Kinetic Substituent and Isotope Effects in the Acid-catalysed Rearrangement of *N*-Phenylhydroxylamines. Are Nitrenium Ions Involved?

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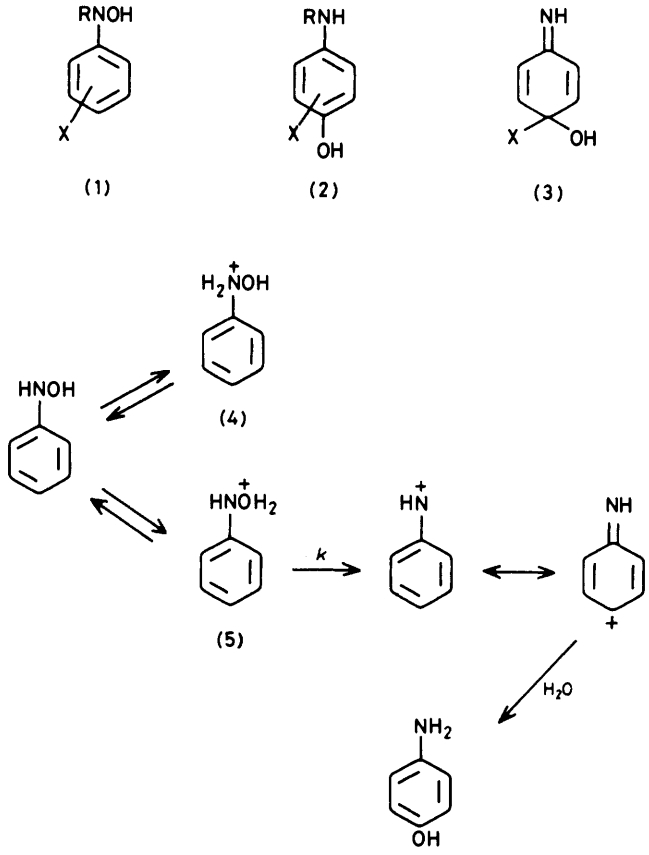
Acidity–rate profiles have been established for the rearrangement of *N*-phenylhydroxylamine and its derivatives in aqueous sulphuric acid and also in D_2SO_4–D_2O. The results, particularly the change in the magnitude of the kinetic solvent isotope effect on increasing the acidity, are consistent only with a reaction mechanism involving unimolecular decomposition of the *O*-protonated species. *N*-Ethyl substitution has only a very small effect on the overall rate of reaction, whereas the rate constant was increased by *ca.* 100 by 4-Me substitution. The substituent effects argue against the involvement of a nitrenium ion intermediate but rather suggest that the intermediate is better represented by an imine structure with the positive charge at the 4-position in the aromatic ring.

It is well known that *N*-phenylhydroxylamines (1) readily rearrange in aqueous acid solution to give the corresponding 4-aminophenols (2). The reaction was discovered and much studied by Bamberger [1] at the turn of the century, but until recently very little mechanistic information has been available (other than the early product studies), particularly in comparison with the effort directed to establishing the rearrangement mechanism of other *N*-substituted aniline derivatives.[2,3] Bamberger showed that the parent compound (R = X = H) gave exclusively 4-aminophenol when the reaction medium was aqueous sulphuric acid, but both 2- and 4-amino ethyl esters when the solvent was ethanol, and also the 2- and 4-chloroamino derivatives when hydrochloric acid was used.[1,4] When X was 4-Me the initial product was the iminocyclohexadienol (3), which was subsequently hydrolysed to the quinone.[5] The early work of Bamberger, together with a few more recent studies, has been reviewed.[6,7]

One fact established with certainty is that the reaction occurs in an intermolecular fashion,[8] since full uptake of ^{18}O occurs in the product (but none in the reactant) when the solvent contains $H_2{}^{18}O$.

