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OXYGEN TRANSFER REACTIONS OF AROMATIC AMINE N-OXIDES. THE CARBOXY INVERSION MECHANISM

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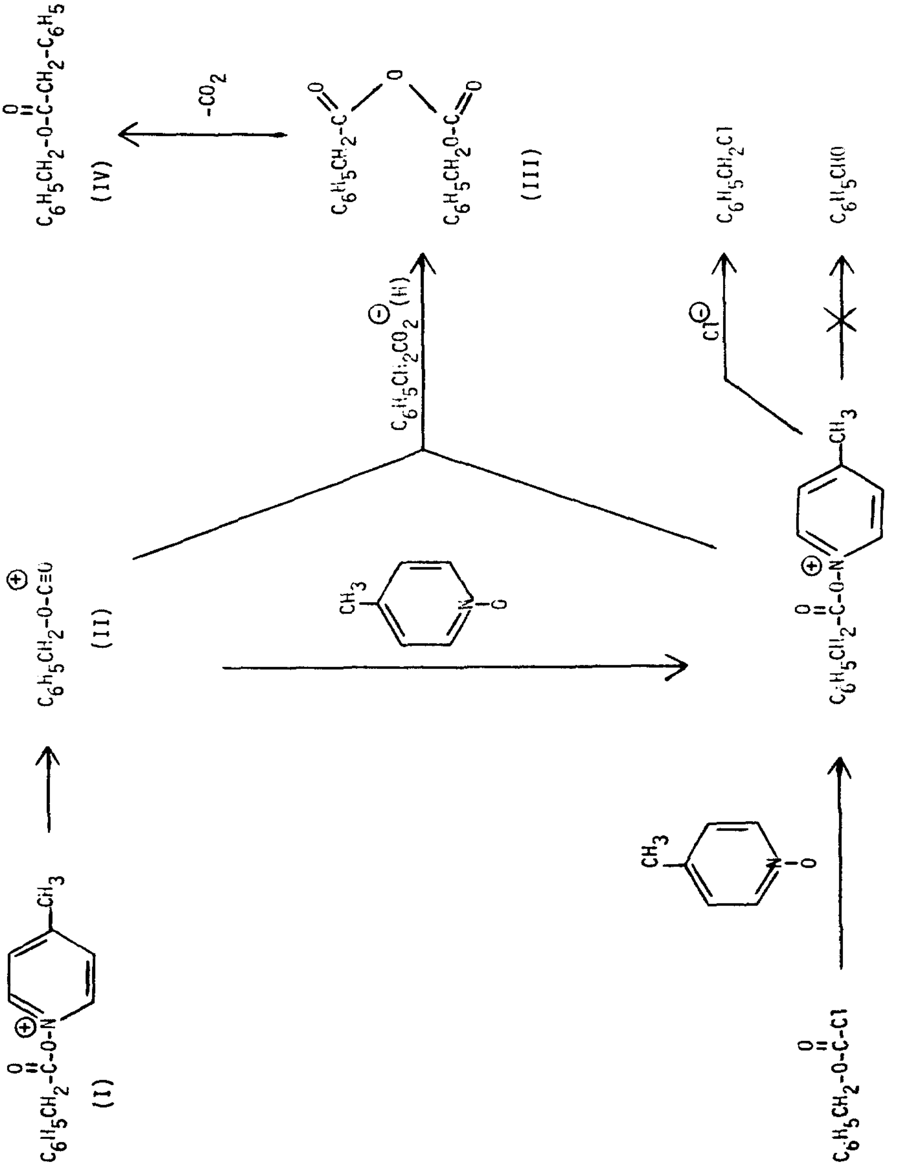
Like other reactions of amine N-oxides with carboxylic acid anhydrides (1), the recently discovered (2,3,4) oxidative decarboxylation of anhydrides with pyridine and picoline N-oxides has developed into a subject of considerable controversy. The most recent report (5) on experiments designed to elucidate the mechanism of this type of reaction contains the proposal of a carboxy inversion step to give an acylonium ion (II) as the key intermediate for the formation of both ester and oxidation products. We had originally proposed this path for the ester formation (4). The experiments detailed below cause us to doubt that such a species is the one responsible for the oxidation reaction which we are studying.

