

IMPLICATION OF SMALL HYDROGEN-DEUTERIUM KINETIC ISOTOPE EFFECT IN THE REACTION  
OF QUINALDINE AND 1-METHYLISOQUINOLINE N-OXIDES WITH ACETIC ANHYDRIDE (1)

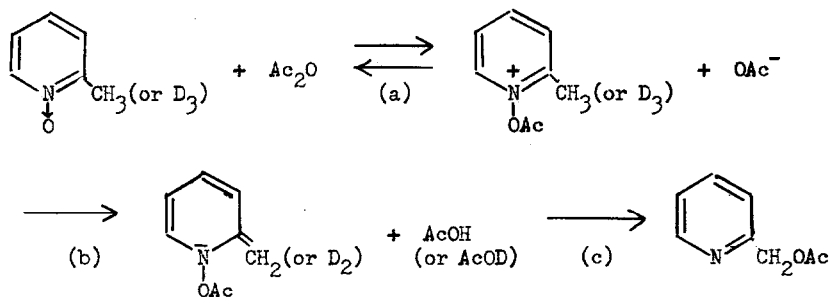
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(Received in Japan 22 July 1968; received in UK for publication 12 August 1968)

The general scheme of the reaction between  $\alpha$ - or  $\gamma$ -alkylated pyridine and quinaldine N-oxides with acetic anhydride can be depicted as shown below (2).



Previously, we have shown that unlike other  $\alpha$ -alkylated pyridine and quinoline N-oxides the reactions of quinaldine and 1-methylisoquinoline N-oxides give rather small kinetic isotope effect, i.e., 1.5 for the former (at  $60^\circ$  in  $\text{CH}_3\text{CN}$ ) and 3.5 for the latter (2). Meanwhile, we have found that the similar reaction of 6-methylquinaldine N-oxide gives a kinetic isotope effect of normal magnitude, i.e.,  $k_{\text{H}}/k_{\text{D}} = 7.4$  (at  $30^\circ\text{C}$ ) depicting the rate-determining step to be the proton removal (b). The small isotope effects observed for these former two N-oxides could mean that the initial pre-equilibrium step (a) is competing with the subsequent proton removal step. However this possibility is excluded, since the addition of lithium perchlorate which is known to shift the equilibrium rapidly to the right hand side of the acetylated intermediate does not change the size of the kinetic isotope effect. Meanwhile if the C-H (or D) bond concerned is not cleaved enough or the bond cleavage is over developed at the transition state, the kinetic isotope effect would be rather small (3), even when the

proton-removal step is the rate-determining step of the reaction, like many examples of E<sub>2</sub> reactions (4). Another possibility is that a slow proton removal (b) precedes in an equilibrium reaction to form the anhydrobase which undergoes cleavage of N-O bond in the slower transition state, like E<sub>1</sub>CB process. In this case, "anhydrobase" should be a fairly stable intermediate, and  $\alpha$ -trideuterated N-oxide will gradually undergo deuterium-hydrogen exchange in the presence of undeuterated acetic acid. We have found this to be the case for quinaldine and 1-methylisoquinoline N-oxide and wish to present a few observations to support it. At first,  $\alpha$ -trideuterated quinaldine N-oxide was subjected to the reaction with acetic anhydride in acetic acid to see the extent of hydrogen-isotopic exchange during the reaction and inspection of the data in Table I reveals that hydrogen isotopic exchange is taking place with this compound. Namely

TABLE I

HYDROGEN-DEUTERIUM EXCHANGE REACTION FOR REACTION OF N-OXIDES WITH Ac<sub>2</sub>O IN AcOH (or AcOD)

	Reaction Temp.	Deuterium or Proton Content %	Reaction %
Quinaldine N-oxide			
1) starting N-oxide	75°	94 % D	
recovered N-oxide		61.5 % H	50
2) starting N-oxide	75°	0 % D	
recovered N-oxide		62 % D	35
6-methylquinaldine N-oxide			
starting N-oxide	75°	0 % D	60
recovered N-oxide		25 % D	

quinaldine N-oxide recovered after 35 % completion of the reaction has lost 60 % of deuterium. Even 6-methylquinaldine N-oxide recovered after 60 % completion lost 25 % of deuterium. The esters obtained were also found to have lost more than one deuterium. Under the same condition, neither these N-oxides nor esters undergo any hydrogen exchange in acetic acid alone without acetic anhydride.

