Reaction between Various Benzaldehydes and Phenylhydroxylamine: Special Behaviour Compared with Other Amines

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The kinetics and mechanism of the reaction between phenylhydroxylamine and benzaldehydes to give nitrones has been studied. Phenylhydroxylamine exhibits special behaviour compared with other amines. We have determined the following. (i) The pH–rate profile of the reaction of phenylhydroxylamine with benzaldehydes does not correspond to any of those previously encountered for this kind of reaction. Unlike amines of similar pK_a values, the pH–rate profile for phenylhydroxylamine does not show a negative break, because the rate-determining step is the dehydration of the dihydroxy intermediate over the entire pH range (pH 1–11). (ii) The point for the reaction of phenylhydroxylamine shows a positive deviation from the Brønsted relation between the hydronium ion catalytic rate constant and the pK_a of the amines. It is evident that this behaviour is caused by a very fast first step for the reaction of phenylhydroxylamine and it is suggested that this is due to a pre-association mechanism of attack of phenylhydroxylamine on carbonyl compounds.

It has been suggested[1] that the addition of amines to carbonyl compounds can exhibit three basic types of pH–rate profile, depending on the relative predominance of an acid catalysed 'concerted mechanism' involving attack of the amine on the carbonyl group or a 'stepwise mechanism' involving initial formation of an unstable zwitterionic intermediate ($T^{\pm}$) which is subsequently trapped by proton transfer to give the dihydroxy intermediate. All the profiles exhibit a non-linear pH–rate relationship in which the deviation is caused by a change in the rate-determining step from the attack of the amine on the carbonyl compound to dehydration of the dihydroxy intermediate to give the final product. Between pH 1 and 11, the reaction between furfurals and phenylhydroxylamine[2] shows only one rate-determining step, *i.e.*, the dehydration of the dihydroxy intermediate. Consequently, the pH–rate profile does not correspond to any of those indicated by Sayer *et al.*,[1] pointing to a special behaviour of phenylhydroxylamine as the nucleophile in this kind of reaction.

Considering that the mechanism of the reaction of amines and benzaldehydes has been widely studied, the reaction of phenylhydroxylamine and benzaldehydes to obtain nitrones was carried out in order to obtain more information about the special nucleophilic behaviour of phenylhydroxylamine, eqn. (1).

$$\mathrm{PhCHO + PhNHOH \longrightarrow PhCH{=}\overset{+}{N}(O^-)Ph + H_2O} \quad (1)$$

Results and Discussion

The pH dependence of the second-order rate constant (k_2), extrapolated to zero buffer concentration, for the reaction of phenylhydroxylamine with benzaldehydes is shown in Fig. 1. The pH–rate profile exhibits three regions: a region of hydronium-ion-catalysed condensation at low pH, a region of hydroxide-ion-catalysed nitrone formation at high pH, and like the reaction of furfurals with phenylhydroxylamine, a region of spontaneous reaction is observed in the pH range 6–8.

Eqn. (2) is consistent with the experimental results and

$$k_2 = k_{obs}/[\mathrm{B}]\{(K_a/K_a + [\mathrm{H^+}])\} = k_\mathrm{H}[\mathrm{H^+}] + k_o + k_\mathrm{OH}[\mathrm{OH}] \quad (2)$$

includes terms for hydronium ion (k_H) and hydroxide ion (k_OH) catalysis and for a spontaneous pathway (k_o). The aldehyde (B) is present in sufficient excess so as to obtain pseudo-first-order reaction conditions and K_a is the dissociation constant of the phenylhydroxylammonium ion. The curves in Fig. 1 were calculated using eqn. (2) together with the rate constants indicated in Table 1 and the acid dissociation constant of the phenylhydroxylammonium ion under the conditions of the reaction [(K_a = 1.96) in 20% aqueous ethanol, at 25 °C and ionic strength 0.5 mol dm^{-3} (KCl)].

