THE JOURNAL OF Organic Chemistry®

VOLUME 44, NUMBER 11

MAY 25, 1979

Flow Nuclear Magnetic Resonance Investigation of the Intermediates Formed by the Attack of Alkoxide Ions on Substituted Pyridinium Ions[1,2]

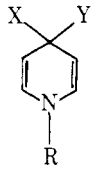
S. W. H. Damji[3] and C. A. Fyfe*

Guelph-Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, University of Guelph, Guelph, Ontario, Canada N1G2W1

Received November 7, 1977

High-resolution flow NMR has been used to detect and to characterize the intermediates formed by the attack of alkoxide ions on substituted pyridinium ions in Me_2SO–methanol solution. The kinetic and thermodynamic distributions of the 1,2 and 1,4 isomers have been determined and the UV–visible spectra of both species have been assigned. The results are discussed with respect to literature data concerning the orientation of the attack of nucleophiles on pyridinium ions.

Pyridinium ions undergo nucleophilic aromatic substitution reactions, the quaternary nitrogen being a very powerful activating group. Because the substrate is positively charged, the intermediate formed in these reactions is neutral, of the general type of structure **1**.



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There has been considerable interest in the attack of nucleophiles on pyridinium ions to yield species of type 1 and the analogous complexes formed by attack in the 2 and 6 positions, due, in part at least, to the biological importance of the reduction of nicotinamide adenine dinucleotide (NAD) in combination with an appropriate coenzyme by a whole variety of substrates to yield a 1,4-dihydropyridine system.

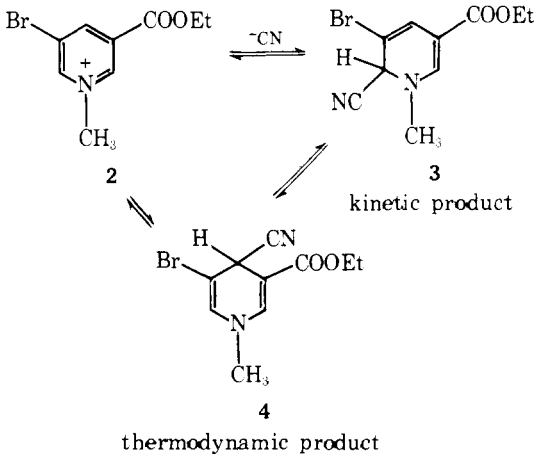
A wide variety of behavior in terms of the position of attack of nucleophiles on the pyridinium ring system has been described,[4] some nucleophiles being reported to yield 1,2-dihydropyridines, and others exclusively 1,4-dihydropyridines. In an attempt to rationalize the literature data on these systems, Kosower[5] related the position of attack by a nucleophile to the possible intermediacy of a "charge-transfer" complex prior to the attack. He postulated that nucleophiles with a low ionization potential which might be expected to easily form such complexes added to the ring at the 4 position, while those nucleophiles which probably would not form such complexes added at the 2 or 6 positions. An alternative explanation correlating the position of attack with the "hardness" or "softness" of the nucleophile has more recently been advanced.[7]

A further complication in these reactions is illustrated by work on the attack of cyanide ion on substituted pyridinium ions.[7,8] In the case of 5-bromo-3-carbomethoxypyridinium methoiodide it was found[7,8] that the attack occurred at the 6 position to yield **3** which subsequently rearranged to give the thermodynamically stable 1,4-isomer **4** (Scheme I).

No such isomerization was observed for 3-X-substituted derivatives, but it was also reported for the attack of cyanide ion on 3,5-dicyano-1-methylpyridinium tosylate.[9,10]

Lyle and Gauthier[7] have argued that these observations represent a general mechanism for the reaction, i.e., that the 6 isomer is always produced under kinetic control, and subsequently rearranges to the more stable 4 isomer, and that the necessity, with cyanide ion at least, of postulating the intermediacy of charge-transfer complexes as suggested by Kosower is eliminated. However, the factors governing the distribution of isomers are not at present clear.[8] Thus, those stabilizing factors which allow for detection of 1,6-isomers

Scheme I



2 3 kinetic product

4 thermodynamic product

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may, in fact, induce their occurrence in the first place, and it may well be wrong to conclude that 1,2 and 1,6 isomers are formed in all cases.[8]

In this and the succeeding paper, we have employed two different but complementary approaches to try and determine if isomerization processes are of general occurrence in these systems or if there is any direct evidence for specific interactions which determine the position of attack.