An up-dated view of the mechanism, based on the ideas of Bamberger, was first set out by Heller *et al.*[9] (see Scheme 1). This involves unimolecular loss of a water molecule from the *O*-protonated form (5), followed by nucleophilic attack at the 4- or in some cases the 2-position in the aromatic ring. It is likely that *N*-protonation is the more extensive but the *N*-protonated form is considered not to be an intermediate in the overall rearrangement. A concerted S_N2-type reaction involving concurrent nucleophilic attack and N–O bond fission has been ruled out by the observation that the reaction rate constant is independent of chloride ion concentration, even though chloroamino products are formed.[9]

Recently, more detailed kinetic studies have been reported.[10,11] The reaction was observed to be first order in phenylhydroxylamine and acid-catalysed up to pH 1; thereafter the rate constant was almost unchanged for a range of acidity up to $H_0 = -1$, after which a further, less marked rate increase was observed. Spectral measurements were consistent with *N*-protonation and a pK_a value of 1.90 was determined. The observed acidity–rate profile does not distinguish between *N*- and *O*-protonated intermediates, but analogies with other *N*- and *O*-protonation sites and a σ–ρ correlation of three 3-substituted phenylhydroxylamines were taken to support the mechanism shown in Scheme 1. Positive entropies of activation were found which again argue against a bimolecular process. The acid catalysis at high acidities was attributed [10] to the incursion of another mechanism involving the diprotonated species $PhN\overset{+}{H}_2\overset{+}{O}H_2$. This pathway had been suggested earlier,[12] but without any experimental evidence, although other polarographic measurements [13] have been interpreted in terms of this doubly protonated species. A similar species, the doubly protonated hydrazobenzene, is now well established as an intermediate in the benzidine rearrangement under certain conditions at high acidities.[14]



Scheme 1.

It was thought that further insight into the mechanism of this reaction, particularly the question of the involvement of nitrenium ion intermediates, could be obtained from kinetic studies using electron-releasing substituents (*a*) at the amino nitrogen and (*b*) at the 4-position of the aromatic ring.

Nitrenium ions have been postulated as intermediates in solvolysis reactions of *N*-chloro amines [15] and in other reactions, but up to the present there is no direct evidence for their existence as stable species.[16] Our results, together with data obtained on the kinetic solvent isotope effects, are presented in this paper. The overall conclusions have already been incorporated into a recent review article [17] covering aspects of the mechanism of aromatic rearrangements.

Experimental

Materials.—Phenylhydroxylamine was prepared by the standard method [18] of reduction of nitrobenzene with ammonium chloride and zinc dust. The crude material was recrystallised from a mixture of benzene and light petroleum (b.p. 40—60 °C) to give white needles, m.p. 80—81 °C (lit.,[1] 80.5—81 °C). It was kept refrigerated under nitrogen and was recrystallised immediately before use in the kinetic experiments. Similarly *N*-(4-methylphenyl)- and *N*-(4-chlorophenyl)-hydroxylamine were prepared from 1-methyl-4-nitrobenzene and 1-chloro-4-nitrobenzene respectively. Both were recystallised; m.p.s 93 °C (4-Me) (lit.,[5] 94 °C) and 87 °C (4-Cl) (lit.,[19] 86.5 °C). *N*-Ethyl-*N*-phenylhydroxylamine was prepared by reaction of *N*-phenylhydroxylamine with freshly distilled ethyl bromide in pyridine solution.[20] The pale yellow crystals were purified by sublimation to give white crystals, m.p. 36—37 °C (lit.,[20] 35—37 °C). All other materials were commercially available and were purified by recrystallisation where necessary.

Products.—The u.v. spectrum of the completed reaction mixture from *N*-phenylhydroxylamine was identical with that of 4-aminophenol in acid solution. For a number of runs at different acidities the mixtures resulting from completed reactions were made alkaline and again their u.v. spectra were examined. The absorption maximum at 310 nm (due to 4-aminophenol) was present in each, with no detectable peak at 297 nm characteristic of the 2-amino isomer.

For *N*-ethyl-*N*-phenylhydroxylamine, the reaction mixture was made alkaline and extracted with carbon tetrachloride; the product was identified as *N*-ethyl-4-hydroxyaniline by i.r. spectroscopy.

The first product from the reaction of *N*-(4-methylphenyl)-hydroxylamine was obtained as a yellow oil by neutralisation of the reaction mixture (originally 0.25M in sulphuric acid) after 40 min and extraction with ether. The i.r. spectrum indicated the presence of NH and OH groups but no carbonyl group. It proved impossible to get a pure sample but the mass spectrum clearly showed the molecular ion at *m/z* 123 expected for the iminocyclohexadienol. The second product was similarly extracted after reaction had been allowed to proceed for 4 days. The oil obtained was sublimed to give a red-brown solid with an i.r. spectrum showing OH and quinone carbonyl absorption (Found: C, 67.7; H, 7.0; N, 0. Calc. for $C_7H_8O_2$: C, 67.7; H, 6.5%). The mass spectrum showed the expected molecular ion at *m/z* 124 and a fragmentation pattern consistent with the presence of the hydroxyquinone.

