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# THE MECHANISM OF THE FISCHER–HEPP REARRANGEMENT OF AROMATIC N-NITROSO-AMINES

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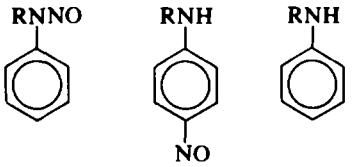
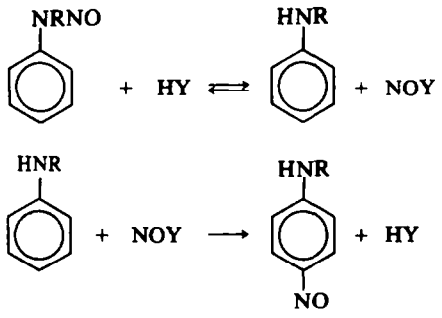
**Abstract**—Rate equations have been deduced for two possible mechanisms for the Fischer–Hepp rearrangement of aromatic N-nitroso-amines in acid solution: (a) for the commonly assumed intermolecular process involving de-nitrosation to the secondary amine and a free nitrosating agent, followed by a direct *C*-nitrosation of the secondary amine by this nitrosating agent, and (b) for a mechanism whereby rearrangement and de-nitrosation occur concurrently, by two separate reactions of the protonated N-nitroso-amine. All the experimental evidence supports mechanism (b), whilst most of it is incompatible with (a). Particularly diagnostic of the mechanism are (1) the observed rearrangement: de-nitrosation product ratios under certain limiting conditions, (2) the question of halide ion catalysis, and (3) the rate form found under the limiting condition of a large excess of added secondary amine.

It has long been known, since the early work of Fischer and Hepp in 1886,[1] that aromatic N-nitroso-amines (**1**) undergo rearrangement in acid solution to give the corresponding *para*-nitroso amines (**2**), together with, under certain conditions, the product of de-nitrosation (**3**). Apart from these early experiments, relatively little work




**1** **2** **3**

has been carried out on this reaction, while it has been much used synthetically. In particular, the reaction has never been the subject of a detailed mechanistic investigation, although rearrangement reactions of other N-substituted aromatic amines have been the focus of much attention: these include the benzidine rearrangement of hydrazobenzenes,[2] the rearrangement of N-nitro-amines[3] and the Orton rearrangement of N-chloroanilides.[4] Nevertheless, the rearrangement of N-nitroso-amines is generally represented in many organic chemistry text books[5] and in review articles[6] in terms of the mechanism given in Scheme 1. Here, reversible de-nitrosation of the reactant is brought about by the acid



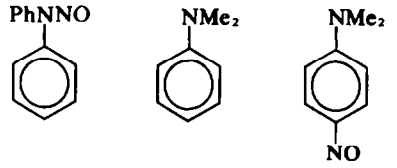

Scheme 1.

HY (e.g. HCl), probably by attack of $Y^-$ on the protonated form of the nitroso-amine; this is followed by a conventional electrophilic substitution at the *para* position of the formed secondary amine by the free nitrosating agent NOY. This mechanism was originally suggested by Houben[7] in 1913, and has apparently been generally accepted since—the results of later experiments have been taken to support this mechanism. The evidence is based entirely upon product analyses and can be summarised by the following four points:

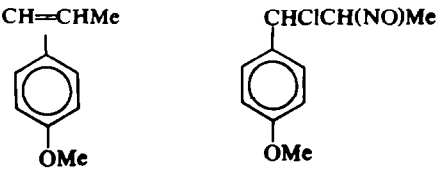
(1) Yields of rearrangement product were found to be greatest with hydrogen chloride as the catalyst. Low yields were reported for reactions in sulphuric acid and nitric acid.[8] This implies that chloride ion plays an important part in the reaction, although interestingly, with hydrogen bromide the main product was that of de-nitrosation (the secondary amine) together with bromo by-products.

(2) Added sodium nitrite increased the overall yield of the rearrangement product.[7]

(3) A number of "cross-over" nitrosations (or trans-nitrosation) have been noted.[7] for example, the reaction of N-nitrosodiphenylamine (**4**) in the presence of N,N-




**4** **5** **6**




**7** **8**

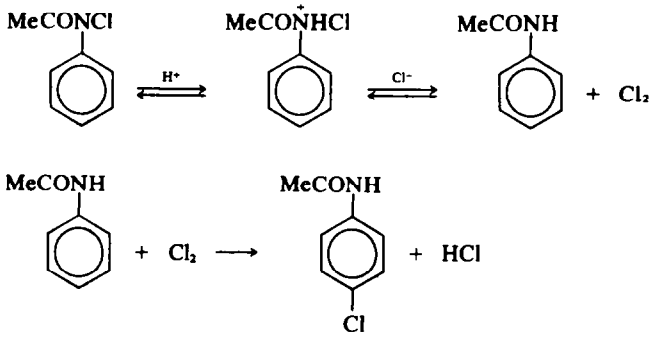
dimethylaniline (**5**) gave in addition to the normal product of rearrangement, *para* nitroso N,N-dimethylaniline (**6**). Similarly the reaction of N-methyl-N-nitrosoaniline (**1**,

