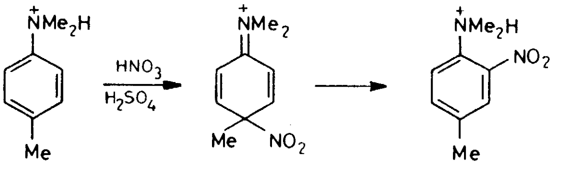
ipso-Attack in the Nitration of Aromatic Amines. Part 1. The Reactions of *NN*-Dimethyl-*p*-toluidine and Some Related Compounds

By **Fatima Al-Omran, Kenji Fujiwara, Janet C. Giffney, John H. Ridd,*** and **Stephen R. Robinson,**
Chemistry Department, University College, 20 Gordon Street, London WC1H 0AJ

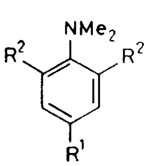
NN-Dimethyl-*p*-toluidine, *NN*-dimethyl-4-ethylaniline and *NN*-dimethyl-2,4,6-trimethylaniline react with nitric acid in aqueous sulphuric acid (*ca.* 70%) to form the *ipso*-Wheland intermediates with an NO_2 group at the 4-position (identified by ^1H and ^{13}C n.m.r. spectroscopy). These reactions cannot derive from direct attack by nitronium ions since they require the presence of traces of nitrous acid. The first example gives rise to an e.s.r. spectrum identified as that of the cation radical $4\text{-}MeC_6H_4NMe_2^{+\cdot}$. Where the *ortho*-positions are unsubstituted, the formation of the *ipso*-Wheland intermediate is followed by a 1,3-rearrangement to give the 2-nitro-product. The rate-determining step of this reaction appears to be the proton loss from the 2-position for there is a large isotope effect (k_H/k_D *ca.* 5) and the rate of the rearrangement decreases with an increase in the acidity of the medium. The 1,3-rearrangement of the nitro-group appears to be mainly intramolecular but studies of isotopic exchange in concurrent rearrangements show that there is also an intermolecular component and this is considered to involve the cation radical ($ArNMe_2^{+\cdot}$) and nitrogen dioxide. Other aromatic amines present in the solution during the rearrangement do not undergo nitration.

As might be expected from earlier studies,[1] the nitration of *NN*-dimethyl-*p*-toluidine in aqueous sulphuric acid (*ca.* 70%) gives a good yield (78%) of the *o*-nitro-derivative. However the n.m.r. spectra of the reaction mixtures shows that this nitration proceeds in two clearly defined stages. In our preliminary communication,[2] the intermediate species was considered to be the σ-complex resulting from *ipso*-attack at the 4-position [equation (1)]. The present paper is concerned with the evidence for this identification and with the reaction paths for the formation and rearrangement of this and related intermediates.

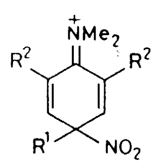


(1)

Identification of the ipso-*Intermediate.*—The changes in the ^1H n.m.r. spectra during the nitration of *NN*-dimethyl-*p*-toluidine are illustrated in Figure 1. The first spectrum (A) was taken a few minutes after the start of reaction and shows the peaks of the anilinium ion together with those of the intermediate. The next spectrum (B) was taken after complete conversion of the anilinium ion into the intermediate and when some product had been formed. The final spectrum (C) was taken when the rearrangement of the intermediate into the 2-nitro-product was almost complete. The relevant chemical shifts of the unprotonated amine and the intermediate are included with those of related amines (I) and intermediates (II) in Table 1.



(I)



(II)

The form of the signals from the ring protons in the intermediate shows that these positions have not undergone substitution. The singlet for the *N*-methyl protons in the intermediate shows that the nitrogen atom in the intermediate is far less basic than that in the initial amine or in the 2-nitro-product. This could derive from the addition of NO_2^+ to the lone pair of electrons on the nitrogen but such a reaction would not explain the high-field shift of the signal for the 4-methyl group, even relative to that in the free amine (Table 1). The identification of the intermediate as a σ-complex resulting from *ipso*-attack at the 4-position explains these observations. The formation of the intermediate is initiated by the attack of a nitrosonium ion on the

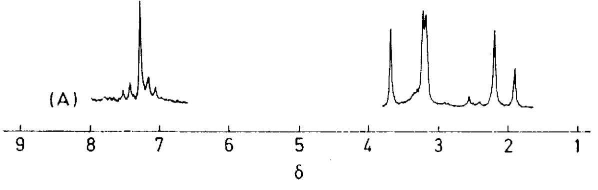


FIGURE 1 ^1H N.m.r. spectra of reaction mixtures during the nitration of *NN*-dimethyl-*p*-toluidine at 0 °C: (A) soon after the start of reaction; (B) when the concentration of the intermediate is a maximum; and (C) when conversion into the 2-nitro-product is almost complete. Spectra (A) and (B) are for $[ArNMe_2] = [HNO_3] = 0.5$ mol dm^{-3} in 77.4% H_2SO_4; spectrum (C) is for $[ArNMe_2] = [HNO_3] = 0.75$ mol dm^{-3} in 73.9% H_2SO_4

protonated amine (see below) but we do not consider that the intermediate can have a nitroso-group at the 4-position since traces of nitrous acid are sufficient to cause the complete conversion of the starting material into the intermediate. The structure of the intermediate is considered therefore to be that shown in equation (1). This structure is supported by analysis of the ^{13}C n.m.r. spectrum (Table 2), for this suggests that the signal for the 4-carbon shifts to high field by 38.4 p.p.m. when the intermediate is formed from the free amine. This is similar to the shift observed[3] for the corresponding carbon atom in the formation of the σ-complex from hexamethylbenzene and the nitronium ion (33.6 p.p.m.) and accords with a change from sp^2 to sp^3 hybridisation.

