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THE RING-OPENING OF N-METHOXYPYRIDINIUM PERCHLORATE BY HYDROXIDE ION*

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Abstract—Hydroxide ions react rapidly but reversibly with 1-methoxypyridinium salts to open the pyridine ring yielding glutaconic dialdehyde mono-O-methyloxime. The known decomposition of N-alkoxypyridium cations to aldehyde and pyridine is an accompanying slow but irreversible reaction. The kinetics and mechanisms of the ring opening are elucidated.

INTRODUCTION

THE potential synthetic utility of N-alkoxypyridinium salts was first investigated by Ochiai *et al*, in 1944.[1] These salts, in the presence of alkali, decompose to the aldehyde and the parent pyridine (Path A, Chart I). This method has been successfully used for the preparation of substituted benzaldehydes.[2] The possible value of this reaction as a mild, non-reductive method for deoxygenating pyridine-N-oxides has also been noted.[3] Here hydroxide acts as a base in *abstracting* a proton from the carbon atom α to the oxygen. Alkoxide[4] and mercaptide[5] ions can act similarly.

N-Alkoxypyridinium salts are also susceptible to nucleophilic *substitution* on the ring. It has been shown[6,7] that 2- and/or 4-cyanopyridines can be conveniently synthesized by treatment of N-alkoxypyridinium salts with cyanide, reaction occurring with concommitant loss of the RO-function as the alcohol[8] (Path B). With mercaptide ions,[9] the reaction is more complex, 3-substituted derivatives being formed in addition to the 2- and 4-mercaptopyridines. The mechanism of the 3-substitution reaction remains unclear.

Another mode of reaction of N-alkoxypyridinium salts with nucleophiles involves *displacement* of pyridine-1-oxide at the alkoxy carbon atom (Path C). Treatment of N-alkoxypyridinium or picolinium salts with thiophenoxide[9a] or benzyloxide[4] yielded the parent N-oxide. Other nucleophiles, such as acetate ion and aniline, act similarly.

Several years ago, one of us[10] observed anomalous behaviour in the reaction of 1-methoxypyridinium salts with hydroxide ion, *viz.* the transient appearance of a

* Part XXVI in the series, N-Oxides and Related Compounds. Part XXV, H. Bauer and A. R. Katritzky, *J. Chem. Soc.* 4394 (1964).

[1] E. Ochiai, M. Katada, T. Naito, *J. Pharm. Soc. Japan* **64**, 210 (1944); *Chem. Abstr.* **45**, 5154 (1954).

[2] W. E. Feely, W. L. Lehn and V. Boekelheide, *J. Org. Chem.* **22**, 1135 (1957).

[3] A. R. Katritzky, *J. Chem. Soc.* 2404 (1956).

[4] N. A. Coats and A. R. Katritzky, *J. Org. Chem.* **24**, 1836 (1959).

[5] L. Bauer and L. A. Gardella, *J. Org. Chem.* **28**, 1320 (1963).

[6] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.* **81**, 4004 (1959).

[7] T. Okamoto and H. Tani, *Chem. and Pharm. Bull.* **7**, 925 (1959).

[8] H. Tani, *Chem. and Pharm. Bull.* **7**, 930 (1959).

[9] L. Bauer and L. A. Gardella, *J. Org. Chem.* **28**, 1323 (1963); [9a] L. Bauer and T. E. Dickerhofe, *Ibid.* **29**, 2183 (1964).

[10] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957).

strong absorption band at ca. 340 mμ in the UV spectrum, and hysteresis effects in potentiometric titrations. We now show that these phenomena can be rationalized in terms of a fourth reaction pathway, the nucleophilic *addition* of hydroxide to the pyridine ring, and subsequent ring opening (Path D). This also appears to be the first example of the ring-opening of a pyridine-N-oxide, although ring-opening reactions of other pyridinium salts[11] and betaines[12] are well known.