Kinetic Measurements.—These were carried out spectrophotometrically at 31.5 °C using a Pye Unicam SP 8000 instrument. Oxidation side reactions were eliminated or kept to a minimum by carrying out the reaction under nitrogen and (for *N*-phenylhydroxylamine and the *N*-ethyl derivative) samples were withdrawn at intervals and the absorbance was measured at 272 nm. For the 4-methyl substrate two reactions were observed, sufficiently different in rate for both first-order rate constants to be measured, by monitoring both the appearance and the disappearance of the absorbance at 247 nm.

Data from a typical run are given in Table 1 for the reaction of *N*-phenylhydroxylamine (5×10^{-4}M) in sulphuric acid (2.5M) at 31.5 °C.

Table 1. A typical kinetic run for the reaction of *N*-phenylhydroxylamine (5×10^{-4}M) in sulphuric acid (2.5M) at 31.5 °C

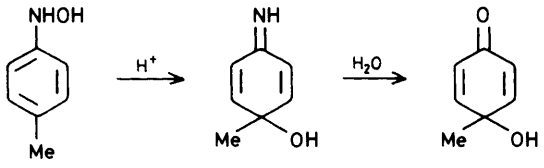
t/s	0	1 660	3 675	5 680	8 320	10 360
Absorbance	0.081	0.129	0.180	0.229	0.293	0.333
$10^5 k_{obs}/s^{-1}$		4.46	4.34	4.38	4.56	4.54
t/s	14 250	17 230	19 840	22 765	25 805	30 460
Absorbance	0.398	0.453	0.479	0.512	0.543	0.585
$10^5 k_{obs}/s^{-1}$	4.48	4.68	4.52	4.50	4.51	4.55
t/s	∞					
Absorbance	0.753					

Mean value of $k_{obs} = 4.50 \pm 0.09 \times 10^{-5}$ s^{-1}.

Results and Discussion

Products.—As noted by Sone *et al.*[10] the rearrangement of phenylhydroxylamine gave in addition to 4-aminophenol, significant quantities of oxidation by-products including azoxybenzene, particularly when the acidity of the reaction medium was low. It is believed that the substrate (in its non-protonated form) undergoes aerial oxidation to yield nitrosobenzene, which then reacts further with the substrate to give azoxybenzene. We were able to isolate azoxybenzene readily, by extraction with carbon disulphide, from a solution of *N*-phenylhydroxylamine left in the air for 2 days without an acid catalyst; this supports an earlier finding.[20] The situation is further complicated by the rearrangement of azoxybenzene under the influence of u.v. light.[21] Oxidation side products were not detected (spectrophotometrically) in reactions at high acidity, and were reduced to a minimum elsewhere by carrying out reactions under nitrogen and removing samples periodically for u.v. absorption measurement. Even so, for the reactions carried out at very low acidity it was not possible to eliminate these side reactions completely, and small corrections were introduced in the appropriate kinetic experiments. Oxidation side products were not observed in the reactions of the *N*-ethyl or the 4-methyl substrate, but were so pronounced with the 4-chlorophenylhydroxylamine that they could not be contained sufficiently for sensible kinetic measurements to be made.

For four different acidities in the range 0.25—2.5M-H_2SO_4, the u.v. spectra of solutions remaining after completion of reactions were consistent with the quantitative production of 4-aminophenol. However it was not possible from the spectra of acid solutions to discount the presence of some 2-aminophenol. When the reaction mixtures were made slightly alkaline, in no case was any indication found of a sharp absorbance at 297 nm characteristic of the 2-isomer. The conclusion is that under these conditions the product of rearrangement is solely 4-aminophenol, when oxidation by-products have been eliminated. Similarly the *N*-ethyl substrate gave only the corresponding 4-hydroxyaniline derivative. The reaction of *N*-(4-methylphenyl)hydroxylamine gave (as previously found by Bamberger [5]) initially the iminocyclohexadienol (3), which, more slowly, was hydrolysed to the quinone (6). Similar behaviour had been found for 2,4-dimethyl- [22] and 2,4,6-trimethyl-phenylhydroxylamine.[23] The final product isolated was not always the quinone correspond-



(3) X = Me (6)

Table 2. pK_a Values of *N*-phenylhydroxylamines at 31 °C

Substrate	Solvent	pK_a *	pK_a †
(1; R = H, X = H)	H_2O	1.90 ± 0.02	1.90 ± 0.02
(1; R = H, X = H)	D_2O	2.43 ± 0.02	2.35 ± 0.03
(1; R = Et, X = H)	H_2O	2.32 ± 0.02	2.37 ± 0.01
(1; R = H, X = Me)	H_2O	2.49 ± 0.06	2.44 ± 0.04

* Measured spectrophotometrically. † Derived from kinetic measurements.

