Nitration of Pyridine Compounds. The Reaction of N-Nitro-1,4-dihydro-4-pyridinesulfonic Acid

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The reactions of N-nitropropyridinium nitrate (1) and 2,6-dideuterio-N-nitropyridinium nitrate (2,6-d$_2$-1) with SO$_2$H$_2$O-HSO$_3$ have been studied. The results are consistent with a reaction scheme in which the formed N-nitro-1,4-dihydro-4-pyridinesulfonic acid (2) did not react directly to give 3-nitropyridine but existed in equilibrium with 1 and 2,6-d$_2$-1 from which N-nitro-1,2-dihydro-2-pyridinesulfonic acid (3) was formed. From 3, 3-nitropyridine was formed by a [1,5] sigmatropic shift of the nitro group.

The successful nitration of pyridine compounds has been achieved by first reacting the substrate with dinitrogen pentoxide (N$_2$O$_5$) in an organic solvent and then mixing the resulting N-nitropropyridinium nitrate (1) with an aqueous solution of SO$_2$H$_2$O-HSO$_3$$. In the water phase, two unstable compounds, the 1,4-dihydro- (2) and 1,2-dihydropyridine (3) derivatives were formed (Scheme 1). Both these reacted further and 3-nitropyridine (6) was formed as the end product. Compound 3 reacted much faster than 2 and at room temperature only 2 was observed. We have presented evidence which indicates that 3 reacts by a [1,5] sigmatropic shift of the nitro group to give the 3-nitro-2,3-dihydropyridine derivative 4. This reacts further to give the tetrahydropyridine compound 5 which finally gives 3-nitropyridine (6). For 2, a sigmatropic shift of the nitro group is not possible for symmetry reasons. The migration of the nitro group from the 1- to the 3-position would therefore have to be by migration of either a nitronium ion or a NO$_2$ radical in a solvent cage. The rate of reaction of the intermediate 2 was not influenced by the polarity of the reaction medium and reaction by an ion pair in a solvent cage therefore appeared less likely. Reaction by radical pairs on the other hand has been shown to take place in many cases for compounds derived from aromatic systems, for instance for the nitramine rearrangement$^3$ and for the nitrocyclohexadienones.$^4$ A third possibility would be that nitro group migration does not take place for the 1,4-dihydropyridine derivative 2 but, instead, formation of 2 from the N-nitropropyridinium ion is reversible and

Scheme 1.

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that 3-nitropyridine is formed from the 1,2-dihydropyr-
idine derivative 3 by a [1,5] sigmatropic shift.

The objective of the present investigation was to
determine which of the two possible reaction paths was
the most likely, either directly to 3-nitropyridine or by
the reversible formation of 3 (Scheme 1). As 3 reacted
faster than 2 under all conditions, we were not able to
study this by the conversion of 2 into 3.

Attempts to establish the reversible reactions of 2 and
3 by saturation transfer NMR experiments were
inconclusive.1

Results and discussion

The reaction 2→3 would presumably go by reversible
reactions via the N-nitropyridinium ion 1. N-Nitopy-
ridinium nitrate has been shown to be a relatively
stable compound which precipitates from dichlorometh-
ane on its formation from pyridine and N₂O₅. From this
suspension 1 could be isolated by rapid filtration and
kept as a solid under nitrogen at −20°C for several
days. This fact made it possible to set up the following
experiments.