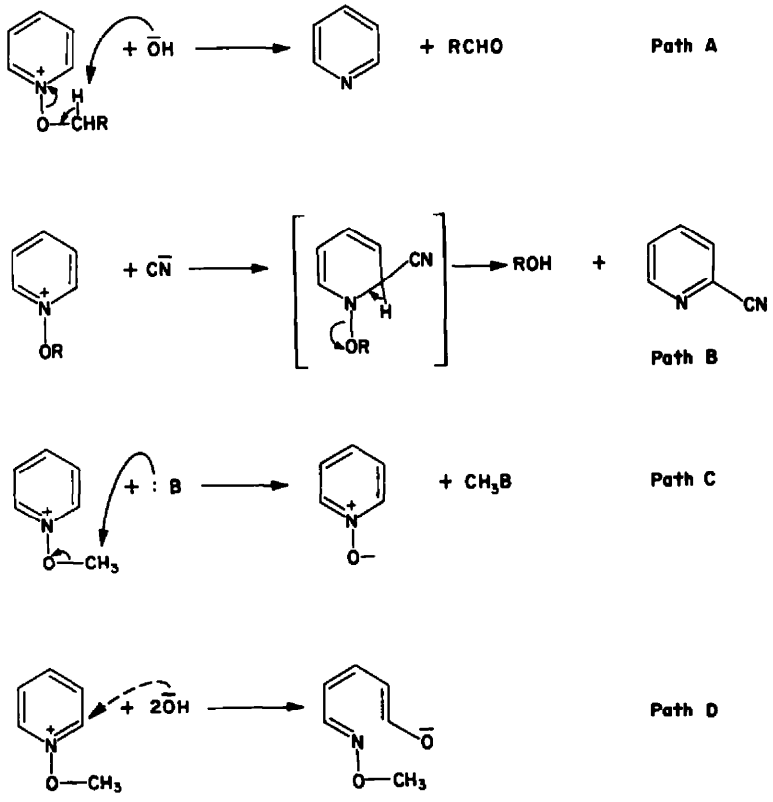


Chart I Modes of Reaction of N-alkoxypyridinium Salts.

EXPERIMENTAL[13]

Materials. O-Methylhydroxylamine hydrochloride, m.p. 150·5–152° (lit.,[16] 151°) (from EtOH–ether) was prepared[14] from dipotassium hydroxylamine disulphonate.[15]

The sodium enolate of glutaconic dialdehyde was prepared[18] from pyridine-N-sulphonate[17] and purified by the method of Koch.[18]

N-Methoxypyridinium perchlorate was prepared from the crude methosulphate[6] obtained from

[11] Th. Zincke, *Liebig's Ann.* **338**, 107 (1905).
[12] P. Baumgarten, *Ber. Dtsch. Chem. Ges.* **59**, 1166 (1926).
[13] M.ps are uncorrected; analysis by Weiler and Strauss, Oxford. UV spectra were obtained with a Perkin-Elmer 137 UV instrument and NMR spectra with a Perkin-Elmer 40 Mc spectrometer.
[14] C. H. Andrews, H. King and J. Walker, *Proc. Roy. Soc.* **B133**, 40 (1946).
[15] G. K. Rollefson and C. F. Oldershaw, *J. Amer. Chem. Soc.* **54**, 977 (1932).
[16] W. Lossen, *Liebig's Ann.* **281**, 217 (1894).
[17] H. Sisler and L. F. Aubrieth, *Inorg. Syn.* **2**, 173 (1946).
[18] C. Schöpf, A. Hartmann and K. Koch, *Ber. Dtsch. Chem. Ges.* **69**, 2766 (1936).

