# REVERSIBLE FORMATION OF A PSEUDOBASE FROM 1-METHYLPYRIDINIUM-3-CARB(OX)ALDEHYDE

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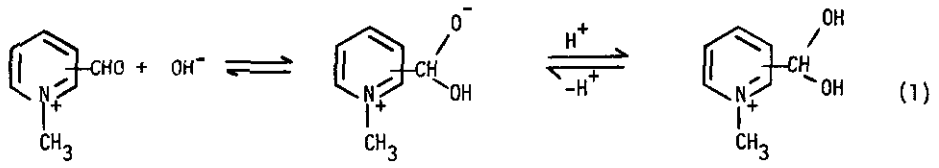
Abstract - The geminal diol anion of 1-methylpyridinium-3-carb(ox)aldehyde hydrate in aqueous alkaline solutions forms an unstable pseudobase by nucleophilic attack of hydroxide ion at the pyridinium ring. This reaction with $pK_a$ = 14.4 is unique among 1-methylpyridiniumcarboxaldehydes for the 3-isomer.

Reversible addition of hydroxide ions to the aldehydic group has been reported for benzaldehydes,[1-3] polycyclic aromatic carboxaldehydes[4] and π-excessive heteroaromatic aldehydes.[5] Formation of a geminal diol anion by addition of hydroxide ion to the unhydrated aldehydic group or by dissociation of the geminal diol group of hydrated pyridinecarboxaldehydes was speculatively proposed more than two decades ago in the interpretation of spectroscopic data.[6] More recently quantitative information about such equilibria has been obtained by spectroscopic and electrochemical studies.[7] On the other hand, some π-deficient N-alkyl heteroaromatic cations are readily attacked by hydroxide ion on the aromatic ring.[8-10] Such reactions, facilitated by the electron-withdrawing, positively charged heterocyclic nitrogen, have been proposed to yield intermediates in numerous reactions of N-alkylpyridinium ions.[10,11] Thus, isomeric, N-substituted pyridiniumcarboxaldehydes in alkaline solutions are subject to nucleophilic attack at the side chain and at the ring. The sequence of such reactions is the subject of this report. Between pH 8 and 12, changes in uv and nmr spectra and in electrochemical behavior in aqueous solutions of N-alkylpyridiniumcarboxaldehydes[12,13] indicated initial reactions of $OH^-$ with the aldehyde group in the following equilibria:




B A C (1)

I: 3-substituted derivative
II: 2-substituted derivative
III: 4-substituted derivative

For 1-methylpyridinium-3-carb(ox)aldehyde (IB), which is of particular interest as a model for nicotinamide adenine dinucleotide (NAD), we have observed additional reactions in more alkaline solutions. In contrast to the major uv band at 260 nm between pH 2 and 9, in solutions of sodium hydroxide at pH > 13 a new strong absorption band was observed at 317 nm, with an absorbance which decreased with time. The absorbance at 317 nm extrapolated to zero time after addition of IB increased with increasing activity of hydroxide ions. This absorbance plotted vs. acidity function $J_-$[14] gave an excellent fit to the theoretical dissociation curve of a monobasic acid with $pK_a$ = 14.4 (Fig. 1). In the same acidity region where the decrease of the absorbance at 317 nm was observed, polarographic limiting current (corresponding to reduction of IB formed from IA and IC in the vicinity of the electrode[14]) showed a decrease with time following first order kinetics. Rate constants of $3 \times 10^{-5}$ $s^{-1}$ and $8 \times 10^{-5}$ $s^{-1}$ were found at $J_-$ = 14.7 and 15.7, respectively. This decrease in the aldehyde wave is accompanied by the growth of a new reduction wave at more negative potentials. These results indicate that IA reacts with hydroxide ions and the product of this reaction undergoes a further chemical transformation.