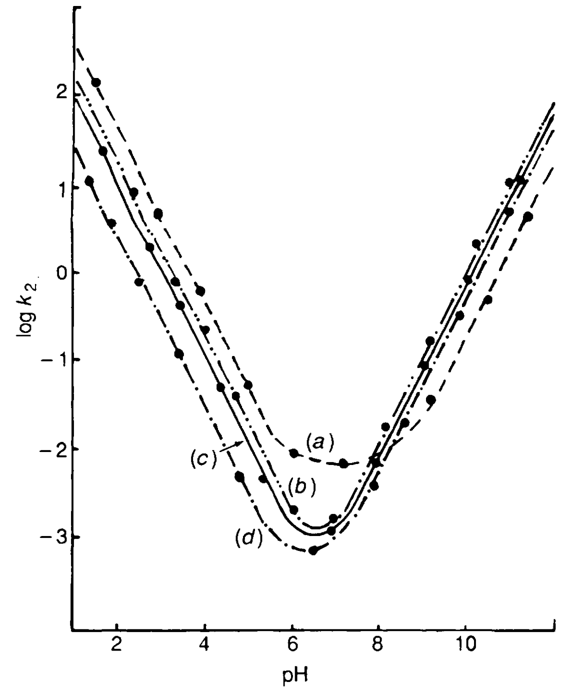


Fig. 1 pH Dependence of the logarithms of second-order rate constants for nitrone formation from phenylhydroxylamine and (*a*) *p*-nitrobenzaldehyde (- - -); (*b*) benzaldehyde (-···-); (*c*) *p*-chlorobenzaldehyde (—); and (*d*) *p*-methoxybenzaldehyde (-··-) in 20% aqueous ethanol at 25 °C and ionic strength 0.5 mol dm^{-3}

The Rate-determining Step of the Reaction.—It is reasonable to assume that this reaction proceeds by a two-step process analogous to that of nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine,[3] namely initial attack of the amine on the carbonyl compound to give a dihydroxy intermediate and a subsequent step in which this intermediate eliminates water to give the product [eqns. (3) and (4)].

$$\mathrm{PhNHOH + PhCHO \rightleftharpoons PhN(OH)CH(OH)Ph} \quad (3)$$

$$\mathrm{PhN(OH)CH(OH)Ph \xrightarrow{slow} Ph\overset{+}{N}(O^-){=}CHPh + H_2O} \quad (4)$$

The profile of log k_2 *vs.* pH (Fig. 1) for the reaction of benzaldehydes with phenylhydroxylamine, like that for the reaction of furfurals with phenylhydroxylamine, shows no evidence of a negative deviation of the type expected for a change in the rate-determining step.[4] Thus, the observed profile is indicative of only one rate-determining step for this reaction over the entire pH range studied (pH 2–12).

Several pieces of evidence suggest that the rate-determining step is dehydration of the intermediate formed upon addition of phenylhydroxylamine to the benzaldehydes. (i) The rate constant for *p*-chlorobenzaldehyde is smaller than that of benzaldehyde in the acidic and basic regions, while *p*-nitrobenzaldehyde exhibits a rate constant larger than benzaldehyde in the acidic region, but smaller in the basic region. This behaviour is inconsistent with rate-determining attack. (ii) As can be observed in Table 2, the ratio between the hydronium ion catalytic rate constants for the reaction of *p*-nitrobenzaldehyde and benzaldehyde with phenylhydrazine under conditions where attack is the rate-determining step is 3.33. For the reaction of these benzaldehydes with phenylhydroxylamine, this ratio is 1.71, a value similar to that (1.87) observed for phenylhydrazine in the region where dehydration of the addition intermediate is rate-determining. (iii) The reaction does not occur in DMSO or THF. For the reaction between furfurals and phenylhydroxylamine,[2] this was attributed to the nature of the dehydration process, the initial carbon–oxygen cleavage being highly unfavourable in DMSO and THF due to their poor anion-solvating ability.

