The reaction mechanism of the nitration of pyridine compounds by N_2O_5–$NaHSO_3$

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Reaction of pyridine compounds in organic solvents with N_2O_5 gives the corresponding *N*-nitropyridinium nitrate. On reaction of this with an aqueous solution of $NaHSO_3$ unstable 1,2- and 1,4-dihydropyridine compounds are formed which react to give β-nitropyridine compounds. The reaction of the 1,2-dihydropyridine compounds have been studied. From pyridine itself compound **2** is obtained which reacts with $\Delta H^{\ddagger} = 18(1)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -5(4)$ cal mol^{-1} K^{-1}. Its rate of reaction is only marginally affected by the polarity of the reaction medium. From 3-acetylpyridine the 1,2-dihydropyridine compound **8a** is obtained from attack of the nucleophile in the 2-position. This then reacts with a regioselective migration of the NO_2 group from the 1- to the 3-position. Analogous results are obtained from 3-methyl- and 2,5-dimethyl-pyridine. These results do not support a reaction *via* the formation of an ion pair (Route B, Scheme 1) but are in accordance with a reaction by a [1,5] sigmatropic shift of the NO_2 group (Route A).

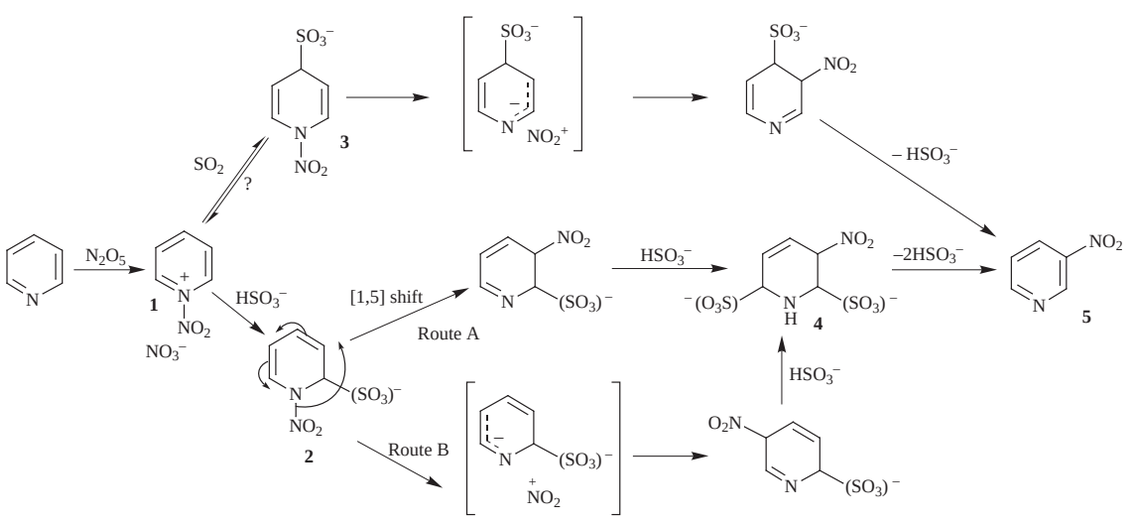
We have reported that the nitration of pyridine and some substituted pyridines with dinitrogen pentoxide gives much higher yields of β-nitropyridine compounds than those obtained by other direct nitration methods.[1] The reaction is therefore of great preparative value. We have also shown that it has a rather complicated reaction path and that it is not a normal electrophilic aromatic substitution reaction.[2]

In a recent report we proposed that this nitration reaction proceeded by one of the reaction paths outlined in Scheme 1. Pyridine reacted with dinitrogen pentoxide (N_2O_5, DNP) in an organic solvent to give *N*-nitropyridinium nitrate (**1**). On reaction of **1** with an aqueous solution of $SO_2 \cdot xH_2O$–HSO_3^-, 1,2-dihydro- (**2**) and 1,4-dihydropyridine (**3**) compounds were formed. Compound **2** reacted rapidly to give the tetrahydropyridine derivative **4**, which gave 3-nitropyridine on further reaction. The reaction of compound **3** was also followed by an increase in the concentration of 3-nitropyridine. Both compounds **2** and **3** reacted by first order rate laws and the reactions appeared to be either intramolecular or to take place in a solvent cage.[2] In that report, the mode of the migration of the nitro group from the 1- to the 3-position of the pyridine ring was discussed: did it take place by a concerted reaction, for instance a sigmatropic shift, or by a migration in a solvent cage of a nitronium ion or nitrogen dioxide radical formed by a heterolytic or homolytic cleavage of the N–N bond of **2** and **3**? We have now made further investigations into the reaction of the 1,2-dihydropyridine derivative **2**.