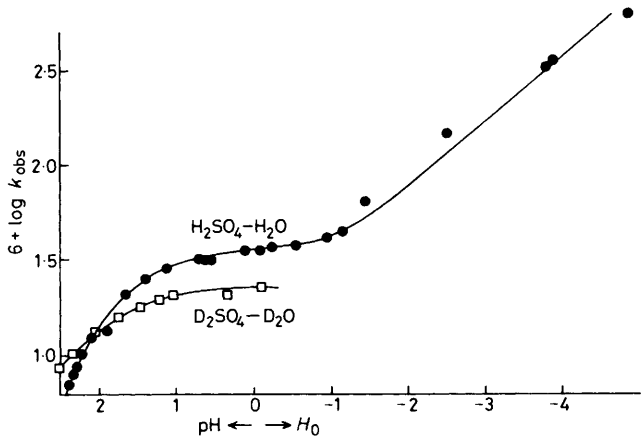


Figure. A plot of log *k* *vs.* H_0 or pH for the rearrangement of *N*-phenylhydroxylamine in H_2SO_4–H_2O and in D_2SO_4–D_2O

Table 3. Substituent effects in *N*-phenylhydroxylamine rearrangement

	0.005M-H_2SO_4		0.3M-H_2SO_4	
Substrate	k_{obs}/s^{-1}	Rel. k_{obs}	k_{obs}/s^{-1}	Rel. k_{obs}
(1; R = H, X = H)	1.3×10^{-5}	1	3.2×10^{-5}	1
(1; R = Et, X = H)	1.5×10^{-5}	1.2	2.2×10^{-5}	0.7
(1; R = H, X = Me)	1.4×10^{-3}	108	1.9×10^{-3}	60

ing to (6), but sometimes a dihydroxy aromatic compound where the 4-methyl substituent has migrated to the 5-position.

The u.v. spectra of the phenylhydroxylamines in water change on acidifying even before rearrangement occurs. This corresponds to significant conversion into the *N*-protonated species, which is virtually complete in 0.5M-H_2SO_4. The pK_a values were readily obtained from absorbance measurements and are shown in Table 2 for (1; R = H, X = H) in water and in D_2O, and also for (1; R = Et, X = H) and for (1; R = H, X = 4-Me). The value for the unsubstituted compound in water agrees well with that reported by Sone *et al.*[10] The larger value in D_2O is as expected as are the increased values on substitution by *N*-Et and 4-Me. The values calculated from the kinetic results agree well with those from spectral measurements.

Kinetics.—The acidity–rate profile for the reaction of (1; R = H, X = H) in sulphuric acid is shown in the Figure for both H_2O and D_2O solvents. The curve for H_2O is essentially the same as that found by Sone *et al.*;[10] indeed our plateau value of k_{obs} of 3.2×10^{-5} s^{-1} (at 31 °C) is in reasonable agreement with the value of 2.3×10^{-5} s^{-1} calculated from the data in ref. 10. Similar rate profiles were obtained for (1; R = Et, X = H) and (1; R = H, X = 4-Me). The solvent isotope effect $k_{obs}(H_2O)/k_{obs}(D_2O)$ changes from being less than 1 at low acidities to 1.5 at the plateau region. These observations can be rationalised by the mechanism in Scheme 1 if we consider the detailed rate equation expected. Let K^O and K^N be the dissociation constants for the *O*- and *N*-protonated form of the reactant respectively, with $K^O \gg K^N$. The rate constant for the decomposition of (5) is *k*. The total substrate concentration is then given generally by [(1)] + [(4)], and the first-order rate constant observed [defined by equation (i)] is given by equation (ii). This readily explains the first-order

$$-d([(1)] + [(4)])/dt = k_{obs}([(1)] + [(4)]) \quad (i)$$

$$k_{obs} = kK^N[H^+]/K^O(K^N + [H^+]) \quad (ii)$$

acid dependence at low acidity and zero-order dependence at higher values (the plateau region). At low acidities k_{obs} is given by equation (iii) and the solvent isotope effect by (iv). Acid

$$k_{obs} = k[H^+]/K^O \quad (iii)$$

$$k_{obs}(H_2O)/k_{obs}(D_2O) = K^O(D_2O)/K^O(H_2O) \quad (iv)$$

dissociation constants are greater in H_2O than in D_2O[24] and so the expected solvent isotope effect is less than 1 as observed. Conversely at high acidities at the plateau region the rate constant is given by equation (v), and the kinetic solvent isotope effect by equation (vi). This now depends on the ratio

