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KINETIC STUDIES ON THE REACTIONS OF 2- AND 4-ALKYL-SUBSTITUTED HETEROAROMATIC N-OXIDES WITH ACETIC ANHYDRIDE[1)]

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The reaction of the N-oxides of 2- and 4-alkyl-pyridines and quinolines with acylating agents have received considerable attentions in recent years.[2)] However, the mechanistic details concerning the mode of the N-O bond cleavage have been the subject of some controversies.[3-6)]

In order to uncover the over-all picture of the whole process and the energy profile of each of these reactions, the kinetic investigations of these reactions have been considered as most desirable. We have found that the over-all reaction rates of these compounds can be followed spectrophotometrically and accumulated sufficient kinetic data on both undeuterated and deuterated compounds and hence wish to discuss the implications of the kinetic results.[7)] Most of these reactions followed the second-order rate equation, $v=k_{obs}\,[\text{N-oxide}] \times [Ac_2O]$ when it was carried out in dioxane or acetonitrile. Table 1 lists the pseudo-first-order rates of 2-(substituted benzyl)pyridine N-oxides as a typical example.

The large kinetic isotope effects, $k_H/k_D=7.6$ (for 2-benzylpyridine N-oxide) indicated that the rate-determining step of the reaction is the deprotonation step and the succeeding steps are fast.

The large kinetic isotope effect means that a negative charge will be developing at the methylenic carbon considerably at the transition state and the

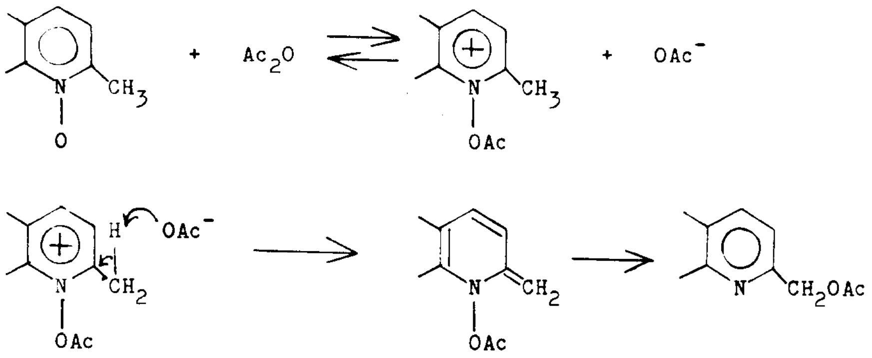
TABLE 1

The Pseudo-First-Order Rate Constants of the Reaction of 2-(Substituted Benzyl) Pyridine N-Oxide with a large excess of Ac_2O in Dioxane at 30°C.

$[Ac_2O] = 5.88$ M

X:	$k \times 10^5$ sec^{-1}
p-NO_2	28.7
p-Cl	10.8
H	7.37
m-CH_3	7.17
p-CH_3	6.76

rate will be markedly enhanced by the electron-withdrowing substituents and hence a large positive ρ-value is expected in the reactions of 2-(substituted benzyl)-pyridine N-oxides, if no other competing reaction is involved. However the rate enhancing effects of electronegative substituents such as p-nitro and p-chloro are relatively small, while the ρ-value was also rather small. The small rate enhancing effect of the electronegative group and the small positive ρ-value (+0.7) are apparently derived from the fact that there is a competing pre-equilibrium reaction which counterbalances the effect of the substituent in the succeeding deprotonation step. In fact, there is a case, namely, the reaction of quinaldine N-oxide in which the substituent effect of the first equilibrium step of the reaction appears to outweigh that of the second rate-determining deprotonation step. Thus the Hammett plot gave a upward curvature rather than a linear line when the rates of 6-substituted quinaldine N-oxides were examined in acetonitrile (Table 4) while the rate was found to increase markedly in a polar solvent (acetonitrile) and also by the addition of lithium perchlorate as one can see in Table 2. Apparently these enhancements are caused by the shift of the first equilibrium toward right hand side. Indeed the addition of lithium perchlorate was found to increase the equilibrium constant. Thus the mechanistic scheme of the over-all reaction can be written as shown below, while



etc.

TABLE 2

The Second-Order-Rate Constant of the Reaction of Quinaldine N-Oxide with Ac_2O.

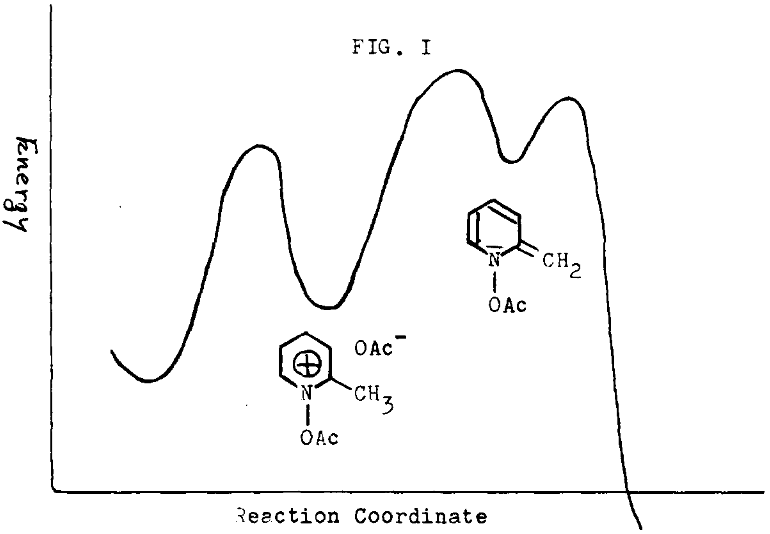
Temp.:$60.10^\circ \pm 0.01$; Solvent:CH_3CN