Solutions containing equimolar amounts of N-
nitropyridinium nitrate and NaHSO₄ in 1H₂O–3H₂O–OH
1:1 were mixed at −40°C. Immediately after this, an
equimolecular amount of 2,6-dideuterio-N-nitropyri-
dinium nitrate (2,6-d₂-1) was added to the solution. The
reaction was then monitored by ¹H NMR spectroscopy
at −22°C. The progress of the reaction was estimated
from the concentration of each compound and from the
incorporation of deuterium into the 2- and 6-positions
of 2 and 3. This incorporation was assessed from the
ratios of the integrals of the signals from the protons in
the 2- or 6-positions of the pyridine ring to those from
the protons in the 3-, 4- or 5-positions. For each com-
pound the signals with the least, or preferably no, overlap
with other signals were used for the estimates. 2,4,6-
Trimethylpyridine was used as an internal standard to
determine the concentration of each compound. The
results are summarised in Table 1. Minor by-products
such as pyridine and 3-pyridinesulfonic acid are not
listed. The precision of the measurements was limited by
the accuracy of the integration of the NMR signals.
Furthermore, we were not able to determine the absolute
purity of 1 and 2,6-d₂-1 as these were precipitated from
dichloromethane but could not be recrystallised owing
to their instability. Because of these points the concentra-
tions of deuterated and non-deuterated compounds
were not exactly equal.

The results in Table 1 show that deuterium was incor-
porated from 2,6-d₂-1 into positions 2 and 6 of both
compounds 2 and 3 and also that the equilibration of 1,
2, 3 and their 2,6-dideuterated analogues was not rapid
on the timescale of the experiment. However, this incor-
poration of deuterium was not unambiguous evidence for
the reversibility of the formation of these compounds
as SO₃·xH₂O–H₂SO₄⁻ formed by the formation of
3-nitropyridine might have reacted with 2,6-d₂-1
(Scheme 1).1

However, the change in the ratio [1][2,6-d₂-1] gave
strong evidence for the reversible formation of 3. If no
reversible reaction took place, this ratio would be con-
stant during the reaction. But Table 1 shows that this
ratio increased during the reaction, a point which can
only be explained by the reversible formation of 1.
However, as the concentration of 2,6-d₂-2 and 2 increased
during the reaction, the reversibility of the formation 2
was not proved by this result.

We therefore performed an additional experiment. To
an aqueous solution of SO₃·xH₂O–H₂SO₄⁻ at room tem-
perture and pH 1.0 was added compound 1. At this
pH, the formation of 2 from 1 is favoured over that of
3.1 To this mixture was then added an equimolecular
amount of 2,6-d₂-1 and the reaction monitored by ¹H
NMR spectroscopy at 21°C. Under these conditions,
compound 2 reacted at a measurable rate and 3 too fast
to be observed. The variations in the concentrations of
1, 2,6-d₂-1, 2, 2,6-d₂-2, 6 and 2,6-d₂-6 are shown in Fig. 1.
From the increase in the concentration of 1 it is clear
that the reaction 1→2 is reversible, as shown in Scheme 1.
This point was not clear from the first experiment.
Nevertheless, from this alone, the direct reaction of 2 to
3-nitropyridine was not excluded.

However, a closer study of the data presented in Fig. 1
further information on this point. We have shown

| Table 1. Variations with time of the concentrations of the compounds present in the reactions of N-nitropyridinium nitrate and 2,6-dideuterio-N-nitropyridinium nitrate with sodium bisulphite. |
|---|---|---|---|---|---|
| t/min | 1 | 2,6-d₂-1 | 2 | 2,6-d₂-2 | 3 | 2,6-d₂-3 | 6 |
| 0 | 5.1 | 36.1 | 5.5 | 2.6 | 34.0 | 15.5 | 1.2 |
| 14 | 5.7 | 33.2 | 5.9 | 2.6 | 32.9 | 16.5 | 2.6 |
| 34 | 7.1 | 28.7 | 6.2 | 2.6 | 27.7 | 18.6 | 8.0 |
| 54 | 7.9 | 24.3 | 6.3 | 2.6 | 23.6 | 19.7 | 12.8 |
| 75 | 8.2 | 20.4 | 6.8 | 2.6 | 20.6 | 19.9 | 17.5 |
| 104 | 7.9 | 15.7 | 7.7 | 2.6 | 17.2 | 20.0 | 23.8 |
| 149 | 6.1 | 10.5 | 8.5 | 2.6 | 13.6 | 18.6 | 23.7 |
| 178 | 5.0 | 7.6 | 9.1 | 2.6 | 12.5 | 17.7 | 37.7 |
| 226 | 3.1 | 4.3 | 10.1 | 12.3 | 10.6 | 14.7 | 44.9 |
that the reaction of 2 follows a first-order rate law. The reactions of 1 and 2,6-d_{2}-1 would also follow a pseudo-first-order rate law as [HSO_{4}] would be small and constant during the reaction. If 3-nitropyridine were from either 1 or 2 we would have:

either \( \frac{d[6]}{dt} = k^1[1] \); \( \frac{d[2,6-d_{2}-6]}{dt} = k^3[2,6-d_{2}-1] \)  

or \( \frac{d[6]}{dt} = k^3[2] \); \( \frac{d[2,6-d_{2}-6]}{dt} = k^3[2,6-d_{2}-2] \)  

From the data in Fig. 1 a regression analysis gave polynomial expressions for [6] and [2,6-d_{2}-6]. From these, equations \( \frac{d[6]}{dt} \) and \( \frac{d[2,6-d_{2}-6]}{dt} \) were calculated. The reactions in Scheme 1 did not show primary deuterium kinetic isotope effects. With the precision of the NMR monitoring employed in the present investigation secondary kinetic deuterium isotope effects would not be detected. Therefore, in interpretation of the results

we can set \( k^1 = k^3 \) [eqn. (1)] and \( k^3 = k^4 \) [eqn. (2)]. From eqn. (1) we then obtain:

\( \frac{d[6]}{dt}/\frac{d[2,6-d_{2}-6]}{dt} = \frac{[1]}{[2,6-d_{2}-1]} \)  

and from eqn. (2):

\( \frac{d[6]}{dt}/\frac{d[2,6-d_{2}-6]}{dt} = \frac{[2]}{[2,6-d_{2}-2]} \)  

In Fig. 2 we have plotted \( \frac{d[6]}{dt}/\frac{d[2,6-d_{2}-6]}{dt} \), \( \frac{[1]}{[2,6-d_{2}-1]} \) and \( \frac{[2]}{[2,6-d_{2}-2]} \) as functions of the reaction time. Fig. 2 shows a good correlation of the deuterium content of the formed 3-nitropyridine (6) with that of N-nitropyridinium nitrate, but no correlation with the deuterium content of the 1,4-dihydropyridine derivative 2.

From this it appears reasonable that 3-nitropyridine (6) was formed mainly from the 1,2-dihydropyridine derivative 3 and that the 1,4-dihydropyridine derivative

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**Fig. 1.** Variations in the concentrations of 1, 2,6-d_{2}-1, 2, 2,6-d_{2}-2, 6 and 2,6-d_{2}-6 with time at 21°C.

**Fig. 2.** Variations in the ratios [1]/[2,6-d_{2}-1]; [2]/[2,6-d_{2}-2]; and in (d[6]/dt)/(d[2,6-d_{2}-6]/dt) with time at 21°C.
2 was in equilibrium with 3 via 1. At most, only a part of 2 reacted directly to give 3-nitropyridine. We have shown that the migration of the nitro group did not take place by a nitronium ion in a solvent cage. The results presented here furthermore show that the migration of the nitro group by a radical pair was not an important reaction path for the 1,4-dihydropyridine derivative 2.

The experimental results from the reaction of the 1,2-dihydropyridine derivative 3 can be explained by a [1,5] sigmatropic shift of the nitro group although a reaction by a radical pair is not excluded. The present results indicate that the reaction by a radical pair is not important for the 1,4-dihydropyridine derivative 2 for which a sigmatropic shift was not possible. The radical pair reaction path may also not be important for the reaction of 3 as a [1,5] sigmatropic shift would be possible for this compound.

Experimental

The spectroscopic and chromatographic equipment used have been described. Dinitrogen pentoxide was prepared from N₂O₅ and ozone. 2,6-Dideuteriopyridine was supplied by CDN Isotopes with 99.7% of the theoretical deuterium content. It was used as received.

