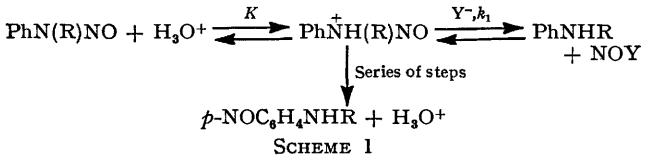
Kinetics and Mechanism of the Fischer–Hepp Rearrangement and Denitrosation. Part 9.[1] Ring-Methyl Substituent Effects

By Ian D. Biggs and D. Lyn H. Williams,* Department of Chemistry, Durham University, Durham DH1 3LE

Rate constants have been obtained for both denitrosation and rearrangement reactions of the 2- and 3-methyl- and 2,6- and 3,5-dimethyl-substituted *N*-methyl-*N*-nitrosoanilines. The very large rate reduction (*ca.* 10^3) observed for the 2,6-compound (compared with the unsubstituted nitroso-amine) for both reactions, is attributable to steric hindrance towards protonation of the amino-nitrogen atom. Otherwise methyl substitution in the ring activates the system to denitrosation, by relatively small amounts in hydrochloric acid (and also for the reactions with added bromide ion), but by greater amounts in the sulphuric acid reactions; these results are taken to support an earlier suggestion, that at high acidities, and in the absence of added nucleophiles, another mechanism of denitrosation becomes important, which involves attack by H_3O^+ at the protonated amino-nitrogen atom, with the concurrent expulsion of NO^+. Both 2- and 3-methyl substitution also increases the reactivity of the nitroso-amines towards rearrangement (Fischer–Hepp), with the 3-methyl group having, as expected the greater effect. Unexpectedly, the 3,5-dimethyl- is significantly less reactive than the 3-methyl-nitroso-amine, suggesting that some steric factor comes into play in the intramolecular rearrangement process.

WE have established[2] that the rearrangement (to the *p*-nitroso-isomer) and denitrosation (to give the secondary amine) of aromatic *N*-nitroso-amines take place concurrently, by separate reactions of the protonated form of the nitroso-amine (see Scheme 1). The observed rate constant for denitrosation is strongly dependent upon the reactivity and concentration of the added nucleophiles (Y^-), whereas that for rearrangement is independent of such species.[2,3] The results are consistent with a mechanism for rearrangement which is intramolecular, and cannot be accounted for in terms of a direct *C*-nitrosation of the formed secondary amine PhNHR and the free nitrosating agent NOY, as had been previously thought.[4] Other evidence, including the constancy of the product ratio (rearrangement : denitrosation) as the concentration and nature of an added trap for NOY (sulphamic acid, *etc.*) is varied,[5] supports such a scheme. Denitrosation and rearrangement can readily be studied separately by carrying out the reaction under two limiting conditions, (*a*) in the presence of a nitrite trap, when denitrosation is irreversible, and normally the rate of rearrangement is much less than that of denitrosation, and (*b*) in the presence of an added excess of the secondary amine, which in effect suppresses denitrosation. Recently[1] the effect of *N*-alkyl substitution upon both reactions has been reported, together with the effect of *para*-substituents in the aromatic ring upon the rate of denitrosation (no rearrangement occurs if the *para*-position is blocked). The results were rationalised in terms of the effect of the substituents upon both K, the equilibrium constant for protonation, and k_1, the rate constant for the rate-limiting step. This paper presents the kinetic results for the denitrosation and rearrangement (which will be discussed separately), of the 2- and 3-methyl- and 2,6- and 3,5-dimethyl-substituted *N*-methyl-*N*-nitroso-anilines. In this way it was hoped to determine the extent of the steric requirements of both reactions, particularly with the intention of obtaining a better picture of the intramolecular rearrangement process.



SCHEME 1

EXPERIMENTAL

All of the substituted nitroso-amines were prepared from the corresponding aniline derivatives by reaction with dimethyl sulphate, according to the method described by Adams and Sundholm,[6] followed by nitrosation of the secondary amines with sodium nitrite and hydrochloric acid at *ca.* 5°. The nitroso-amines were distilled at reduced pressure before use in the kinetic experiments, and had b.p.s which agreed with the literature values.