Results

Kinetics

The reaction of the 1,2-dihydropyridine derivative **2** was too fast at room temperature to be monitored by NMR spectroscopy.[2] As the reaction took place in water, the range of temperatures possible for the investigation was too small to obtain reliable activation parameters. We have therefore extended this range by using a mixture of water and a water-miscible organic solvent as the medium for the reaction. By this means we were able to obtain kinetic data for the reaction of **2**



Scheme 1

Table 1 Rate of reaction of the 1,2-dihydropyridine derivative **2** in ^2H_2O–[$^2H_6$]acetone 1 : 1 (v : v), $[2]_0 = 0.14$ M, [salts] = 0.87 M, salts were $NaHSO_3$ and HNO_3, pH = 1.8, 2,4,6-trimethylpyridine as internal standard. The reaction was monitored by ^1H NMR spectroscopy

Run	θ/°C	$k_1/10^{-5}$ s^{-1}	r^2
1	−5.3	82(1)	0.9992
2	−12.4	43.8(5)	0.9974
3	−17.7	19.0(2)	0.9984
4	−21.2	12.57(6)	0.9998
5	−24.3	5.94(5)	0.9987
6	−28.5	3.47(7)	0.9947

for the temperature range from −29 to −5 °C. The results are given in Table 1. For all runs the data were in accordance with a rate law first order in **[2]**. From the data in Table 1, the activation parameters $\Delta H^{\ddagger} = 18(1)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -5(4)$ cal mol^{-1} K^{-1} were obtained.

We have also conducted kinetic investigations in different solvent and solvent mixtures at −12 °C. The results are given in Table 2. In Table 2 are also given the results from reactions in media with differing concentrations of ionic compounds.

NMR studies

We have studied the nitration reaction of some 3- and 4-substituted pyridines by low temperature NMR spectroscopy. The spectral assignments were made from the observations of ^1H and ^{13}C 1D spectra together with ^1H–^1H and ^1H–^{13}C correlation spectra. The techniques and arguments used have been reported.[2] The data from these experiments are given in the Experimental section.

Discussion

In Scheme 1 two possible routes for the migration of the nitro group from the 1- to the 3-position of **2** are shown, one a concerted reaction involving a [1,5] sigmatropic shift, the other a reaction in a solvent cage. The activation parameters obtained for the reaction, particularly the entropy of activation, had rather large limits of error, $\Delta H^{\ddagger} = 18(1)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -5(4)$ cal mol^{-1} K^{-1}. Nevertheless, two points are clear: the enthalpy of activation was rather small and the entropy of activation was close to zero, not large and positive. These two points would be in accordance with a concerted reaction. Thus, Harbraken *et al.*[3] reported the isomerisation of *N*-nitropyrazole by a [1,5] sigmatropic shift. The entropy of activation for that reaction varied from −3 to +7 cal mol^{-1} K^{-1} depending on the solvent, that is, near zero. For substituted *N*-nitropyrazoles the entropy of activation was slightly positive, 2–7 cal mol^{-1} K^{-1}. The enthalpy of activation for these reactions was *ca*. 30 kcal mol^{-1}. This was considered too low for an N–NO_2 homolysis giving a radical pair.[3] For [1,5] shifts with carbon as the migrating group, the entropy of activation has been reported as negative or slightly positive.[4] We therefore find that the reaction of **2** by a [1,5] sigmatropic shift (Route A, Scheme 1) is not excluded by these results.

The change in solvent necessary for the determination of the rate of reaction of **2** at low temperatures made it possible to study the influence of the medium on the rate of reaction. The results in Table 2 are from runs in solvent or solvent mixtures that represent a variation in the ionization power of the medium. The concentration of salts was also varied. For convenience the *Y*-values of the Grunwald–Winstein equation[5] were included in the Table. These are a measure of the ionization power of each solvent mixture. In the present case, the Grunwald–Winstein equation as such was not applicable due to the presence of ionic compounds. However, if the reaction of **2** proceeded by an ionic mechanism (Route B, Scheme 1) we would expect an increase in k_1 if the concentration of salts was increased or if the *Y*-value of the medium was increased or both.