TABLE 1

^1H Chemical shifts (δ values) for the amines (I), the corresponding *ipso*-intermediates (II) and the differences between these values ($\Delta\delta$)

Substrate	H-2 and -6	H-3 and -5	Me-4	Me-2 and -6	MeN
(I; $R^1 = Me$, $R^2 = H$) [a]	6.63	7.01	2.23		2.82
(II; $R^1 = Me$, $R^2 = H$) [b]	7.14	7.52	1.93		3.68
$\Delta\delta$	0.51	0.51	-0.30		0.86
(I; $R^1 = R^2 = Me$) [a]		6.77	2.22	2.24	2.76
(II; $R^1 = R^2 = Me$) [c]		6.86	1.99	2.39	3.84
$\Delta\delta$		0.09	-0.23	0.15	1.08
			CH_2-4	MeC	
(I; $R^1 = Et$, $R^2 = H$) [a]	6.64	7.05	2.54	1.18	2.83
(II; $R^1 = Et$, $R^2 = H$) [c]	7.08	7.41	2.32	0.82	3.65
$\Delta\delta$	0.44	0.36	-0.22	-0.36	0.82

[a] In $CDCl_3$ at 0 °C. [b] In 77.1% H_2SO_4 at 0 °C. [c] In 73.5% H_2SO_4 at 0 °C.

A number of other aromatic amines have been found to form such intermediates but with some amines the formation of the intermediate is followed by rapid subsequent reactions that have not yet been fully elucidated. The results for two others are included in Table 1. As might be expected, the evidence for the formation and structure of the *ipso*-intermediate in the nitration of the *NN*-dimethyl-*p*-ethylanilinium ion closely parallels that for the *p*-methyl compound. The 2,4,6-trimethyl-amine (I; $R^1 = R^2 = Me$) could, in principle, form an *ipso*-intermediate at both the *ortho*- and *para*-positions but the singlet for the aromatic proton absorption in the ^1H n.m.r. spectrum of the intermediate indicates that only the *ipso*-intermediate at the *para*-position is formed [(II; $R^1 = R^2 = Me$)]. The comparison of the ^{13}C n.m.r. spectra of this intermediate and the corresponding free amine shows the expected high field shift (46.2 p.p.m.) of the signal for the 4-carbon atom in forming the intermediate (Table 2). This intermediate is stable for many hours at 0 °C.

TABLE 2

^{13}C Chemical shifts (p.p.m. from Me_4Si) for the amines (I), the corresponding *ipso*-intermediates (II) and the differences between these values ($\Delta\delta$)

Substrate	C-1	C-2 and -6	C-3 and -5	C-4	Me-4	Me-2 and -6	Me-N
(I; $R^1 = Me$, $R^2 = H$) [a]	148.5	112.6	129.2	124.6	19.8		40.1
(II; $R^1 = Me$, $R^2 = H$) [b]	161.7	121.1	148.9	86.2	25.5		45.4
$\Delta\delta$	13.2	8.5	19.7	-38.4	5.7		5.3
(I; $R^1 = R^2 = Me$) [c]	146.7	136.6	129.3	133.9	20.5	18.9	42.3
(II; $R^1 = R^2 = Me$) [d]	175.9	137.4	142.5	87.7	24.4	20.5	49.7
$\Delta\delta$	29.2	0.8	13.2	-46.2	3.9	1.6	7.4

[a] In [$^2H_6$]DMSO at 25 °C. [b] In 74.5% H_2SO_4 at -10 °C. [c] In $CDCl_3$ at 0 °C. [d] In 72.3% H_2SO_4 at 0 °C.

The Formation of the ipso-*Intermediate*.—The analysis of the reaction mixtures in the nitration of the *NN*-dimethyl-*p*-toluidinium ion has been based mainly on the height of the C-Me peaks in the ^1H n.m.r. spectrum. The positions of these peaks in the initial anilinium ion, the intermediate and the product are sufficiently separate for overlap to be ignored (Figure 1) and so the percentage of each species present has been calculated from the ratio of the height of the corresponding peak to the sum of the height of all three peaks. In kinetic runs carried out in >75% sulphuric acid a small amount of 3-nitro-*NN*-dimethyl-*p*-toluidine is formed (by direct nitration of the protonated amine) and the fourth peak has then to be included in the above analysis. This can be seen at δ 2.6 in spectra (A) and (B) in Figure 1. The results for a typical kinetic run are shown in Figure 2.

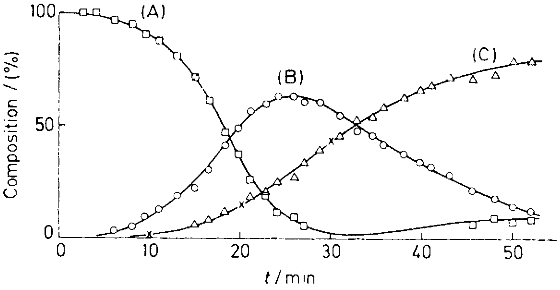
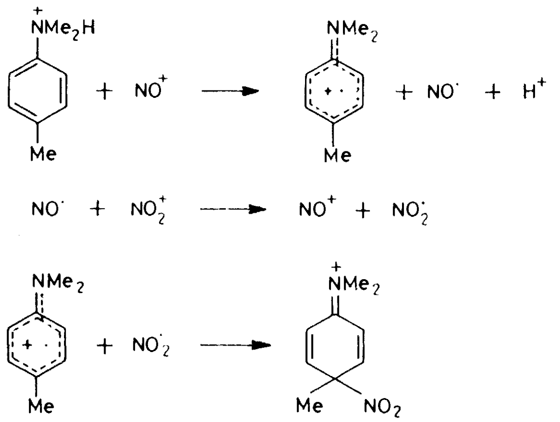