Rate measurements were carried out spectrophotometrically at 31° in water containing a small quantity (*ca.* 1%) of methanol, as the stock solutions of the nitroso-amines were made up in methanol for easy solution. First-order rate coefficients were obtained by noting the decreasing absorption of the reactant (*ca.* 275 nm) or, in the case of rearrangement, the increasing absorption of the *p*-nitroso-product (*ca.* 350 nm). Good first-order behaviour was obtained over about three half-lives, and the rate constants were reproducible to ±3%. A typical run is given for the denitrosation of 3,5,*N*-trimethyl-*N*-nitroso-aniline (1.7×10^{-4}M) in hydrochloric acid (3.80M) containing sulphamic acid (2.4×10^{-3}M):

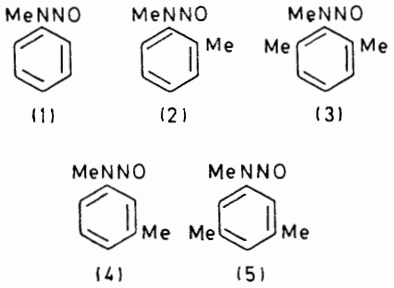
t (30 s units)	0	1	2	3	4	5
OD	0.897	0.768	0.656	0.572	0.500	0.441
$10^4k_0/s^{-1}$		66.7	69.0	67.7	68.0	68.3
t (30 s units)	6	7	8	9	∞	
OD	0.391	0.352	0.319	0.292	0.185	
$10^4k_0/s^{-1}$	69.0	69.0	69.7	70.0		

RESULTS AND DISCUSSION

(1) *Denitrosation.*—The nitroso-amines (2), (4), and (5) underwent quantitative denitrosation to the corresponding secondary amines in hydrochloric acid (over

[1] Part 8, I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1976, 691.
[2] T. D. B. Morgan, D. L. H. Williams, and J. A. Wilson, *J.C.S. Perkin II*, 1973, 473; D. L. H. Williams, *Internat. J. Chem. Kinetics*, 1975, 215.
[3] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.
[4] H. J. Shine, 'Aromatic Rearrangements,' Elsevier, Amsterdam, 1967, pp. 231—235.
[5] D. L. H. Williams, *J.C.S. Perkin II*, 1975, 655.
[6] R. Adams and N. K. Sundholm, *J. Amer. Chem. Soc.*, 1948, **70**, 2667.

the range 2—5M), all at very similar rates. The interpolated rate constants for reaction in 2.0M-hydrochloric acid are shown in Table 1. The 3,5-dimethyl-nitroso-amine is clearly the most reactive, there being hardly



any change under the reaction conditions for the 2,6-isomer (3). A measure of the reactivity of (3) was obtained from the bromide ion-catalysed reactions, where the observed rate constants k_0 are much greater. The results are shown in Table 2 and are presented in

TABLE 1

Rate constants for denitrosation in 2.0M-HCl

Substrate	$10^4 k_0/s^{-1}$
(1)	3.6
(2)	4.8
(4)	4.8
(5)	8.3
(3)	Too slow to measure

k_0 is defined by $-d[S]/dt = k_0[S]$, where S is the substrate.

terms of k_1K (where $k_0 = k_1K[Br^-]h_0$, if a h_0 dependence is assumed for the protonation equilibrium). Here again (1) and (2) show a comparable reactivity, as for the chloride ion reaction, but (3) is less reactive by a factor of *ca.* 10^3. These rate constants are not corrected for the salt effect of added bromide nor for the consequent change upon the H_0 values. This is unlikely to alter significantly the fact that (1) and (2) have a similar reactivity which is an order of magnitude greater than that of (3) in these reactions. This must result from a steric effect, since it appears that the overall electronic effect of an *o*-methyl group is very small in these reactions (see Table 1). There are of course two possibilities here since k_0 contains the product k_1K; any substituent effect could arise from a change in k_1, K, or in both, not necessarily in the same direction.

TABLE 2

The product k_1K for denitrosation by Br^-

Substrate	$10^4 k_1K$
(1)	18 [a]
(2)	18 [a]
(3)	0.020 [b]
(3)	0.017 [c]

[a] 3.18M-H_2SO_4, 0.23M-Br^-. [b] 5.10M-H_2SO_4, 0.57M-Br^-. [c] 4.90M-H_2SO_4, 1.13M-Br^-.