52·3 g pyridine-N-oxide (0·55 mole) and 70 g (0·55 mole) of methyl sulphate. Following the addition of 85 ml abs. EtOH, 55 ml 70% perchloric acid, and 400 ml ethyl acetate, thorough cooling gave the *perchlorate* which was recrystallized from 95% EtOH, (88·7 g) m.p. 69–70°. (Found: N, 6·51. $C_6H_6NO_6Cl$ requires: N, 6·68%.) Light absorption max at 258 mμ (ε 4100) in water. An additional 3·3 g product was obtained by concentrating the mother liquors to 250 ml, washing with benzene, and adding 1000 ml dry ethyl acetate; total yield 92·0 g (80%).

Spectral observations. The reaction of O-methyl-hydroxylamine (OMH) with glutaconic dialdehyde (GDA) was investigated as follows: A solution containing equimolar quantities of OMH and GDA was examined at various pH in the 365 mμ region (the λ_{max} of NaGDA). The most favourable pH for reaction was ca. 4·75 (at pH 9·15 very little reaction occurs). The spectral observations were themselves made at pH 9 to analyse for unreacted GDA by its intense peak at 365 mμ in alkali. A typical run was as follows: 3·5 ml of $5·49 \times 10^{-3}$ M NaGDA plus 1 ml 2·00 M OMH.HCl were diluted to 100 ml with 0·02 M acetate buffer (pH 4·75). Periodically, 1 ml aliquots were diluted to 10 ml with 0·01 M borax buffer (pH 9·1). Since GDA is itself unstable in acidic media a control of GDA under the same conditions was run concurrently. In 50 min the absorbance shown by the aliquots at 365 mμ dropped from 1·36 to 0·38 O.D. units; the control diminished only by 0·02 O.D. units.

The reaction of N-methoxypyridinium perchlorate with methoxide ion in MeOH was studied by examining the time dependence of spectra of solutions of the perchlorate in methanolic MeONa of strengths from 0·10 to 1·0 N. No absorbance was noted above 275 mμ and the spectrum of the pyridinium salt rapidly changed to that of pyridine (Fig. 1).

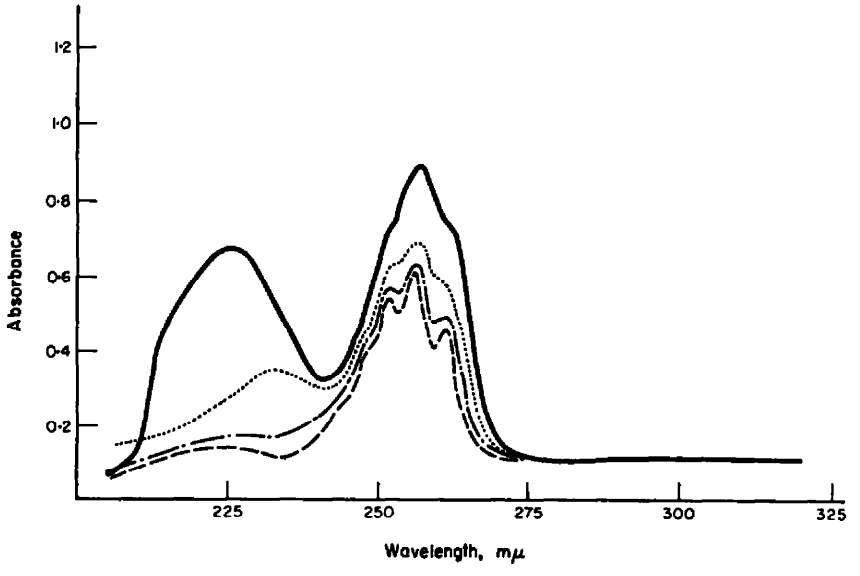


FIG. 1 Variation of the spectrum of N-methoxypyridinium perchlorate with time (initial conc. $2·6 \times 10^{-4}$ M) in 0·50 N methanolic sodium methoxide.
——at 0 min, · · · · · · after 1·5 min,
– · – · – 3 min, – – – 10 min and 30 min