Table 2 Rate of reaction of the 1,2-dihydropyridine derivative **2** in mixtures of ^2H_2O and deuterated solvents and with different concentrations of ionic compounds, $[2]_0 = 0.14$ M, 2,4,6-trimethylpyridine as internal standard, reaction temperature −12.4 °C. Percentage in the Solvent column is percentage of the solvent in ^2H_2O (v : v). The reactions were monitored by ^1H NMR spectroscopy. Salts were $NaHSO_3$ and HNO_3, pH = 1.8

Run	Solvent	$k_1/10^{-5}$ s^{-1}	Y_{OTos} [a]	[salts]/M	r^2
1	Methanol, 60%	70.5(9)	1.52	0.70	0.9973
2	Acetone, 20%	52.4(6)	3.05	1.39	0.9983
3	Acetone, 30%	57(1)	2.5	1.20	0.9943
4	Acetone, 50%	43.8(5)	1.26	0.87	0.9974
5	Water, 100%	99(5) [b]	4.1	1.20	0.9895
6	Methanol, 42% [c]	31.5(4)	2.4	0.15	0.9984
7	Methanol, 42% [d]	33.4(3)	2.4	0.61	0.9995

[a] See ref. 6. [b] Ice formed during run. [c] Temperature −15 °C. [d] Temperature −15 °C, in addition to $NaHSO_3$ and HNO_3, $[LiClO_4] = 0.46$.

The results presented in Table 2 show that this was not the case. For instance Run 2, in which both *Y* and [salts] were increased as compared to Run 1, showed a lower k_1 than that of Run 1. The same conclusion was obtained by comparing runs 6 and 7 for which *Y* was constant but for which there was a significant change in [salts]. For an ionic mechanism we would have expected a large increase in k_1 by going from [salts] of 0.15 to 0.61 M.[7] However, only a small increase, almost within the limits of error, was observed.

Reactions by intimate ion pairs, analogous to the reaction of **2** by Route B, show normal dependence on both the Grunwald–Winstein equation and Winstein's equation for the rate dependence on [salts], see for instance the solvolysis of pinacolyl bromide and 1-adamantyl tosylate[8] and the solvolysis of 2-(*p*-methoxyphenyl)-2-butyl brosylate.[9] The observed activation parameters and the polarity dependence of the reaction of **2** were thus in accordance with Route A in Scheme 1, a [1,5] sigmatropic shift, but not with a reaction that proceeded by a highly charged transition state as exemplified by Route B and the reaction of **3** in Scheme 1.

Product studies of the reaction gave further information. The nitration of the pyridine compounds was highly regioselective as the nitration took place in the β-position in all cases. Thus, with 3-substituted substrates, the nitration took place in the 5-position. In general, the yields were lower for 3- than for 4-substituted substrates. For instance, nitration of 4-acetylpyridine gave a 67% yield of 4-acetyl-3-nitropyridine while nitration of 3-acetylpyridine gave only a 19% yield of 3-acetyl-5-nitropyridine.[1] We have now studied the nitration of some substituted pyridines by low temperature (−55–0 °C) NMR spectroscopy.

In the nitration of 3-acetylpyridine, three unstable intermediates were observed from 3-acetyl-*N*-nitropyridinium nitrate (**6a**, Scheme 2). These were the 1,4-dihydropyridine derivative **7a** and two *N*,α-dihydropyridine compounds, **8a** and **9a**, in a *ca*. 0.4 : 1 : 0.15 ratio.

The *N*,α-dihydropyridine derivatives **8a** and **9a** reacted rapidly with similar first order rate constants (*ca*. 4×10^{-4} s^{-1} at 0 °C). In Fig. 1 are shown the variations in the concentration of these intermediates with time. For the first 55 min the temperature was −30 °C, for the next 180 min 0 °C and then +7 °C. The observed rate constants are not accurate, especially that for **9a**.

Due to its low concentration, it was not possible to determine the product of the reaction of **9a**. However, from Fig. 1, the reduction in the concentration of **8a** was accompanied by an increase in that of the tetrahydropyridine intermediate **11a**, implying that **11a** was formed from **8a**. This shows a regioselective migration of the nitro group from the *N*- to the β-position