R=Me) in the presence of the reactive olefin (7) gave its nitroso-chloride adduct (8) among the products. In general when the *para* position of the nitroso-amine is blocked, de-nitrosation rather than rearrangement occurs, but the nitroso group can be transferred to another molecule such as an amine.

(4) Reaction of *meta*-nitro N-methyl-N-nitrosoaniline in the presence of a large excess of urea gave *only* the product of de-nitrosation.[9]

Each of these points is apparently consistent with the proposed mechanism, although many authors[3,6a] have pointed out that the detailed kinetic evidence for such a mechanism is lacking. Dewar[10] goes further: "The mechanism of the Fischer–Hepp rearrangement of N-nitrosoanilines to *para*-nitrosoanilines is commonly assumed to be intermolecular, although there is in fact no definite evidence concerning its mechanism, apart from the inconclusive information that cross-migration can take place". It was our intention at the start of this work to provide the necessary detailed kinetic evidence which would either support or refute this plausible, but unproved mechanism.

This reaction has a certain formal similarity with the Orton rearrangement of N-chloroanilides. The generally accepted mechanism is given in Scheme 2. Here




Scheme 2.

de-chlorination of the reactant occurs by nucleophilic attack by chloride ion yielding the free anilide and chlorine, which then form the C-chloro product by an electrophilic substitution. Cross-chlorination to a more reactive substitute (such as a phenol[11]) can occur (just as for the nitroso-amine reaction), free chlorine can be aspirated from the reaction solution,[12] and exchange of $^{36}Cl$ label can be effected between chloride ion and N-chloroanilide.[13] Kinetic evidence supports the intermolecular mechanism. The rate equation for the disappearance of reactant was found to be:[11]

$$\text{Rate} = k[\text{N-chloroacetanilide}][H^+][Cl^-]$$

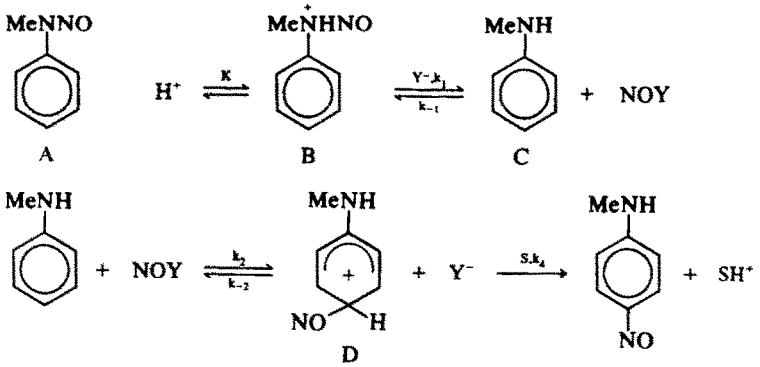
i.e. the rate is proportional both to hydrogen ion and chloride ion concentration and is readily interpretable in terms of attack by chloride ion upon the protonated form of N-chloroacetanilide. Other experiments confirm the mechanism given by Scheme 2.*

The question of the *intra*- or *inter*-molecularity of rearrangement reactions has often been decided by noting the pick up, or otherwise, of isotopic label in the products, from non-labelled reactants, when reaction is carried out in the presence of a labelled species which can exchange with any fragment likely to be formed from the reactant. Thus, the rearrangement of phenylhydroxylamine to *para* amino phenol takes place with full uptake of $^{18}O$ in the product from $H_2{}^{18}O$ solvent,[15] confirming the intermolecularity of the change. Conversely, the failure to observe any incorporation of $^{15}N$ in the products of rearrangement of N-nitroaniline from added $^{15}NO_3^-$ or $^{15}NO_2^-$, has been taken[3a] as evidence of the intramolecularity of the reaction. However, no clear cut distinction can be made in the Fischer–Hepp rearrangement on the basis of labelling experiments of this kind, since it has been found[16] that N-methyl-N-nitrosoaniline exchanges $^{15}N$ label with added sodium nitrite in acid solution, at a rate far in excess of that of the rearrangement. Additionally it has been shown, by using ring-deuterated material, that N-methyl-N-nitrosoaniline can transfer the nitroso group to N-methylaniline at a rate much greater than that of rearrangement.