Specifically here, this steric effect could be due to either steric hindrance by the 2,6-methyl groups to protonation of the amino-nitrogen atom, or to nucleophilic attack by bromide ion at the nitroso-nitrogen atom. There is evidence available [1] which shows that the bulky *N*-t-butyl group does in fact hinder the approach of the larger nucleophiles Br^- and I^-, but the effect is not very great. It seems more likely, from the consideration of molecular models, that for the 2,6-dimethyl-nitroso-amine, there is steric hindrance towards the initial protonation, *i.e.* that the observed effect is due to the reduction of K. 2,6-Dimethylaniline has a much smaller pK_a value than does aniline itself. This is generally ascribed [7] to a steric effect, but there has been some controversy [8] regarding the detailed nature of such an effect. Wepster has claimed that the ion form is destabilised when there are *o*-alkyl groups, by reduction of the solvation shell around the positive charge on the amino-nitrogen atom, whereas Brown has considered that a steric interference of groups attached to different atoms (*F* strain) is responsible for the base-weakening effect. The situation is more complex for *N*-substituted anilines. For example, 2,6-dimethyl substitution in *NN*-dimethylaniline actually increases the pK_a value, but not by as much as does a single *o*-methyl group. Two factors are thought to be involved now, which operate in different directions. Firstly there is the steric effect observed in the aniline series which reduces the pK_a and secondly it is believed that steric inhibition of resonance occurs which strengthens the base increasing the pK_a value. This effect is not important in the aniline series where there are no bulky *N*-groups to interact with any *o*-groups. It appears that the latter effect outweighs the former in the *NN*-dimethylaniline case, but the data suggest that the former effect (which reduces the pK_a) becomes progressively more important as *N*-substitution is increased. It is not therefore unreasonable to suppose that the base-weakening steric effect (whatever its nature) might even be more important for the nitrosoamines where the –N=O group contributes to the steric crowding. It has been reported [9] that the angle of twist θ about the aromatic C–N bond is very large (*ca.* 90°) when 2,6-dimethyl substituents are present in nitroso-amines. Compound (3) also undergoes rearrangement very slowly indeed, whereas the 3,5-dimethyl isomer (5) reacts readily to give the corresponding rearrangement product. It seems reasonable again to attribute the failure of (3) to react readily to a steric effect upon K, particularly since it is known that rearrangement does not involve attack by a nucleophile. The low reactivity of the 2,6-dimethyl-nitroso-amine may be important in another area; it has been reported [10] that whereas *N*-nitrosopiperidine and its 2-, 3-, and 4-monomethyl derivatives are powerful carcinogens when introduced into rats, the 2,6-dimethyl-nitroso-amine and the 2,2,6,6-tetramethyl compound show no carcinogenic activity.

[7] J. W. Smith, 'The Chemistry of the Amino Group,' ed. S. Patai, Interscience, New York, 1968, pp. 184—187.
[8] B. M. Wepster, *Rec. Trav. chim.*, 1957, **76**, 357; H. C. Brown and A. Cahn, *J. Amer. Chem. Soc*, 1950, **72**, 2939.
[9] J. T. D'Agostino and H. H. Jaffé, *J. Amer. Chem. Soc.*, 1970, **92**, 5160.
[10] W. Lijinsky and H. Wayne Taylor, *Int. J. Cancer*, 1975, **16**, 318.

It may well be that this is due to the failure of these compounds (because of a steric effect) to undergo