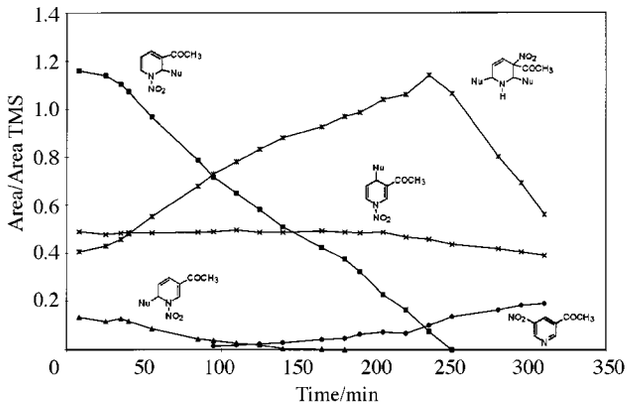
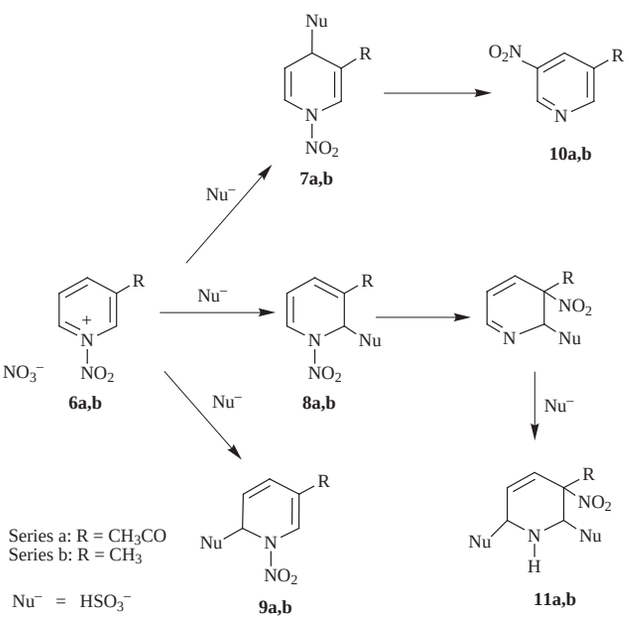


Fig. 1 Variations in concentrations with time of intermediates formed from the reaction of 3-acetyl-*N*-nitropyridinium nitrate in ^2H_2O–$C^2H_3O^2H$, 1 : 1, determined by integration of NMR spectra.



Scheme 2

of the pyridine ring followed by addition of a nucleophile to give **11a** (Scheme 2).

For the reaction of 3-methylpyridine the results were analogous to those of 3-acetylpyridine. However, only one 1,2-dihydropyridine intermediate, **8b** was observed and this reacted faster than the analogous 3-acetyl intermediate (**8a**). The dihydropyridine derivative **8b** reacted to give the tetrahydropyridine intermediate **11b**. Again, the migration of the nitro group appeared to be regioselective. The decrease in the concentration of the 1,4-dihydropyridine derivative **7b** was accompanied by an increase in the concentration of 3-methyl-5-nitropyridine (**10b**). This may indicate that **7b** was the precursor of **10b**.

For the reaction of 4-acetylpyridine, two unstable intermediates from the reaction of 4-acetyl-*N*-nitropyridinium nitrate (**12a**) were observed, the 1,4-dihydropyridine derivative (**13a**) and the 1,2-dihydropyridine derivative **14a** in a *ca.* 1 : 10 ratio (Scheme 3). At the applied reaction temperature, −3 °C, **14a** reacted rapidly and **13a** very slowly (Fig. 2). Fig. 2 indicated that the tetrahydropyridine derivative **15a** was formed from **14a** and that it reacted to give 4-acetyl-3-nitropyridine (**16a**). The high starting concentration of **15a** (Fig. 2) is explained by the rapid reaction of **14a** by analogy with the results from the nitration of pyridine itself.[2]

4-Methyl-*N*-nitropyridinium nitrate (**12b**) reacted rapidly with both SO_2 and HSO_3^- and the dihydropyridine intermedi-

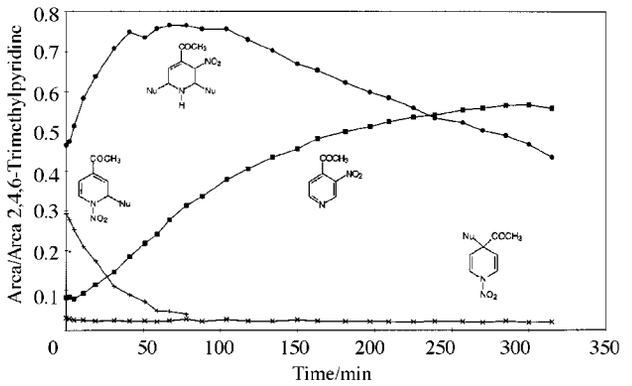
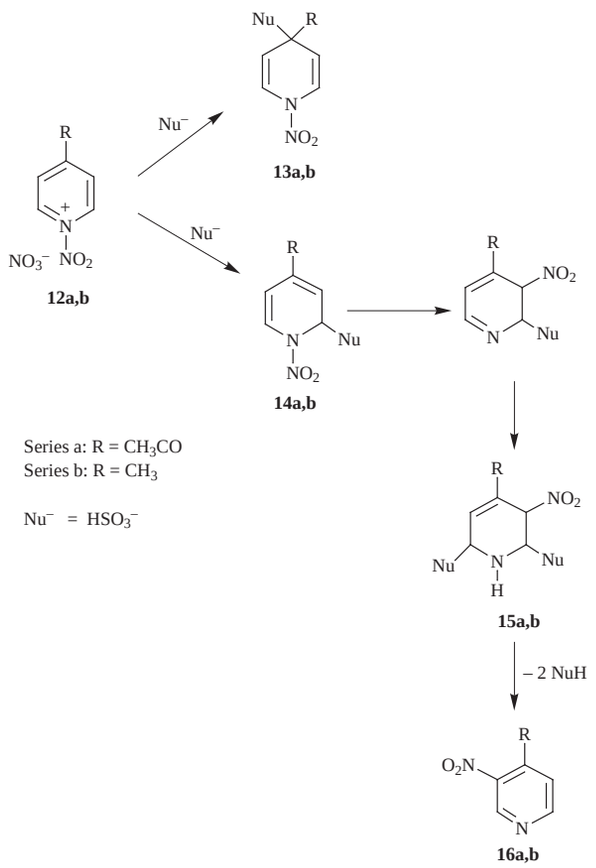


