

GENERAL-ACID, SPECIFIC-BASE AND INTRAMOLECULAR CATALYSIS OF THE DEHYDRATION STEP IN NITRONE FORMATION FROM FURFURALS AND PHENYLHYDROXYLAMINE

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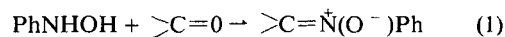
Nitrone formation from furfural and 5-nitrofurfural with phenylhydroxylamine was studied in water at 25 °C and ionic strength 1.0 (KCl). The reaction exhibits general acid catalysis ($\alpha = 0.52$), specific base catalysis and a pH-independent process. The results are consistent with a mechanism where dehydration of an *N,N'*-dihydroxy addition intermediate, formed by a rapid pre-equilibrium, is the only rate-determining step over the pH range studied (1-11). In contrast, nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine exhibits a clear change of rate-determining step, from dehydration of the addition intermediate to attack of the nucleophile on the aldehyde, with increase in pH. The profile of $\log k_2$ ($k_2 =$ second-order rate constant) vs pH indicates, by comparison with the corresponding profile for similar reactions, that phenylhydroxylamine exhibits unexpected nucleophilic behaviour in this reaction. The pH-independent dehydration process, which has a higher rate constant than that predicted from the Brønsted line for the water catalysis, appears to involve intramolecular catalysis rather than bifunctional catalysis by water.

INTRODUCTION

The mechanism and catalysis of nitrone formation from aldehydes and hydroxylamines has been little studied, although interest in nitrone chemistry has grown considerably owing to its use in cycloadditions¹ and natural products synthesis.² Reimann and Jencks³ studied the reaction between *p*-chlorobenzaldehyde and *N*-methylhydroxylamine and showed that it occurs in a two-step process in which acid-catalysed dehydration of the carbinolamine intermediate is rate determining at neutral and weakly acidic pH and attack of free hydroxylamine on the carbonyl group is rate determining at low pH. Masui and Yijima⁴ observed similar results for the reaction between *N*-cyclohexylhydroxylamine and aliphatic aldehydes, which led them to suggest that at neutral and weakly acidic pH the hydronium ion-catalysed attack of free *N*-cyclohexylhydroxylamine on the carbonyl group is rate determining and at basic pH dehydration of the carbinolamine intermediate is rate determining.

To broaden the experimental basis of the mechanism and specially of catalysis in this kind of reaction,

nitrone formation from furfurals and phenylhydroxylamine was studied [equation (1)].



Although this study, in part, reinforces previous conclusions, some interesting differences and new facts appear.

RESULTS AND DISCUSSION

The pH dependence of the second-order rate constants (k_2) extrapolated to zero buffer concentration for the reaction of phenylhydroxylamine with furfural and 5-nitrofurfural is shown in Figure 1. The pH-rate profile indicates hydronium ion-catalysed condensation reaction at low pH, hydroxide ion-catalysed nitrone formation at high pH and a pH-independent pathway in the pH range 5-8.

Equation (2) is consistent with the experimental results:

$$k_2 = k_{\text{obs}}/[\text{F}] (K_a/K_a + [\text{H}^+]) = k_{\text{H}}[\text{H}^+] + k_0 + k_{\text{OH}}[\text{OH}] \quad (2)$$

including terms for hydronium ion (k_{H}) and hydroxide

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ion (k_{OH}) catalysis and the pH-independent pathway (k_0); $[F]$ is the furfural concentration that is in the necessary excess to obtain pseudo-first-order reaction conditions and K_a is the dissociation constant of phenylhydroxylammonium ion. The lines in Figure 1 were calculated using equation (2) with the rate constants given in Table 1 and the acid dissociation constant of phenylhydroxylammonium ion [$K_a = 0.0109$ at 25°C , ionic strength $\mu = 1.0$ (KCl)].

