Kinetics and Mechanism of the Fischer–Hepp Rearrangement and Denitrosation. Part 10.[1] Reactions of 3-Methoxy-*N*-methyl-*N*-nitrosoaniline

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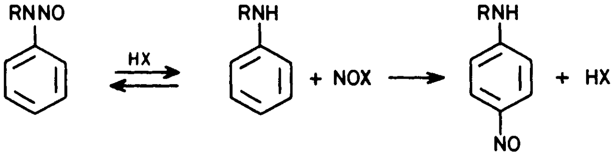
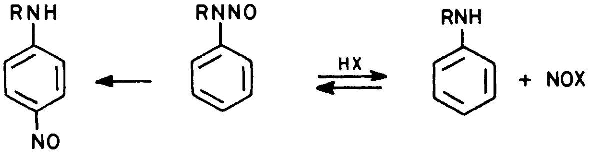
Further evidence is presented in favour of an intramolecular mechanism for the acid-catalysed Fischer–Hepp rearrangement of aromatic *N*-nitrosamines, both in water and in ethanol solvent. In aqueous acid 3-methoxy-*N*-methyl-*N*-nitrosoaniline (IV) gives the rearrangement product 3-methoxy-*N*-methyl-4-nitrosoaniline (V) in >90% yield. This figure drops a little to a constant 85% in the presence of one of three conventional ' nitrite traps ', hydrazoic acid, hydrazine, and sulphamic acid, and over a five-fold range of concentration of each. Additionally the observed first-order rate constant (k_0) is the same in the whole series. When nucleophilic species [Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$] are added the yield of (V) drops and the product of denitrosation, 3-methoxy-*N*-methylaniline (VI), is also observed. The effect is most marked for the most powerful nucleophiles [SCN^- and $SC(NH_2)_2$]. At the same time k_0 increases with increasing nucleophile concentration. The results are wholly consistent with a mechanism involving parallel reactions of the protonated *N*-nitrosamine to give either the product of denitrosation (by nucleophile attack) which is normally reversible, or that of rearrangement where the nucleophile is not involved, and which is irreversible. The results cannot be accounted for in terms of the older intermolecular mechanism whereby the rearrangement product arises by conventional electrophilic *C*-nitrosation involving both the products of denitrosation. This implies strongly that the rearrangement is an intramolecular process. Similar results are reported for the variation of yields and rate constants with added nucleophiles for the same reaction in acidified ethanol, so that it is very likely that the same mechanism operates in that solvent.

EARLY work on the acid-catalysed rearrangement of aromatic *N*-nitrosamines (the Fischer–Hepp rearrangement) led to the formulation of this reaction in terms of a reversible denitrosation followed by a conventional electrophilic aromatic substitution by a carrier of NO^+ (NOX) as set out in Scheme 1. The evidence in favour of Scheme 1 is summarised elsewhere [2,3] and is based entirely on a collection of product analyses. It was thought that the anion X^- (typically Cl^-) played an important role in the reaction analogous to the situation in the Orton rearrangement [4] of *N*-nitroacetanilide. However, closer examination of the experimental evidence shows that this outline mechanism whilst being consistent with the experimental facts is not specificially required, and an alternative Scheme 2, where the rearrangement proceeds intramolecularly and is parallel with reversible denitrosation, is equally compatible with the facts. A distinction between these two possibilities cannot be made using labelled materials,[5] but has been achieved for R = Me on the basis of a number of kinetic investigations for reactions in water.[3] The most compelling evidence comes from observing the yield of 4-nitroso-product as a function of the concentration of an added ' nitrite trap.' These species which include sulphamic acid or hydrazine *etc.* react rapidly and irreversibly with NOX. Scheme 1 predicts that the yield of (II) should decrease to zero as the concentration of the ' nitrite trap ' is increased, since there is now direct competition for NOX. Scheme 2 however requires that the yield of (II) should decrease to a constant value, as the formation of (III) becomes irreversible and results in two parallel reactions. A set of results was presented [6] for R = Me where the yield of rearrangement product (for a given acidity) was constant for a range of different ' nitrite traps ' and also for a range of concentrations. The intermolecular mechanism cannot cope with these findings. An earlier observation [7] that rearrangement does occur even in the presence of urea or sulphamic acid also argues against Scheme 1 and in favour of Scheme 2.