The rate of reaction of N-methyl-N-nitrosoaniline in acid solution is conveniently followed spectrophotometrically either by the disappearance of the absorption due to the reactant at 275 nm, or by the appearance of the peak at 350 nm, which is due to the protonated form of the product C-nitroso isomer. Early experiments by us[17] showed (a) that the overall rate of disappearance of the reactant in hydrochloric acid was approximately proportional to $h_0$ and not to the product $h_0[Cl^-]$, and (b) that rearrangement occurred even in the presence of quite large amounts of urea, which is a well known trap for nitrous acid and nitrosyl chloride. These observations led us to suggest that rearrangement might occur intramolecularly and concurrently with reversible de-nitrosation. This mechanism could also account qualitatively for the early product analyses. Russian workers[18] had also observed rearrangement in the presence of nitrite traps and had suggested the possibility of an intramolecular route to the product. More recently we have set out to distinguish unambiguously between the two possible intermolecular and intramolecular mechanisms by a more detailed kinetic study.

Mechanism (a), which is set out in detail below, represents the generally accepted intermolecular mechanism involving prior de-nitrosation followed by a direct electrophilic substitution by the free nitrosating agent NOY at the *para* position of the formed secondary amine. In general $Y^-$ could be any nucleophile such as halide ion, thiocyanate ion or in the absence of any of these, a water molecule. X is a nitrite trap such as, urea, sulphamic acid, hydrazoic acid, hydroxylamine, aniline, hydrazine etc. In the absence of any added X it is likely that NOY

*For a more detailed account see Ref. 6*a* pp. 221–230 and Ref. 14.




Mechanism (a)

undergoes decomposition by reaction with the solvent, as all our work was carried out at 31° in aqueous solution.

It is assumed that the initial protonation of the nitroso-amine is fast and that the extent of protonation is small. These assumptions are borne out (a) by the absence of a primary hydrogen isotope ($k_H > k_D$) effect when the reaction is carried out in $D_2O$ and (b) by analysis of the uv spectra of neutral and acid solutions of the nitroso-amine. The final proton loss from D is probably brought about by a base S (e.g. $H_2O$), but its concentration has been incorporated into $k_4$ for convenience.

*Derivation of a rate equation*

A first-order rate coefficient $k_0$ is defined by

$$\frac{-d[A]}{dt} = k_0[A]$$

If A exists in rapid equilibrium with a small quantity of its protonated form B, and if A behaves as a Hammett base then [B] is given by $Kh_0[A]$. Application of a steady state treatment to both reactive intermediates D and NOY then results[19] in the expression given by equation (1).

$$k_0 = \frac{k_1[Y^-]Kh_0(k_3[X] + k_2'[C])}{k_3[X] + [k_{-1} + k_2'][C]} \qquad (1)$$

where

$$k_2' = k_2 - \frac{k_{-2}k_2[Y^-]}{k_{-2}[Y^-] + k_4} \text{ (i.e. } k_2' < k_2).$$

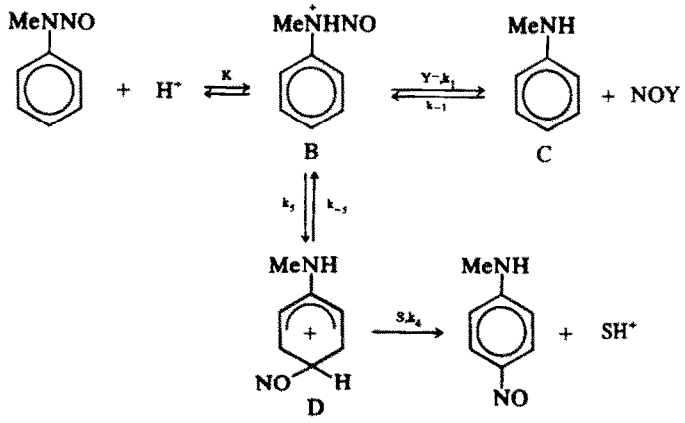
In mechanism (b), which is set out below, the rearrangement now occurs *intramolecularly* and concurrently with de-nitrosation. For simplicity in the kinetic treatment we have written the stage B→D in one stage. Clearly there must be some intermediate between B and D as the distance from the nitroso nitrogen atom to *para* carbon atom is so large, but this will not affect the overall kinetic form. The nature of such an intermediate will be discussed later.

