Kinetics and Mechanism of the Fischer–Hepp Rearrangement and Denitrosation. Part VIII.† Substituent Effects on Denitrosation of Aromatic *N*-Nitroso-amines

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The kinetic effects of various *N*-, *meta*-, and *para*-substituents on the denitrosation of aromatic N-nitroso-amines have been measured, both for the halide ion (Cl^-, Br^-, and in some cases I^-) catalysed reaction and also for reaction brought about by the solvent in sulphuric acid solution. The results are discussed in terms of the effect of substitution upon the basicity of the nitroso-amines, as well as the effect upon the rate-determining step of nucleophilic substitution at the nitroso-nitrogen atom. In the sulphuric acid reactions *para*-substituent effects are reversed when compared with the halide ion reactions: this is taken to support an earlier suggestion of the incursion of a second mechanism of denitrosation, particularly evident at high acidities, where reaction occurs between H_3O^+ and the protonated form of the nitroso-amine. Steric hindrance to attack by the nucleophile is evident in the halide ion reactions of *N*-t-butyl-*N*-nitrosoaniline as shown by the decreasing ratio of the rate constants for the *N*-methyl and *N*-t-butyl compounds along the series Cl^-, Br^-, and I^-. Rate constants have also been determined for the rearrangement (to the *para*-nitroso-isomers) of the *N*-alkylated series (*N*-Me, Et, Pr^i, and Bu^t). The results can be explained in terms of the substituent effects on the initial protonation of the reactant, although steric effects are operative for the *N*-t-butyl compound, which was hitherto thought not to undergo the Fischer–Hepp rearrangement.

N-NITROSO-AMINES can readily be converted to their corresponding secondary amines (a denitrosation process) by reaction with a number of nucleophilic species in acid solution. Normally this process is reversible with the equilibrium lying well over on the side of the nitroso-amine; this is the usual method of preparation of nitroso-amines. Ridd and his co-workers [1] have established the various mechanisms of *N*-nitrosation by nitrous acid and nitrosyl halides, *etc.*, derived from aqueous solutions of nitrous acid. If the free nitrosating species, which is formed on denitrosation along with the secondary amine, is removed very rapidly by, for example, reaction with sulphamic acid, then it is possible to examine mechanistic features of the denitrosation process, without complication due to the reversibility of the reaction. In an earlier paper [2] we have examined the reaction of *N*-methyl-*N*-nitrosoaniline with a number of nucleophilic species Y^-(Cl^-, Br^-, SCN^-, and I^-) and have established that nucleophilic attack occurs at the nitroso-nitrogen atom. More recently [3] it has been shown that a similar denitrosation is brought about by thiourea. All the available results accord with a mechanism (see Scheme 1)

$$PhNMeNO + H^+ \underset{}{\overset{K}{\rightleftharpoons}} Ph\overset{+}{N}H(Me)NO$$

$$Ph\overset{+}{N}H(Me)NO + Y^- \xrightarrow{k_1} PhNHMe + NOY$$

$$NOY + X \xrightarrow{k_2} \text{Various products}$$

SCHEME 1

whereby the nitroso-amine undergoes a fast, reversible protonation (probably at the amino-nitrogen atom) which is followed by nucleophilic attack by Y^- at the nitroso-nitrogen atom in the rate-limiting step to give the secondary amine and the free nitrosating agent NOY directly. The latter is destroyed rapidly by reaction with a suitable nitrite trap X, such as sulphamic acid, hydrazoic acid, urea, *etc.* The reaction is particularly sensitive to the reactivity of the nucleophile Y^-, a range of 15 000 in the observed rate constant covers the change Cl^- to I^-. The observed rate constant, in fact, enables the product k_1K to be obtained for each reaction. In general K values for the protonation of nitroso-amines have not been measured, presumably because of the instability of these compounds in acid solutions, when denitrosation and sometimes rearrangement occur. Jaffé and his co-workers [4] have examined the u.v. spectra of a number of aliphatic nitroso-amines in acid solutions, and have concluded that a number of protonated species can be found, although the precise structure of these species was not established. We have estimated the pK_a value of *N*-methyl-*N* nitrosoaniline to be in the region of *ca.* −2, from the rate–acidity profile of denitrosation.