The rates of reactions of  $\alpha$ -trideuterated N-oxides with acetic anhydride in glacial acetic acid were then followed and the results are tabulated in Table II. One finds that lepidine, 2-benzylpyridine, 6-methylquinaldine N-oxides which exhibit large isotope effects of more than ?

TABLE II

REACTION OF VARIOUS DEUTERATED N-OXIDES WITH ACETIC ANHYDRIDE IN GLACIAL ACETIC ACID (error  $\pm$  3%)

Deuterated N-oxide	Ac <sub>2</sub> O M	Reaction Temp °C	Reaction %	k x 10 <sup>5</sup> sec <sup>-1</sup>	app. k <sub>H</sub> /k <sub>D</sub>
2-Benzylpyridine	2.48	77.8	0	4.90	7.6
			50	5.05	7.4
Lepidine	4.76	65.0	0	2.95	7.7
			50	3.02	7.5
6-Methylquinaldine	2.62	60.3	0	13.5	7.4
			50	14.70	6.8
1-Methylisoquinoline	2.54	40.0	0	1.33	3.5
			50	2.75	1.7
Quinaldine	2.64	50.0	0	2.81	2.0
			50	3.99	1.4
6-Chloroquinaldine	2.27	60.3	0	5.30	2.2
			50	6.35	1.8

do not show any marked rate-acceleration with reaction time. For example, the rate constants at 0 and 50 % completion of the reaction of 6-methylquinaldine N-oxide are 13.4 and  $14.7 \times 10^{-5} \text{sec}^{-1}$ , indicating that the hydrogen isotopic exchange cannot compete with the breaking of the N-O bond and hence undeuterated N-oxide will not be accumulate enough at 50 % completion of the reaction to increase the rates. Whereas with  $\alpha$ -trideuterated quinaldine N-oxide a substantial rate acceleration is observed from the initial stage to that of 50 % of the reaction while the rate of the undeuterated N-oxide remains identical,  $5.52 - 5.53 \times 10^{-5} \text{sec}^{-1}$  all through the reaction. 1-Methylisoquinoline N-oxide also have similarly. Obviously, with these compounds the hydrogen isotopic exchange is competing with the succeeding N-O bond cleavage, thus resulting in the ion of undeuterated N-oxide to increase the rate as the reaction proceeds further. This is reflected in the changes of apparent kinetic isotope effects at the initial stage and 50 % completion of the reactions of various N-oxide. Those which give large k<sub>H</sub>/k<sub>D</sub> values do not reduce the values or give very little reduction, as the reactions proceed while the small isotope effects exhibited by other N-oxides are reduced to even smaller values due to the gradual deuterium exchange during the reaction.

All these observations suggest strongly that "anhydrobase" is a definite intermediate in any of these reactions and the proton-removal step (b) to go back to the N-acetoxy ion is quite rapid. Apparently the reaction of quinaldine, or 6-chloroquinaldine N-oxide involve slow deprotonation (or dedeuteration)-protonation (deuteration) equilibrium followed by slower rate-determining N-O bond cleavage, whereas with lepidine, and 2-benzylpyridino N-oxides the rate-determining step is the deprotonation. Perhaps with 6-methylquinaldine N-oxide both step

(b) and (c) reactions have nearly identical energy barriers.

This is in keeping with the activation parameters of these N-oxides. Namely, the activation energies of lepidine and 2-benzylpyridine N-oxides are 2 - 3 Kcal/mol higher than those of quinaldine and 1-methylisoquinoline N-oxide. These higher activation energies are undoubtedly associated with more difficult proton removal (b) and hence relatively facile N-O bond cleavage in the succeeding step.

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