Rate measurements. In preliminary studies, N-methoxypyridinium perchlorate in alkali was found to exhibit a strong absorbance band with λ_{max} at 343 mμ, the intensity of which was time-dependent (Fig. 2). (Acidification caused this peak to disappear.) The rate of development of this peak was dependent on the concentration of both hydroxide ion and the pyridinium salt. The kinetics of this reaction were studied by the method of initial rates. The initial concentration of one of the reactants was held constant while that of the other reactant was varied over a number of runs. At least two runs were made for each initial set of conditions. The NaOH solution (50 ml) was pipetted into the reaction vessel and this, together with the appropriately diluted stock solution of the pyridinium salt

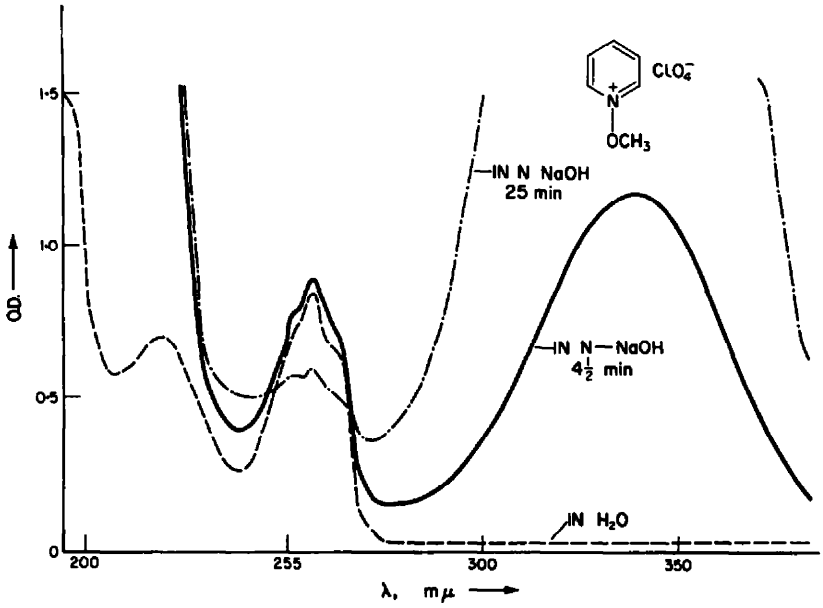


FIG. 2 Action of hydroxide ion on N-methoxypyridinium perchlorate.
– – – in H_2O, – · – · – in N NaOH after 25 min,
——— in N NaOH after 4·5 min.

(substrate), was thermostatted in a water bath at 25·0 ± 0·1° for 1 hr. The substrate solution (5 ml) was transferred to the reaction vessel by pipette, (zero time was taken when half the contents of the pipette were discharged) and the whole rapidly agitated. The reaction was followed in the spectrometer sample cell (Unicam SP 500 with cell holder thermostatted at 25°). Optical density readings at 343 mμ were taken at 30 sec intervals initially, the increment being increased as the rate became smaller.

The initial rates were determined directly from plots of O.D. *vs.* time. The initial portions of these were linear, and a least squares treatment was applied to those points lying along the line. The calculated slope, which differed little from that visually estimated, was taken as the initial rate. The results are given in Table 1.

Detection of intermediate by NMR. The spectra of 1·4 M solutions of N-methoxypyridinium perchlorate were recorded in D_2O and in 2·0 N NaOD. t-Butyl alcohol was employed as internal reference.[19] In D_2O the methoxyl protons absorbed (sharp singlet) at 3·24 ppm downfield from t-BuOH. In NaOD an additional singlet appeared at 2·56 ppm downfield from t-BuOH (Fig. 3). The