Comparison with Other Amine Nucleophiles.—For the reaction between *p*-chlorobenzaldehyde and different amines as nucleophiles, it was demonstrated that, at low pH, attack of the nucleophile on the carbonyl group is the rate-determining step.[1,5]

Table 1 Rate constants for nitrone formation from phenylhydroxylamine and various benzaldehydes[a]

Benzaldehyde	k_H/dm^6 mol^{-2} s^{-1}	k_0/10^{-4} dm^3 mol^{-1} s^{-1}	k_{OH}/dm^6 mol^{-2} s^{-1}
p-Nitrobenzaldehyde	2 200	63.00	1 780
Benzaldehyde	1 280	3.47	8 900
p-Chlorobenzaldehyde	780	3.64	7 080
p-Methoxybenzaldehyde	360	4.34	5 050

[a] In 20% ethanol, at 25 °C, ionic strength 0.5 mol dm^{-3} (KCl).

In the reaction between *p*-chlorobenzaldehyde and thiosemicarbazide,[6] a nucleophile of similar basicity (1.88) to phenylhydroxylamine, the pH–rate profile is of type A with a negative deviation between *ca.* pH 4 and 5. One would thus expect[1] that in view of its similar basicity, phenylhydroxylamine should present the same profile. However, the experimental profile does not correspond to any of those indicated by Sayer *et al.*[1] This new kind of profile, which we classify as type D, corresponds to the case in which dehydration of the addition intermediate is the rate-determining step over the whole pH range.

In order to evaluate the relationship between basicity and the nucleophilicity of the different amines, a Brønsted-type relation, eqn. (5), was used to correlate the hydronium ion catalytic rate constants for the attack step and pK'_a (pK'_a = pK_a under the same conditions used for rate determinations) for eleven nitrogen nucleophiles (Table 3).

$$\log k_H = \beta \mathrm{p}K'_a + \mathrm{cte} \quad (5)$$

The logarithmic plot shown in Fig. 2 covers a range of nucleophile basicity of 10^5 and exhibits good linearity with β = 0.46 and correlation coefficient r = 0.925.

The experimental value of the rate constant for phenylhydroxylamine is 3.7 times greater than the value corresponding to the Brønsted line. Since the rate-determining step for this reaction is the dehydration of the addition intermediate, the attack step must be faster than this, indicating special behaviour for phenylhydroxylamine as compared with other amines.

In the reaction with nitrosobenzene, phenylhydroxylamine

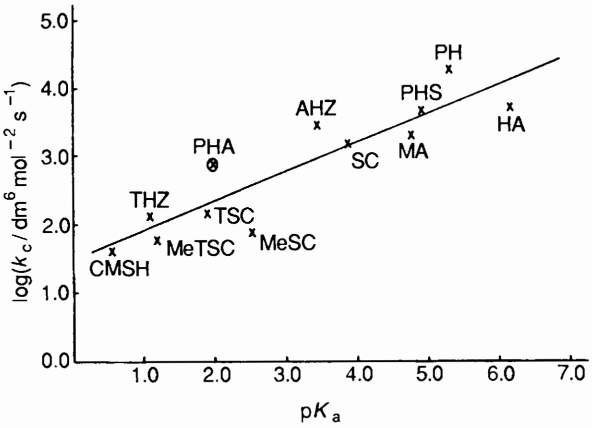


Fig. 2 Brønsted plot for hydronium-ion-catalysed attack step for reaction between *p*-chlorobenzaldehyde and different nitrogen nucleophiles. CMSH = chloromethanesulphonylhydrazine; THZ = toluene-*p*-sulphonohydrazide; MeTSC = 2-methyl-3-thiosemicarbazide; TSC = thiosemicarbazide; PHA = phenylhydroxylamine; MeSC = 2-methylsemicarbazide; AHZ = acetohydrazide; SC = semicarbazide; MA = methoxylamine; PHS = phenylhydrazine-*p*-sulphonate; PH = phenylhydrazine; and HA = hydroxylamine