*Derivation of rate equation*

As for mechanism (a) we can apply steady-state treatments to both NOY and D, define $k_0$ by $(-d[A]/dt) = k_0[A]$, and write $[B] = Kh_0[A]$. The expression for $k_0$ is then given by equation (2).

$$k_0 = \frac{k_4k_5Kh_0}{k_4 + k_{-5}} + \frac{k_1[Y^-]Kh_0k_3[X]}{k_3[X] + k_{-1}[C]} \qquad (2)$$

Eqs (1) and (2), whilst having certain common features (such as a first-order $h_0$ dependence under all conditions),




Mechanism (b)

have sufficiently different forms to enable a distinction between them to be made and hence to establish either mechanism (a) or (b)

(1) *Reactions at high [X]*

As the concentration of X (a nitrite trap such as urea) is increased it is conceivable that $k_3[X]$ should eventually become much greater than both $k_{-1}[C]$ and also $k_2'[C]$. Under these circumstances Eqs (1) and (2) take the limiting forms of Eqs (3) and (4) respectively.

$$k_0 = k_1[Y^-]Kh_0 \quad (3)$$

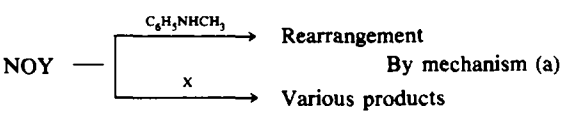
$$k_0 = \frac{k_4k_5Kh_0}{k_4 + k_{-5}} + k_1[Y^-]Kh_0 \quad (4)$$

Both mechanisms thus predict that at high [X] the reaction becomes zero order in X. $k_0$ should thus be constant at any one hydrochloric acid concentration. This is shown in Table 1 which reports values of $k_0$ for a variety of X species and concentration for reaction in 3·05M HCl. As expected $Cl^-$, $Br^-$ and $H^+$ catalysis are all observed.

Table 1.

| Added X | [X]/M | $10^4\ k_0/s^{-1}$ |
|---|---|---|
| $HN_3$ | $1 \times 10^{-3}$ | 16·6 |
| $HN_3$ | $3 \times 10^{-3}$ | 17·3 |
| $HN_3$ | $5 \times 10^{-3}$ | 16·4 |
| $HN_3$ | $5 \times 10^{-3}$ [+0·52M $Cl^-$] | 23·0 |
| $HN_3$ | $5 \times 10^{-3}$ [+0·52M $Br^-$] | 176 |
| $HN_3$ | $5 \times 10^{-3}$ [ 4·47M total $H^+$] | 32·3 |
| $NH_2SO_3H$ | $3 \times 10^{-3}$ | 16·7 |
| $NH_2SO_3H$ | $5 \times 10^{-3}$ | 16·9 |
| $NH_2OH$ | $5 \times 10^{-3}$ | 14·4 |
| $C_6H_5NH_2$ | $1 \times 10^{-3}$ | 13·9 |
| $C_6H_5NH_2$ | $5 \times 10^{-3}$ | 13·7 |
| $CO(NH_2)_2$ | 0·10 | 14·2 |

Equation (4) is made up of two terms—the first representing rearrangement and the second de-nitrosation (now irreversible). It is therefore expected by mechanism (b) that the ratio % rearrangement: % denitrosation should be constant at any one acidity and $Y^-$ concentration—and in particular that this ratio should be independent of the nature and concentration of X. Mechanism (a) meanwhile, although predicting that the value of $k_0$ should be independent of X, predicts that the % rearrangement should decrease towards zero as the concentration of X is increased. This is because there is always a direct




competition between added X and N-methylaniline for capture of NOY at this, the product-determining stage, which occurs after the rate-determining stage of de-nitrosation. This then affords a direct test of mechanism. In hydrochloric acid, except at very low acid concentration (where the rates are inconveniently slow) no rearrangement is observed i.e. according to equation (4) $k_1[Y^-] \gg (k_4k_5/k_4 + k_{-5})$ so no comparison can be made, but for reaction in sulphuric acid where $Cl^-$ is replaced by $H_2O$ as the nucleophile, rearrangement is not swamped by denitrosation (as $k_1$ is now much reduced for the weaker nucleophile). Table 2 shows the results of experiments in

Table 2.

| Added X | [X]/M | $10^4\ k_0/s^{-1}$ | % Rearrangement |
|---|---|---|---|
| $HN_3$ | $6·53 \times 10^{-4}$ | 0·65 | 21 |
| $HN_3$ | $16·3 \times 10^{-4}$ | 0·67 | 21 |
| $NH_2SO_3H$ | $3·1 \times 10^{-3}$ | 0·65 | 21 |
| $NH_2SO_3H$ | $7·8 \times 10^{-3}$ | 0·64 | 22 |
| $CO(NH_2)_2$ | 0·10 | 0·62 | 21 |
| $NH_2OH$ | $2·58 \times 10^{-3}$ | 0·62 | 20 |
| $NH_2NH_2$ | $1·56 \times 10^{-3}$ | 0·66 | 20 |