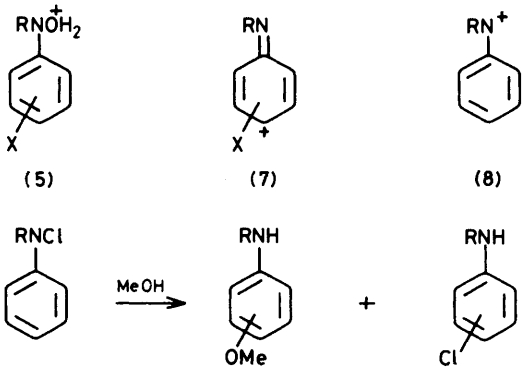
$$k_{obs} = kK^N/K^O \quad (v)$$

$$k_{obs}(H_2O)/k_{obs}(D_2O) = \frac{K^N(H_2O)}{K^N(D_2O)} \Big/ \frac{K^O(H_2O)}{K^O(D_2O)} \quad (vi)$$

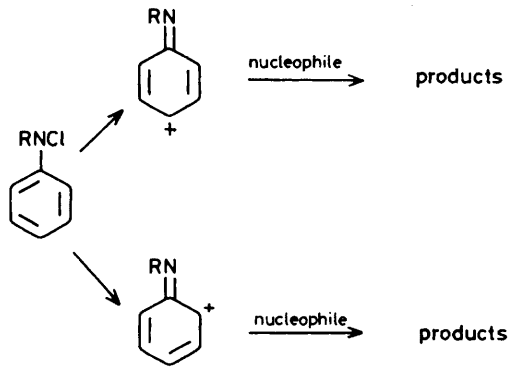
of the $K(H_2O)/K(D_2O)$ values for the *N*- and *O*-protonated forms. It is known that $K(H_2O)/K(D_2O)$ values are a function of the acid strength, being greater for the weaker acids (see ref. 24). $K^N(H_2O)/K^N(D_2O)$ is thus expected to be greater than $K^O(H_2O)/K^O(D_2O)$, yielding a kinetic solvent effect >1 as compared with 1.5 observed experimentally.

A mechanism based on the reaction of the *N*-protonated form (which has been suggested [25]) can explain the kinetic solvent isotope effect only at low acidity. Thus the changeover observed as the acidity is increased provides definite kinetic evidence for reaction *via* the *O*-protonated species. Similar results were obtained for the *N*-Et and 4-Me substrates, where $k_{obs}(H_2O)/k_{obs}(D_2O)$ values were 1.4 and 1.5, respectively, at the plateau, and <1 in both cases at low acidities. Whilst these explanations of the kinetic isotope effects are reasonable in terms of the given reaction mechanism, it is possible that secondary effects are also involved.

Another striking feature of the kinetic substituent effect is that *N*-Et substitution has relatively little effect on the overall rate constant for reaction both at low acidity and in the plateau region, whereas in both regions 4-Me substitution has a large accelerating effect of *ca.* 100 (see Table 3). The quoted rate constants for the 4-Me compound refer to the first



Scheme 2.

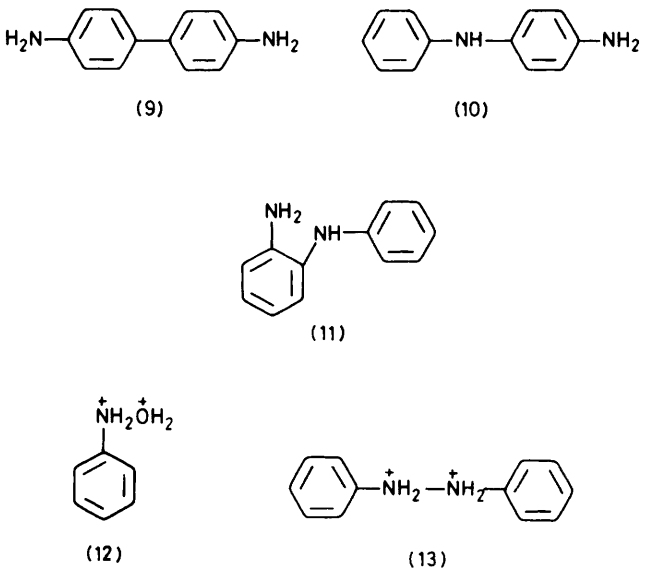


Scheme 3.

reaction to form the iminocyclohexadienol (3), *e.g.* 1.9×10^{-3} s^{-1} at 0.3M-H_2SO_4, whereas the imine hydrolysis to give (6) has a rate constant of 1.6×10^{-5} s^{-1}.