When freshly distilled benzyl chloroformate (b.p. 76-78° at 1-2 mm) is added to a solution of 4-picoline N-oxide in acetonitrile at room temperature, an immediate yellow color developes followed by precipitation of a yellow solid. Gas (carbon dioxide) is evolved slowly from this mixture (50% complete in ca. 1 hour). The materials isolated from such a mixture after stirring overnight in nearly quantitative amounts are benzyl chloride and 4-picoline N-oxide. We propose these observations are the result of formation of the chloride salt of V which suffers decarboxylative substitution by the chloride ion.

When this complex is treated immediately with triethyl amine at room temperature, gas evolution is more rapid but the product remains benzyl chloride. When the complex is treated with tetraethylammonium phenylacetate, the gas formation is very rapid and the product obtained is benzyl phenylacetate (IV) in high yield. When this latter reaction is carried out with oxygen-18 enriched phenylacetate ion, the carbon dioxide evolved contains 1,03 labeled oxygen atoms per molecule. This suggests that the carbonic acid anhydride (III) is an intermediate in the formation of the ester (6). The ester is also formed from treatment of the complex with phenylacetic acid and


(I)
(II)
(III)
(IV)
$-CO_2$
$C_6H_5CH_2CO_2^{\ominus}$ (H)
$Cl^{\ominus}$
$C_6H_5CH_2Cl$
C_6H_5CHO

triethyl amine together. Under none of the above conditions was benzaldehyde a detected product (7).

It should be strongly emphasized that these conditions are quite comparable to those under which the anhydride oxidation occurs. A solution of phenylacetic anhydride (0.1 M) and 4-picoline N-oxide (0.2M) in acetonitrile gives 16-20% benzaldehyde and carbon dioxide on stirring at room temperature overnight. We therefore consider the carboxy inversion process a likely competing path leading to ester formation but not aldehyde formation under our conditions.

This most recent paper (5) also criticized our kinetic studies on the basis that the yields of benzaldehyde and carbon dioxide were only 16% and 3% respectively under kinetic conditions". We have, therefore, rechecked our previous results on this point. These data are summarized in Table I.

TABLE I

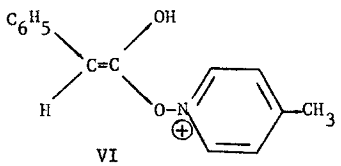
Products from 4-Picoline N-Oxide and Acid Anhydrides in Refluxing Acetonitrile.

Anhy.[M]	N-Oxide[M]	Acid[M]	CO_2[a]	$T_{1/2}CO_2$[b]	DNP[c]
0.11[d]	0.20		70%	4	62%
0.10[d]	0.20		65%	4	57%
0.10[d]	0.20		70%	4	55%
0.10[d]	0.20	0.11	61%	15	52%
0.10[d]	0.20	0.21	61%	30	43%
0.24[d]	0.42		61%	4	60%
0.48[d]	0.82		65%	3	45%
0.02[d]	0.04		65%	6	-
0.10[e]	0.21	-	80%	$\sim$0.5	60%[f]
0.10[e]	0.21	0.10	70%	10	
0.01[e]	0.02	-	71%	6	

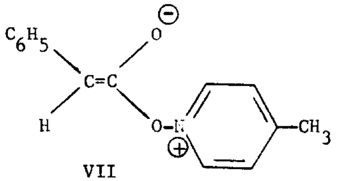
a) Yields of carbon dioxide by gas evolution based on 1/2 the moles N-oxide present. b) Estimated time for half the eventual carbon dioxide to be evolved (minutes). c) Yields of benzaldehyde dinitrophenylhydrazone based on 1/2 the moles N-oxide present. d) Phenylacetic anhydride. e) Diphenylacetic anhydride. f) Benzophenone by n.m.r.