It is of interest to examine the effects of substituents upon the reactivity of nitroso-amines particularly with regard to their separate contributions to K and k_1 in denitrosation. This paper reports the results of *N*-substitution (CH_3, C_2H_5, Pr^n, Pr^i, and Bu^t) on denitrosation and rearrangement separately and of *para*- (CH_3, OCH_3, Cl, NO_2) and *meta*- (OCH_3, NO_2) substitution in the aromatic ring. Russian workers [5] have reported some kinetic results for the denitrosation reaction of aromatic nitroso-amines, but their mechanistic conclusions are far from clear. Suggestions were made that a hydrogen bonded complex between the nitroso-amine and an acid HA was formed, which either lost NO^+ unimolecularly or underwent reaction with Cl^- or HSO_4^- to form the amine in both cases. Later [6] it was proposed that maybe a doubly protonated form of the nitrosoamine was involved in the reaction path. These mechanisms were

† Part VII, I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1976, 601.

[1] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418 and references quoted.

[2] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.

[3] D. L. H. Williams, *J.C.S. Chem. Comm.*, 1975, 375.

[4] W. S. Layne, H. H. Jaffé, and H. Zimmer, *J. Amer. Chem. Soc.*, 1963, **85**, 1816.

[5] B. A. Porai-Koshits, E. Y. Belyaev, E. Szadowski, and V. I. Zaionts, *Doklady Akad. Nauk S.S.S.R.*, 1964, **167**, 629; B. A. Porai-Koshits, E. Y. Belyaev, and J. Szadowski, *Reakts. Spos. org. Soedinenii*, 1964, **1**, 10; E. Y. Belyaev and B. A. Porai-Koshits, *ibid.*, p. 204.

[6] E. Y. Belyaev, T. I. Nikulicheva, and B. A. Porai-Koshits, *Zhur. org. Khim.*, 1965, **5**, 2141 (English translation).

not formulated in detail and it seems to us that the experimental evidence by no means specifically demands any one of them.

EXPERIMENTAL

N-Methyl-, *N*-ethyl-, *N*-n-propyl- and *N*-isopropyl-*N*-nitrosoanilines were all prepared by direct nitrosation of the corresponding secondary amines with acidified sodium nitrite. *N*-t-Butylaniline was prepared by reaction of t-butyl iodide with aniline,[7] separated from unchanged aniline by fractionation and converted to the *N*-nitroso-compound in the usual way. The *para*- and *meta*-substituted compounds were all made from the correspondingly substituted aniline by *N*-methylation with dimethyl sulphate, followed by nitrosation with sodium nitrite in hydrochloric acid. All were recrystallised from aqueous ethanol or from light petroleum (b.p. 60—80°), and gave satisfactory elemental analysis and m.p.s.

Kinetic measurements were made as before [2] in a recording u.v.–visible spectrophotometer by noting the decreasing absorption due to the reactant at fixed wavelength as a function of time, or by scanning an appropriate region of the spectrum at fixed time intervals. Denitrosation gave quantitative conversion to the secondary amine. Good first-order rate constants were obtained in all cases with a reproducibility of ±3%. A typical run is shown for the reaction of *N*-methyl-*p*-nitro-*N*-nitrosoaniline (1×10^{-4}M) with hydrochloric acid (4.14M) containing sulphamic acid (2×10^{-3}M). All rate measurements were done in aqueous solution at 31 °C.

t/s	0	60	90	120	150	180	210	240
O.D. (310 nm)	0.871	0.540	0.440	0.366	0.313	0.270	0.238	0.213
$10^4\,k$/s^{-1}		102	101	100	98	98	99	100
t/s	270	300	∞					
O.D. (310 nm)	0.197	0.182	0.147					
$10^4\,k$/s^{-1}	99	101						