To identify the unstable intermediate of the reaction of IA with hydroxide ion, 60 $MH_z$ proton nmr spectra were recorded immediately after dissolving aldehyde IB in $D_2O$ solutions containing NaOD. In 0.016 M NaOD (pD = 12.2) and in unbuffered $D_2O$ an aromatic four-proton pattern was observed centered around $\delta$ = 8.6 (tetramethylsilane reference) with the proton on the exocyclic carbon at $\delta$= 6.9. These spectra are attributed to IC and IA which predominate in these solutions. The aromatic coupling pattern was identical to that of 1-methyl-3-cyanopyridinium ion, interpreted by Damji and Fyfe.[15] In 5.2 M NaOD ($J_-$ = 15.4) four distinctly separated ring proton resonance peaks were found (Fig. 2) and assigned as follows: a relatively uncoupled peak at $\delta$ = 8.7(H-2), and coupled peaks at $\delta$ = 6.8(H-6), 5.9(H-5), and 4.8(H-4) ppm. The proton on the exocyclic carbon gave a line at $\delta$= 7.8. The integral of each peak corresponded to one proton. The peak assigned to the methyl protons observed at $\delta$ = 4.7 ppm at pD = 12.2 was shifted upfield to $\delta$ = 3.7 ppm in 5.2 M NaOH, consistent with removal of positive charge on the adjacent nitrogen. Assignments of the ring protons were made by reference to the spectrum of 1-methyl-3-cyano-4-methoxy-1,4-dihydropyridine, which has been interpreted in detail.[15] Assignments for the latter were confirmed by deuterium substitution,[15] and the pattern of coupling of ring protons was nearly identical to that in Fig. 2. Nmr data are consistent with nucleophilic addition of hydroxide ion to IA yielding the 1,4-dihydropyridine pseudobase IV:

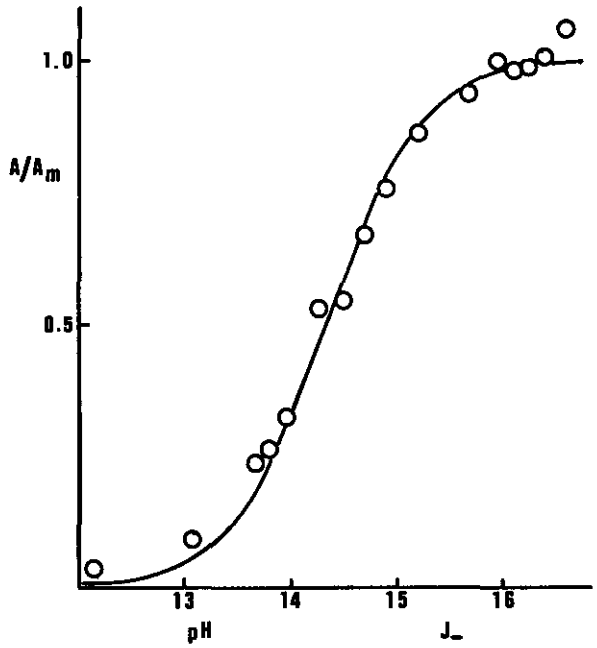



Figure 1. Influence of acidity on absorbance of 0.10 mM 1-methylpyridinium-3-carb(ox)aldehyde at zero time. $A_m$ is the average extrapolated absorbance at $J_- > 16$. Circles are experimental; line is theoretical dissociation curve for a monobasic acid with $pK_a = 14.4$.

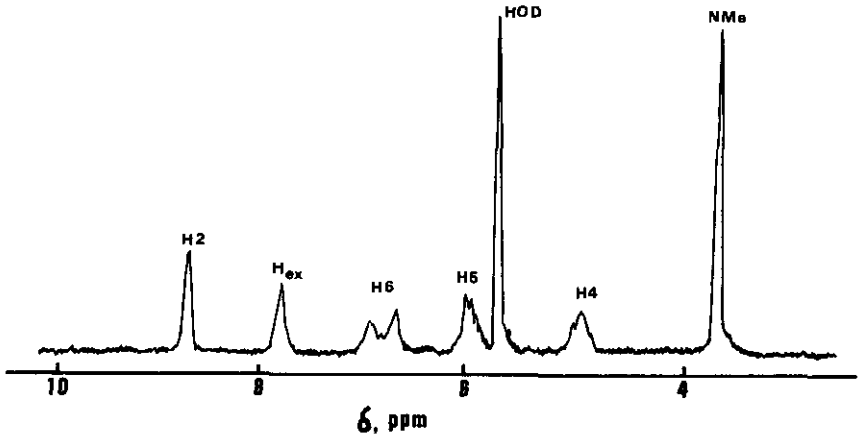
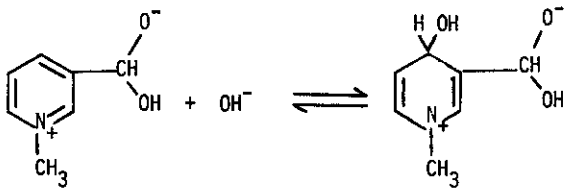



Figure 2. Proton nmr spectrum of 15% 1-methylpyridinium-3-carb(ox)aldehyde in 5.2 M NaOD in $D_2O$ taken immediately after mixing (TMS external reference).