FIGURE 2 The composition of a reaction mixture for the reaction of *NN*-dimethyl-*p*-toluidine (0.5 mol dm^{-3}) with nitric acid (0.5 mol dm^{-3}) in 73.9% sulphuric acid at 0 °C: (A) the initial amine, (B) the *ipso*-intermediate, and (C) the 2-nitro-product. The points indicated by × are calculated concentrations (see text)

Such plots show that the formation of the intermediate is an autocatalytic reaction. The reaction is inhibited by the presence of hydrazine and strongly catalysed by traces of nitrous acid. It appears therefore that the formation of the intermediate does not result from the attack of a nitronium ion at the 4-position but is initiated by traces of nitrous acid and then catalysed by the nitrous acid produced in side-reactions accompanying the formation of the intermediate.

No systematic kinetic study of this reaction has been carried out since the overall rate and kinetic form appear very similar to the reaction of the *NN*-dimethylanilinium ion under the same conditions. At the acidities used in the present work, the reaction of the *NN*-dimethylanilinium ion leads almost completely to benzidine derivatives,[4] but accompanied by an increasing amount of *NN*-dimethyl-*p*-nitroaniline as the acidity is increased. The proposed mechanism involves the intermediate formation of the cation radical PhNMe$_2^{+\cdot}$ as a result of the attack of the nitrosonium ion on the protonated amine. This cation radical is considered to react either by coupling at the *para*-position with an identical cation radical or amine molecule to form derivatives of benzidine or by the addition of nitrogen dioxide at the *para*-position to form eventually *NN*-dimethyl-*p*-nitroaniline. The presence of the *p*-methyl group in the cation radical from *NN*-dimethyl-*p*-toluidine should hinder the coupling reaction and so, by analogy, the formation of the *ipso*-intermediate should occur as shown in Scheme 1. The mechanism shown for the oxidation of nitric oxide in this scheme may be an over-simplification but it illustrates the stoicheiometry involved.

An alternative and simpler reaction path for the formation of the *ipso*-intermediate would involve the attack of NO$^+$ at the *para*-position to form the related *ipso*-intermediate with NO in place of NO$_2$ followed directly by the oxidation of this nitroso-group to a nitro-group. However, this interpretation provides no explanation of why the corresponding reaction of the *NN*-dimethylanilinium ion leads to the formation of benzidines instead of to *para*-nitration. The mechanism in Scheme 1 also receives support from the e.s.r. spectrum of the reaction mixture for this is very similar to that expected for the cation radical of *NN*-dimethyl-*p*-toluidine (Figure 3). The hyperfine coupling constants used for the simulated spectrum in Figure 3 are slight modification of those in the literature [5] (given in parentheses): a_N 11.70 (11.06); a_H(N-Me) 10.60 (12.20); a_H(*ortho*) 5.30 (5.30); a_H(*meta*) 1.35 (1.35); a_H(C-Me) 10.60 (10.00) G. The literature values were obtained from the electrochemical generation of the cation radical in acetonitrile and could therefore differ from those of the cation radical in *ca.* 70% sulphuric acid. When the *ipso*-intermediate is generated in the presence of excess nitric acid, the e.s.r. spectrum shown in Figure 3 disappears when the conversion of the initial anilinium ion to the intermediate is complete. When the amine is in excess, the e.s.r. spectrum can still be observed for much of the rearrangement stage. Unfortunately these observations do not prove that the cation radical is on the reaction path for *ipso*-nitration for it could also derive from one of the side reactions (see below).



SCHEME 1

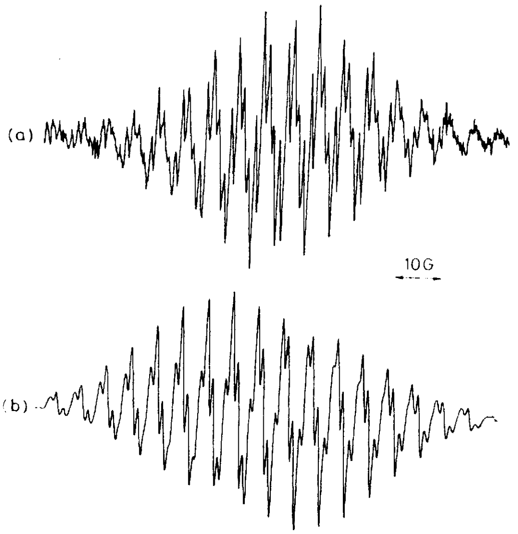


FIGURE 3 (a) The e.s.r. spectrum of a reaction mixture with *NN*-dimethyl-*p*-toluidine (0.75 mol dm^{-3}) and nitric acid (0.75 mol dm^{-3}) in 75.9% sulphuric acid at 0 °C. The spectrum was taken 37 min after mixing the reactants. (b) The calculated spectrum for the cation radical *p*-MeC$_6$H$_4$NMe$_2^{+\cdot}$. For details see text

The formation of the *ipso*-intermediate from the *ortho*-substituted amine (I; R^1 = R^2 = Me) requires catalysis by added sodium nitrite and the reaction mixture gives no e.s.r. absorption. The slower rate of this reaction is as expected from the secondary steric effect of the *o*-methyl groups [6] and the absence of the e.s.r. spectrum could be explained from the lower stability and hence lower concentration of the cation radical. Whether or not cation radicals are involved in all these nitrous acid catalysed *ipso*-nitrations is not yet clear.

