Acknowledgments. This research was supported by National Institutes of Health Grant No. GM 12633-10 (R. H. A.), National Institutes of Health Special Fellowship 1 F03 GM 55300-01 to R. C. H., and National Institutes of Health Special Fellowship 5 F02 GM 40063-02 to A. L. M.

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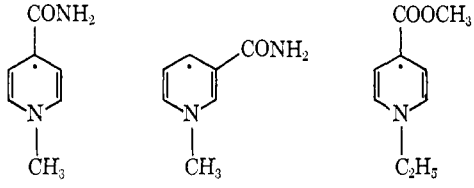
Received June 14, 1973

Bimolecular Disappearance of Pyridinyl Radicals in Water

Sir:

The 1-ethyl-4-carbamidopyridinyl radical is stable



4a 3a 4e

for hours in acetonitrile.[1] We now report that the related 1-methyl radical (**4a**) disappears in water at a rate which is proportional to the square of the radical concentration and has the unusual feature of being strongly pH dependent.

Pyridinyl radicals were generated through one-equivalent reduction of the corresponding pyridinium ion[2-4] in aqueous buffers containing the appropriate combinations of sodium formate and formic acid, phosphate, or sulfuric acid, using 2–5 μsec pulses of 10 MeV electrons.[5] Optical transmission was monitored with an EMI 9558 photomultiplier. Dosimetry was based on the absorptions due to **3a**.[3]

The **4a** radical was found to disappear by second-order kinetics with rate constants k (defined by $d[Py\cdot]/dt = -k[Py\cdot]^2$) at pH 6.9 and 4.0 of 2.5×10^4 and 6.8×10^8 M^{-1} sec^{-1}, respectively. Rate constants measured for intermediate pH values suggested a second-order dependence on $[H^+]$, as illustrated in Figure 1. The rate constant for the disappearance of **3a** was 6.7×10^7 M^{-1} sec^{-1}, in agreement with the previous determination,[2] and was independent of pH in the range over which k_{4a} varied.

The absorption spectrum of **4a** was the same at pH 6.9 and 4.0 and exhibited a narrow peak with a maximum close to 305 nm and a broader peak with a maximum at 405 nm. Extensive protonation at pH 4.0 is therefore excluded. In more acid solutions (below H_0 of about -2) spectra were observed in which the 405-nm peak was somewhat lower in intensity and shifted to 425 nm, perhaps because of protonation of the amide group, as reported for benzamide in the same acidity

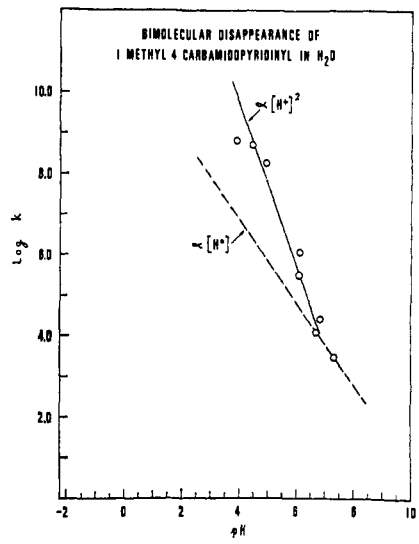


Figure 1. Log k, bimolecular rate constant for disappearance of 1-methyl-4-carbamidopyridinyl radical in water solution, plotted against pH. The dashed line represents a process linear in $[H^+]$ and the solid line a process proportional to $[H^+]^2$.

range.[6] The products of the reaction of **4a** radicals could not readily be determined, but the pyridinyl radical **4e** can conveniently be prepared in a pure form[7-9] and has previously been found to react fairly rapidly in water. By mixing small amounts of dilute acetonitrile solutions of **4e** with an aqueous buffer in a quartz cell in a Cary spectrophotometer, the radical has now been found to disappear in a second-order reaction with a rate constant at pH 8.0 of 3.8×10^3 M^{-1} sec^{-1}. Addition of modest amounts of acetonitrile dramatically decreased the rate of disappearance. Using larger quantities of **4e**, the products of the reaction have been found to be the corresponding pyridinium ion and the hydrolysis products of the dihydropyridine in *ca.* 1:1 ratio, based primarily on nmr spectra. The pH-dependent disappearance of the **4a** radicals can be explained by Scheme I. This mechanism accounts

Scheme I

$$Py\cdot + Py\cdot \rightleftharpoons [Py\cdot, Py\cdot \rightleftharpoons Py^+, Py^-] \quad (a)$$

$$[Py^+, Py^-] + H^+ \rightleftharpoons [Py^+, PyH] \quad (b)$$

$$[Py^+, PyH] \longrightarrow Py^+ + PyH \quad (c)$$

$$[Py^+, PyH] \xrightarrow{H^+} Py^+ + PyH_2^+ \quad (d)$$

$$PyH \xrightarrow[H_2O]{H^+} \text{products} \quad (e)$$

$$PyH_2^+ \xrightarrow{H_2O} \text{products} \quad (f)$$

for the products of the reaction of the **4e** radicals, which are taken to be like those of **4a**. It also explains the stability of the radicals in less-polar solvents, since the electron-transfer equilibrium shown in the first step would be shifted to the left by amounts which could readily be estimated from the Z values for the solvents.[9-11]

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(11) **4e** is stable indefinitely in a 0.05 M solution in acetonitrile at 5°.