TABLE 1. INITIAL RATES FOR THE REACTION OF N-METHOXYPYRIDINIUM PERCHLORATE WITH SODIUM HYDROXIDE IN WATER AT 25°

Initial concentrations (moles/l) $[C_5H_5NOCH_3^+] \times 10^5$	$[OH^-] \times 10$	No. runs	Average initial rate (O.D. units/sec)	% mean deviation
8·119	2·593	2	$1·518 \times 10^{-4}$	1·0
8·119	4·673	2	$4·814 \times 10^{-4}$	0·5
8·119	7·408	3	$1·087 \times 10^{-3}$	1·2
8·119	14·8	3	$3·919 \times 10^{-3}$	1·4
8·119	9·673	4	$1·843 \times 10^{-3}$	1·6
4·060	9·673	2	$9·346 \times 10^{-4}$	0·7
1·624	9·673	2	$3·706 \times 10^{-4}$	0·3

[19] R. A. Y. Jones, A. R. Katritzky, J. N. Murrell and N. Sheppard, *J. Chem. Soc.* 2576 (1962).

methoxyl peak of spectra of OMH·HCl in D_2O and NaOD appeared at 2·70 and 2·36 ppm (downfield from t-BuOH) respectively.

Trapping of intermediate. 50% NaOH aq (24 g) was added to 2·1 g (0·01 mole) N-methoxypyridinium perchlorate and 10·4 g (0·08 mole) aniline hydrochloride in 40 ml water at 0°, with stirring. After 20 sec the deep red mixture was made strongly acidic by the addition of 40 ml conc. HCl aq. The resulting ppt, a partially solidified reddish-black gum with a green lustre (1·2 g) was dried in air,

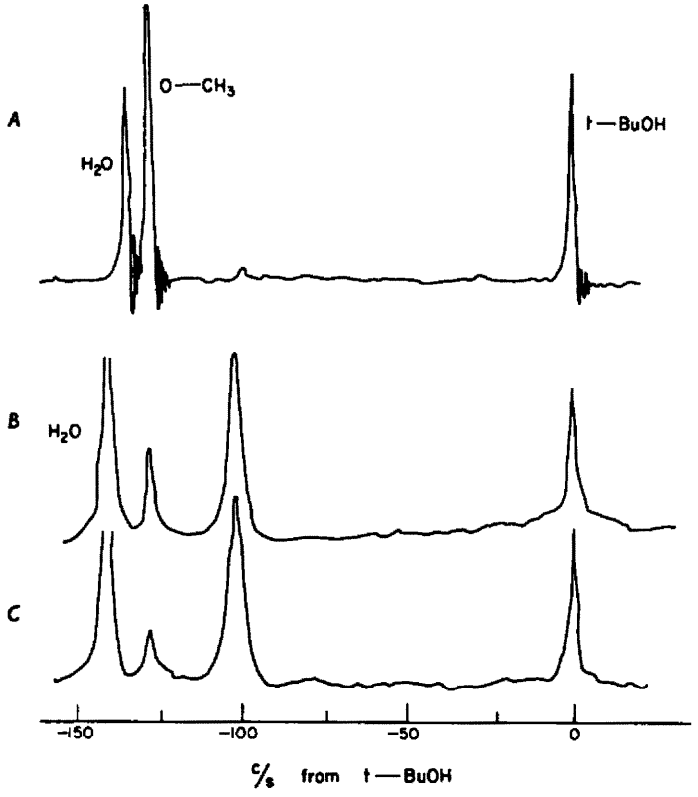


FIG. 3 40 Mc NMR spectra of N-methoxypyridinium perchlorate; (int. ref. t-butyl alcohol): *A* in D_2O; *B* in 2·0 N NaOD after ~3 min *C* in 2·0 N NaOD after ~7 min.

and ground with small quantities of warm acetone. The acetone extracts were cooled and filtered leaving a residue of 150 mg of carmine crystals of the hydrochloride of glutaconic aldehyde dianil, m.p. 168° (lit.[20] m.p. 165–167°). The UV spectrum in EtOH (containing a trace of HCl) had λ_{max} 496 mμ[21] (log ε, 4·81): no reaction was noted between N-methoxypyridinium perchlorate and aniline at room temp in the absence of added hydroxide.