Table 2 Hydronium catalytic rate constants k_H for the reaction between phenylhydroxylamine and phenylhydrazine with various benzaldehydes at 25 °C

		Phenylhydrazone[b]	
	Nitrone[a]	Attack[c]	Overall reaction[d]
Benzaldehyde	k_H/10^5 dm^6 mol^{-2} min^{-1}	k_H/10^5 dm^6 mol^{-2} min^{-1}	k_H/10^8 dm^6 mol^{-2} min^{-1}
p-Nitrobenzaldehyde	1.32	30	4.5
Benzaldehyde	0.77	9	2.4
p-Chlorobenzaldehyde	0.47	12	3.0
p-Methoxybenzaldehyde	0.22	1.6	0.7

[a] This work. [b] Ref. 5. [c] pH 1–6. [d] pH 6–14.

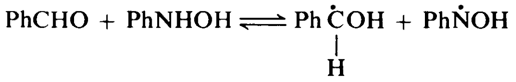
Table 3 Rate constants k_H for dihydroxy intermediate formation from nitrogen nucleophiles and *p*-chlorobenzaldehyde[a]

Nucleophile	Formula	pK'_a	$K_{ad}/dm^3\ mol^{-1}$	$k_H/dm^6\ mol^{-2}\ s^{-1}$
Chloromethanesulphonohydrazide	$ClCH_2SO_2NHNH_2$	0.55	—	43
Toluene-*p*-sulphonohydrazide	$H_3CC_6H_4SC_2NHNH_2$	1.09	—	132
2-Methyl-3-thiosemicarbazide	$H_2NC(S)N(CH_3)NH_2$	1.20	0.23	63
Thiosemicarbazide	$H_2NC(S)NHNH_2$	1.88	—	156
Phenylhydroxylamine	PhNHOH[b]	1.96	—	795
2-Methylsemicarbazide	$H_2NH(O)N(CH_3)NH_2$	2.54	0.90	77
Acetohydrazide	$H_3CC(O)NHNH_2$	3.44	—	3 000
Semicarbazide	$H_2NC(O)NHNH_2$	3.86	3.10	1 600
Methoxylamine	H_3CONH_2	4.73	13.4	2 070
Phenylhydrazine-*p*-sulphonate	$^-O_3SC_6H_4NHNH_2$	4.90	—	5 500
Phenylhydrazine	$PhNHNH_2$[c]	5.27	—	20 000
Hydroxylamine	$HONH_2$	6.15	23.5	5 800

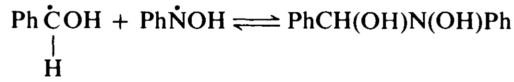
[a] Values from ref. 1 except where otherwise noted. [b] This work (in 20% ethanol). [c] From ref. 5.

also exhibits special behaviour. Thus, this reaction shows a rapid pre-equilibrium in which nitrosobenzene is reduced to phenylhydroxylamine which is then oxidized to nitrosobenzene.[7] Between pH 1–5 the rate constant for the reaction between phenylhydroxylamine and nitrosobenzene, corresponding to rate-determining hydronium-ion-catalysed dehydration of the addition intermediate,[8] is three times larger than that for rate-determining hydronium-ion-catalysed attack of aniline on the nitrosobenzene.[9] Consequently, the attack step of phenylhydroxylamine on the nitrosobenzene should be noticeably faster than that of aniline, in spite of the fact that phenylhydroxylamine is 500 times less basic.