The dependence of the second-order rate constant (k_2) on acetate buffer for reaction of phenylhydroxylamine with furfural is shown in Figure 2. The reaction is general acid catalysed; least-squares fits correlating the third-order rate constants with the molar fraction of free acids gave straight lines (plots not shown) whose right intercepts (where the fraction of free acid equals 1) give the catalytic constants for the acidic component of the buffers (k_{AH} in Table 2) and whose left intercepts (where the fraction of free acid equals 0) are zero. Changing the ionic strength from 0 to 1.2 (KCl) does not affect the second-order rate constants.

General acid catalysis

The Brønsted plot for the formation of furfuralide-aniline *N*-oxide catalysed by different acids is shown in Figure 3 ($\alpha = 0.52$, correlation coefficient = 0.998;

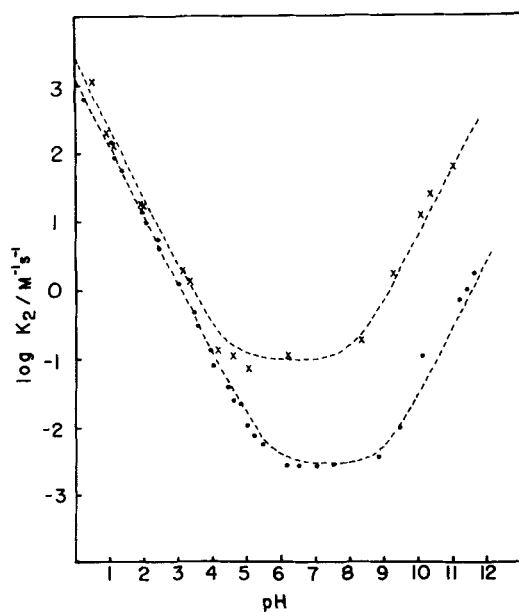


Figure 1. pH dependence of the logarithms of second-order rate constants for nitrone formation from furfural (0.01 M) and 5-nitrofurfural (0.001 M) with phenylhydroxylamine (10^{-4} M) in water at 25°C and ionic strength 0.5. All rate constants have been extrapolated to zero buffer concentration. (●) Furfural; (x) 5-nitrofurfural

statistical corrections were applied according to the method of Bell and Evans⁵). Nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine gives a higher value of α (0.77).³ To determine the

Table 1. Rate constants for formation of nitrone from furfural and phenylhydroxylamine^a

Rate constant	Value
k_H	$1.50 \times 10^3 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$
k_0	$2.80 \times 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$
k_{OH}	$2.50 \times 10^2 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$

^a Water, 25°C , ionic strength 1.0 (KCl).

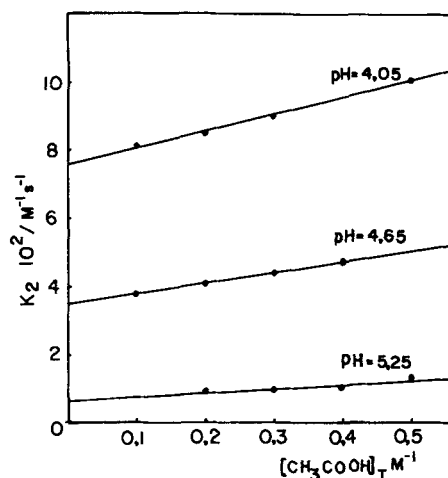


Figure 2. Second-order rate constants for nitrone formation from furfural (0.01 M) and phenylhydroxylamine (10^{-4} M) in water at 25°C and ionic strength 0.5 plotted against the concentration of acetic acid-acetate buffer at three pH values

Table 2. Rate constants for general-acid catalysed nitrone formation from furfural and phenylhydroxylamine^a

Catalyst	$\text{p}K'_a$	k_{AH} ($\text{l}^2 \text{ mol}^{-2} \text{ s}^{-1}$)
Hydronium ion	1.74 ^b	1.50×10^3
Formic acid	3.56 ^c	2.60×10^{-1}
Acetic acid	4.65 ^c	6.50×10^{-2}
Succinate monoanion	5.48 ^d	4.50×10^{-2}
Phosphate monoanion	6.60 ^d	1.40×10^{-2}
Imidazolium	7.21 ^c	3.00×10^{-3}
Water	15.74 ^b	5.00×10^{-5}

^a In water, 25°C , ionic strength 1.0 (KCl).

