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

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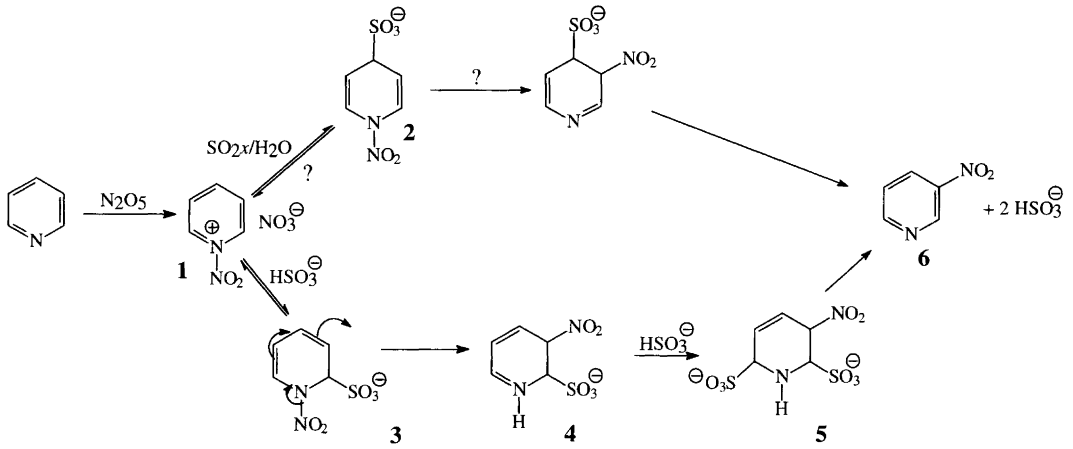
The reactions of *N*-nitropyridinium nitrate (**1**) and 2,6-dideuterio-*N*-nitropyridium nitrate (2,6-d_2-**1**) with SO_2xH_2O–HSO_3^- have been studied. The results are consistent with a reaction scheme in which the formed *N*-nitro-1,4-dihydro-4-pyridinesulfonic acid (**2**) did not react directly 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_2O_5) in an organic solvent and then mixing the resulting *N*-nitropyridinium nitrate (**1**) with an aqueous solution of SO_2xH_2O–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.[1] 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**).[2] 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.[1] 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.[2] 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*-nitropyridinium ion is reversible and



Scheme 1.

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that 3-nitropyridine is formed from the 1,2-dihydropyridine 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*-Nitropyridinium nitrate has been shown to be a relatively stable compound which precipitates from dichloromethane on its formation from pyridine and N_2O_5. 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 equimolecular amounts of *N*-nitropyridinium nitrate and $NaHSO_3$ in ^2H_2O–$C^2H_3O^2H$ 1:1 were mixed at −40 °C. Immediately after this, an equimolecular amount of 2,6-dideuterio-*N*-nitropyridinium nitrate (2,6-d_2-**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 compound 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-d_2-**1** as these were precipitated from dichloromethane but could not be recrystallised owing to their instability. Because of these points the concentrations of deuteriated and non-deuteriated compounds were not exactly equal.

The results in Table 1 show that deuterium was incorporated from 2,6-d_2-**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-dideuteriated analogues was not rapid on the timescale of the experiment. However, this incorporation of deuterium was not unambiguous evidence for the reversibility of the formation of these compounds as SO_2xH_2O–HSO_3^- formed by the formation of 3-nitropyridine might have reacted with 2,6-d_2-**1** (Scheme 1).[1]

However, the change in the ratio [**1**]/[2,6-d_2-**1**] gave strong evidence for the reversible formation of **3**. If no reversible reaction took place, this ratio would be constant 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-d_2-**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 SO_2xH_2O–HSO_3^- at room temperature 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-d_2-**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-d_2-**1**, **2**, 2,6-d_2-**2**, **6** and 2,6-d_2-**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 gave 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 bisulfite.