2·75M $H_2SO_4$. Obviously the reaction is zero order in X and also the % rearrangement is constant. Similarly at 4·75M $H_2SO_4$ the % rearrangement is constant at 10% (denitrosation and rearrangement have slightly different acid dependencies, hence the ratio is not independent of $[H^+]$) for a wide variety of concentration and nature of X. The same effect is apparent in the chloride ion catalysed reactions but only when the concentration of chloride is small, since otherwise no rearrangement is detectable (no rearrangement is observed when the more powerful nucleophiles $Br^-$, $SCN^-$ and $I^-$ are present). Thus for reaction in 2·52M sulphuric acid containing 0·2M $Cl^-$, 7% rearrangement occurs and $k_0$ is $14·0 \times 10^{-5}\ s^{-1}$ for added sulphamic acid of $2·9 \times 10^{-3}$M and also for $4·58 \times 10^{-3}$M. Rearrangement and de-nitrosation appear to have different acidity dependencies of $(h_0)^{1·2}$ and $(h_0)^{1·6}$ respectively. It is believed that this is due to the incursion of a second mechanism of de-nitrosation involving attack by $H_3O^+$ upon the protonated form of the nitrosoamine (see section 5). This second mechanism becomes progressively more important at higher acidities; obviously this will affect the rearrangement: de-nitrosation product ratio as the acidity changes.

The experimental evidence thus enables a clear distinction to be made between the two mechanisms on the basis of the variation of yield of rearrangement at high X concentration. The results are consistent only with mechanism (b).

(2) *Reactions at high concentrations of* N-*methylaniline* (*C*)

(a) *Halide ion catalysis.* Another limiting form of the general expression for $k_0$ occurs when $k_{-3}[C] \gg k_3[X]$, i.e. when reaction is carried out in the presence of a large excess of added N-methylaniline. Under these conditions Eq (2) from mechanism (b) reduces to equation (5).

$$k_0 = \frac{k_4k_5Kh_0}{k_4 + k_{-5}} \quad (5)$$

This predicts that $k_0$ should become independent of $[Y^-]$ ($Cl^-$, etc.), added N-methylaniline (C) and added X (urea, etc.). We have found[20] (see also later in (2) (b)) that at one acidity $k_0$ decreases to a limiting value as [C] is increased. Under these circumstances virtually quantitative rearrangement occurs. Table 3 shows that this limiting value of $k_0$ is totally independent of the concentration of added chloride and bromide ion, as predicted by Eq (5). In

Table 3.

| [N-methylaniline] added/M | [Halide ion] added/M | $10^4\ k_o/s^{-1}$ |
|---|---|---|
| $4 \times 10^{-3}$ | 0 | 1·75 |
| $4 \times 10^{-3}$ | 0·2M NaCl | 1·79 |
| $4 \times 10^{-3}$ | 0·1M NaBr | 1·77 |

physical terms this means that de-nitrosation can be completely suppressed by the addition of an excess of N-methylaniline so that the rate of N-nitrosation is sufficiently increased and no free nitrosating agent NOY is lost by reaction with X or the solvent. This, of course, explains the early observation[7] that added nitrite gave increased yields of rearrangement product. Halide ion is thus not involved in that part of the reaction leading to rearrangement—in fact we have obtained high yields of rearrangement in sulphuric acid solution, so long as excess N-methylaniline is added to suppress de-nitrosation. No doubts high yields could also be obtained in any acid medium by a similar procedure.

Baliga[21] has also noted the absence of chloride ion catalysis in the rearrangement of N-nitrosodiphenylamine in methanol. A mechanism was tentatively proposed whereby nitrosyl chloride was lost *via* a 4-centred transition state. This is inconsistent with many of our results and will be discussed more fully later.

It is not immediately obvious what form of halide ion catalysis is predicted for mechanism (a) *via* Eq (1) at the limit of high [C], since $[Y^-]$ appears in the $k_2'$ term in both the numerator and denominator. However if Eq (1) is rewritten as Eq (6),

$$k_0 = k_1[Y^-]Kh_0\left[1 - \frac{k_{-1}[C]}{k_3[X] + [k_{-1} + k_2'][C]}\right] \qquad (6)$$

then it is clear that $k_0$ should never be independent of $[Y^-]$-contrary to what is observed experimentally. This test again clearly comes down in favour of mechanism (b).

(b) *Dependence of $k_0$ upon* [N-*methylaniline*] (*C*). Eq (5) gives the limiting form of $k_0$ according to mechanism (b). As the concentration of N-methylaniline is increased $k_0$ should decrease towards this limiting value. Table 4 gives the results of such a study of the reaction in 5·90M HCl.