We have developed the technique of flow NMR[1,11] which enables high-resolution NMR spectra to be recorded on flowing, chemically reacting systems and have used it to detect transient species in several different types of reaction.[12-18] In the present work, we have applied this technique and the previously described equipment to the investigation of the reaction of alkoxide ions with pyridinium ions in Me_2SO–methanol solution. This particular system was chosen because all of the species involved in the reaction are soluble in the solvent system, and it is possible to measure all the spectra "in situ" without any ambiguities which might arise through isolation procedures.

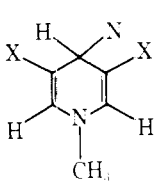
Experimental Section

Chemicals were from commercial sources or were prepared by literature methods and had melting points and/or spectral data consistent with their proposed structures.

Flow NMR and flow UV spectra were obtained using the equipment previously described[1,11] which was thermostated at 30 °C. The basic NMR spectrometer was a Varian H.A. 100 and the basic UV–vis spectrophotometer was a Unicam SP800. Microanalyses were carried out in the department and mass spectra were run on a Varian CH7 mass spectrometer.

Results and Discussion

A. Structure Determination: Orientation of Attack. UV–vis spectroscopy is a relatively nondiagnostic technique, and at least part of the problem with the variety of products which have been reported in the literature is that in most cases structural assignments have been made on the basis of UV–vis spectra. High-resolution NMR is much more diagnostic, but in some cases the spectra can still be ambiguous. For a symmetrically 3,5-disubstituted pyridinium ion, the two isomeric products **5** and **6** produced by the attack of a nucleophile N^-



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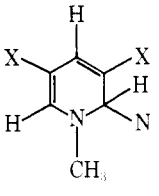

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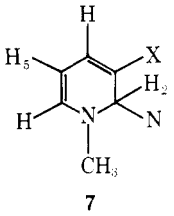
can be clearly differentiated on the basis of their NMR spectra; thus, **5** will exhibit two signals in the ratio of 2:1 at predictable chemical shift values and **6** will exhibit three signals in the ratios of 1:1:1, again at roughly predictable chemical shifts.

With 3-substituted pyridinium ions, the situation is more complex. The three possible isomers that may be formed are **7–9**. **7** may be easily distinguished from **8** and **9** by the occurrence of the signal due to H_2 (which will be only slightly coupled into the other nuclei) at relatively high field since it is



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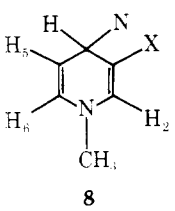

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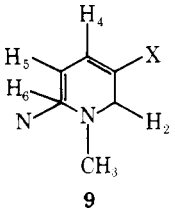

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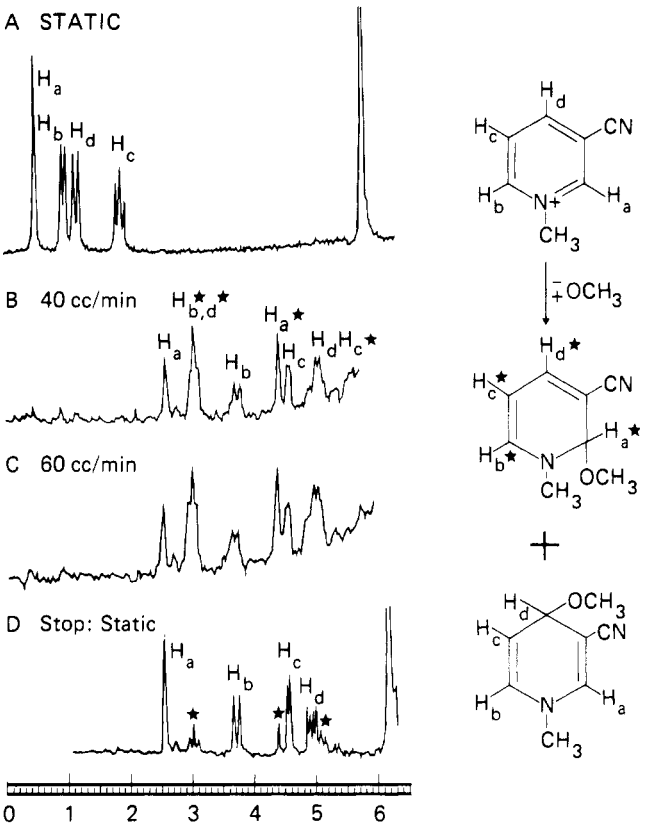
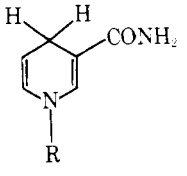