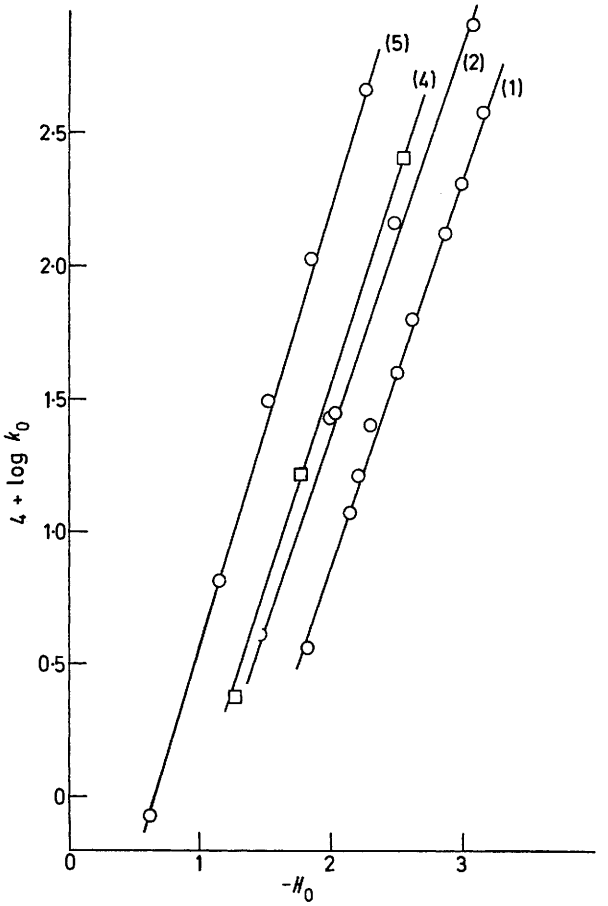


FIGURE 1 Variation of the rate constants for denitrosation of the nitroso-amines (1), (2), (4), and (5) with acidity in H_2SO_4

TABLE 3

Denitrosation rate constants expressed as log $k_0 = -AH_0 - B$ for reaction in H_2SO_4

Compound	A	B
(1)	1.46	6.03
(2)	1.47	5.57
(4)	1.54	5.50
(5)	1.68	5.11

denitrosation when the nitroso-group is transferred to a suitable nucleophilic site.

In sulphuric acid solution, without any added nucleophiles, denitrosation occurs, as expected, much less readily than in hydrochloric acid. The results are presented in Figure 1, for a range of acid concentration 1.5—6.5M. Again we observe the same reactivity order (5) > (4) ~ (2) > (1) ⋙ (3) (not shown), but the range of reactivity along this series is now greater. For example (5) is now *ca.* 25 times more reactive than (1) whereas the figure is 2.5 for the hydrochloric acid reaction. An explanation for this greater reactivity range in sulphuric acid is that, at these higher acidities, a second mechanism of denitrosation becomes important. This mechanism is thought to involve attack by H_3O^+ at the amino-nitrogen atom of the protonated form of the nitroso-amine, with the concurrent expulsion of NO^+. This was suggested in an earlier paper,[4] to account for the observed dependence of k_0 upon the acidity, and later gained some support in the interpretation of *para*-substituent effects.[1] Such a mechanism, in the reverse sequence of steps was proposed some years ago by Ridd and his co-workers [11] in the nitrosation of aromatic amines, to account for the observed acidity dependence of the rate constant in the ' moderate ' acidity range. It is to be expected that ring methyl substituents would, in our case, not only increase K as before, but also probably favour the rate-determining electrophilic attack by H_3O^+. This would account for the increased reactivity as methyl groups are progressively introduced into the ring. This effect is evidently not sufficiently powerful in the case of the 2,6-dimethyl-nitroso-amine to overcome the very large steric effect on the initial protonation.

(2) *Rearrangement.*—Compounds (1), (2), (4), and (5) gave the corresponding *p*-nitroso-isomers in high yield (>80%) in acid solution, when in each case reaction was carried out in the presence of an excess of the corresponding secondary amine, and without added sulphamic acid, *etc.* This ensures that essentially no overall denitrosation occurs and thus the rearrangement reaction can be examined without complication. The results are displayed in Figure 2, again for a range of sulphuric acid concentrations. In each case methyl