RESULTS AND DISCUSSION

(1) *Halide Ion Catalysed Denitrosation.*—Table 1 shows the rate constants for the reaction of the series of *N*-alkylated nitroso-amines in sulphuric acid containing added sodium bromide and excess of sulphamic acid. Results are presented for each of two acidities. Under these conditions, denitrosation is irreversible [2] and the rate of rearrangement is negligibly small compared with that for denitrosation. Further, the rate of the non-catalysed reaction (*i.e.* denitrosation brought about by the solvent) is also negligibly small, so that the reaction represents attack by bromide ion at the protonated nitroso-amine. At both acidities the rate sequence NMe < NEt ~ NPr^n < NPr^i is apparent, with a factor of *ca.* 10 covering the whole reactivity range. For the *N*-t-butylnitroso-amine the reactivity lies between that of the NMe and NEt compounds which suggests that some steric effect operates. A similar, but not identical, rate sequence occurs for the chloride ion reaction, represented in Figure 1 as a dependence upon H_0. Here the *N*-t-butylnitroso-amine shows much the same reactivity as the NPr^n and is slightly less than that of NEt compound. Table 2 shows the rate constant ratios for *N*-t-butyl : *N*-methyl for a variety of nucleophilic reagents. It is clear that as the size of the nucleophile increases the relative reactivity of the Bu^t compound decreases, such that for the iodide reaction the Me compound is the more reactive. The steric effect must represent here the difficulty of approach of a large nucleophile to the nitroso-nitrogen centre, when the bulky t-butyl group is present at the amino-nitrogen. This effect is not evident for the isopropyl group where the corresponding rate ratios are virtually independent of the size of the nucleophile.

TABLE 1

Rate constants for the bromide ion catalysed denitrosation of *N*-alkyl-*N*-nitrosoanilines

N-Alkyl substituent	3.18M-H_2SO_4 0.23M-Br^- $10^4\,k_0$/s^{-1}	Rel k	2.15M-H_2SO_4 0.24M-Br^- $10^4\,k_0$/s^{-1}	Rel k
Me	122	1	39	1
Et	318	2.6	88	2.2
Pr^n			95	2.4
Pr^i	1 050	9	432	11
Bu^t	183	1.5		

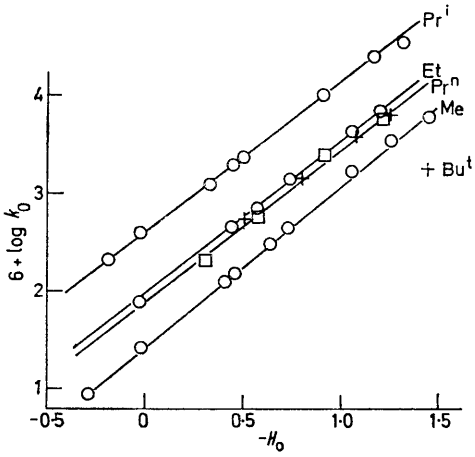


FIGURE 1 Rates of denitrosation of *N*-alkylnitrosoanilines in HCl

TABLE 2

Relative reactivity of NBu^t and NMe as a function of the nucleophile

Nucleophile	k_0(Bu^t) : k_0(Me)
Cl^-	2.45
H_2O	2.39
Br^-	1.45
I^-	0.94

The effect of substitution in the aromatic ring on the rate of denitrosation has been similarly investigated. Table 3 shows the rate constants for a number of *para*- and *meta*-substituted nitroso-amines in their reactions with acidified bromide ion solutions. The range of reactivity here is quite small, but the trend is quite clear in that electron-releasing substituents retard reaction, whereas electron-attracting substituents increase the overall reactivity. The same overall effects have been found for the chloride ion reaction; the results are reported graphically in Figures 2 and 3 for a range of

[7] W. J. Hickinbottom, *J. Chem. Soc.*, 1933, 946.

hydrochloric acid concentrations. In general the plots are approximately parallel with the notable exceptions of the *para*- and *meta*-nitro-substituents. It appears

TABLE 3

Rate constants for the bromide ion catalysed denitrosation of ring substituted *N*-nitrosoanilines