Figure 1. Static and flow 100 MHz ^1H NMR spectra of 3-cyanopyridinium methiodide (0.5 M in Me_2SO) during its reaction with methoxide ion (0.5 M in 87.5% Me_2SO–12.5% MeOH) at 30 °C: (A) static spectrum of 3-cyanopyridinium methiodide (0.5 M in Me_2SO); (B) flow spectrum, 0.79 s after mixing; (C) flow spectrum, 0.52 s after mixing; (D) static spectrum, 10 min after mixing.

attached to an sp^3 hybridized carbon. Not so obvious is the fact that it will not, in general, be possible to distinguish **8** and **9** on the basis of their NMR spectra. Thus, the signals due to H_4, H_2, H_5, and H_6 in **8** would occur at similar chemical shift values to those of H_6, H_2, H_5, and H_4 in **9**. We have made this distinction by specifically deuterating various positions in the pyridinium ion substrates and identifying these in the product spectra. However, an unambiguous structure assignment must at some point still be made to deduce the position of the deuterium incorporation. This unambiguous assignment comes from the X-ray structure determination of the product of the dithionite reduction of *N*-benzylnicotinamide as **10**[19] with R = benzyl and *N*-propylnicotinamide as **10** with R =



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propyl,[20] i.e., in this reaction the reduction is definitely in the 4 position. By performing the reduction of N-substituted 3-cyanopyridinium iodides with dithionite in D_2O and oxidizing the resulting 1,4-dihydropyridines back to the pyridinium ions, position 4 may be identified in these and in any adducts subsequently produced, thus differentiating clearly between **8** and **9**. The deuteration was performed by four successive oxidation–reduction cycles for the substrates studied. It was also checked by using these 4-deuterated substrates that deuteration by sodium carbonate in D_2O yielded deuterium

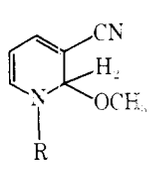
Table I. Kinetic and Thermodynamic Parameters for the Reaction of Methoxide Ion with Pyridinium Ion Substrates in 94% Me_2SO–6% MeOH at 30 °C

substrate	registry no.	% of 1,2 isomer[a] $t = 0$	% of 1,2 isomer[a] at equil	% of 1,4 isomer[a] $t = 0$	% of 1,4 isomer[a] at equil	k_3,[b] s^{-1}	k_{-3},[b] s^{-1}	K_3[c]
3,5-dichloropyridinium methiodide	23029-86-9	97.5[e]	68.5	2.5[f]	31.5	7.20×10^{-3}	1.58×10^{-2}	0.460
N-benzyl-3,5-dichloropyridinium chloride	68843-55-0	84.1	45.1	15.9[h]	54.9	1.748×10^{-3}	1.436×10^{-3}	1.217
3-cyanopyridinium methiodide	1004-16-6	58[i]	20	42[j]	80	9.07×10^{-3}	2.27×10^{-3}	4.0
N-benzyl-3-cyanopyridinium chloride[d]	14535-08-1	45.2[k]	17	35.8[l]	64	8.5×10^{-3}	2.26×10^{-3}	3.76

[a] Estimated error = ±5%. [b] Estimated error = ±10%. [c] Estimated error = ±7%. [d] 1,6 isomer also present in mixture. [e] Registry no. 68854-40-0. [f] Registry no. 68854-41-1. [g] Registry no. 68854-42-2. [h] Registry no. 68854-43-3. [i] Registry no. 68854-44-4. [j] Registry no. 68854-45-5. [k] Registry no. 68854-46-6. [l] Registry no. 68854-47-7.

in the 2 and 6 positions as previously assumed.[8] In practice, this is a much simpler procedure which enables the same distinction between **8** and **9** to be made.