(I) (III) (II)

SCHEME 1



(II) (I) (III)

SCHEME 2

Further evidence for an intramolecular rearrangement comes from a kinetic study of the rearrangement as a function of the added nucleophile X^-. It is known [8] that the denitrosation process is very sensitive to the concentration and nature of X^- and the rate-limiting step for denitrosation is thought to be the attack of the nucleophile at the protonated nitrosamine [equation (1)]. The rearrangement can be separated from denitrosation by the addition of an excess of the secondary amine product PhN(R)H. Under these conditions the rate constant decreases to a limiting value, and the yield of rearranged product increases to a limiting value as [PhN(R)H] is increased. At the limit there is no kinetic

$$\mathrm{Ph\overset{+}{N}(R)H(NO)} + X^- \longrightarrow \mathrm{PhN(R)H} + \mathrm{NOX} \qquad (1)$$

dependence[9] upon Cl^- or Br^-, as expected from Scheme 2 but contrary to the predictions from Scheme 1.

Another investigation of this reaction[10] still argues in favour of an intermolecular mechanism. The results of our investigations were discounted[11] since it was claimed that many of the materials used by us as ' nitrite traps ' also have substantial nucleophilic reactivity. This is of course true in neutral or alkaline solution for N_3^-, NH_2NH_2, and $C_6H_5NH_2$ for example, but in the strongly acidic solution used in these reactions, these species exist virtually quantitatively in their protonated forms HN_3, $NH_2\overset{+}{N}H_3$, and $C_6H_5\overset{+}{N}H_3$, which will have negligible nucleophilic reactivity. Indeed this is borne out experimentally quite clearly by the constancy of the observed rate constants as [' nitrite trap '] is increased; a true zero-order condition prevails, whereas there is (except at very high nucleophile concentration and in solvents other than water) a true first-order dependence upon the nucleophile concentration for Cl^-, Br^-, SCN^-, I^-, and $SC(NH_2)_2$, in increasing order of reactivity. On the other hand species capable of acting as nitrite traps, but with no measurable nucleophilic reactivity towards the protonated nitrosamine under acid conditions are (again in order of increasing reactivity), $CO(NH_2)_2$, $\overset{+}{N}H_3OH$, $C_6H_5NH_2$, NH_2SO_3H, ascorbic acid, 2- and 4-nitroaniline, $NH_2\overset{+}{N}H_3$, and HN_3.

In this paper studies on the Fischer–Hepp rearrangement have been extended to an examination of the reactions of 3-methoxy-*N*-methyl-*N*-nitrosoaniline (IV) in acid solution particularly with a view to establishing the generality or otherwise of the intramolecularity of the change. This substrate was chosen because it is known[12] that it gives a much higher yield of the rearrangement product than does the nitrosamine without ring-substitution under the same experimental conditions.

EXPERIMENTAL

The 3-methoxy-nitrosamine (IV) and its 2,4,6-trideuterio-isomer were prepared as described previously.[12] Reactions were carried out in water and in ethanol solvents and were studied kinetically (spectrophotometrically) at 31 °C. Rate measurements were made at 320 nm, the maximum absorption of the rearrangement product in acid solution (ε 20 200 measured in water), and the absorption noted as a function of time. The product was not generally completely infinitely stable in acid solution, so the Guggenheim method was used to measure the first-order rate constants k_0. The yields were calculated from the ∞ readings at 320 nm and are all adjudged to be within $\pm 2\%$. In some cases the product of denitrosation, 3-methoxy-*N*-methylaniline, was observed at 278 nm.