The Kinetics of the Rearrangement.—The kinetic study of the rearrangement stage of Scheme 1 by n.m.r. spectroscopy presents a number of difficulties. One arises from the requirement for high concentrations of the reactants, for this restricts the range of concentrations that can be used and also implies that a change in these concentrations can cause a significant change in the reaction medium. Thus, an increase in the concentrations of the amine and nitric acid increases the percentage of water in the solvent during the rearrangement, for one molecule of water is formed for each molecule of the *ipso*-intermediate. We have taken account of this by specifying both the initial composition of the solvent and the composition of the solvent during the rearrangement. The calculation of the latter also takes account of the initial protonation of the amine when this is added as the neutral molecule.

Another complication arises because the concentrations of the *ipso*-intermediate and the product do not follow a simple kinetic form until the conversion of the initial amine to the *ipso*-intermediate is complete. In the earlier experiments, the rate coefficient of the rearrangement was determined by a conventional first-order plot of the height of the N-Me or C-Me peaks in the ^1H n.m.r. spectrum of the *ipso*-intermediate using the later part of the composition–time curve (*cf.* Figure 1). To avoid this restriction, this method has been supplemented by the calculation of k_1 by equation (2). In this equation, [II] represents the concentration of the *ipso*-intermediate and $[P]_t$ the concentration of the product at time t. The integral was evaluated from the main part of the composition–time curves using Simpson's approximation (see Experimental section). Both methods imply that the rearrangement is first order with respect to the *ipso*-intermediate but, if this is not true, the fact should be apparent from the variation in the value of k_1.

$$[P]_{t_2} - [P]_{t_1} = k_1 \int_{t_1}^{t_2} [II]\,dt \qquad (2)$$

The two methods for the calculation of k_1 involve different assumptions. The calculation of k_1 from the first-order plots based on the concentration of the intermediate implies that *all* the intermediate reacts to form the 2-nitro-product. The calculation of k_1 from equation (2) implies that *all* the 2-nitro-product is derived from the intermediate. The values of k_1 by the two methods were normally in agreement to within the usual limits (*ca.* 15%) of kinetic studies by n.m.r. but the use of equation (2) gave more consistent results. The possibility that some of the 2-nitro-product was obtained by direct substitution at the 2-position was checked by determinining the value of k_1 from equation (2) for *ca.* 75% reaction and by using this value of k_1 in equation (2) to calculate the first part of the percentage–time curve for the product. The good agreement of the observed and calculated results is shown in Figure 2. However, in some runs in which nitrous acid was present at the start of reaction, the initial percentages of the 2-nitro-product exceeded the values calculated from equation (2) and so some direct attack at the 2-position may then occur. For such runs, the rate coefficients have been calculated from the slopes of the first-order plots.

One further complication comes from the existence of certain side-reactions that accompany the rearrangement. These have not yet been investigated in detail but mass spectrometric analysis of the reaction products suggest that they derive from demethylation at the nitrogen atom. The products of these side reactions are not easily detected in the n.m.r. spectra when excess nitric acid is present but become significant when excess amine is used and become important when, in addition, the 2,6-positions of the amine are deuteriated. When the side reactions are important, the rate of disappearance of the *ipso*-intermediate exceeds the rate of formation of the 2-nitro-product but both reaction rates appear greater than those observed under conditions where the side-reactions are absent. To avoid these complications, the kinetic form of the rearrangement has been determined from experiments using excess nitric acid.

The values of k_1 [equation (2)] from experiments under these conditions are listed in Table 3. The eight kinetic runs carried out with the initial concentration of sulphuric acid at 73.8% and with $[Ar\overset{+}{N}Me_2H]$ 0.5 mol dm^{-3} show that the rate of reaction is insensitive to the excess of nitric acid during the rearrangement when this is varied over the range 0.125—0.5 mol dm^{-3}. However, the following group of seven runs show that the first-order rate coefficient is sensitive to the initial concentration of the amine. The interpretation of this is not entirely clear (see later) but because of these results the experiments on the acidity dependence of k_1 have been carried out with a constant initial concentration of the amine (0.5 mol dm^{-3}). The results are given in Table 3 and are plotted against the effective concentration of sulphuric acid in Figure 4. The rate coefficient decreases with acidity, the slope of the logarithmic plot varying from —0.07 to *ca.* —0.13. A trace of sodium nitrite was added initially for the runs at the lowest acidity to facilitate the formation of the intermediate and these rate coefficients were therefore calculated from the slopes of first-order plots.

TABLE 3

First-order rate coefficients [k_1, equation (2)] for the rearrangement of the *ipso*-intermediate (II; $R^1 = Me$, $R^2 = H$) in aqueous sulphuric acid at 0 °C

H_2SO_4 (%)		$[Ar\overset{+}{N}Me_2H]$ mol dm^{-3}	$[HNO_3]$ mol dm^{-3}	$10^4k_1/s^{-1}$	
Solvent	Solution				
64.1	62.4	0.5	0.625	28.5 [a]	28.6
64.1	62.4	0.5	0.625	28.6 [a]	
69.7	68.3	0.5	0.625	12.1	12.0
69.7	68.3	0.5	0.625	11.8	
73.8	72.5	0.5	0.625	5.81	5.56
73.8	72.5	0.5	0.625	5.17	
73.8	72.5	0.5	0.625	6.32	
73.8	72.5	0.5	0.625	4.95	
73.8	72.5	0.5	0.75	5.91	5.59
73.8	72.5	0.5	0.75	5.26	
73.8	72.5	0.5	1.0	5.61	5.48
73.8	72.5	0.5	1.0	5.34	
73.8	73.2	0.625 [b]	0.75	5.73	5.25
73.8	73.2	0.625 [b]	0.75	4.66	
73.8	73.2	0.625 [b]	0.75	5.35	
73.8	73.5	0.375 [b]	0.75	3.61	3.70
73.8	73.5	0.375 [b]	0.75	3.79	
73.8	73.6	0.25 [b]	0.75	2.50	2.51
73.8	73.6	0.25 [b]	0.75	2.53	
79.6	78.5	0.50	0.75	1.17	1.17
79.6	78.5	0.50	0.75	1.16	

[a] Calculated from the slope of a first-order plot. [b] Added as the hydrogensulphate salt.