B. Reaction of 3-Cyanopyridinium Iodides (0.5 M in Me_2SO) with Methoxide Ion (0.5 M in 87.5% Me_2SO–12.5% MeOH). Figure 1 shows the spectra recorded under static and flowing conditions for the reaction of 3-cyanopyridinium methiodide. The top spectrum shows the ring proton signals of the substrate before reaction. The second spectrum is recorded under flowing conditions at a flow rate of 40 mL/min (0.79 s after mixing). There has been the immediate disappearance of the absorptions due to the pyridinium ion and the appearance of a new set of absorptions at higher fields.



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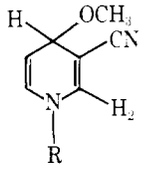

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As the flow rate is increased, that is the time between mixing and observation decreased, the relative intensities of the peaks in the spectrum change, reaching the limiting situation shown in spectrum C. The spectrum changes on stopping the flow to yield the equilibrium situation shown in the spectrum D.

The final, equilibrium spectrum may be interpreted as being due to mainly the two isomers **11** and **12**, R = CH_3, as indicated. As discussed above, the assignments can be checked by the use of specifically deuterated substrates. Particularly important in the assignments is the identification of the position of the H_2 resonances. In isomer **11** (R = CH_3) the H_2 resonance occurs at δ 5.70, whereas in isomer **12** (R = CH_3) it occurs at much lower fields, δ 7.53. There is also a small signal at δ 7.35 due to the presence of a small amount (6% assuming it is due to a single proton) of another species. The concentration of this species remains constant, and it has not been included in the kinetic analyses.

From a comparison of the spectra in Figure 1 it is evident that both isomers **11** and **12**, R = CH_3, are present in both the kinetic and thermodynamically controlled mixtures. Further, the composition of the mixture changes in favor of the 1,4 isomer.

The change from kinetic to thermodynamic control is slow enough that it can be followed by stopping the flow and quickly and repeatedly scanning a small spectral region containing absorptions from both isomers. The sum of the concentrations of **12** (R = CH_3) and **11** (R = CH_3) and the data give a good first-order plot (Figure 2) from which reasonable kinetic data may be obtained. These are given in Table I.

Very similar spectral changes are observed in the reaction of *N*-benzyl-3-cyanopyridinium chloride under these conditions: Both isomers are again formed under kinetic control and

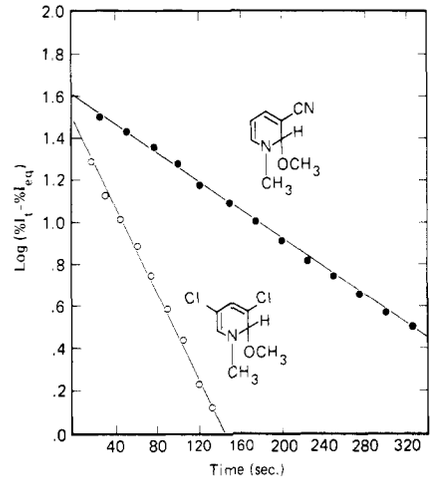
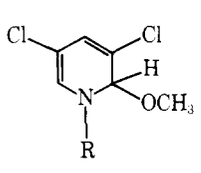


Figure 2. Plot of log $]11_t - 11_{eq}]$ against time (s) for the decrease in the proton resonance signal of the H_2 hydrogen in the 1,2 isomer **11**, R = CH_3, formed by the attack of methoxide ion on 3-cyanopyridinium methiodide (A) and for the decrease in the H_2 hydrogen in the 1,2 isomer **13**, R = CH_3, formed by the attack of methoxide ion on 3,5-dichloropyridinium methiodide (B). The solid lines are least-squares fits to the data yielding the kinetic parameters listed in Table I.

the system again adjusts in favor of the 4-substituted isomer **12**, R = benzyl. In this case, the 1,6 isomer is also formed in the reaction, accounting for ~20% of the reaction mixtures formed under both kinetic and thermodynamic control. By using the techniques outlined above, kinetic data relating to the 1,2 and 1,4 isomers may again be obtained. These are presented in Table I.