RESULTS

The kinetics of the appearance of the 343 mμ peak could not be determined directly since the molar extinction coefficient is not known. If the absorption at 343 mμ is due to a single substance and follows Beer's Law, the rate expression is

[20] A. E. van Dormall and J. Nys, *Bull. Soc. Chim. Belg.* **61**, 614 (1952); *Chem. Abstr.* **48**, 7005 (1954).
[21] W. König, *Z. Angew. Chem.* **38**, 743 (1925).

given by Eq. 1. Then, from Eq. 2, log-log plots (Fig. 4) of the two sets of data, i.e. in which $[OH^-]$ or $[Py^+]$ was varied, the other being held constant, are

$$\text{rate} = k_{obs}[OH^-]^n[Py^+]^m \text{ where } [Py^+] = [C_6H_5N^+OMe] \qquad \text{Eq. 1.}$$

$$\log \text{rate} = \log k_{obs} + n \log [OH^-] + m \log [Py^+] \qquad \text{Eq. 2.}$$

linear of slope n or m respectively. The calculated slopes gave values for the order of the reaction of 1·9 with respect to hydroxide, and 1·0 with respect to the pyridinium

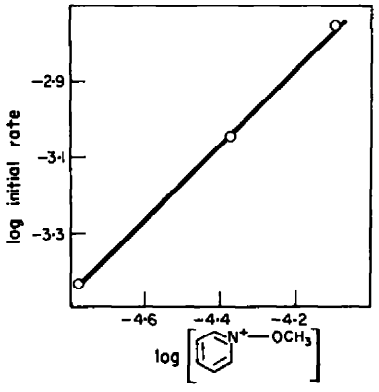


FIG. 4a Log-log plot of initial rate *vs.* conc. of N-methoxypyridinium perchlorate. Hydroxide ion conc. held constant at 9·673 × 10^{-1} M

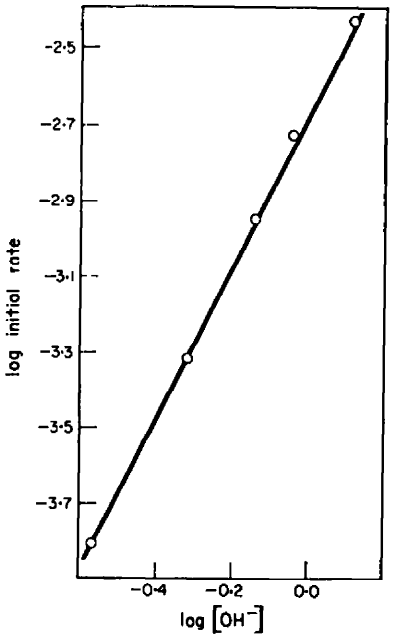
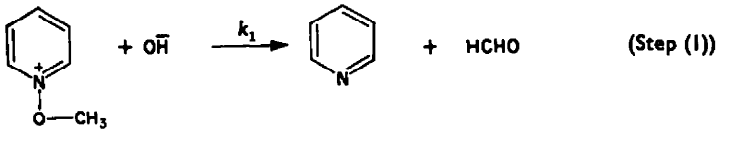


FIG. 4b Log-log plot of initial rate *vs.* conc. of hydroxide ion. Conc. of N-methoxypyridinium perchlorate held constant at 8·119 × 10^{-5} M

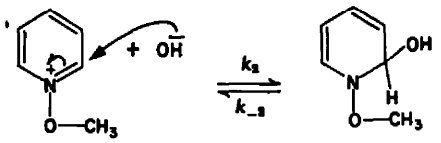
salt (correlation coefficients for both plots > 0·99). A check on the validity of the method was made by comparison of the k_{obs} values which can be calculated from the y-intercept for each set of data: the rate data at constant $[OH^-]$ and constant $[Py^+]$ gave k_{obs} values of 23·0 and 23·7 respectively.