Fig. 2 Variations in concentrations with time of intermediates formed from the reaction of 4-acetyl-*N*-nitropyridinium nitrate in ^2H_2O–$C^2H_3O^2H$, 1 : 1, determined by integration of NMR spectra.

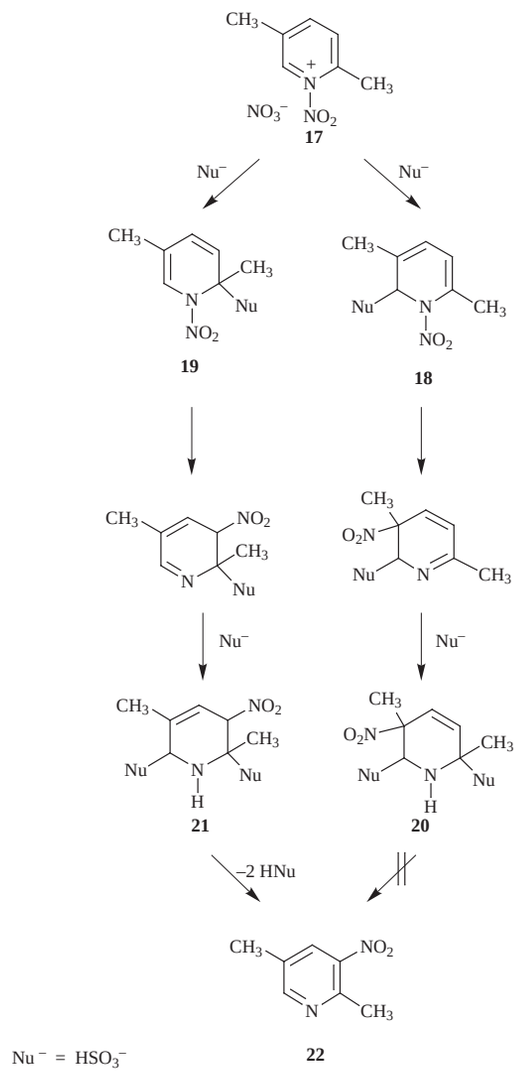


Scheme 3

ates **13b** and **14b** were not observed, only a tentative observation of the tetrahydropyridine derivative **15b** was possible.

We have reported the results from the nitration of dimethylpyridines.[1,2] Of these, the 2,5-isomer gave a low yield (<3%) of 2,5-dimethyl-3-nitropyridine (**22**). We have now investigated the reaction of 2,5-dimethyl-*N*-nitropyridinium nitrate (**17**, Scheme 4) at 0 °C by NMR spectroscopy. The main intermediate was the tetrahydropyridine derivative **20**. By analogy with the results from the nitration of the 3-substituted pyridines discussed above, it is not unreasonable to propose that **20** was formed from the *N*,*α*-dihydropyridine derivative **18** which was formed by nucleophilic attack in the 6-position (Scheme 4).

A low yield of 2,5-dimethyl-3-nitropyridine (**22**) was obtained. This was presumably formed from the two (not observed) intermediates **19** and **21**. As dimethylpyridines are activated for normal electrophilic nitration, **22** might have been formed directly in a reaction with N_2O_5. However, this was not the case as it was not formed when the product from the



Scheme 4

reaction with N_2O_5 was poured into water without sodium bisulfite.