C. 3,5-Dichloropyridinium Ions (0.5 M in Me_2SO) plus Methoxide Ion (0.5 M in 87.5% Me_2SO–12.5% MeOH). Figure 3 shows the spectral changes in the reaction of 3,5-dichloropyridinium methiodide with methoxide ion. In this case there is no ambiguity about the position of attack, and deuteration of the substrate is not essential. The conclusions were checked, however, by deuteration in the 2 and 6 positions. The top spectrum shows the ring proton absorptions of the dichloropyridinium ion. The middle spectrum was recorded under flowing conditions at a flow rate of 72 mL/min (0.44 s after mixing). On stopping the flow, the spectrum changes to the limiting situation described by the bottom spectrum. In the two lower spectra, both the 1,2 and 1,4 isomers (**13** and **14**,



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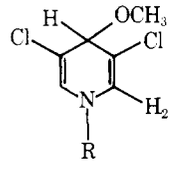

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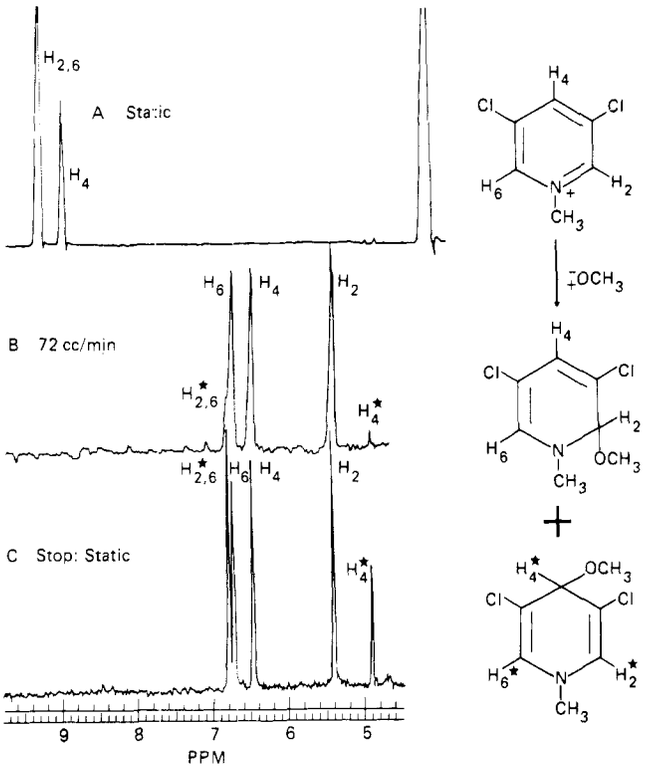
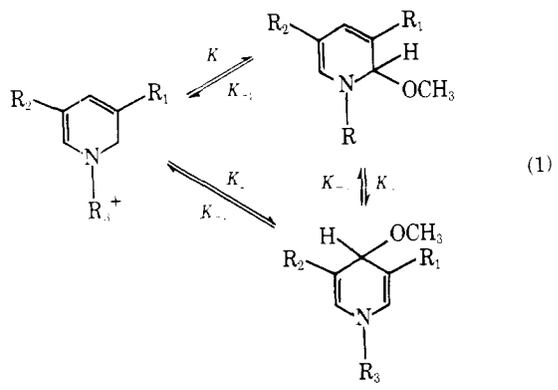


Figure 3. Static and flow 100 MHz ^1H NMR spectra of 3,5-dichloropyridinium methiodide (0.5 M in Me_2SO) during its reaction with methoxide ion (0.5 M in 87.5% Me_2SO–12.5% MeOH) at 30 °C: (A) static spectrum of 3,5-dichloropyridinium methiodide; (B) flow spectrum, 0.44 s after mixing; (C) static spectrum, 10 min after mixing.