We are at a loss to explain this apparent discrepancy in experimental results (8). We do observe a minor trend towards decreased aldehyde product with increased acid concentration. This and the general observation of less than quantitative aldehyde formation offer no serious challenge to the kinetic studies since the formation of other oxidation products such as diphenyl maleic anhydride also occurs in these reactions (3,9). Such side reactions could account for the upward curvature of the rate plots after 60% reaction. Our previous conclusions were not based on the overall kinetics but on the correlation of initial rates with added acid and this correlation is not subject to the criticisms raised by Rüchardt. A more serious problem with the interpretation of the kinetic results arises from our recent observation that added acetic acid also inhibits the rearrangement reaction of 4-picoline N-oxide with acetic anhydride. This general inhibition by added acid may be a result of hydrogen bonding between the N-oxide and the added acid rather than of reversible proton transfer, though both effects may actually be operative. In any case, the implications of this inhibition are ambiguous for the present.

This situation makes Cohen's enol intermediate (VI) a kinetically allowable possibility rather than demanding a deprotonated species (such as VII) as previously proposed.



VI



VII

The absence of an increased yield of benzophenone from the decomposition of *di-t*-butylperoxy diphenylmalonate (5,8) in the presence of N-oxide is a powerful argument against the α-lactone mechanism (4). The enol (VI) mechanism thus becomes the one which deserves further testing.

If the enolization (I→VI) is rate determining, then the reaction should be first order each in N-oxide and anhydride with the acid inhibition superimposed, exactly the same as that expected for the α-lactone mechanism. The integrated form of this rate

$$\frac{dP}{dt} = k\,\frac{(N\text{-}O)\,(AN)}{(Acid)} \qquad (1)$$

law predicts no dependence of the half time of reaction on initial reactant concentration but 280 times the half time for 99% reaction as well as the linear dependence of half time on initial acid concentration mentioned previously. The data of the table for the phenylacetic anhydride reaction strongly support this rate law for gas formation in agreement with the previous infrared studies.

If the attack of the second N-oxide on the enol is rate determining then the rate law should be second order in N-oxide, first order in anhydride with the acid inhibition superimposed. The integrated form of this rate law predicts an inverse

$$\frac{dP}{dt} = \frac{k\ (\text{N-oxide})^2(\text{Anhy.})}{(\text{Acid})^2} \qquad (2)$$

proportion between the initial reagent concentration and the half time of the reaction. Also initial addition of 1 equivalent of acid (based on anhydride) is calculated to increase the half time by ca. 13 fold at the same reagent concentration. The data of the table for diphenylacetic anhydride appear to be in accord with these predictions. If this rate law proves to be correct then it could provide substantial support for the enol mechanism.

Finally, it should be pointed out that the conditions of Rüchart's studies are so different from our own that the data may not be mutually applicable. A change in mechanism is quite conceivable on going to such drastic temperatures compared to 40-80°. The reaction (4) between diphenylketene and N-oxide is now made more interesting by these results (8).

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7. Similar results have been obtained by C. Rüchart, private communication.

8. The acetonitrile used in our studies was distilled (b.p. 81.5-82°) from phosphorus pentoxide onto activated molecular sieves. The solvent used by Rüchardt was finally distilled from anhydrous potassium carbonate. We have found that this final distillation adds enough water to the solvent to hydrolyze most of the anhydride. This conclusion has been verified by Rüchardt's group.

9. T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1966).

10. T. Barklow, unpublished work in these laboratories. There is a possibility that two separate molecules which might be described as α-lactones (planar and non-planar) exist and are separated by an appreciable rotational energy barrier. Extended Hückel molecular orbital calculations suggest this may be the case. If so, then which species is formed in which reaction is, in itself, an interesting question.