^b L. P. Hammett, *Physical Organic Chemistry*, 2nd ed. p. 23. McGraw-Hill, New York (1970).

^c J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.* **91**, 6353 (1969).

^d Ref. 2.

^e W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* **90**, 2622 (1968).

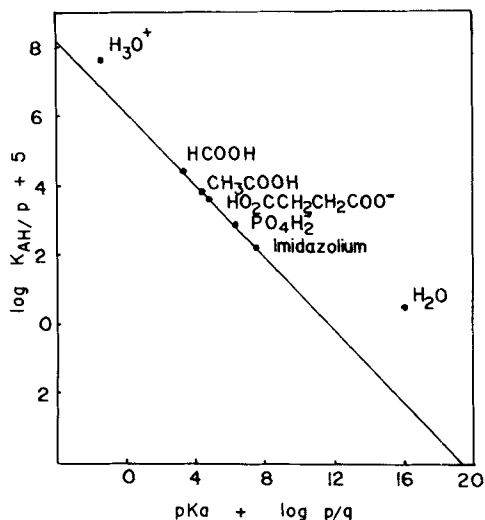


Figure 3. Brønsted plot for general-acid catalysed formation of nitrone from furfural and phenylhydroxylamine in water at 25 °C and ionic strength 0.5

mechanistic nature of the general acid-catalysis, experiments were carried out at pH 5.21 with different concentrations of imidazole. The reaction was catalysed, which shows that there is true general acid catalysis since at this pH the concentration of the free base is negligible and the catalysis corresponds to that effected by imidazolium ion.

The hydronium ion catalytic rate constant is approximately four time larger than that expected from the Brønsted plot (Figure 3).

Catalysis by the hydroxide ion

The reaction of furfural and 5-nitrofurfural with phenylhydroxylamine is hydroxide ion catalysed (Figure 1), which is an important difference from the reactions of nitrone formation from *p*-chlorobenzaldehyde³ and aliphatic aldehydes⁴ with *N*-methylhydroxylamine and *N*-cyclohexylhydroxylamine, respectively, where this kind of catalysis is not detected. Some evidence indicates that the hydroxide ion catalysis is specific because (i) there is no general base catalysis in the pH range studied; (ii) the significantly smaller values of the enthalpy and entropy of activation for the base-catalysed region (Table 3) suggest that in this region there is a different mechanism; and (iii) as noted below, the pK_a of the proposed tetrahedral addition intermediate is consistent with this behaviour.

Rate-determining step and reaction mechanism

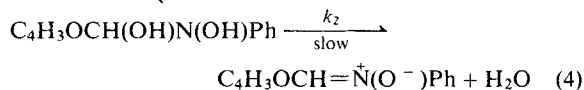
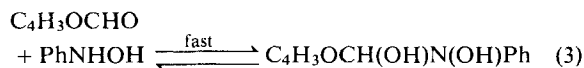
A two-step process generally fits the experimental data for nitrone formation from aldehydes and hydroxyl-

Table 3. Activation enthalpies, entropies and free energies for the reaction of nitrone from furfural and phenylhydroxylamine at different pH^a

pH	ΔH^\ddagger (kcal mol ⁻¹)	ΔS^\ddagger (e.u.)	ΔG^\ddagger (kcal mol ⁻¹)
3.2	7.73	-35.21	19.63
6.5	11.35	-33.94	21.65
11.0	2.26	-64.41	21.82

^a In water, 25 °C, ionic strength 1.0 (KCl).

amines.^{3,4} In the reaction between furfurals and phenylhydroxylamine, no intermediate could be shown experimentally. However, our results indicate that the mechanism, over the pH range studied, involves fast addition of phenylhydroxylamine to furfurals to give a tetrahedral addition intermediate followed by slow dehydration of this intermediate to the final product:



The evidence is provided by the following observations. First, it is known that in this kind of reaction an intermediate, which does not accumulate in detectable concentrations, gives rise to non-linear pH-rate relationships in which a negative deviation may be caused by a change in the rate-determining step⁶. Reimann and Jencks,³ considering this behaviour, postulated this change of rate-determining step in the nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine. The absence of this negative deviation in the profile of $\log k_2$ vs pH for the reaction between furfurals and phenylhydroxylamine is evidence that this reaction has only one rate-determining step over the pH range studied. Other evidence is obtained by comparison with the similar reaction of furfurals and phenylhydrazine to give phenylhydrazone⁷ (Table 4). The initial attack of phenylhydrazine on furfural and 5-nitrofurfural can be measured under conditions in which dehydration is fast (*ca* pH 1–6). At higher pH (6–11) dehydration becomes rate limiting and the rate constants for the hydronium ion-catalysed, hydroxide ion-catalysed and uncatalysed processes under this limiting condition are given in Table 4. The pH-rate profile of the nitrone formation from furfural and 5-nitrofurfural corresponds to the profile of dehydration as the rate-determining step of the phenylhydrazone formation from furfural and 5-nitrofurfural. Thus, the values of the hydronium ion catalytic rate constant (k_H) are very similar for furfural and 5-nitrofurfural in both reactions. This means that the acid-catalysed pathway is insensitive to the polar substituent, which is reasonable

Table 4. Rate constants for the hydronium ion- and hydroxide ion-catalysed and for the uncatalysed reaction of nitrone and phenylhydrazone formation from furfurals at 25 °C

Furfural	Nitrone ^a	Phenylhydrazone ^b	
		Attack ^c	Overall reaction ^d
k_H (l ² mol ⁻² s ⁻¹)			
5-H	1.5×10^3	5.5×10^3	1.3×10^6
5-NO ₂	2.5×10^3	1.0×10^5	1.5×10^6
k_0 (l mol ⁻¹ min ⁻¹)			
5-H	2.8×10^{-3}	3.0	3.3×10^{-3}
5-NO ₂	0.1	4.2	0.125
k_{OH} (l ² mol ⁻² s ⁻¹)			
5-H	2.5×10^2	—	—
5-NO ₂	6.7×10^4	—	3.33×10^3

^a This work.

^b Ref. 10.

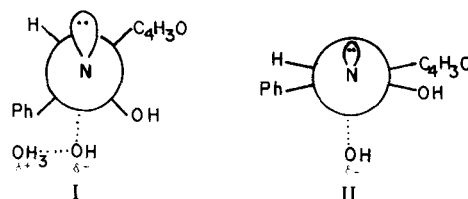
^c pH 1–6.

^d pH 6–11.

for the dehydration step, because the unfavourable effect of the nitro group on the rate of dehydration is compensated for by its favourable effect on the equilibrium formation of the addition intermediate. Similar observations have been made for related reactions.^{8–10} In contrast with this behaviour, in the region where the rate-determining step is attack of phenylhydrazine on the furfurals, the hydronium ion catalytic rate constant for 5-nitrofurfural is 18 times larger than that for furfural. In the uncatalysed process, the second-order rate constant (k_0) for reactions of 5-nitrofurfural is 35 and 37 times larger than that for furfural in the formation of nitrone and phenylhydrazone, respectively, i.e. there is a high sensitivity to the polar substituent effect in this region. Finally, the hydroxide ion-catalysed process cannot be compared because the catalytic constant for hydroxide ion (k_{OH}) for the reaction between furfural and phenylhydrazine could not be observed.⁷