Isolation of N-nitropyridinium nitrate (1). N₂O₅ (2.16 g, 20 mmol) was dissolved in CH₂Cl₂ (20 ml) at 4 °C under nitrogen. Pyridine (0.79 g, 10 mmol) in CH₂Cl₂ (10 ml) was slowly added and the mixture was stirred at 4 °C for 15 min. The white precipitate formed was then filtered off, washed with CH₂Cl₂, immediately placed into a flask and dried at 4 °C in a stream of nitrogen for 2 h. N-Nitropyridinium nitrate could be stored for several days under nitrogen at −20 °C.

Experiment 1. N-Nitropyridinium nitrate (1, 74.8 mg, 0.4 mmol) was dissolved in D₂H₂O·C₂H₅O·H (1:1 v/v, 2 ml) at −40 °C under nitrogen. NaH₂O₂ (41.6, 0.4 mmol) dissolved in D₂H₂O·C₂H₅O·H (1:1 v/v, 1 ml) was added and the mixture was stirred at −40 °C for 3 min. N-Nitro-2,6-dideuteriopyridinium nitrate (2,6-d⁻¹) (75.7 mg, 0.4 mmol) dissolved in D₂H₂O·C₂H₅O·H (1:1 v/v, 1 ml) was then added and a sample for NMR study was withdrawn immediately and kept at low temperature during transfer to NMR spectrometer. The ¹H NMR experiment was performed and the spectra recorded at a constant temperature of −22 °C with 2,4,6-trimethylpyridine as an internal standard.

Experiment 2. N-Nitropyridinium nitrate (1, 187.1 mg, 1.0 mmol) was dissolved in D₂H₂O (4 ml) and acidified (pH 1) with D₂HNO₃ at room temperature under nitrogen. NaH₂O₂ (72.8 mg, 1.0 mmol) dissolved in acidified D₂H₂O (4 ml) was then added and the mixture was stirred for 10 min at room temperature to allow the 1,2-dihydroadduct 3 to react to give 3-nitropyridine (6). N-Nitro-2,6-dideuteriopyridinium nitrate (2,6-d⁻¹) (189.1 mg, 1.0 mmol) dissolved in acidified D₂H₂O (2 ml) was then added and the mixture was stirred for 10 min at room temperature. The mixture was then extracted with CH₂Cl₂ (2 × 10 ml) and CCl₄ (10 ml) to remove 3-nitropyridine formed mostly from the 1,2-dihydroadduct (3), and the phases separated. A sample was then withdrawn from the aqueous phase. The ¹H NMR experiment was performed and spectra recorded at a constant temperature of 21 °C with 2,4,6-trimethylpyridine as an internal standard. The relative concentration of each compound at different time intervals was thus determined and the rates d[6]/dt and d[2,6-d⁻¹-6]/dt were calculated.

The plot of the increasing concentration of 3-nitropyridine with time was fitted to two mutually linked polynomials and the rates d[6]/dt and d[2,6-d⁻¹-6]/dt calculated by differentiation of these polynomials.


$$[6] = 2.84484 + 0.05203t - 3.57661E - 4t^2$$
$$+ 8.82186E - 6t^3 - 5.04499E - 8t^4; t = 0-80 \text{ min}$$

$$[6] = 4.49057 + 0.00632t + 4.79501E - 4t^2$$
$$- 2.32756E - 6t^3 + 3.23065E - 9t^4; t = 80-160 \text{ min}$$

$$[2,6-d⁻¹-6] = 1.1049 + 0.34874t - 0.00305t^2$$
$$+ 1.35641E - 5t^3; t = 0-30 \text{ min}$$

$$[2,6-d⁻¹-6] = 3.32922 + 0.22268t - 7.96282E - 4t^2$$
$$+ 1.10435E - 6t^3; t = 30-160 \text{ min}$$

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References


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