Substituent	3.18M-H_2SO_4 0.23M-Br^- $10^4\ k_0/s^{-1}$	Rel k	2.15M-H_2SO_4 0.24M-Br^- $10^4\ k_0/s^{-1}$	Rel k
H	122	1	39	1
p-Me	69.5	0.6	23.7	0.6
p-OMe	38.3	0.3	13.7	0.3
p-Cl	223	1.8	63.7	1.6
p-NO_2	202	1.7	50.8	1.3
m-OMe	225	1.8		
m-NO_2	214	1.8		

that all the *N*-alkyl and *para*- and *meta*-substituted nitroso-amines except the nitro-compounds respond in approximately the same way to the Hammett acidity function H_0. This feature shows up again in the reaction in sulphuric acid, and can make comparison of relative reactivities (particularly for the nitro-compounds) a function of the acidity chosen and therefore can lead to meaningless conclusions. Analysis of the substituent

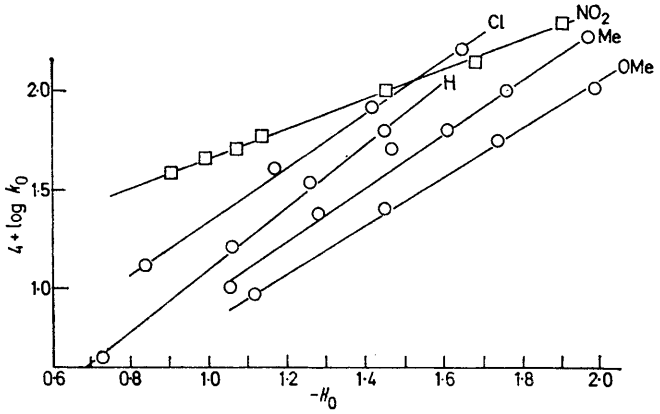
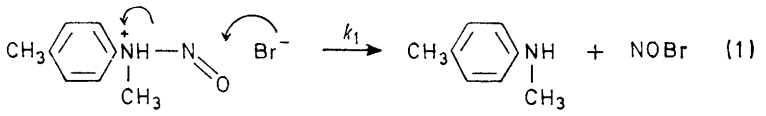


FIGURE 2 Rates of denitrosation of *para*-substituted *N*-methylnitrosoanilines in HCl

effects is complicated by the fact that the observed rate constant is a function of the product k_1K, *i.e.* the rate constant for the rate-determining nucleophilic attack and also the equilibrium constant for the initial protonation. Unfortunately those K values are not known for nitroso-amines, but it is perhaps to be expected that they should



show the same trends as those of the correspondingly substituted anilines. Values of pK_a for these are shown [8] in Table 4. It can be argued that the trend in the rates of denitrosation *N*-methyl < *N*-ethyl ~ *N*-n-propyl < *N*-isopropyl could simply represent the increasing value of K along the series, although it is perhaps surprising that k_1 should not be adversely affected by increasing *N*-alkyl substitution. The steric effect referred to earlier

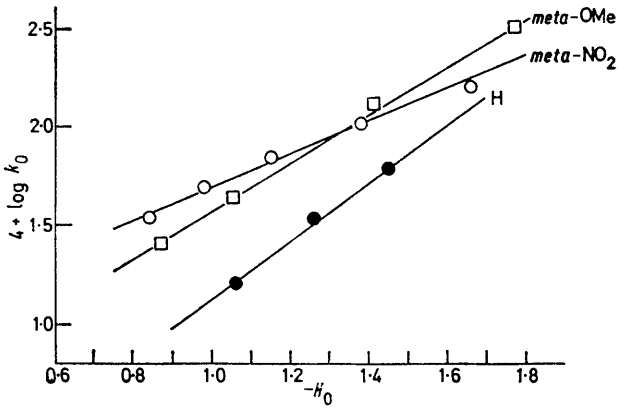


FIGURE 3 Rates of denitrosation of *meta*-substituted *N*-methylnitrosoanilines in HCl

clearly affects the reactivity of the *N*-t-butylnitroso-amine, reducing the overall reactivity in spite of an expected large increase in K, by comparison with the aniline series. The result of substitution in the aromatic ring (*para* and *meta*) is however not readily understood simply on the basis of the effect of these substituents