The form of the rate profile suggested that the proton loss could be rate-determining and so experiments were carried out with the deuteriated amine (II; $R^1 = Me$, $R^2 = D$). The results are given in Table 4 and included in Figure 4. The isotope effect is large at the higher acidities but appears to decrease significantly as the acidity is lowered. In the presence of excess nitric acid, the isotope effect from the slopes of first-order plots is essentially the same as that obtained from equation (2); thus for reaction in 73.8% sulphuric acid the former gives k_H/k_D 4.9. However, this is not true when excess amine is present for with $[Ar\overset{+}{N}Me_2H]$ 0.75 and $[HNO_3]$ 0.5 mol dm^{-3} in 73.6% sulphuric acid, the value of k_H/k_D is 1.9 when followed from the disappearance of the *ipso*-intermediate but 4.9 when followed from the appearance of the 2-nitro-product [equation (2)]. Presumably the side-reactions involving the *ipso*-intermediate and the excess amine occur at the same rate with the deuteriated and undeuteriated species and thus reduce the isotope effect for the overall reaction.

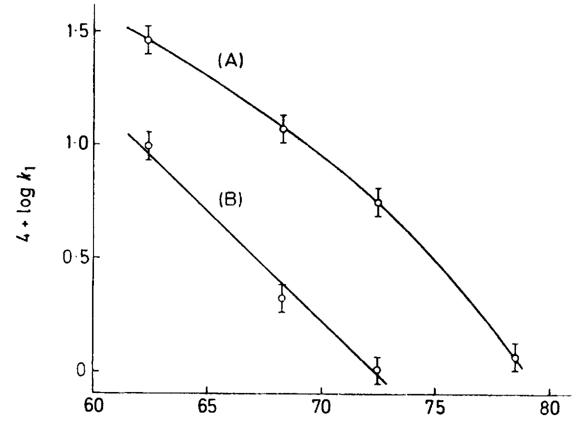


FIGURE 4 Rate profiles for the rearrangement of the *ipso*-intermediates (II; $R^1 = Me$, $R^2 = H$) (A) and (II; $R^1 = Me$, $R^2 = D$) (B). $[Ar\overset{+}{N}Me_2H]$ 0.5 mol dm^{-3}, $[HNO_3]$ 0.625 mol dm^{-3}. The error bars correspond to ±15%

TABLE 4

First-order rate coefficients [k_1, equation (2)] for the rearrangement of the deuteriated *ipso*-intermediate (II; $R^1 = Me$, $R^2 = D$) in aqueous sulphuric acid at 0 °C

$[Ar\overset{+}{N}Me_2H]$ = 0.5 mol dm^{-3} $[HNO_3]$ = 0.625 mol dm^{-3}

H_2SO_4 (%)				
Solvent	Solution	$10^4k_1/s^{-1}$		k_1^H/k_1^D
64.1	62.4	9.14 [a]	9.77	2.9
64.1	62.4	10.4 [a]		
69.7	68.3	1.76	2.13	5.6
69.7	68.3	1.71		
69.7	68.3	2.07		
69.7	68.3	2.98		
73.8	72.5	1.11	1.0	5.6
73.8	72.5	0.88		

[a] Footnote *a*, Table 3.

The consequence of adding various species to the reaction mixture at the time when concentration of the intermediate is a maximum ($NaNO_2$, $N_2H_5HSO_4$, 2-nitro-product) or at the start of the reaction ($KHSO_4$) is shown in Table 5. None of these species appear to have a marked effect on the rate of the rearrangement reaction.

Isotopic Studies with ^{15}N *and 'Crossover' Experiments.*—A number of experiments have been carried out to determine whether the rearrangement of (II; $R^1 = Me$, $R^2 = H$) is inter- or intra-molecular. One set of experiments involved carrying out this rearrangement in the presence of other species and determining whether the other species had undergone nitration. A reaction mixture with equal concentrations of *NN*-dimethyl-*p*-toluidine and nitric acid in 73.5% sulphuric acid at 0 °C was followed by n.m.r. spectroscopy until the concentration of the intermediate was a maximum and then an approximately equal amount of *NN*-dimethyl-*p*-ethylaniline in the same concentration of sulphuric acid was added. Analysis of the reaction product by t.l.c. gave no evidence of the 2-nitro-derivatives of *NN*-dimethyl-4-ethylaniline. The experiment was repeated using 80.5% sulphuric acid followed by analysis of the reaction product by mass spectrometry but with essentially the same result: the height of the peak corresponding to the 2-nitro-derivative of the added amine was only 2% of that of *NN*-dimethyl-2-methyl-*p*-toluidine. The first of the above experiments was repeated in the reverse direction by adding a solution of *NN*-dimethyl-*p*-toluidine after the complete formation of the *ipso*-intermediate from *NN*-dimethyl-4-ethylaniline and nitric acid but again none of the 2-nitro-derivative of the added amine could be detected in the reaction product.