From the study of the nitration of these three substituted pyridines together with those from the nitration of pyridine itself[2] the following points emerge: 1. The *N*,*α*-dihydropyridine derivative formed by a nucleophilic attack on the corresponding *N*-nitropyridinium ion reacted by first order reactions with low activation enthalpy (18 kcal^{-1} mol^{-1}) and a small negative activation entropy (−5 cal mol^{-1} K^{-1}). 2. The rate of reaction of the 1,2-dihydropyridine derivative **2** was not influenced by the ionising power of the reaction medium. 3. The migration of the nitro group from the pyridine *N*-atom to the β-position was highly regiospecific.

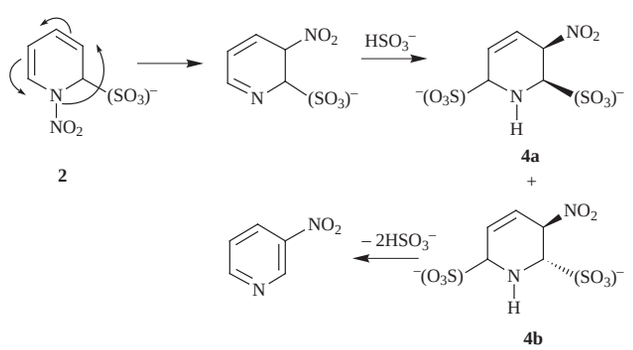
Route A in Scheme 1 by which the nitro group migrates by a [1,5] sigmatropic shift is in accordance with these three points. The ordered TS of a sigmatropic shift would result in a negative or small positive entropy of activation. This has been observed for analogous [1,5] shifts (Point 1). The non-polar TS of a [1,5] shift would explain the lack of influence of the polarity of the solvent (Point 2). Furthermore, the observed regioselectivity would also be expected for such a rearrangement (Point 3).[3,4] The observed data are therefore all explained by Route A in Scheme 1.

The data also exclude a reaction by an ion pair as in Route B. For that type of reaction one would expect a larger influence of the ionising power of the reaction medium than that observed (Table 2).

One possibility that may be considered is a reaction by a radical pair, that is by Route B in Scheme 1 but with a homolytic instead of a heterolytic cleavage of the N–NO_2 bond. This would be analogous to the mechanism for the migration of NO_2 in the aromatic nitramine rearrangement[10] and to that of the migration of NO_2 in the nitrocyclohexadienones.[11] The activation parameters of the nitramine rearrangement do not appear to have been determined but those for the reaction of nitrocyclohexadienones have been reported. For 2-methyl-2-nitrocyclohexa-3,5-dienones, $\Delta H^{\ddagger} = 74.0$ to 118 kJ mol^{-1} and $\Delta S^{\ddagger} = -4$ to 112 J K^{-1} mol^{-1}, depending on acid concentration and substituents, were obtained. For 4-methyl-4-nitrocyclohexa-2,5-dienone $\Delta H^{\ddagger} = 98.4$ kJ mol^{-1}, $\Delta S^{\ddagger} = 14$ J K^{-1} mol^{-1} were reported.[11] Thus, both the enthalpy and entropy of activation for these reactions were similar to those found for the rearrangement of **2**.

We are aware that for [1,5] sigmatropic shifts with groups other than hydrogen atoms migrating, the energetics of the reaction may be similar for a sigmatropic shift and for a reaction by a radical pair.[12] However, the regiospecificity of the reaction of **2** is not easily explained by the migration of a NO_2 radical. For 2-methyl-2-nitrocyclohexa-3,5-dienone the regioselectivity was proposed to be caused by an interaction of the migrating NO_2 with the aryloxy radical.[11] An analogous interaction would be more difficult in our system as a delocalisation of a radical electron to the nucleophile in the 2-position would not be possible.

Furthermore, if the migration of the nitro group did proceed *via* the nucleophile in the 2-position, only one stereoisomer of migration product would be formed, giving only one stereoisomer of the tetrahydropyridine derivative **4** (Scheme 1). Indeed, in our earlier work only one stereoisomer of **4**, the *cis* isomer (**4a**, Scheme 5), was observed.[2] As we have now studied



Scheme 5

the reaction at a lower temperature, one more stereoisomer of **4** has been observed. Its ^{1}H NMR chemical shifts and scalar coupling patterns were similar to those observed for **4a**, except for one coupling constant. For **4a**, $^3J_{2,3} = 4.19$ Hz was observed, for the new one, 8.87 Hz. This identifies the new compound as the *trans* isomer, **4b**. At −20 °C these two compounds were formed in *ca*. 1:1 ratio, with **4b** reacting at a higher rate than **4a**. This shows that the migration of the nitro group did not take place *via* the nucleophile in the 2-position, at least not exclusively by that pathway.