DISCUSSION

The available evidence is rationalized by the following mechanism:

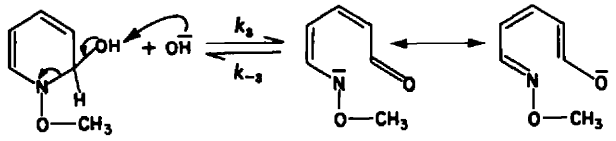


I



(Step (2))

II

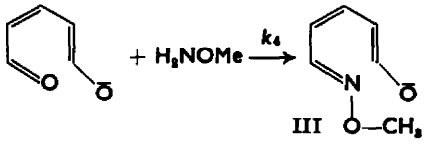


(Step (3))

III

Step (1) is identical with Path A, Chart I, and is irreversible. The strong transient absorbance which appears at 343 mμ in alkaline solution is ascribed to the intermediate III, the enolate of the O-methyl ether of glutaconic aldehyde mono-oxime. The postulation of III rather than II as the moiety exhibiting the 343 mμ peak is consistent with the predicted behaviour of the chromophore of III. The sodium enolate of glutaconic dialdehyde has λ_{max} at 365 mμ; in chromophores of this type, replacement of $-\overset{|}{C}=O$ by $-\overset{|}{C}=NH$ usually results in hypsochromic shifts of about 35 mμ.[22] The inductive effect of the methoxy group would tend to lessen this shift. Unfortunately no direct comparison can be made as regards the predicted absorbance of II since simple 1,2-dihydropyridine derivatives analogous to II have not been studied.[23]

Glutaconic aldehyde reacts with O-methylhydroxylamine (OMH) at pH 4·75 to yield III (Step 4) but examination of the product mixture at p H9 reveals



Step (4)

that further reaction proceeds rapidly through II to I (as shown by the lack of absorption at 343 mμ). This indicates that at pH 4·7 the reversal of steps (2) and (3) is rapid compared with forward reaction (4). That (2) and (3) are rapidly reversed at pH 4·7 is also shown by the observation that acidification of alkaline solutions of N-methoxypyridinium salts results in loss of the 343 mμ absorption and regeneration of the spectrum of I. The forward reactions, (2) and (3), were shown experimentally to be too slow to be observed at pH 9, or indeed at any pH < 12.

Conventional kinetic measurement of the reaction would be very complex owing to the reversibility of steps (2) and (3) and the occurrence of the irreversible side reaction (1). We therefore used the initial rate method, since all steps other than those

[22] A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy* p. 113, Edward Arnold, London (1954).

[23] The absorption, in the 350 mμ region, of dihydropyridines containing a conjugated electron withdrawing group in the 3-position is well known to be due to the $-\overset{|}{N}-\left(-\overset{|}{C}=\overset{|}{C}-\right)_2-\overset{|}{O}=C$ chromophore.[8]

represented by k_2, k_{-2} and k_3 can be neglected. Thus, in terms of initial rates, Eq. 3 can be taken as the rate expression.[24]

$$\frac{d[III]}{dt} = \frac{k_2 k_3 [I][OH^-]^2}{k_{-2} + k_3[OH^-]} \qquad \text{Eq. 3.}$$

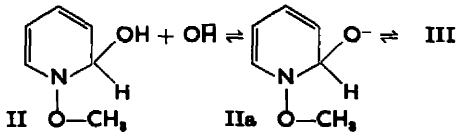
If $k_{-2} \gg k_3[OH^-]$, Eq. (3) becomes rate $= k_2 k_3 [I][OH^-]^2/k_{-2}$ which is entirely consistent with the observed kinetics, where $k_{obs} = k_2 k_3/k_{-2}$. (The slightly low value of order 1·9 in hydroxide may be due to an insufficiently large difference in magnitude between k_{-2} and $k_3[OH^-]$.[25]) The kinetic study of a related reaction, that of aromatic amines with N-2,4-dinitrophenylpyridinium chloride, led to similar mechanistic conclusions.[26]