a_0	$(Ac_2O) \times 10^2$ M	$(LiClO_4)$	$k \times 10^4$ (M^{-1} sec^{-1})
3.646	10.337	-	7.68
3.6135	10.377	0.0596	30.2
3.548	10.355	0.119	49.5
3.497	0.4626	0.200	76.1
0.1745	0.4626	0.186	120
0.1658	0.4626	0.766	510
0.1721	0.4626	0.955	354
3.470	43.110	-	0.647 (in Dioxane)

a_0 : the initial concentration of quinaldine N-oxide $\times 10^2$ M

the energy profile can be illustrated as shown in Fig. 1.

FIG. I



Other compounds were also subjected to the similar kinetic experiments and the results are shown in Table 3.

TABLE 3

The Kinetic Isotope Effects and First-Order Rate Constants of Various N-Oxides in Dioxane $[Ac_2O] = 5.98$ M at 30°C

N-oxides	k_H/k_D	Pseudo-1st.-order rate constants $\times 10^5$ sec^{-1}
2-Picoline	3.1 (50% D-content)	0.418
4-Picoline	4.6	0.998
6-Phenyl-2-picoline	-	7.30
2-Benzylpyridine	7.6	7.40
Lepidine	7.7	11.5
Quinaldine	1.5	24.5
1-Methylisoquinoline	3.5	112

In all the other cases the kinetic isotope effects were found to be quite substantial, indicating that the rate determining step of the reactions of all these compounds is the proton removal by acetate anion.

Only in the reaction of quinaldine N-oxide, relatively small value of kinetic isotope effect i.e., $k_H/k_D=1.5$ was found. Undoubtedly the position of the transition state along the reaction coordinate is quite important in the consideration of the energy profile of the reaction. Probably the activated complex of this particular reaction assumes a very similar structure to that of the N-acetoxy quinaldinium ion as compared to those of the other N-oxides, therefore the C-H bond cleavage is less developed at the transition state, thus giving the rather small kinetic isotope effect.

One notices relatively small variation of rates i.e., only within 10^2 fold difference from 2-picoline to 1-methylisoquinoline N-oxides. Since the acidity of the methyl group of the activated complex of any of the N-oxides is mainly caused by the positive acyloxy ammonium function which is common to all the N-oxides studied here, the relatively small effect is transmitted from elsewhere. The higher rates of the quinoline, especially, the isoquinoline derivatives are obviously derived from the electron-withdrowing effect of benzo group attached to the pyridine ring.

In the same molecular skeleton where the acidity of methyl group is relatifely unaltered, the 1st step of acylation equiliblium apparently controls the rates though the rate varies relatively little, thus the rate of 6-methyl or 6-methoxy quinaldine N-oxide is higher than the unsubstituted compound which in turn is 3 times more reactive than 6-chloro compound. (Table 4)
The kinetic data in Table 4 and the work of Traynelis and his coworkers also support that the N-O bond cleavage is relatively unimportant in the rate-determining step of the over-all reaction, because the polar effect would be markedly larger in case if the cleavage of the N-O bond would be involved in the rate-controlling step. The fact that the following succeeding step is rapid is also supported by uneven distribution of the ^{18}O in the resulting esters which is the subject of the following communication.

The detail account of the experimental procedures, data and the discussions will be reported in a series of full papers soon.

TABLE 4

The Reaction of 6-Substituted Quinaldine N-Oxide with Ac_2O in Acetonitrile at 30°C

N-Oxide[a]	Rate Constant[b] (sec^{-1})	Rel.Rate	k_H/k_D	Rate Constant[c] (sec^{-1})	Rel.Rate
6-Methoxyquinaldine	1.54×10^{-4}	1.19	-	0.73×10^{-4}	0.67_8
6-Methylquinaldine	2.41×10^{-4}	1.87	7.4	2.22×10^{-4}	2.05
Quinaldine	1.29×10^{-4}	1.00	2.0	1.07×10^{-4}	1.00
6-Chlroquinaldine	0.38×10^{-4}	0.29_8	-	$0.66_1 \times 10^{-4}$	0.618

a) $[\text{N-Oxide}] = 3.4 \times 10^{-3}$ M b) $[Ac_2O] = 1.16$ M at 30°C

c) $[Ac_2O] = 0.53$ M, $[LiClO_4] = 2.0 \times 10^{-2}$ M at 10°C

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