The Attack Step.—The above discussion indicates that the attack of phenylhydroxylamine on benzaldehydes is faster than the acid-catalysed 'concerted mechanism' of attack of the other amines. This could be explained by a different reaction mechanism, such as that proposed by Kozakova *et al.*[10] and indicated in eqns. (6)–(8).



$$\mathrm{PhCHO + PhNHOH \rightleftharpoons Ph\dot{C}(H)OH + Ph\dot{N}OH} \quad (6)$$



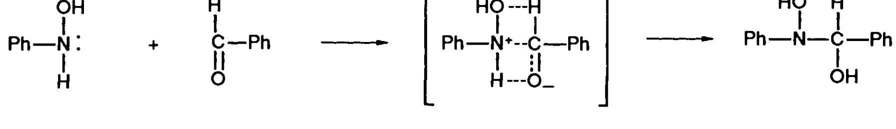
$$\mathrm{Ph\dot{C}(H)OH + Ph\dot{N}OH \rightleftharpoons PhCH(OH)N(OH)Ph} \quad (7)$$

$$\mathrm{PhCH(OH)N(OH)Ph \longrightarrow PhCH{=}\overset{+}{N}(O^-)Ph + H_2O} \quad (8)$$

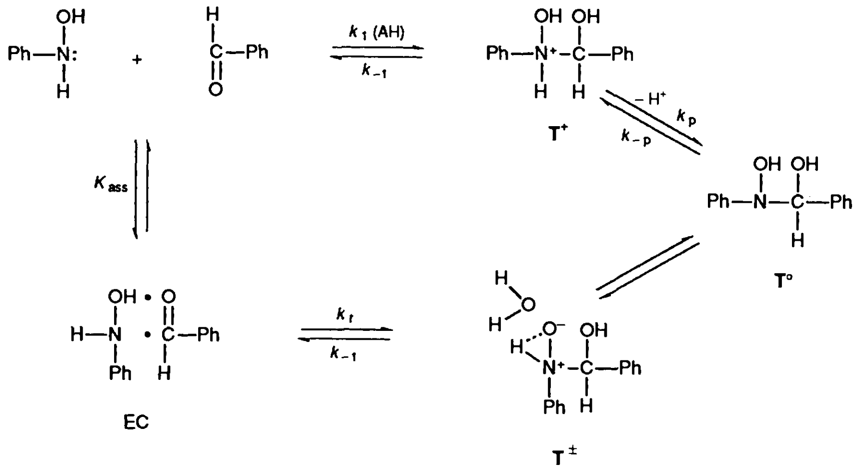
In order to test this mechanism, two types of radical scavenger were added to the reaction between benzaldehydes and phenylhydroxylamine: (i) iron(II) sulphate, which reacts with radical intermediates by donating electrons and (ii) hydroquinone and BHT (2,6-di-*tert*-butyl-4-methylphenol), which react with radical intermediates by donating hydrogen atoms. The results demonstrate that the scavengers do not interfere with the nitrone formation. Although this result is not a conclusive proof that dihydroxy intermediate formation does not proceed *via* free radicals, several pieces of evidence suggest an alternative mechanism. This evidence is: (i) the possibility of an ionic mechanism of the type suggested for the reaction between *p*-chlorobenzaldehyde and *N*-methylhydroxylamine.[3] (ii) The value of β for complete formation of the carbon–nitrogen bond in the reaction between amines and *p*-chlorobenzaldehyde, obtained from the plot of the logarithm of the known equilibrium constants of the amines (Table 3) *vs.* their pK_a, is 0.43. This value is very similar to the β value (0.46) obtained from the correlation of the logarithm of the constants for the attack step with pK_a. This fact is an indication, according to the Hammond postulate, that the energy of the transition state is very near to that of the product and, consequently, that the formation of the carbon–nitrogen bond between amines and *p*-chlorobenzaldehyde must be very advanced in the transition state. (iii) Reimann and Jencks[3] have suggested that a concerted intramolecular proton transfer occurs from the nitrogen of the amine to the oxygen of the carbonyl group in the attack step of the reaction of *N*-methylhydroxylamine with *p*-chlorobenzaldehyde. Thus, an alternative mechanism for the attack step of the reaction of phenylhydroxylamine with benzaldehyde is a concerted proton transfer together with C–N bond formation, as indicated in eqn. (9).