The UV spectrum of I in methanolic sodium methoxide (Fig. 1) was rapidly converted to that of pyridine. No absorption above 275 mμ was observed. The reaction of methoxide with I is fast compared with that of hydroxide with I. This is to be expected because of the difficulty of a step corresponding to (3) occurring with methoxide. Significantly, the ratio of the absorbances at λ_{max} at the beginning and the end of the reaction is identical to the ratio of the ε_{max} values of I and pyridine. This ability to confine the general reaction of N-alkoxypyridinium salts with base completely to Path A by proper choice of reagent offers attractive possibilities for widening the scope of the reaction as a synthetic tool.[27]

Detection of the intermediate (III) by NMR was based on the fact that in going from I to II to III, the nitrogen atom becomes progressively more negatively charged. The consequent change in the inductive effect will cause the methoxyl protons to become more highly shielded. Provided that equilibration between I and III is not too rapid, the NMR spectrum in base will exhibit a second methoxyl peak at higher field than the methoxyl peak in the pyridinium salt. The spectra are shown in Fig. 3. The new methoxyl peak is assigned to the methoxy group in III rather than II, since the kinetic results indicate that there will be very little II present at any given time. The expected direction of shift of the methoxy peak was verified by comparison with the spectra of OMH in acidic and basic solution (Experimental).

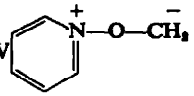
[24] Eq. 3 is derived on the basis of the assumptions made above utilizing a steady-state approximation for the concentration of intermediate II.

[25] An additional refinement, which is neither excluded nor required by the available data, is the involvement of IIa, the valence tautomer of III, as a reactive intermediate such that



If IIa and III are in rapid equilibrium, the involvement of IIa would not be kinetically observable.

[26] E. Dunghan, J. Nasielski and P. von Laer, *Bull. Soc. Chim. Belg.* **66**, 661 (1957).

[27] As regards the mechanism of Path A, it is not known whether the zwitterion IV 

is involved as a discrete intermediate or if proton abstraction and N—O bond cleavage are synchronous.

In analogy to early work with pyridinium-N-sulphonate and related compounds,[12,28] attempts were made to trap intermediate III as the sodium salt, barium salt, benzoyl derivative or dianil. Only the dianil was isolable, and that in very low yield and accompanied by a large amount of gum. The occurrence of tarry materials was frequently encountered in working with I in alkaline media; glutaconic aldehyde derivatives and dihydropyridines are known to polymerise readily.[28,29]

The occurrence of ring opening reactions of pyridine-N-oxide derivatives may be more widespread than is normally apparent. For example, in a study of reaction Path C, a number of organic bases of widely varying types (e.g. Grignard reagents, amines, carboxylate salts) was caused to react with N-methoxypyridinium tosylate.[4] The yields of pyridine-N-oxide varied between 15 and 30%. However, hydroxylamine was found to give a 55% yield of pyridine-N-oxide. This anomolous result could well be indicative of the operation of a different mechanism, *viz.* Path D, involving ring opening, condensation with hydroxylamine, and ring closure with elimination of OMH. Work currently in progress in this laboratory indicates that this type of reaction may be fairly general.

Acknowledgement—We are pleased to acknowledge the support of this work by the U.S. Public Health Service through a National Institutes of Health Postdoctoral Fellowship, no. CPD-15, 745, to R. E.

[28] P. Baumgarten, L. Merlander, and H. Olshausen, *Ber. Dtsh. Chem. Ges.* **66**, 1802 (1933).

[29] E. N. Shaw, ch. III, *Pyridine and Its Derivatives, Part Two* (Edited by E. Klingsberg) p. 47. Interscience, New York (1961).