acridine[5] seems to disfavour the free radical pair process.

However, neither the cyclic process alone, nor the sliding migration mechanism also can explain these results. A possible, and probably the only conceivable explanation of the results of ^{18}O tracer experiments and those of the kinetic study by Markgraf *et al.*[5,6] will be that the rearrangement is an intramolecular process in which the following two intramolecular processes, i.e., the cyclic (VI) and the sliding (VII) rearrangements of acetoxy group are both involved.



These ^{18}O analytical results apparently indicate that the incorporation of ^{18}O in the product is largely affected not by the amount of acetic anhydride used but by the nature of the solvent used. The increasing incorporation of ^{18}O in the product obtained in a large excess of acetic anhydride (Expt. 4) is probably due to the change of the nature of the solvent. It is interesting to note here that the ^{18}O incorporation in the product was unaltered even when the molar ratio of acetic anhydride to the N-oxide was changed in a ratio 3·6 to 11 (Expt. 12, 13) if the amount of the mixture of the solvent and acetic anhydride was kept the same for the reaction.

When the reaction was carried out using an equimolar or small excess of acetic anhydride without using any additional solvent, or in sulfolane, the sliding rearrange ment was favoured over the cyclic process. In other cases, the cyclic process became predominant.

[9] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962).
[10] S. Oae and S. Kozuka, *Tetrahedron* **20**, 2671 (1964).

It appears that the ratio of these two competing intramolecular pathways is not particularly associated with the polarity of the solvent used.* However in all the cases, the use of a large amount of solvent seems to increase the amount of the ^{18}O incorporation, namely, to favour the cyclic process. It might be that a large amount of solvent would cluster around the rearranging cation (III) so that it would force the acetoxy group to assume a conformation for a facile cyclic rearrangement (VI), while making the free sliding of acetoxy group from nitrogen to the 9 position more difficult.

More extensive experiments on the incorporation of ^{18}O are desired in order to clarify these views by using many other solvents with different polarity, dielectric constant, viscosity etc. However, unfortunately there are very little choice of solvents applicable for the tracer study because only a very few solvents have a good solubilities for acridine N-oxide and not to react with acetic anhydride.

EXPERIMENTAL

Materials. Acridine N-oxide (m.p. 167·5°–168·5°) was prepared by oxidizing acridine in $CHCl_3$[2] with perbenzoic acid.

Preparation of the labelled Ac_2O and the isotope analyses for both the starting material and the product were performed by the same procedure described in the earlier paper of this series.[8]

The reaction of acridine N-*oxide with* ^{18}O-*labelled* Ac_2O. Acridine N-oxide (308 mg, $1·58 \times 10^{-4}$ mole) was sealed in a small glass ampoule with the labelled Ac_2O (351 mg, $3·44 \times 10^{-4}$ mole) and heated in a bath up to 140° for 30 min. After cooling, the residual solid was washed with ether, obtaining crude acridone. m.p. 350° (dec.) (253 mg, 82% yield). Recrystallization from isoamyl alcohol gave light yellow crystals. m.p 362–365° (dec.) The reaction with an excess Ac_2O was also carried out in a similar manner. No difference in product yield was observed. The ^{18}O analytical results of these experiments are shown in the Table 1.

The reaction of the N-*oxide with the labelled* Ac_2O *in other solvents.* A typical run was as follows: to a $CHCl_3$ (10 ml) solution of acridine N-oxide (207 mg, $1·06 \times 10^{-4}$ mole), the labelled acetic anhydride (110 mg, $1·08 \times 10^{-4}$ mole) was added and the whole mixture was refluxed for 3 hr. After evaporation to dryness under red. press., the residual mass was washed with ether to obtain crude acridone, mp. 350–355°/(dec.) (164 mg, 79·5% yield). Isotope analysis was made after recrystallization from isoamyl alcohol to afford purified acridone of m.p. 362–364° (dec.).

The varieties and the amounts of solvents used, molar ratio of Ac_2O to the N-oxide and the analytical results are given in Table 2.

The reaction of acridine N-oxide with ^{18}O-labelled Ac_2O–AcOH mixture and the reaction of the N-oxide in non-labelled AcOH with ^{18}O-Ac_2O was also performed. These results are shown in Table 3.

The oxygen exchange reaction of acridone with the labelled Ac_2O *or* AcOH–Ac_2O *mixture.* Acridone (207 mg), unlabelled with any excess ^{18}O was heated with the labelled Ac_2O (562 mg, 0·86 atom% ^{18}O) in a ampoule up to 140° for 30 min. The recovered acridone (94% recovered. yield) revealed no excess ^{18}O (0·20 atom%). The recovered acridone after heating with the labelled AcOH–Ac_2O mixture (about 1:1 mole mixt. 1·10 atom% ^{18}O) also contained no excess ^{18}O. (0·21 atom%).

* Cf., ε: $CHCl_3$, 4·64, AcOH, 6·18, Ac_2O, 20, sulfolane 44.[11]

[11] E. M. Arnett and C. F. Douty, *J. Amer. Chem. Soc.* **86**, 409 (1964).