RESULTS AND DISCUSSION

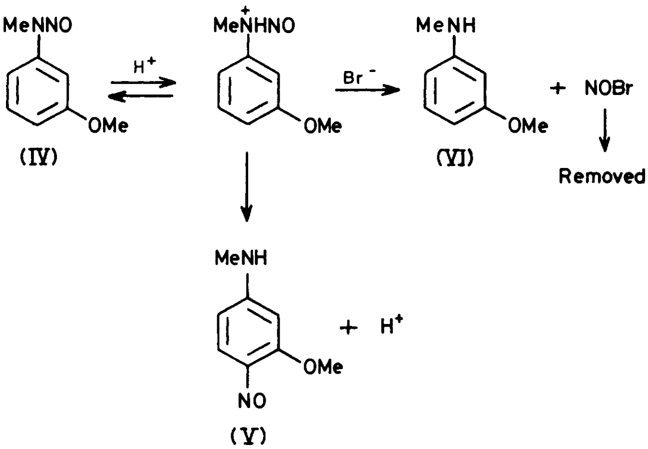
In sulphuric acid solution rearrangement of (IV) occurred in the absence of any added nucleophile or nitrite trap to an extent of 85—95%. The reaction was acid-catalysed as expected (see Table 1) and log k_0 correlated quite well with H_0 with a slope of —0.9.

TABLE 1

Variation of rate constant and yield of rearrangement product with acidity for the reaction of (IV) in sulphuric acid

$[H_2SO_4]$/M	10^4k_0/s^{-1}	Rearrangement (%)
0.79	1.08	85
1.59	3.75	95
2.37	8.55	92
3.15	18.5	95

When ' nitrite traps ' are added (sodium azide, hydrazine sulphate, sulphamic acid) at one acidity the yield of rearrangement product drops slightly but consistently from 95 to 85% and is constant, within experimental error, for the range of ' nitrite traps ' and also for a five-fold range of concentrations for each. At the same time the rate constant increases by a small amount (deemed to be outside the experimental error) from 2.94×10^{-3} s^{-1} to an average value of 3.29×10^{-3} s^{-1}. The results are presented in Table 2. These results are only consistent with the outline mechanism given in Scheme 2. The concentration of ' nitrite traps ' used here are sufficient to ensure the irreversibility of the denitrosation process. Independent work on the denitrosation reaction alone has confirmed this for this and other substituted *N*-nitrosamines.[13] This then leaves the situation of two parallel reactions from the same intermediate, the protonated form of the nitrosamine (Scheme 3), and the product ratio should be quite independent of the ' nitrite trap ' concentration, so long as it exceeds some threshold value which ensures the irreversibility of the denitrosation



SCHEME 3

TABLE 2

Variation of rate constant and yield of rearrangement product with added ' nitrite traps ' for the reaction of (IV) in 3.5M-H_2SO_4

' Nitrite trap '	10^3k_0/s^{-1}	Rearrangement (%)
0	2.94	95
HN_3 1×10^{-3}M	3.10	84
HN_3 5×10^{-3}M	3.22	85
$\overset{+}{N}H_3NH_2$ 1×10^{-3}M	3.25	85
$\overset{+}{N}H_3NH_2$ 5×10^{-3}M	3.39	85
NH_2SO_3H 1×10^{-3}M	3.33	84
NH_2SO_3H 5×10^{-3}M	3.48	84

process. The observed rate constant k_0 represents now the sum of the rate constants for both processes and again should be independent of the 'nitrite trap' concentration. The small increase observed compared with the value in the absence of any trap is compatible with the effective removal of the reverse step (*N*-nitrosation). Scheme 1 predicts that the yield of (II) should also decrease with added 'nitrite trap' but should go to zero. It is impossible to rationalise the constant product ratio obtained (and the constant rate constants) with that mechanistic framework. The very fact that rearrangement occurs in high yield in the presence of *e.g.* 5×10^{-3}M-HN_3 argues very strongly against Scheme 1 since it is known that this concentration of HN_3 is more than sufficient to suppress *N*-nitrosation, and therefore by implication *C*-nitrosation.