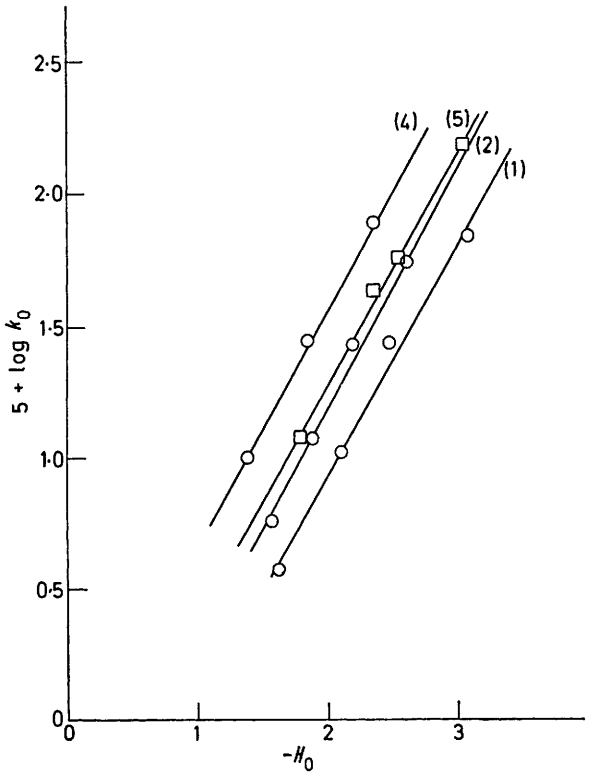


FIGURE 2 Variation of the rate constants for rearrangement of the nitroso-amines (1), (2), (4), and (5) with acidity in H_2SO_4

[11] E. C. R. de Fabrizio, E. Kalatzis, and J. H. Ridd, *J. Chem. Soc.* (*B*), 1966, 533.

substitution in the aromatic ring substantially increases the rate of the reaction, except again for the 2,6-dimethyl compound, for which reaction was just detectable over a period of days. Its estimated rate constant at

TABLE 4

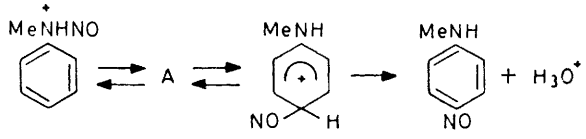
Rearrangement rate constants expressed as log $k_0 = -AH_0 - B$ for reaction in H_2SO_4

Compound	A	B
(1)	0.88	5.82
(2)	0.91	5.64
(5)	0.88	5.48
(4)	0.89	5.23

3.41M-H_2SO_4 was 1×10^{-7} s^{-1} which makes it *ca.* 3×10^4 times less reactive than the unsubstituted compound. This rate ratio is of the same order of magnitude as was found for denitrosation, and is consistent with the steric hindrance to protonation discussed earlier.

The 3-methyl substituent activates the reaction significantly more than does the 2-methyl substituent, by a factor of 2.5, whereas in denitrosation their effects were almost identical. This is to be expected for an electrophilic substitution reaction at the 4-position in the ring, when electron-releasing substituents in the 3-position can stabilise the transition state leading to the formation of the σ complex (Wheland intermediate). It had already been noted [2] that 3-methyl and 3-methoxy-substituents favour rearrangement, whereas 3-chloro- and 3-nitro-substituents reduced the rate of rearrangement to such an extent that denitrosation only occurred. This means that although rearrangement is subject to a ring deuterium isotope effect of 2.4, the final proton-loss cannot be wholly rate-limiting, rather k_0 must be a composite quantity which includes the rate constant for the proton loss and those involved in the reversible formation of the Wheland intermediate.[12]

An interesting though unexpected result however, is found for the rearrangement of (5) which is less reactive by a factor of *ca.* 2 than is (4), *i.e.* the introduction of a second *m*-methyl group actually reduces the rate of the reaction. This is difficult to explain in terms of a change in the basicity of the nitroso-amine, particularly since in denitrosation (5) is more reactive than (4). The effect must arise from one of the steps leading from the protonated form of the nitroso-amine to the final product. In the conventional electrophilic substitution processes of halogenation and hydrogen exchange, the addition of the second methyl group in a position equivalent to the *meta*-position here, increases the reactivity considerably.[13] Previously [12] we have envisaged that rearrangement occurs by way of some intermediate A (in Scheme 2) in which the nitrosonium ion NO^+ is bound to the ring system (possibly as a π complex) without its becoming kinetically free. It is conceivable that 3,5-dimethyl substituents could sterically



hinder the formation of such an intermediate to such an extent as to more than counteract the extra electronic effect of the second methyl substituent, and so lead to the observed order of reactivity.

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[12] D. L. H. Williams, *Tetrahedron*, 1975, 1343.
[13] R. O. C. Norman and R. Taylor, ' Electrophilic Substitution in Benezenoid Compounds,' Elsevier, Amsterdam, 1965, pp. 142, 211.