R = CH_3) are present. The spectra may be assigned to the two species as indicated in the lowest spectrum. It is clear that again both species are formed under kinetic control and that again the composition of the mixture alters in favor of the 1,4 isomer.

The kinetic profile of the change was obtained by stopping the flow and quickly and repeatedly scanning the region from δ 7.0 to 4.5 which contains absorptions of both species. A good first-order plot was obtained for the isomerization process (Figure 2) and the kinetic and thermodynamic parameters are presented in Table I.



(1)

Very similar spectral changes are observed for the reaction of *N*-benzyl-3,5-dichloropyridinium chloride. Again both isomers were produced under kinetic control and the system again adjusted in favor of the 1,4 isomer **14**, R = benzyl. The data are presented in Table I.

D. Assignment of UV–Vis Spectra. As indicated previously, UV–vis spectroscopy is relatively nondiagnostic, and at least part of the confusion in these systems arises because most structural assignments have been made using this technique. The UV–vis spectra of the systems studied here have been assigned, by recording these spectra under very similar conditions to the flow NMR experiments using a very short path length (~0.1 mm) UV–vis cell. It was not possible to exactly duplicate the concentrations of the flow NMR experiments due to the very high concentrations used in these experiments, but it was possible to make measurements on solutions which were 0.05 M in substrate, and it was checked that there were no large differences in the general spectral profiles observed over a 100-fold range of concentration up to this point.

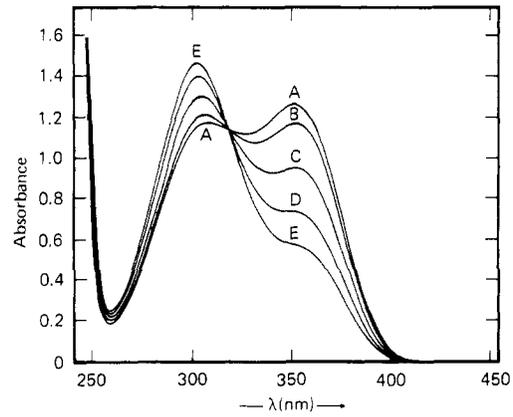


Figure 4. UV–vis spectra of the adducts formed by the addition of methoxide ion (0.05 M in 87.5:12.5 Me_2SO–methanol (v/v)) to 0.05 M 3-cyanopyridinium methiodide in Me_2SO at 30 °C. The spectra were recorded at the following times after mixing: (A) 1 min; (B) 2 min; (C) 5 min; (D) 10 min; (E) 20 min.

Table II. UV–Vis Spectral Data for the Adducts Formed by the Action of Methoxide Ion on 3-Cyano- and 3,5-Dichloropyridinium Ions (30 °C in 94% Me_2SO–6% MeOH)

compd	1,4 isomer λ_1, nm	1,2 isomer λ_2, nm
3-cyanopyridinium methiodide	313	360
N-benzyl-3-cyanopyridinium chloride	276	315
N-benzyl-3,5-dichloropyridinium chloride	276	315

Figure 4 shows the time evolution of the UV–vis spectrum of the reacting solution of 0.05 M 3-cyanopyridinium methiodide in Me_2SO and methoxide ion (0.05 M in 87.5% Me_2SO–12.5% methanol) at 30 °C. Initially there are two absorbances at 313 and 360 nm. The absorption at 360 nm decreases with time with a corresponding increase in the 313 nm absorption, and an isobestic point is observed (Figure 4). On the basis of the NMR data presented above (Table I), the two absorptions may be assigned to the 1,2 isomer (360 nm) and the 1,4 isomer (313 nm). Similar results were obtained for *N*-benzyl-3-cyanopyridinium chloride (1,2 isomer, 315 nm; 1,4 isomer, 276 nm). In both cases, clean isobestic points are observed. One would expect very similar spectral changes for the 3,5-dichloropyridinium methiodide in light of the NMR data on this system (Table I), but very inconsistent results were obtained. It is not at present clear why this system is different from the others studied. The *N*-benzyl-3,5-dichloropyridinium chloride gave clear changes consistent with previous data. The results for the different systems are summarized in Table II.