The results reported here are thus better explained by a [1,5] sigmatropic shift reaction than by a formation of a radical pair. However, the bond breaking and bond formation in the reaction may not be synchronous and this will determine the radical character of the reaction.

Experimental

The spectroscopic equipment and the NMR pulse programmes applied, the purification of reagents and solvents and the preparation of N_2O_5 have been reported.[2]

For the kinetic runs, the pyridine compound (3.1 mmol) was added to N_2O_5 (*ca*. 6.4 mmol) in nitromethane (6 ml)

at 0 °C. After 5 min the suspension of the appropriate *N*-nitropyridinium nitrate was poured into ^2H_2O (6 ml) containing $NaHSO_3$ (15.2 mmol) and 2,4,6-trimethylpyridine (0.8 mmol, internal standard) kept at −5 °C. A sample of the aqueous phase was transferred as rapidly as possible (less than 1 min) to an NMR tube containing a deuterated water miscible organic solvent and the monitoring of the reaction by ^1H NMR spectroscopy started. The temperature of the NMR spectrometer was checked by the signals from a MeOH sample.[13] This procedure was used both for kinetic runs and for obtaining ^1H–^1H and ^1H–^{13}C correlation spectra.

Identification of intermediates

From the reaction of 3-acetylpyridine. *Compound **7a**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −10 °C) 8.70 (s, H^2), 7.76 (dd, H^6, $J_{6,5}$ 7.39, $J_{6,4}$ 1.42), 5.64 (dd, H^5, $J_{5,6}$ 7.39, $J_{5,4}$ 5.88), 4.90 (dd, H^4, $J_{4,5}$ 5.88, $J_{4,6}$ 1.42) 2.5 (CH_3); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −10 °C) 125.1 (C^6), 107.7 (C^5), 54.6 (C^4), 25 (CH_3). Shift values for (C^2), (C^3) and (CO) not observed.

*Compound **8a**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −10 °C) 7.85 (dd, H^4, $J_{4,5}$ 6.54, $J_{4,6}$ 1.32), 7.48 (dd, H^6, $J_{6,5}$ 7.48, $J_{6,4}$ 1.32), 7.10 (s, H^2), 5.93 (dd, H^5, $J_{5,4}$ 7.85, $J_{5,6}$ 7.48), 2.5 (CH_3); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −10 °C) 134.1 (C^6), 130.0 (C^4), 108.8 (C^5), 68.5 (C^2), 25 (CH_3). Shift value for (C^3) not observed.

*Compound **9a**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −10 °C) 8.60 (s, H^2), 6.81 (dd, H^4, $J_{4,5}$ 9.67, $J_{4,6}$ 1.61), 6.50 (dd, H^6, $J_{6,5}$ 10.19, $J_{6,4}$ 1.61), 6.17 (dd, H^5, $J_{5,4}$ 9.67, $J_{5,6}$ 10.19), 2.5 (CH_3). ^{13}C spectrum not obtained.

*Compound **11a**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −10 °C) 6.61 (dd, H^4, $J_{4,5}$ 11.13, $J_{4,6}$ 1.03), 6.43 (dd, H^5, $J_{5,4}$ 11.13, $J_{5,6}$ 2.59), 5.47 (s, H^2), 4.83 (dd, H^6, $J_{6,5}$ 2.59, $J_{6,4}$ 1.03), 2.00 (s, $COCH_3$); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −10 °C) 130.5 (C^5), 123.0 (C^4), 72.3 (C^2), 69.0 (C^6). Shift values for (C^3) and ($COCH_3$) not observed.

From the reaction of 3-methylpyridine. In this case, 3-methylpyridine (0.853 g, 9.16 mmol) in dichloromethane (12.5 ml) was reacted with N_2O_5 (1.35 g, 12.5 mmol) at 0 °C for 10 min, the obtained slurry filtered and the crystals (3-methyl-*N*-nitropyridinium nitrate, **6b**) washed with dichloromethane, dried with N_2 and placed at −20 °C over night. **6b** (0.12 g, 0.60 mmol) was dissolved in 0.5 mL solvent in an NMR tube, and sodium bisulfite (0.15 g, 1.44 mmol) in solvent (0.5 ml) added at −78 °C. The NMR tube was then placed in the NMR instrument at the appropriate temperature.

*Compound **7b**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −50 °C) 7.69 (dd, H^6, $J_{6,5}$ 7.98, $J_{6,4}$ 1.52), 7.54 (s, H^2), 5.56 (dd, H^5 $J_{5,6}$ 7.98, $J_{5,4}$ 5.62), 4.33 (dd, H^4, $J_{4,5}$ 5.62, $J_{4,6}$ 1.52), 2.05 (s, CH_3); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −50 °C) 126.5 (C^6), 123.1 (C^2), 109.5 (C^5), 63.5 (C^4), 20.6 (CH_3). Shift values for C^3 not observed.