TABLE 5

Effect of added species (X) on the values of k_1 [equation (2)] for the rearrangement of the *ipso*-intermediate (II; $R^1 = Me$, $R^2 = H$) at 0 °C

Conditions	X	$\frac{[X]}{mol\ dm^{-3}}$	$10^4k_1/s^{-1}$
a			5.47
a	$NaNO_2$	0.07	5.58
a	$N_2H_5HSO_4$	0.01	6.60
b			9.18 [d]
b	2-Nitro-product	0.79	7.74 [d]
c			3.57
c	$KHSO_4$	0.5	3.43

[a] $[Ar\overset{+}{N}Me_2H]$ 0.5 mol dm^{-3}, $[HNO_3]$ 0.625 mol dm^{-3}, 73.6% H_2SO_4. [b] $[Ar\overset{+}{N}Me_2H]$ = $[HNO_3]$ = 0.75 mol dm^{-3}, 73.8% H_2SO_4. [c] $[Ar\overset{+}{N}Me_2H]$ 0.5 mol dm^{-3} (added as hydrogen-sulphate) $[HNO_3]$ 0.75 mol dm^{-3}, 73.8% H_2SO_4' [d] From the slopes of first-order plots.

A more sensitive test of the nitration of added species was provided by the addition of a solution of *p*-methylbenzyltrimethylammonium perchlorate in 80.5% sulphuric acid at 0 °C to a reaction mixture with equimolar concentrations of *NN*-dimethyl-*p*-toluidine and nitric acid at this temperature and acidity after complete formation of the *ipso*-intermediate. The n.m.r. spectrum of the reaction mixture after rearrangement showed no peaks corresponding to the nitration of the quaternary salt. At this temperature and acidity, the half-life for the nitration of this quaternary salt with equimolar reactants (0.1 mol dm^{-3}) would be *ca.* 6 s.*

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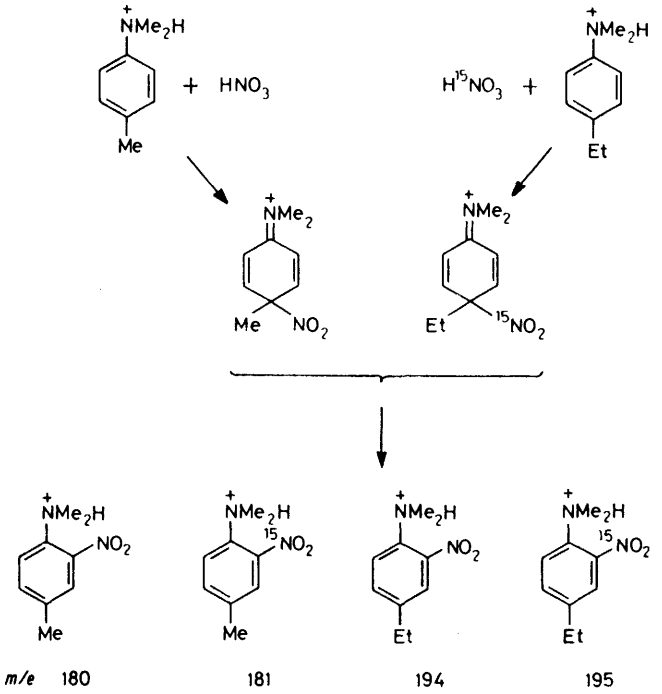
* Calculated by an extrapolation of previous results.[7]

The above results suggest that the rearrangement is intramolecular but there is some evidence to the contrary. When equal amounts of the two *ipso*-intermediates in Scheme 2 were formed separately in 80.5% sulphuric acid then allowed to rearrange in the same solution, the nitro-products from the two amines each contained *ca.* 12% of the other isotope of nitrogen. This estimate is based on a comparison with the mass spectrum of the product obtained by mixing the solutions after rearrangement was complete. When an amount of $H^{15}NO_3$ in 73.8% sulphuric acid at 0 °C was added during the rearrangement of an equal amount of the intermediate (II; R^1 = Me, R^2 = H) at this temperature and acidity, 11% of the product contained ^{15}N. Thus, under these conditions, some exchange does occur.



SCHEME 2

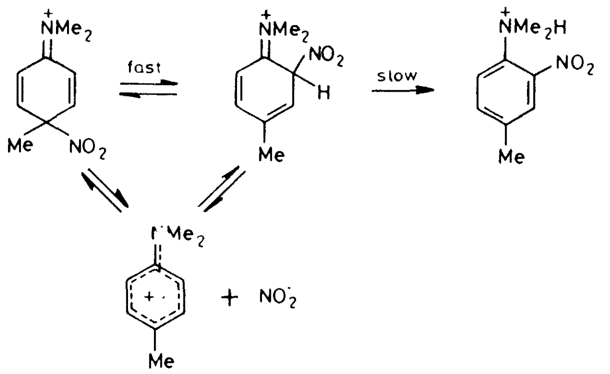
In assessing the significance of these results, it is necessary to remember that 20—30% of the 2-nitro-product is formed before the solution with the 'other' isotope is added, for the mixing cannot be carried out until after complete formation of the *ipso*-intermediate(s). A random distribution of the nitrogen isotopes after mixing would therefore lead to an incorporation of 35—40% of the 'other' isotope in the product. Thus, the observed exchange is *ca.* 1/3 of that expected for complete exchange after mixing.

DISCUSSION

This discussion is limited to the mechanism of the rearrangement stage of equation (1). It is convenient to consider first the rate-determining step and then the more fragmentary evidence on the earlier stages of the reaction path.