Table 4.

| $10^3$[C] added/M | $10^4\ k_o/s^{-1}$ | % Rearrangement |
|---|---|---|
| 0 | 5·07 | 28 |
| 0·44 | 3·74 | 54 |
| 0·94 | 3·61 | 60 |
| 3·08 | 2·80 | 76 |
| 3·96 | 2·78 | 78 |
| 5·71 | 2·84 | 80 |

The yield of *para*-nitroso product increases beyond 80% as [C] is increased, and correspondingly $k_0$ decreases to a definite limit of $2{\cdot}80 \times 10^{-4}\ s^{-1}$. It is found that $(k_0)_{limit}$ obtained in this way is proportional to $h_0^{1\cdot2}$ and is independent of the concentration of halide ions. Similar behaviour is obtained when excess urea or hydroxylamine is present, although, as expected, a higher concentration of N-methylaniline is required to achieve the limiting value of $k_0$. Measurements on this system have enabled the relative reactivities of a number of X compounds (relative to N-methylaniline) towards nitrosyl chloride to be obtained.[22]

The corresponding limit of $k_0$ at high [C] according to mechanism (a) is easily seen fromEq (6) in the preceeding section. At high [C], if $k_{-1}[C]$ becomes much greater than $k_3[X]$, then $k_0$ should take a value very close to zero. This is because $k_2[C]$, the rate of C-nitrosation is likely to be several orders of magnitude smaller than the corresponding rate of N-nitrosation, $k_{-1}[C]$ and since $k_2' < k_2$, it follows that the term inside the bracket in Eq (6) will be extremely small. Eq (6) thus predicts the wrong dependence upon N-methylaniline as well as that on halide ion.

(3) *Substituent effects*

The effect of *meta* substituents on the yield of rearrangement and on $k_0$ for reaction in 3M HCl is shown in Table 5.[20] These results are for reactions without either

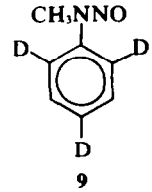
Table 5.

| Substituent | $k_o/s^{-1}$ | % Rearrangement |
|---|---|---|
| None | $3{\cdot}6 \times 10^{-5}$ | 32 |
| meta OMe | $1{\cdot}0 \times 10^{-3}$ | 92 |
| meta $CH_3$ | $9{\cdot}1 \times 10^{-5}$ | 40 |
| meta Cl | $3{\cdot}7 \times 10^{-6}$ | 14 |
| meta $NO_2$ | Very slow | 0 |

added N-methylaniline or nitrite trap X. Electron withdrawing groups *meta* Cl and *meta* nitro reduce the yield of rearrangement and also reduce the value of $k_0$ whilst *meta* OMe and *meta* Me increase the rate of reaction and also the yield of rearrangement (although the *meta* Me yield seems a little low). These results are in agreement with scheme (b) where de-nitrosation and rearrangement are concurrent (rather than consecutive) processes. It is to be expected that *meta* substituents would have only a secondary effect upon the rate of de-nitrosation ($k_1$) because of its relatively remote position, whereas *meta* electron releasing groups would be expected to increase the rate constant of an electrophilic substitution at the *para* position ($k_5$). This is borne out by the experimental results—the *meta* OMe group increases the rate of rearrangement to such an extent that no de-nitrosation occurs, whereas at the other extreme *meta* $NO_2$ decreases the rate of rearrangement so much that only de-nitrosation now occurs. The earlier observation of Macmillen and Reade[9] that no rearrangement occurs with the *meta* nitro compound in the *presence* of urea, must now be taken together with the result of this experiment, i.e. no rearrangement occurs even in the *absence* of urea. This demolishes the evidence of the Macmillen and Reade experiment in favour of the intermolecular mechanism.

(4) *Isotope effects*

(a) *Aromatic ring effect.* The reaction of (9) in 5·5M HCl occurs more slowly [17] than the non-deuterated substrate by a factor of 1·7. This implies that the final proton transfer from the *para* position in the ring to the solvent (step $k_4$) is at least in part rate-determining. This is

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not generally true of electrophilic aromatic substitution reactions but is found also in other nitrosation reactions such as the nitrosation of phenols[23] and other aromatic systems.[24] Under "rearrangement only" conditions, i.e. with added N-methylaniline or using the *meta* OMe substrate, this isotope effect is increased to 2·4.[20] This is readily explained by mechanism (b) and Eq (2) since $k_4$ appears only in the first term (the contribution of $k_0$ to rearrangement); under the high [C] limiting conditions the second term disappears. In physical terms this means that when de-nitrosation (for which there is no ring isotope effect) is suppressed, the maximum ring isotope effect of rearrangement is found.