(2)

IV

Because of similarities of nmr spectra for possible isomers,[15,16] the presence of a small amount of the isomeric 1,2-dihydropyridine pseudobase in equilibrium with IV cannot be ruled out. The uv band at 317 nm is more consistent with IV, since absorption of the 1,2-dihydro isomer is expected at longer wavelengths. Thus, IV seems the likely structure for the pseudobase formed from IA (eq 2). Formation of a pseudobase similar to IV was proposed to account for the appearance of new uv-absorption bands in alkaline solutions of nicotinamide.[17,18] Formation of the pseudobase IV is reversible, as proved by identity of spectra of alkaline solutions of IV rapidly acidified to pH < 8 with spectra of IB added directly to buffers of pH < 8. Furthermore, spectra of these acidified solutions did not vary with time.

It is noteworthy that pseudobases were not detected in strongly alkaline solutions of 1-methylpyridinium-4- or 2-carb(ox)aldehydes (IIB and IIIB, respectively). Solutions of IIB and IIIB at pH > 13 showed only a decrease in the absorbance at 280-300 nm and a corresponding decrease of polarographic limiting currents with time.[12] Their uv spectra extrapolated to zero time showed no new bands at longer wavelengths, even in 8 M NaOH. Similarly, no new polarographic waves were observed at potentials more negative than that of the aldehydic forms IIB and IIIB. Finally, proton nmr of rapidly prepared solutions of IIB and IIIB in 5.2 M NaOD/$D_2O$ retained the aromatic resonance pattern observed at lower pH.

Thus, the formation of a pseudobase (IV) from 1-methylpyridinium-3-carb(ox)aldehyde is unique among its positional isomers. However, it is not the parent compound IB, but the geminal diol zwitterion IA formed in eq 1 which undergoes attack by hydroxide on the aromatic ring (eq 2). Increased reactivity of the aromatic system in the presence of the geminal diol anion substituent was also observed for reactions of 5-nitrofurfural.[19] Similar activation in a benzenoid system was noted for nitrobenzaldehydes, where Meisenheimer addition occurs for the geminal diol anionic form.[20] Pseudobase (IV) in strongly alkaline media undergoes further slow chemical reactions, which were not investigated in detail.

REFERENCES


1. W. J. Bover and P. Zuman, J. Electrochem. Soc., 1975, 122, 368.
2. J. H. Sedon and P. Zuman, J. Org. Chem., 1976, 41, 1957.
3. P. Greenzaid, J. Org. Chem., 1973, 38, 3164.
4. D. Defries, Senior Thesis, Clarkson College of Technology, Potsdam,NY, 1974.
5. W. J. Scott, W. J. Bover, K. Bratin, and P. Zuman, J. Org. Chem., 1976, 41, 1952.
6. K. Nakamoto and A. E. Martell, J. Am. Chem. Soc., 1958, 81, 5857.
7. J. F. Rusling and P. Zuman, J. Electroanal. Chem., 1986, 213, 255, 277.
8. J. W. Bunting and W. G. Meathrel, Can. J. Chem., 1972, 50, 917.
9. J. W. Bunting and W. G. Meathrel, Can. J. Chem., 1974, 52, 981.
10. J. W. Bunting, Adv. Heterocyclic Chem., 1979, 25, 1-82.
11. (a) R. A. Abramovitch (Ed.), V. 14, Supplement, Part One, Interscience, NY, 1974 (b) O. R. Rodig in "Pyridine and its Derivatives" R. A. Abramovitch (Ed.), V. 14, Supplement, Part One, Interscience, NY, 1974, pp. 309-430.
12. J. F. Rusling, J. P. Segretario, and P. Zuman, J. Electroanal.Chem., 1983, 143, 291.
13. J. F. Rusling and P. Zuman, J. Electroanal.Chem., 1983, 143, 283.
14. W. J. Bover and P. Zuman, J. Am. Chem. Soc., 1973, 95, 2531.
15. S. W. H. Damji and C. A. Fyfe, J. Org. Chem., 1979, 44, 1757.
16. R. E. Lyle in "Pyridine and its Derivatives", R. A. Abramovitch (Ed.), V. 14, Supplement, Part One, Interscience, NY, 1974, pp. 137-182.
17. R. M. Burton and N. O. Kaplan, Arch. Biochem. Biophys., 1963, 101, 139.
18. R. B. Martin and J. G. Hull, J. Biol. Chem., 1964, 239, 1237.
19. D. Murphy, Senior Thesis, Clarkson College of Technology, Potsdam, NY, 1978.
20. A. Dombrowski, H. Schultze, P. Zuman, Clarkson College of Technology, Potsdam, NY, 1978, unpublished results.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