This is consistent with the suggestion of an advanced transition state in which the amine nitrogen should have developed a full positive charge, increasing the acidic character of the proton. However, given that the same possibility exists for thiosemicarbazide and other amines with pK_as similar to phenylhydroxylamine, and that semicarbazide exhibits a mechanism of nucleophilic attack 'concerted' with hydronium ion catalysis rather than the mechanism suggested in eqn. (9), it is clear that this last mechanism cannot satisfactorily explain the behaviour of phenylhydroxylamine.

A most attractive possibility is that phenylhydroxylamine and benzaldehydes form an encounter complex with hydrogen bonding between the hydroxy group of phenylhydroxylamine and the carbonyl group of the benzaldehydes, following a pre-association mechanism[11] that is faster than the acid-catalysed concerted mechanism. Scheme 1 summarizes the possible mechanisms of attack of phenylhydroxylamine on benzaldehydes. Concerted acid catalysis gives the intermediate T^+, which is converted into the dihydroxy intermediate T^0 by proton transfer to the solvent. In the pre-association mechanism, initial formation of the encounter complex EC is followed by proton transfer from the hydroxy group of the phenylhydroxylamine to the carbonyl oxygen of the benzaldehydes by a five-membered cyclic transition state,[4,12] giving the intermediate $T^{\pm}$. This is possible because the transition state is advanced and



(9)



Scheme 1

this kind of proton transfer, with a non-linear trajectory, is compatible with rapid kinetics.[13] The subsequent proton transfer from the nitrogen to the negatively charged oxygen of phenylhydroxylamine should proceed very rapidly, with or without participation of water molecules. This last extreme form of proton transfer was suggested by Jencks[14] in the nucleophilic attack of the hydroxylamine oxygen on esters. The mechanism of pre-association should proceed by the lowest energy path.

Experimental

Materials.—The organic reagents employed were commercially available products and were either redistilled or recrystallized. Inorganic chemicals and formic and acetic acids used in buffers were reagent grade and used without further purification. Solutions of various *para*-substituted benzaldehydes were prepared just prior to use, as were those of carboxylic acids in 20% aqueous ethanol to avoid esterification.

Phenylhydroxylamine was prepared according to the method of Smissman and Corbett[15] and was purified by recrystallization from benzene–light petroleum (b.p. 40–60 °C).

Kinetic Procedure.—The solvent in most of the kinetic measurements was 20% aqueous ethanol at ionic strength 0.5 mol dm^{-3} (KCl). The reactions between benzaldehydes and phenylhydroxylamine were followed at 25 °C on a Varian DMS 80 spectrophotometer by monitoring the formation of the nitrone at 320, 330, 351 or 318 nm (benzaldehyde, *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde or *p*-chlorobenzaldehyde, respectively).

The reaction between benzaldehyde and phenylhydroxylamine was also carried out in 50% aqueous ethanol at ionic strength 0.5 mol dm^{-3} (KCl). The rate constants are about the same as those mentioned above.

The initial concentration of phenylhydroxylamine was 4×10^{-4} mol dm^3. A sufficient excess of benzaldehyde was employed to ensure pseudo-first-order kinetic behaviour. First-order rate constants were calculated from the standard rate equation. Second-order rate constants were calculated from eqn. (2).

Experiments with Scavengers.—The experiments with scavengers were carried out as before.[8]

pK_a Determination.—The pK_a of phenylhydroxylamine in 20% aqueous ethanol at ionic strength 0.5 mol dm^{-1} (KCl) was determined following the spectrophotometric method of Albert and Sergeant.[16] The pH meter was standardized following the method of Bates.[17]

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