(b) *Solvent isotope effect.* In $D_2O$ solvent the value of $k_0$ for the reaction under non-limiting conditions is increased by a factor of about 2·5. This is wholly consistent with any mechanism involving a fast reversible proton transfer to a base *A* followed by some rate determining reaction of $AH^+$. Since both de-nitrosation and rearrangement are thought to arise by separate reactions of $AH^+$, both reactions should show similar isotope effects. This is confirmed by our experiments for both limiting cases. We have considered reaction to occur via the amino nitrogen protonated form of the nitroso-amine. There are indications[25] however that several different kinds of protonated species exist in solution at different acidities, although their exact composition has not been established. As far as we are aware $pK_a$ values of aromatic nitroso-amines have not been determined, presumably because of the reactivity of the protonated forms to rearrangement and de-nitrosation. Our results argue strongly against a rate-determining proton transfer which was suggested[26] for the nitrosation of N-methylaniline by N-nitrosodiphenylamine, and there appears to be no reason to suggest some rate-determining intramolecular rearrangement[27] of one protonated form to another.

(5) *De-nitrosation*

Since de-nitrosation occurs concurrently with rearrangement, it is important to establish its mechanism. Apparently no systematic mechanistic study of de-nitrosation has been carried out prior to this work, even though the reaction is quite well-known experimentally: de-nitrosation of nitrosoamines can readily be accomplished by heating in hydrochloric acid with an excess of urea,[9] or ferrous ion.[28] Presumably the urea removes the nitrosyl chloride formed and prevents the reverse reaction of N-nitrosation. Our work with the rearrangement reaction earlier showed that one limiting form of the general equation represents the de-nitrosation reaction alone i.e. when a sufficient quantity of a nitrite trap X is present. Then, particularly if an efficient nucleophile is present, no rearrangement occurs. It has been established[29] that of the conventional nitrite traps, urea is the least reactive, and is only efficient if present in concentrations greater than 0·1M, whereas sulphamic acid and hydrazoic acid are much more reactive and so are required only in very small amounts. The rate of de-nitrosation in hydrochloric acid or in sulphuric acid containing added chloride ion was proportional to $h_0[Cl^-]$ and not simply to $h_0$ or $[Cl^-]$,[30] i.e. very much like the de-chlorination of N-chloroacetanilide.[11] This is readily interpreted as nucleophilic attack by chloride ion on the protonated form of the nitroso-amine. The observed

$$C_6H_5\overset{+}{N}H(Me)\text{–}NO \overset{\overset{\curvearrowleft}{Cl^-}}{\underset{}{\overset{k_1}{\longrightarrow}}} C_6H_5NHMe + NOCl$$

$$NOCl + NH_2SO_3H \xrightarrow{\text{fast}} N_2 + SO_3 + H_2O + HCl$$

deuterium solvent isotope effect of *ca.* 2·7 supports this mechanism. The effect of other nucleophiles was obtained from rate measurements in sulphuric acid containing sodium bromide, sodium iodide and potassium thiocyanate. In each case, good straight lines resulted from plots of $k_0$ vs [nucleophile], from which the product $k_1K$ was obtained from the slope, for each nucleophile. The results are shown in Table 6, for a number of different acid

Table 6.

| Catalyst | Acid | $k_1Kh_0$ | $10^5\ k_1K$ |
|---|---|---|---|
| $Cl^-$ | 0·4–5·0 M HCl | – | 0·45 |
| $Cl^-$ | 2·52M $H_2SO_4$ | $55·0 \times 10^{-5}$ | 0·41 |
| $Cl^-$ | 3·96M $H_2SO_4$ | $27·8 \times 10^{-4}$ | 0·42 |
| $Cl^-$ | 4·75M $H_2SO_4$ | $72·0 \times 10^{-4}$ | 0·43 * |
| $Br^-$ | 2·52M $H_2SO_4$ | $2·84 \times 10^{-2}$ | 21·1 |
| $Br^-$ | 3·96M $H_2SO_4$ | $1·57 \times 10^{-1}$ | 23·8 |
| $CNS^-$ | 2·52M $H_2SO_4$ | 2·99 | 2217 |
| $I^-$ | 2·52M $H_2SO_4$ | 8·50 | 6300 |

* Experiments using hydrazoic acid as the nitrite trap

concentrations, and usually in the presence of excess sulphamic acid. The increasing reactivity of the nucleophiles $Cl^- < Br^- < CNS^- < I^-$ is quite marked. This contrasts with the corresponding reactions of these nucleophiles with the nitrous acidium ion $H_2\overset{+}{N}O_2$ where a factor of 1·5 covers the whole reactivity range.[31] It is thought that the rates of the $H_2\overset{+}{N}O_2$ reactions approach the diffusion controlled limit. Application of the Swain–Scott equation[32] to our data gives an excellent correlation between log $k_1K$ and the nucleophilic constant n. The slope of the line gives s, the susceptibility constant (analogous to $\rho$) as 2·1. This compares with values of s of 0·7 for $S_N2$ substitution reactions of ethyl tosylate and 0·9 for the ring-opening of epichlorohydrin. This shows that the de-nitrosation process is very sensitive to the nature and reactivity of the nucleophile.