	Concentration (%)						
t/min	**1**	2,6-d_2-**1**	**2**	2,6-d_2-**2**	**3**	2,6-d_2-**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	32.8	16.5	2.6
34	7.1	28.7	6.2	3.8	27.7	18.6	8.0
54	7.9	24.3	6.3	5.3	23.6	19.7	12.8
75	8.2	20.4	6.8	6.6	20.6	19.9	17.5
104	7.9	15.7	7.7	7.7	17.2	20.0	23.8
149	6.1	10.5	8.5	9.9	13.9	18.5	23.7
178	5.0	7.5	9.1	10.7	12.3	17.7	37.7
226	3.1	4.3	10.1	12.3	10.6	14.7	44.9

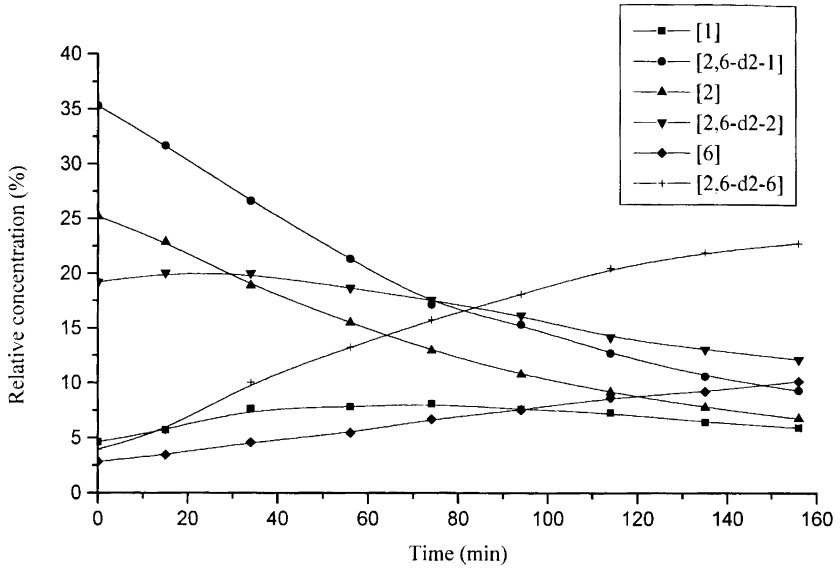

Fig. 1. Variations in the concentrations of **1**, 2,6-d_2-**1**, **2**, 2,6-d_2-**2**, **6** and 2,6-d_2-**6** with time at 21 °C.

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_3^-] would be small and constant during the reaction. If 3-nitropyridine were formed from either **1** or **2** we would have:

either $d[\mathbf{6}]/dt = k^1[\mathbf{1}]$; $d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt = k^2[2,6\text{-}d_2\text{-}\mathbf{1}]$ (1)

or $d[\mathbf{6}]/dt = k^3[\mathbf{2}]$; $d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt = k^4[2,6\text{-}d_2\text{-}\mathbf{2}]$ (2)

From the data in Fig. 1 a regression analysis gave polynomial expressions for [**6**] and [2,6-d_2-**6**]. From these, equations $d[\mathbf{6}]/dt$ and $d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt$ 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 $k^1 = k^2$ [eqn. (1)] and $k^3 = k^4$ [eqn. (2)]. From eqn. (1) we then obtain:

$$(d[\mathbf{6}]/dt)/(d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt) = [\mathbf{1}]/[2,6\text{-}d_2\text{-}\mathbf{1}] \quad (3)$$

and from eqn. (2):

$$(d[\mathbf{6}]/dt)/(d[2,6\text{-}d_2\text{-}\mathbf{6}])/dt = [\mathbf{2}]/[2,6\text{-}d_2\text{-}\mathbf{2}] \quad (4)$$

In Fig. 2 we have plotted $(d[\mathbf{6}]/dt)/(d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt)$, $[\mathbf{1}]/[2,6\text{-}d_2\text{-}\mathbf{1}]$ and $[\mathbf{2}]/[2,6\text{-}d_2\text{-}\mathbf{2}]$ 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