TABLE 4

pK_a Values of substituted anilines

N-Substituent	pK_a	Substituent	pK_a
H	4.60	*p*-Me	5.10
Me	4.85	*p*-OMe	5.34
Et	5.11	*p*-Cl	3.98
Pr^n	5.02	*p*-NO_2	1.11
Pr^i	5.77	*m*-OMe	4.21
Bu^t	7.00	*m*-NO_2	2.47

upon the pK_a value of the substrates. The relatively small magnitude of the effects suggests that probably two opposing forces are at work. If it were merely a case of substituent effects upon the pK_a, then one would expect electron-releasing substituents to increase the reactivity and *vice versa*. It appears that these substituents exert a considerable influence upon k_1, outweighing the effect upon the basicity of the nitroso-amine. This represents an example of the effect of substituents in the leaving group of a nucleophilic substitution at a nitrogen centre [equation (1)]. The question arises as to why substitution at the amino-nitrogen atom and in the aromatic ring are apparently so different. The answer possibly lies in the nature of the substituent effects on the basicity of the *N*-alkylated nitroso-amines. It is known that the observed increases in the base strength on substitution of the *N*-hydrogen atoms in aniline by alkyl

[8] Taken from J. W. Smith 'The Chemistry of the Amino Group,' ed. S. Patai, Interscience, New York, 1968, pp. 182, 188.

groups are too large to be accounted for simply by the electronic effects of these groups, and it has been suggested that the steric effects are important. The precise nature of such effects has not been formulated mainly because of lack of accurate data such as the enthalpy and entropy changes accompanying protonation. At least two views have been put forward. Brown [9] has discussed the effects in terms of various steric strains, whereas Wepster [10] has interpreted the data in terms of the solvation energies of the protonated forms of the amines. Whatever the nature of the effects, it is not unreasonable to expect their magnitude to be greater in tertiary amines such as the *N*-alkyl-*N*-nitrosoanilines, so that the base-strengthening effects of *N*-alkylation (whatever their cause) outweigh the inductive effects of these substituents upon the rate-determining nucleophilic substitution step. The exception to this is of course the t-butyl compound where a further steric effect, steric hindrance to the approach of the nucleophile in the slow step, is operative. For the *meta*- and *para*-substituted series no steric complications exist and the situation is resolved in terms of a balance between the opposing substituent effects upon K and k_1. The net result is that the effects are nearly cancelled out but with the change on k_1 marginally outweighing that on K.

(2) *Denitrosation in Sulphuric Acid.*—In the absence of halide ion or other strong nucleophilic species such as thiourea,[3] denitrosation can still occur in acid solution such as sulphuric acid, although generally at a rate much less than that for the corresponding acidity in hydrochloric acid. There is no catalysis by hydrogen sulphate or sulphate ions as expected from their relatively weak nucleophilicity. Here it is presumed that denitrosation occurs [2] by attack of a water molecule as the nucleophile, although our results would not exclude a unimolecular fission to give NO^+. This is considered to be unlikely at the acidities studied since the reverse reaction (nitrosation of aromatic amines) is thought to occur [1] by attack of the nitrous acidium ion $H_2\overset{+}{N}O_2$. For *N*-alkyl substituents, the pattern of reactivity is very similar to that found for the halide ion reactions *i.e.* the sequence *N*-methyl < *N*-ethyl < *N*-isopropyl, with *N*-t-butyl lying close to *N*-ethyl (Figure 4). Again, it would appear that the dominant factor is the substituent effect upon the basicity of the nitroso-amine, although the origin of such an effect may be obscure. It is suggested that, as before, the apparent low reactivity of the t-butyl compound is due to steric hindrance to attack by the water molecule in the rate-determining step. Russian workers [5] had previously noted this order of reactivity for denitrosation in sulphuric acid for *N*-alkylated *p*-nitro- and *p*-methyl-nitroso-amines. The effect of *para*-substitution is shown in Figure 5. Here again the *p*-nitro-group appears to produce anomalous behaviour, in that the slope of the line is markedly different from those of other substituents Here we have a reversed order of reactivity, when compared with the corresponding reactions in hydrochloric