At the higher acidities the slope of the rate profile in Figure 4 approaches that for the corresponding variation of H_0 (−0.15); this suggests that proton loss from the *ipso*-intermediate is occurring before or during the rate-determining step. The isotope effect resulting from deuteriation at the 2-position (Table 4) shows that this C–H bond is being broken in the rate-determining step. Taken together, these results suggest that the rate-determining step is the proton transfer shown in the final stage of Scheme 3.

One difficulty with this interpretation is that the first-order rate coefficients depend on the initial concentration of the amine and hence on the concentration of the *ipso*-intermediate (Table 3). The differences are greater than would be expected from the corresponding change in the acidity of the solutions. However, it is difficult to interpret this variation as a true second-order reaction with respect to the *ipso*-intermediate since the first-order rate coefficients calculated from the overall reaction account for the amount of product formed in the initial stages of the reaction when the concentration of the *ipso*-intermediate is low [see calculated points (×) in Figure 2]. Preliminary kinetic studies of the rearrangement * using much lower concentrations of the *ipso*-intermediate (*ca.* 10^{-3} mol dm^{-3}) and followed by u.v. spectroscopy have given rate coefficients within a factor of two of those reported here. We prefer therefore to assume that the higher concentration of amine used in some of the experiments gives rise to a medium effect which facilitates the uptake of a proton by the solvent.



SCHEME 3

The above interpretation implies that the migration of the nitro-group between the 2- and 4-positions is fast and reversible in comparison with the rate of proton loss. This migration cannot occur through the formation of the amine molecule and a separate nitronium ion for other aromatic molecules in the solution of comparable or greater reactivity do not undergo nitration. However, the presence of some exchange during the concurrent rearrangements (Scheme 2) and in the presence of $H^{15}NO_3$ shows that the rearrangement is not exclusively intramolecular. The presence of an intermolecular component can be reconciled with the absence

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* Carried out by Mr. P. Helsby.

of nitration of the other species present provided the exchange occurs *via* the formation of nitrogen dioxide and the cation radical as shown in Scheme 3. The concentration of the cation radical must, however, be very low since an e.s.r. spectrum is not always observed during the rearrangement (see above).

There are two considerations which, taken together, suggest that the intermolecular path is relatively unimportant in the overall reaction. One comes from the fact that the extent of exchange is only *ca.* 1/3 of what would be expected from complete mixing of the isotopically labelled species. The other is that the recombination of the cation radical with nitrogen dioxide should reform the *ipso*-intermediate. This comes partly from the relative spin densities in the cation radical * and partly because, from the k_H/k_D isotope effect, the Wheland intermediate resulting from the attack of nitrogen dioxide at the 2-position should normally rearrange to form the *ipso*-intermediate instead of undergoing proton loss to form the product. Thus the contribution of the intermolecular path to the overall reaction rate should be much less than the proportion of isotopic exchange in the product. The main reaction appears to involve the intramolecular 1,3-rearrangement. This may, of course, occur *via* the radical pair $Ar\overset{+\cdot}{N}Me_2\ NO_2\cdot$ but since many 1,3-rearrangements must occur for each overall reaction it is a little surprising that so little isotopic exchange is observed. If the rearrangement is represented in this way, it is probably necessary to assume that some interaction keeps the radical pair from separating during most of the migrations.

The mechanism presented in Scheme 3 is consistent with earlier work in the literature. An isotope effect on the rate of *ortho*-nitration of *NN*-dimethylaniline has not been observed previously but deuteriation of the aromatic ring does modify the *ortho* : *para* ratio in the rearrangement of *N*-nitroaniline in a way which suggests that the migration of the nitro-group between these positions can compete under some conditions with the rate of proton loss.[9] Methylation of the amino-group should hinder this proton loss by providing steric hindrance to the formation of the *o*-nitro product. The intermolecular reaction path in Scheme 3 is analogous to that proposed for the 1,3-rearrangement of nitrocyclohexadienones,[10] although the dissociation is then considered to be rate limiting.

Further work is in progress on the side-reactions, the effect of additional substituents, and on other methods of following these rearrangements.

EXPERIMENTAL

Materials.—Fuming nitric acid, sulphuric acid, and sodium nitrite were AnalaR reagents. Nitric acid (100%) was prepared by distillation under reduced pressure of a solution of fuming nitric acid in concentrated sulphuric acid and was used for the kinetic runs. Nitric acid labelled with ^{15}N (95.8 atom %) was obtained from Prochem. 2,4,6-Trimethylaniline, *p*-ethylaniline, and *NN*-dimethyl-*p*-toluidine were laboratory reagents. *NN*-Dimethyl-*p*-ethylaniline and *NN*-dimethyl-2,4,6-trimethylaniline were prepared by *N*-methylation of the corresponding free amines with trimethyl phosphate [11] and were purified by distillation under reduced pressure. The amine hydrogensulphates were prepared as described previously[12] The deuteriation of *NN*-dimethyl-*p*-toluidine was carried out by dissolving the amine (2 g) in D_2SO_4–D_2O (3 mol dm^{-3}, 25 ml) and heating at 80 °C for one week.[13] The product after neutralisation and extraction gave 2,6-dideuterio-*NN*-dimethyl-*p*-toluidine (1.7 g). The purity of the above compounds was checked by g.l.c., n.m.r., or elemental analysis and was shown to be satisfactory.