Recent data have strengthened previous suggestions as to the possibility of one-electron intermediates in the reactions of pyridine nucleotides.[12-15]

Ion pairs of the type postulated in the present work have been suggested on the basis of the pH dependence of the products from dihydropyrimidinyl radicals formed in radiolysis of dihydropyrimidines.[16] It may be of significance to the consideration of the role of NAD^+ in the enzymatic oxidation of alcohols that photoexcited 9-phenylacridine is reduced to a radical by electron transfer rather than hydrogen atom transfer.[17] The resulting radical pair must then continue to final products by one electron steps. We have pointed out elsewhere the existence of this possibility for NAD^+ in enzymatic reactions,[13,18] and the substituent and isotope effects reported by Klinman are still consistent with this idea.[19]

In the interesting thermal disproportionation reaction of *N,N'*-dicarboethoxy-4,4'-tetrahydrobipyridyl,[20] the transfer of the carboethoxy group and the formation of pyridine might be readily explained by the intervention of an ion pair formed by electron transfer after the formation of the initial radical pair.

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(21) Support from the Army Research Office (Durham) is gratefully acknowledged.

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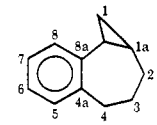
Received April 21, 1973

Ipso Nitration of an Unsymmetrical Arene.[1] Selective Adduct Formation and Multistep Nitro Group Migrations

Sir:

The importance of electrophilic attack at a substituted position (*ipso* attack[2]) in nitration of certain benzene derivatives has become increasingly clear recently, emphasized by isolation of numerous 1,4 *ipso* adducts.[3] A key experiment by Myhre[4] showed that 1,4 (nitro, acetoxy) adducts of *o*-xylene are converted in strongly acidic media to 3-nitro-*o*-xylene. Postulation of a 1,2-nitro shift sufficed to account for this result; no indications were found of more extensive nitro shifts. We now report that exposure of *ipso* adducts of 1,1a,2,3,4,8b-hexahydrobenzo[*a*]cyclopropa[*c*]cycloheptene (**1**) to strongly acidic media affords

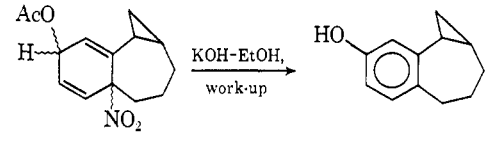


1

evidence that a nitro group can have significantly more mobility in intramolecular rearrangement than previously seen.

Compound **1** appears almost uniquely well suited for the study reported here. The 5-, 6-, 7-, and 8-nitro derivatives of **1** are readily separable and/or distinguishable by pmr analysis,[5] as are the 6- and 7-acetoxy[6] and 6- and 7-hydroxy[6] derivatives. Nitration of **1** (6 mmol in 2 ml of acetic anhydride) with acetyl nitrate (preformed from 9 mmol of 100% nitric acid and 2 ml of acetic anhydride) gave up to 60% of *ipso* adducts, in addition to "normal" nitration products, as indicated by comparison of pmr integrated intensities of vinyl (δ 6.01–5.95) *vs.* aryl (δ 8.17–7.18) proton resonances.[3] The nitro derivative mixture consisted of 40% each of 6- and 7-nitro-**1**, 11% of 5-nitro-**1**, and 9% of 8-nitro-**1**.[7]

Welcome simplification of the adduct identification problem was provided by treatment of the crude nitration mixture with ethanolic alkali; work-up yielded a nearly quantitative amount of a mixture of all four nitro derivatives and 7-hydroxy-**1**. The absence of detectable amounts of 6-hydroxy-**1** showed that essentially exclusive formation of adducts having gross structure **2** had occurred.



2

Rapid chromatography of the crude reaction mixture over deactivated alumina afforded a stable stereoisomer of **2**: colorless crystals; mp 86–87.5°; pmr (CCl_4) δ 6.01 (broad s, 2 H), 5.95 (m, 1 H), 5.53 (m, 1 H), and 2.08 (s, 3 H).[9] Passage of this pure adduct through a silica gel column effected conversion to pure 7-acetoxy-**1**.[6] However, when the adduct was solvolyzed in 78% sulfuric acid (2 min, 25°), in addition to the 5-nitro-**1** expected from a 1,2-nitro shift (41%), there was obtained 54% of 8-nitro-**1** and *ca.* 5% of a mixture of 6- and 7-nitro-**1**.[10]

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