*Compound **8b**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −55 °C) 7.4 (d, H^6, $J_{6,5}$ 7.9), 6.3 (s, H^2), 6.2 (d, H^4, $J_{4,5}$ 7.4), 5.7 (dd, H^5, $J_{5,4}$ 7.4, $J_{5,6}$ 7.9); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −55 °C) 123.91 (C^4), 123.3 (C^6), 112.9 (C^5), 76.6 (C^2). Shift value for (C^3) not observed.

*Compound **11b**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −50 °C) 6.26 (dd, H^5, $J_{5,4}$ 9.99, $J_{5,6}$ 3.05), 6.11 (dd, H^4, $J_{4,5}$ 9.99, $J_{4,6}$ 2.34), 5.29 (s, H^2), 4.68 (dd, H^6, $J_{6,5}$ 3.05, $J_{6,4}$ 2.34), 1.86 (s, CH_3); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −50 °C) 132.9 (C^4), 128.2 (C^5), 74.2 (C^2), 71.6 (C^6), 22.9 (CH_3). Shift value for C^3 not observed.

From the reaction of 4-acetylpyridine. *Compound **13a**:* $\delta_H(^2H_2O$, −2 °C) 7.76 (d, $H^{2,6}$, $J_{2,3}$ 5.24), 6.52 (d, $H^{3,5}$, $J_{2,3}$ 5.24), 2.44 (s, CH_3).

*Compound **14a**:* $\delta_H(^2H_2O$, −2 °C) 7.52 (dd, H^6, $J_{3,6}$ 1.15, $J_{5,6}$ 8.19), 7.13 (dd, H^2, $J_{2,3}$ 6.35, $J_{2,5}$ 1.73), 6.84 (dd, H^3, $J_{2,3}$ 6.35, $J_{3,6}$ 1.15), 6.15 (dd, H^5, $J_{2,5}$ 1.73, $J_{5,6}$ 8.19), 2.49 (s, CH_3).

*Compound **15a**:* $\delta_H(^2H_2O$, −2 °C) 7.56 (d, H^5, $J_{5,6}$ 2.7), 5.89 (d, H^3, $J_{2,3}$ 1.5), 5.11 (d, H^6, $J_{5,6}$ 2.7), 5.08 (d, H^2, $J_{2,3}$ 1.5), 2.55 (*s, CH_3*). Correlation and ^{13}C spectra were not obtained.

From the reaction of 4-methylpyridine. Compound ***13b**:* $\delta_H(^2H_2O$, pH 1, 25 °C) 6.02 (d, H^5, $J_{5,6}$ 2.9), 5.32 (d, H^3, $J_{2,3}$ 4.59), 4.93 (d, H^2, $J_{2,3}$ 4.59), 4.6 (d, H^6, $J_{5,6}$ 2.9), 1.81 (s, CH_3). Correlation and ^{13}C spectra were not obtained.

From the reaction of 2,5-dimethylpyridine. *Compound **20**:* $\delta_H(^2H_2O$, 0 °C) 6.11 (d, H^3, $J_{3,4}$ 10.06), 5.97 (d, H^4, $J_{3,4}$ 10.06), 5.50 (s, H^6), 1.70 (s, CH_3), 1.51 (s, CH_3); $\delta_C(^2H_2O$, 0 °C) 128.3 (C^4), 127.3 (C^3), 83.8 (C^2), 70.6 (C^5), 69.3 (C^6), 21.3 (CH_3), 15.7 (CH_3).

From the reaction of pyridine. *Compound **4b**:* $\delta_H(^2H_2O$–$C^2H_3O^2H$, −21 °C) 6.23 (ddd, H^4, $J_{3,4}$ 2.4, $J_{4,5}$ 10.15, $J_{4,6}$ 2.1), 5.96 (ddd, H^5, $J_{3,5}$ 2.1, $J_{4,5}$ 10.15, $J_{5,6}$ 2.4), 5.39 (ddd, H^3, $J_{2,3}$ 8.87, $J_{3,4}$ 2.4, $J_{3,5}$ 2.1), 4.58 (dd, H^6, $J_{4,6}$ 2.1, $J_{5,6}$ 2.4), 4.41 (d, H^2, $J_{2,3}$ 8.87); $\delta_C(^2H_2O$–$C^2H_3O^2H$, −21 °C) 129.3 (C^4), 125.1 (C^5), 82.8 (C^3), 70.8 (C^6), 70.4 (C^2).

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