Products.—All reactions were carried out at 0 °C. A solution of the amine (usually 2 ml, 0.5—1.5 mol dm^{-3}) in sulphuric acid was mixed with an equal volume of a solution of nitric acid of equal or slightly greater molarity in the same concentration of sulphuric acid. When reaction was complete, the mixture was poured onto ice, neutralised with ammonia, extracted with chloroform, and separated by t.l.c. using the procedure described previously.[4] The reaction of *NN*-dimethyl-*p*-toluidine under these conditions in 74.9% sulphuric acid gave a 78% yield of the 2-nitro-derivative. When a second aromatic compound was present during the rearrangement, this was added as an approximately equimolar solution in sulphuric acid of the same concentration after the conversion of the initial amine to the *ipso*-intermediate was complete. The products were then analysed as described above. A similar procedure was used for the rearrangement carried out in the presence of $H^{15}NO_3$. In experiments involving two concurrent rearrangements, each was started as described above and then the two reacting solutions were mixed after the conversion of each amine to the corresponding *ipso*-intermediate was complete. After complete reaction, the products were separated as described above and the mass spectrum determined. Thus, in the experiment outlined in Scheme 2, the relative intensities were 181/180, 0.30; 194/195, 0.35. The corresponding intensities in the spectrum of the product obtained by mixing the reacting solutions after each rearrangement had been completed were 181/180, 0.15; 194/195, 0.23. The mass spectra were measured on AEI MS 902 or VG 7070 instruments.

E.s.r. and N.m.r. Spectra.—The e.s.r. spectra were measured on a Varian E4 spectrometer. The ^1H and ^{13}C n.m.r. spectra were measured on Varian HA 100 and Varian CFT 20 spectrometers respectively. Some of the ^{13}C chemical shifts given here are slightly different from those initially reported [2] since the latter were based on the central line of [$^2H_6$]DMSO (taking this as δ 39.59) and the present results are based on Me_4Si in an internal capillary.

Kinetic Measurements.—A solution of nitric acid (0.5—2.0 mol dm^{-3}, 1 ml) in sulphuric acid at 0 °C was added to a solution of the amine or amine hydrogensulphate (0.5—1.5 mol dm^{-3}, 1 ml) in the same concentration of sulphuric acid at 0 °C and the mixture was stirred for *ca.* 1 min. Part of the solution was then transferred to an n.m.r. tube and the reaction was followed on a Varian HA 100 spectrometer. The percentages of the initial amine, the *ipso*-intermediate, and the 2-nitro-product were calculated from the heights of the corresponding C-Me peaks relative to the sum of the heights of the three peaks. A composition–time curve as shown in Figure 2 was constructed for each run and the rate coefficient calculated by two methods: (a) from

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* As judged from the hyperfine coupling constants (see p. 520) taking a_H(C–Me) as similar to a_H(*para*).[8]

equation (2) after numerical integration of the composition curve for the intermediate using the standard program for Simpson's approximation in a Texas Instruments T.I.58 calculator and (b) from the slope of a least-squares plot of the logarithm of the concentration of the intermediate against time. Such plots gave correlation coefficients of 0.97—0.99. Neither approach gave wholly satisfactory results but, as can be seen from Table 3, the deviation from the mean of the rate coefficients in repeated runs is normally within ±10%. When the nitric acid was in excess, the rate coefficients calculated by method (b) were *ca.* 10% lower than those by method (a) but the differences were not such as to change any of the conclusions reached above. When the concentration of the amine was equal to or exceeded the concentration of the nitric acid the results were less reproducible. Product analysis by mass spectroscopy–g.l.c. shows that significant demethylation then occurs and the *N*-methyl-*p*-toluidine formed may interfere with the later stages of the reaction.

The effective percentage of sulphuric acid in the solvent during the rearrangement reaction was obtained by working out the actual molarities of sulphuric acid and water at this stage after allowing for the water created in forming the *ipso*-intermediate and, where relevant, the sulphuric acid consumed in protonating the amine. These calculations assume that the density of the solution is the same as that of the solvent. The calculated percentage of sulphuric acid was then obtained from the weights of sulphuric acid and water associated with these molarities.

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REFERENCES

[1] H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 1930, 277.

[2] K. Fujiwara, J. C. Giffney, and J. H. Ridd, *J. Chem. Soc., Chem. Commun.*, 1977, 301.

[3] G. A. Olah, H. C. Lin, and D. A. Forsyth, *J. Am. Chem. Soc.*, 1974, **96**, 6908.

[4] J. C. Giffney and J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2*, 1979, 618.

[5] E. T. Seo, R. F. Nelson, J. M. Fritsch, L. S. Marcoux, D. W. Leedy, and R. N. Adams, *J. Am. Chem. Soc.*, 1966, **88**, 3498.

[6] N. V. Sidgwick, 'The Organic Chemistry of Nitrogen,' revised by T. W. J. Taylor and W. Baker, O.U.P., Oxford, 1937, p. 218.

[7] T. A. Modro and J. H. Ridd, *J. Chem. Soc. B*, 1968, 528.

[8] M. K. Carter and G. Vincow, *J. Chem. Phys.*, 1967, **47**, 292 302.

[9] D. V. Banthorpe, E. D. Hughes, and D. L. H. Williams, *J. Chem. Soc.*, 1964, 5349.

[10] C. E. Barnes and P. C. Myhre, *J. Am. Chem. Soc.*, 1978, **100**, 973.

[11] J. H. Billman, A. Radike, and B. W. Mundy, *J. Am. Chem. Soc.*, 1942, **64**, 2977.

[12] J. R. Blackborow, D. P. Clifford, I. M. Hollinshead, T. A. Modro, J. H. Ridd, and M. C. Worley, *J. Chem. Soc., Perkin Trans. 2*, 1980, 632.

[13] *Cf.* D. J. Mills, Ph.D. Thesis, London, 1976, p. 131.