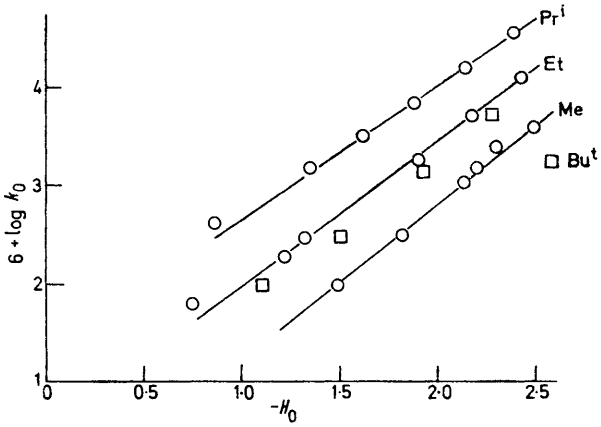


FIGURE 4 Rates of denitrosation of *N*-alkylnitrosoanilines in H_2SO_4

acid, *i.e.* $CH_3 \sim OCH_3 > H > Cl$. The overall effects are again small, implying that two opposing effects operate, but it is clear now that electron-releasing groups activate the nitroso-amine. In an earlier paper [2] we proposed that a second mechanism of denitrosation becomes important at high acidities. This mechanism [equation (2)] involves attack of H_3O^+ at the amino-nitrogen atom, displacing the NO^+ group, perhaps *via* a ring-bonded species to the solvent. The evidence for

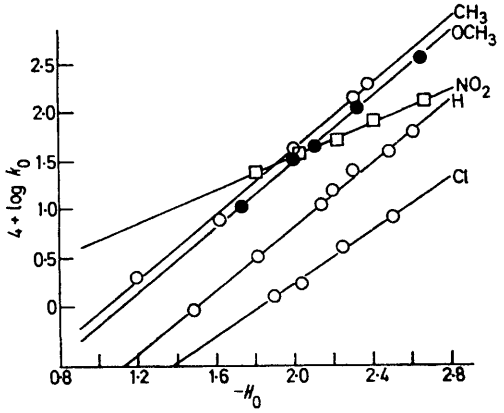


FIGURE 5 Rates of denitrosation of *para*-substituted *N*-methylnitrosoanilines in H_2SO_4

the incursion of this mechanism was from the observed dependence of the rate constant upon the acidity (Ch_0

$$PhN\overset{+}{H}(Me)NO + H_3O^+ = PhN\overset{+}{H}_2Me + \overset{+}{H}_2NO_2 \quad (2)$$

and $C'h_0^2$). Further, a similar mechanism was proposed some years ago by Ridd and his co-workers [11] for the reverse reaction (nitrosation and diazotisation of aromatic amines) in which the nitrous acidium ion reacted

[9] H. C. Brown, D. H. McDaniel, and O. Häfliger in 'Determination of Organic Structures by Physical Methods,' eds. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, p. 607.

[10] B. M. Wepster, *Rec. Trav. chim.*, 1957, **76**, 357.

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

with the protonated form of the amine. We consider that our reversed trend of substituent effects in the sulphuric acid reaction lends further support to this mechanism. Both mechanisms (attack by H_2O at the nitroso-nitrogen and H_3O^+ at the amino-nitrogen) involve reaction *via* the protonated nitroso-amine, so the changes in K will effect both in the same way. However in the high acidity mechanism, rate-determining electrophilic attack by H_3O^+ occurs, which will be facilitated by electron-releasing *para*-substituents. A combination of both mechanisms would account for the observed results.

Russian workers [5,6] have also measured the rates of denitrosation in sulphuric acid of a number of *para*-substituted aromatic nitroso-amines. They concluded from the variation of substituent effects, and in particular from a minimum in the log k against σ plot [12] that two mechanisms acted concurrently, although details of neither were established. It is worth noting that for reactions which proceed *via* a protonated substrate as here, it is futile to carry out a Hammett σ–ρ analysis of this type at one acidity unless all the substrates show exactly the same acidity dependence for the initial protonation *i.e.* that all the log k against H_0 lines are parallel. This is patently not so in the present work as shown by the very different slopes *e.g.* for *p*-NO_2 and *p*-CH_3. At some acidities the *p*-NO_2 group appears to be overall activating (relative to the unsubstituted nitroso-amine) whilst at other acidities it is overall deactivating for denitrosation in both acid systems.