De-nitrosation can also be brought about by the water molecule acting as a nucleophile although, as expected, this process is slower than the halide ion reactions. There is also evidence, from reaction rates at high acidities, that a reaction between the protonated nitroso-amine and $H_3O^+$ occurs, resulting in de-nitrosation. Although further work is needed to establish the mechanism unambiguously, it is interesting to note that at this sort of acidity Ridd and

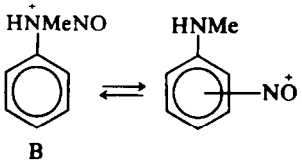
$$C_6H_5\overset{+}{N}H(Me)NO + H_3\overset{+}{O} \rightleftharpoons C_6H_5\overset{+}{N}H(Me) + H_2\overset{+}{N}O_2$$

co-workers[33] have concluded that N-nitrosation of N-methylaniline occurs by a reaction between the protonated amine and the positively charged nitrous acidium ion. It is to be expected that the forward and back reactions have the same mechanistic pathway in reverse sequence.

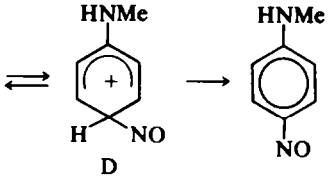
(6) *Conclusion*

The case has been argued that the rearrangement of aromatic N-nitroso-amines occurs intramolecularly and

concurrently with reversible de-nitrosation. It is not possible, on the available evidence to formulate this intramolecular process fully. The *meta* substituent effects indicates that the overall process is one of electrophilic substitution, whilst the ring deuterium isotope effect establishes that the final proton loss occurs from the $\sigma$-complex or Wheland intermediate D. It would seem likely that another intermediate occurs between B and D.



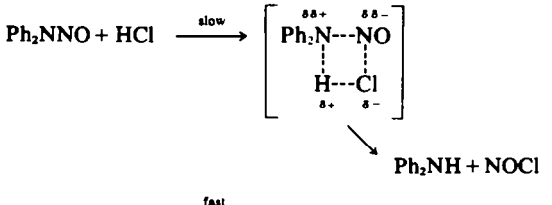

B

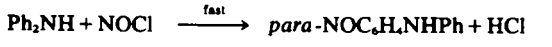



D

We have written this above as some sort of $\pi$ complex but there is in fact no evidence regarding its structure. It is not easy to devise experiments which would produce such evidence.

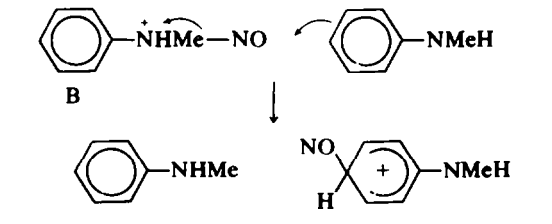
Baliga[21] also found no chloride ion catalysis and proposed a mechanism involving slow formation of the secondary amine and nitrosyl chloride via a four centre




transition state, followed by a fast C-nitrosation. This mechanism is not consistent with many of our experimental observations. In particular we have ruled out, from work with high [X] (Section (1)), any C-nitrosation via a free nitrosating agent. Further it is not possible to account for the observed solvent isotope effects and the ring deuterium isotope effect by such a mechanism. Finally, it would not explain the observed[29] acid catalysis at any one chloride ion concentration.

Other mechanisms are of course feasible, for example it is worth considering the possibility of a direct transfer of the nitroso group from the protonated nitroso-amine to the *para* position of the secondary amine, i.e. an $S_E2$ reaction. This would be consistent with a number of our findings, such as the absence of chloride and other halide ion catalysis. Two factors however argue strongly against this mechanism, (1) nitrosyl chloride and the nitrous acidium ion $H_2NO_2^+$, or any free nitrosating agent




generally, do not effect such a C-nitrosation as shown by the elimination of mechanism (a) for the rearrangement, so it seems unlikely that the protonated nitroso-amine, a likely weaker electrophile, can do so, and (2) there is no direct transfer of the –NO group from B to other nucleophilic sites, such as urea, hydrazoic acid etc. (since at high [X] the reaction is zero order in X), nor to the *para* position of aniline even though it is added in a tenfold excess, so again it seems very unlikely that direct transfer to the relatively weakly nucleophilic carbon site in N-methylaniline can occur.

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