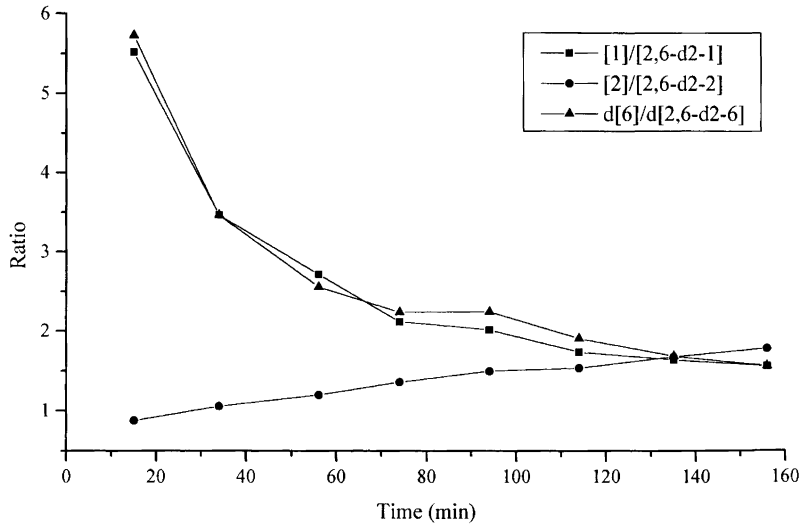

Fig. 2. Variations in the ratios [**1**]/[2,6-d_2-**1**]; [**2**]/[2,6-d_2-**2**]; and in $(d[\mathbf{6}]/dt)/(d[2,6\text{-}d_2\text{-}\mathbf{6}]/dt)$ with time at 21 °C.

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.[2] 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.[2] 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.[1] Dinitrogen pentoxide was prepared from N_2O_4 and ozone.[5] 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**). N_2O_5 (2.16 g, 20 mmol) was dissolved in CH_2Cl_2 (20 ml) at 4 °C under nitrogen. Pyridine (0.79 g, 10 mmol) in CH_2Cl_2 (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 CH_2Cl_2, 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 ^2H_2O–$C^2H_3O^2H$ (1:1 v/v, 2 ml) at −40 °C under nitrogen. $NaHSO_3$ (41.6, 0.4 mmol) dissolved in ^2H_2O–$C^2H_3O^2H$ (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_2-**1**) (75.7 mg, 0.4 mmol) dissolved in ^2H_2O–$C^2H_3O^2H$ (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 ^2H_2O (4 ml) and acidified (pH 1) with $^2HNO_3$ at room temperature under nitrogen. $NaHSO_3$ (72.8 mg, 1.0 mmol) dissolved in acidified ^2H_2O (4 ml) was then added and the mixture was stirred for 10 min at room temperature to allow the 1,2-dihydro-adduct **3** to react to give 3-nitropyridine (**6**). *N*-Nitro-2,6-dideuteriopyridinium nitrate (2,6-d_2-**1**) (189.1 mg, 1.0 mmol) dissolved in acidified ^2H_2O (2 ml) was then added and the mixture was stirred for 10 min at room temperature. The mixture was then extracted with CH_2Cl_2 (2 × 10 ml) and CCl_4 (10 ml) to remove 3-nitropyridine formed mostly from the 1,2-dihydro-adduct (**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_2-**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_2-**6**]/dt calculated by differentiation of these polynomials.

$$[\mathbf{6}] = 2.84484 + 0.05203t - 3.57661\mathrm{E}-4t^2 + 8.82186\mathrm{E}-6t^3 - 5.50449\mathrm{E}-8t^4;\ t = 0\text{–}80\ \mathrm{min}$$

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

$$[2,6\text{-}d_2\text{-}\mathbf{6}] = 1.1049 + 0.34874t - 0.00305t^2 + 1.35641\mathrm{E}-5t^3;\ t = 0\text{–}30\ \mathrm{min}$$

$$[2,6\text{-}d_2\text{-}\mathbf{6}] = 3.32922 + 0.22268t - 7.96282\mathrm{E}-4t^2 + 1.10435\mathrm{E}-6t^3;\ t = 30\text{–}160\ \mathrm{min}$$

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