The product ratio of rearrangement : denitrosation will be decided by the various factors affecting these processes. Both are known [8,13] to be acid-catalysed and so the product ratio should not change with acidity. However whereas denitrosation is brought about by nucleophilic attack [8] (*e.g.* by Br^- as in Scheme 3), rearrangement is believed to be an intramolecular process not involving a nucleophilic species.[3] Thus increasing the nucleophile concentration should decrease the yield of rearrangement, as should the change to a more powerful nucleophile. The reactivity sequence of nucleophiles has been established [8] as $Cl^- < Br^- < SCN^- < I^- < SC(NH_2)_2$. Table 3 shows the effect on the product ratio (and the rate constants) of changing both the concentration and the nature of the added nucleophile. It was more convenient experimentally to follow kinetically the appearance of the rearrangement product (V), but it was also possible to observe qualitatively the presence of the denitrosation product (VI). All these reactions were carried out in the presence of added sodium azide (5×10^{-3}M) to ensure the complete irreversibility of denitrosation.

TABLE 3

Rearrangement yields and rate constants for the reaction of (IV) (in 3.5M-H_2SO_4 containing HN_3 5×10^{-3}M) in the presence of added nucleophiles

Nucleophile	$10^3k_0/s^{-1}$	Rearrangement (%)
(H_2O)	3.27	80
0.077M-Cl^-	3.51	73
0.077M-Br^-		16
0.077M-SCN^-		0
0.077M-$SC(NH_2)_2$		0
0.004M-Br^-	3.86	65
0.008M-Br^-	4.14	56
0.016M-Br^-	6.6	36
0.032M-Br^-	9.4	29
0.077M-Br^-		16
0.100M-Br^-		11
0.600M-Br^-		~2

As shown in Table 3 the effect of changing the nucleophile from Cl^- to Br^- to SCN^- to $SC(NH_2)_2$ (all at 0.077M) markedly decreases the yield of rearrangement product as expected. Indeed for the most reactive nucleophiles, no rearrangement at all is observed, since the rate of denitrosation is now so large as to dominate. Similarly, for one nucleophile (bromide ion) increasing the concentration has the same effect. The rate constants increase since k_0 is the sum of the values for rearrangement and for denitrosation, and the latter increases with $[Br^-]$ (since the first-order rate constant for denitrosation includes the $[Br^-]$ term), and also on changing to a more powerful nucleophile. Where the yield of rearrangement was $<16\%$ it was not possible to obtain a reliable value for k_0 because of the relatively small changes in absorption occurring.

The rate constants for the rearrangement of the 2,4,6-trideuterio-isomer of (IV) were measured under the same conditions as the protio compound. The deuterium kinetic isotope effect k_H/k_D was found to be 1.44 at 0.792M-H_2SO_4, 1.46 at 1.59M-H_2SO_4, 1.82 at 2.37M-H_2SO_4, and 2.37 at 3.15M-H_2SO_4. Clearly as in the case of the earlier work with *N*-methyl-*N*-nitrosoaniline [12] the final proton loss to the solvent from the 4-position is in part rate determining. The increasing k_H/k_D values with increasing acidity could well be due to the reducing water activity at the higher acidities. Similar effects were found in hydrochloric acid solution, k_H/k_D 1.84 at 3.7M-HCl and 1.93 at 5.6M-HCl.

Reactions in Ethanol Solvent.—All the work presented here (and in earlier parts of this series) has referred to reactions in water solvent. For preparative purposes the rearrangement reaction is most often carried out in alcohol solvents, usually ethanol. It has been suggested [14] that maybe the reaction in ethanol has a different mechanism from that in water, hence we have set out to examine mechanistically the rearrangement in ethanol, using the 3-methoxynitrosamine (IV). With *N*-methyl-*N*-nitrosoaniline itself [15] the rate of denitrosation is much increased relative to rearrangement in ethanol compared with water, which makes it more difficult to examine the rearrangement reaction. However the 3-methoxy-substituent serves to promote the rearrangement reaction.