These results strongly suggest that in the transition state deriving from unimolecular reaction of the *O*-protonated species (5), the positive charge is being developed at the 4-position in the aromatic ring rather than at the nitrogen atom since stabilisation by the electron-releasing 4-Me substituent is so marked, whereas the *N*-Et substituent has very little effect. The intermediate is then the imine (7) rather than the nitrenium ion (8). Support for this suggestion comes from an examination of the ^{18}O work of Kukhtenko:[8] incorporation of ^{18}O from the solvent occurred in the product, *but not* in the reactant. If a nitrenium ion intermediate were involved, then attack by the solvent at the nitrogen atom should occur and lead to some ^{18}O incorporation in the reactant. From our results, particularly those at the higher acidity at the plateau region (0.3M-H_2SO_4) where substituent effects on the initial *N*-protonation equilibria are not involved, it is quite clear that the electron releasing *N*-ethyl substituent reduces the observed rate constant slightly whereas the 4-methyl substituent produces a large rate enhancement.

Nitrenium ions have been postulated as intermediates in a number of reactions in an attempt to rationalise the observed products, but direct evidence for their existence as stable species is missing.[16] The evidence in favour of nitrenium ion intermediates arises from the observation of carbocation-like rearrangements in the solvolysis of some *N*-chloro bicyclic systems,[15] and from product and kinetic studies of the solvolyses of *N*-chloroaniline derivatives[26] (Scheme 2). In particular the correlation of rate constants with σ^+ with a ρ value of -6.35 indicated that an electron-deficient species such as a nitrenium ion is being generated. Reactions of



hydroxylamines, including *O*-substituted derivatives, have also been rationalised on the basis of nitrenium ion or nitrenium ion–anion pair intermediates.[27] However, none of these results specifically requires the formation of a discrete nitrenium ion species; they could also be interpreted in terms of concerted reactions where rearrangement and departure of the leaving group occur simultaneously, or in the case of the aniline derivatives, *N*–Cl bond fission is synchronous with electronic movements within the aromatic system, forming directly (Scheme 3) the 2- and 4-positively charged intermediates. Our results suggest, at least with the phenylhydroxylamines, that this is the case, and there is no significant charge development on nitrogen.

It is not clear why in some cases, for example where the nucleophile is water, only the 4-isomer product is formed from phenylhydroxylamine, whereas in other cases *e.g.* when chloride ion is present, both 2- and 4-chloro isomers are formed.

Some of the early product analyses reported by Bamberger[4] suggest that under certain conditions a transition state may exist with a degree of positive charge located at the nitrogen atom. Thus when phenylhydroxylamine is heated with anilinium sulphate in aniline solution, the products are benzidine (9) and the semidines (10) and (11). Small quantities of (9) and (10) were also formed when anilinium sulphate in water was used; the major product was 4-aminophenol. It seems that the semidine products arise by nucleophilic attack by aniline at the 2- and 4-positions, but benzidine could be formed by nucleophilic attack at nitrogen, followed by the benzidine rearrangement.

At quite high acidities (>2M-H_2SO_4) we find, as did Sone *et al.*,[10] a rate constant increase with acidity for all three substrates studied. This has been interpreted[10] as the incursion of another mechanism involving the diprotonated species (12). This cannot be identified spectrophotometrically and there appears to be no suitable H^+ function available for correlation with the rate constants. A similar diprotonated species (13) is believed to be involved in the benzidine rearrangement of hydrazobenzenes[28] at high acidities. However in that case the second protonation also follows H_0 to a good approximation.[29] We and Sone *et al.*[10] find a slope of *ca.* 0.3 for log *k vs.* $-H_0$ at higher acidities, which seems to us rather low for the involvement of intermediate (12). An alternative suggestion for the rate increase in this region is that it arises from a medium or salt effect at these rather high acid concentrations,

but it is difficult to be more precise with the limited experimental data available.

Acknowledgements

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