E. Conclusions. The NMR results clearly indicate that stable σ complexes are formed by the attack of alkoxide ions on the 3-substituted and 3,5-disubstituted pyridinium ions studied. In all cases a *mixture* of the 1,2 and 1,4 isomers is

formed under kinetic control, and this adjusts in favor of the 1,4 isomer to give a different mixture under thermodynamic control. In no case was the exclusive formation of one isomer observed either initially or in the equilibrium mixture. There is an indication that the 1,2 isomer is less favored for the *N*-benzyl derivatives compared to the corresponding *N*-methyl derivatives both initially and in the equilibrium mixtures, which may be due to steric interactions. However, it should be noted that only very small differences in energy would be needed to cause these changes.

In all cases, the 1,2 isomer absorbs at higher wavelength than the 1,4 isomer and both isomers show single absorptions. It is thought that one of the most important applications of the flow NMR technique has been the unambiguous assignment of UV–vis absorptions which now makes possible kinetic studies in dilute, ideal solutions.

Acknowledgments. The authors would like to thank the National Research Council of Canada for a grant in aid of research (C.A.F.) and the Canadian Government for the award of a Commonwealth Fellowship (S.W.H.D.). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (C.A.F.).

Registry No.—Methoxide, 2143-68-2.

References and Notes

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Nuclear Magnetic Resonance Investigation of the Adducts Formed by the Attack of Carbanions on Substituted Pyridinium Ions[1,2]

S. W. H. Damji,[3] C. A. Fyfe,* D. Smith, and F. J. Sharom

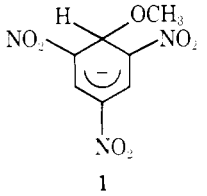
Guelph-Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, University of Guelph, Guelph, Ontario, Canada N1G2W1

Received November 7, 1977

High-resolution NMR has been used to characterize the adducts formed by the attack of nitroalkane carbanions on 3-substituted and 3,5-disubstituted pyridinium ions in aqueous solution and to assign their UV–vis spectra. In all cases studied, only the 1,4-dihydro compound formed by attack of the nucleophile at the 4 position in the ring was found, suggestive of either a very fast isomerization and extreme thermodynamic stability of the 1,4-dihydro compound or a specific interaction between the pyridinium cation and the attacking nucleophile which yields only a single isomer under kinetic control.

In the previous paper we have presented the results of a flow NMR investigation of the attack of alkoxide ions on substituted pyridinium ions carried out to try to determine the relationship between the kinetic and thermodynamic distributions of the isomers formed. It was found that a mixture of 1,2 and 1,4 isomers was formed under kinetic control and that this adjusted in favor of the 1,4 isomer to give the final thermodynamically stable mixture of isomers. In the present paper we present the results of another approach to this problem using the carbanions formed from nitroalkanes as the attacking nucleophiles where it was hoped, on the basis of previous work on nitroaromatic compounds, that there would be no further reaction of the mixture formed under kinetic control.

There exist several examples of the relative stability of the adducts of carbanions with nitroaromatics: Thus, the methoxide adduct **1** of 1,3,5-trinitrobenzene will react with acetone to produce the corresponding acetonate ion adduct **2**, but this reaction cannot be reversed, nor is there any exchange with CD_3COCD_3 even in the presence of base.[4] Similar reactions are observed with the adducts formed by attack of carbanions formed from nitroalkanes.[5]



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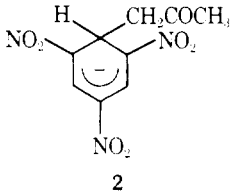

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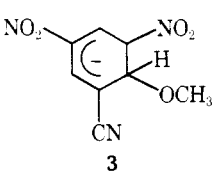
Further, if an unsymmetrical nitroaromatic is used, e.g., 3,5-dinitrocyanobenzene, attack of alkoxide ion yields the thermodynamically stable mixture of isomers, in this case almost exclusively the isomer **3**.[6] It has more recently been shown by stopped-flow UV–vis spectroscopy and flow NMR spectroscopy that under kinetic control a mixture of the two isomers **3** and **4** is in fact formed which then extremely rapidly



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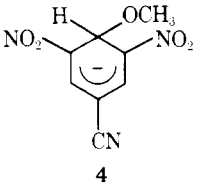

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