Unfortunately it has not been possible to repeat the experiments carried out in water noting the variation of rearrangement with added 'nitrite trap' since the conventional 'nitrite traps' are not sufficiently soluble in this solvent. It is to be expected however that the solvent itself acts in this capacity forming ethyl nitrite in an equilibrium reaction lying well over towards the side of ethyl nitrite.[16] It has been shown recently [17] that propyl nitrite in propan-1-ol acts as a nitrosating agent only in the presence of a strong nucleophile (such as Br^-) and involves the initial formation of a free nitrosating agent (such as NOBr). So the fact that rearrangement occurs at all in H_2SO_4–EtOH solvent is indicative of an intramolecular mechanism. Addition of urea or ascorbic acid had no effect upon the formation of ethyl nitrite (as detected by its u.v. spectrum around 360 nm) from sodium nitrite and HCl–EtOH, indicating that the nitrosating agent is 'tied up' as ethyl nitrite and is unreactive. Neither of these conventional 'nitrite traps' had any effect upon the rate constant or the rearrangement yield from the reaction of (IV) in acidified ethanol.

Table 4 shows the expected acid catalysis for this solvent and also for HCl–EtOH. There is no evidence that the HCl reactions are more rapid than the H_2SO_4 reactions, in fact the reverse is the case at the higher acidities. In H_2SO_4–EtOH rearrangement was essentially quantitative, whereas with HCl–EtOH there was *ca.* 70% rearrangement and *ca.* 30% denitrosation (the latter was detected spectrophotometrically at 278 nm).

TABLE 4

Acid catalysis in EtOH solvent

$[H_2SO_4]$/M	$10^4k_0/s^{-1}$	[HCl]/M	$10^4k_0/s^{-1}$
0.13	0.61	0.14	0.65
0.33	0.85	0.36	1.00
0.65	1.98	0.72	1.47
0.98	3.47	1.08	1.73
1.31	5.41	1.44	2.36
1.63	8.21	1.80	2.65

TABLE 5

Rearrangement of (IV) in H_2SO_4–EtOH containing added thiourea

$[H_2SO_4]$/M	10^3 [Thiourea]/M	$10^4k_0/s^{-1}$	Rearrangement (%)
1.02	0	3.46	100
0.99	0.4	3.71	91
1.02	1.0	4.93	74
1.02	2.0	6.28	59
1.02	4.0	8.03	43
1.02	10.0	11.7	21

Baliga[18] had noted a first-order dependence upon HCl and no catalysis by Cl^- for the rearrangement of *N*-nitrosodiphenylamine in methanol.

The effect of added nucleophiles is shown in Tables 5 and 6 for added thiourea. Similar but less marked effects were observed also with added bromide ion. The pattern of behaviour is exactly as was found for reaction in water solvent for both H_2SO_4–EtOH and HCl–EtOH, in that the yield of rearrangement decreases with added [thiourea] and a marked increase in the rate constant k_0 is observed. This again is consistent with the outline mechanism given in Scheme 2 for parallel reactions of rearrangement and denitrosation, only the latter being dependent upon the concentration of nucleophile present.

TABLE 6

Rearrangement of (IV) in HCl–EtOH containing added thiourea

[HCl]/M	10^3 [Thiourea]/M	$10^4k_0/s^{-1}$	Rearrangement (%)
1.03	0	2.34	70
1.02	0.24	2.69	53
1.02	0.48	3.17	43
1.03	1.0	5.02	27
1.02	2.0	8.70	18
1.03	4.0	17.2	9
1.03	10.0	36.7	6

These results whilst clearly demonstrating the intramolecular nature of the rearrangement both in water and ethanol, yield no further information as to the detailed mechanism of the rearrangement process. Indeed the experiments were not designed to do so. The kinetic isotope effect confirms that proton loss from a Wheland intermediate is partly rate determining. At this stage the details of the rearrangement process are a matter of conjecture; possible models have been suggested and have been discussed elsewhere.[19]

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