(3) *Rearrangement in Sulphuric Acid.*—We have measured the rate constants for rearrangement of the *N*-alkylnitroso-amines, using the technique developed in earlier work,[13] where reaction is carried out in the presence of an excess of the corresponding secondary amine. This in effect cuts out the denitrosation path, by so increasing the rate of *N*-nitrosation that only intramolecular rearrangement occurs. Generally, so long as the concentration of the added secondary amine exceeds some minimum value, the reaction rate is independent of its concentration. The yield of the Fischer–Hepp rearrangement product, the *p*-nitroso-isomer, is almost quantitative under these circumstances. The results, shown in Figure 6, demonstrate the reactivity sequence *N*-methyl < *N*-ethyl < *N*-isopropyl for rearrangement, which can readily be accounted for in terms of the basicity of the nitroso-amines along this series. The t-butylnitroso-amine reaction shows a complicating feature. Whilst rearrangement clearly takes place, as observed spectrophotometrically, its rate, particularly at high acid concentration, is not independent of the concentration of added t-butylaniline. There appears to be some reaction between the nitroso-amine and the secondary amine resulting in an increased rate of disappearance of the nitroso-amine and a decreasing yield of the *p*-nitroso-rearrangement product. This reaction, which has not yet yielded an identifiable product has been noted at higher acidities with other reactive nitroso-amines, *e.g.* *m*-methoxy-*N*-methyl-*N*-nitrosoaniline. However at a lower acidity, where a high yield of rearrangement product is observed *N*-t-butyl-*N*-nitrosoaniline shows a reactivity comparable with the *N*-ethyl compound. It is probable that the origin of the reduced reactivity of the *N*-t-butyl compound is steric. It is claimed in the literature [7,14] that *N*-t-butyl-*N*-nitrosoaniline and other nitroso-amines with bulky *N*-alkyl groups do not undergo the Fischer–Hepp rearrangement, and an explanation involving steric inhibition of resonance has been advanced. In our work *N*-t-butyl-*N*-nitrosoaniline does undergo rearrangement to the *p*-nitroso-isomer in aqueous sulphuric acid, although the rate constant is not as large as that expected from a consideration of the electronic effects alone of the *N*-t-butyl group. The fact that this nitroso-amine undergoes both rearrangement and denitrosation at about the same rate as does the *N*-ethyl compound suggests that there may be steric hindrance to protonation of the substrate, a step which is common to both reations.

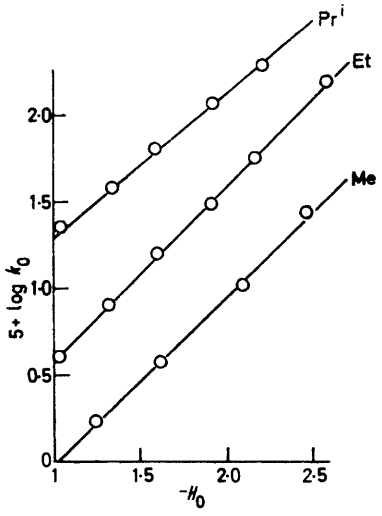


FIGURE 6 Rates of rearrangement of *N*-alkylnitrosoanilines

We thank the S.R.C. and the Royal Society for financial support.

[5/1781 *Received*, 16*th September*, 1975]

[12] J. Shorter, 'Correlation Analysis in Organic Chemistry—An Introduction to Linear Free Energy Relationships,' Clarendon Press, Oxford, 1973, p. 20.

[13] T. D. B. Morgan, D. L. H. Williams, and J. A. Wilson, *J.C.S. Perkin II*, 1973, 473.

[14] H. J. Shine, 'Aromatic Rearrangements,' Elsevier, Amsterdam, 1967, p. 235 and references quoted.