To explain the different sensitivity to the substituent effect in the acid and uncatalysed region, Do Amaral⁷ suggested that the transition states for the two reactions could differ in the extent of carbon–oxygen bond cleavage. Sayer and Jencks¹¹ showed that in the acid-catalysed dehydration step of semicarbazone formation from benzaldehydes the transition state formation involves extensive carbon–oxygen bond cleavage but relatively little electron donation by delocalization from the benzene ring or the nitrogen atom. In the reaction between furfural and phenylhydroxylamine, the value of the Brønsted coefficient α implies that both significant transfer of the proton and cleavage of the carbon–oxygen bond should have occurred in the transition

state. In the uncatalysed process, with the poor leaving hydroxide ion, it is reasonable to postulate a transition state with extensive carbon–oxygen cleavage but relatively large electron donation by delocalization of the non-bonded lone pair from the nitrogen atom that should provide the driving force for antiperiplanar expulsion of the leaving group. There should therefore be a greater interaction by resonance between the reaction centre and the nitro group, which explains the stabilization of the transition state by this group. The transition states of the acid-catalysed (I) and uncatalysed reactions (II) should exhibit, fundamentally, dif-



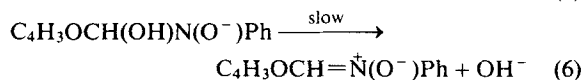
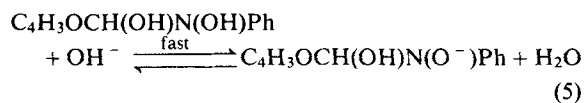
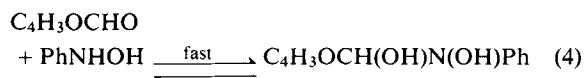
ferent degrees of carbon–nitrogen double bond formation.

According to the general mechanism for the formation of tetrahedral addition compounds (Carbinolamines) from carbonyl compounds and nitrogen nucleophiles described by Sayer *et al.*,¹² three types of pH–rate profiles can be observed. The reaction between furfurals and phenylhydrazine⁷ exhibits a profile of type A where only one change in rate-determining step is observed as a function of the pH, corresponding to the transition from formation to dehydration of the carbinolamine intermediate. The prediction¹² is that reaction between furfurals and phenylhydroxylamine, a less basic nucleophile, must exhibit the same kind of profile. However, the profile in Figure 1 is not of type A and does not correspond to any other profile discussed by Sayer *et al.*¹² We can assume that the change in the rate-determining step occurs at a very high hydronium ion concentration given a profile of type C, similar to that observed by Reimann and Jencks³ for the nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine, which implies a special and unexpected behaviour of phenylhydroxylamine as a nucleophile.

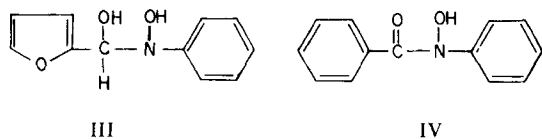
The profile determined by Masui and Yijima⁴ for the reaction of aliphatic aldehydes and *N*-cyclohexylhydroxylamine between pH 2 and 9 corresponds to the acid-catalysed and uncatalysed regions shown in Figure 1 and could better be interpreted by the hypothesis that there is not a rate-determining change and that dehydration of the tetrahedral intermediate is the only rate-determining step.

The carbinolamine intermediate suggested for nitrone formation from furfurals and phenylhydroxylamine is consistent and supports specific base catalysis by

hydroxide ion:



The pK_a for the ionization of the hydroxyl group bonded to the nitrogen of the intermediate (III) can be calculated¹³ from the pK_a of *N*-phenylbenzohydroxamic acid (IV) (9,15)¹⁴ by considering the



change caused by replacement of the $-\text{COPh}$ group by $-\text{CH(OH)C}_4\text{H}_3\text{O}$. The acid-strengthening effect of a $-\text{COPh}$ group in C_α calculated from the $\sigma^* = 2.26$ ¹⁴ (using the equation $\Delta pK_a = 0.06 + 0.63\sigma^*$ ¹⁴) is -1.45 log units. As this group is directly bonded to the functional group, considering that in this position its behaviour is normal, the effect will be $-1.45/0.4 = -3.61$. The $-\text{CH(OH)C}_4\text{H}_3\text{O}$ group can be considered to be formed by the $-\text{C}_4\text{H}_3\text{O}$ and $-\text{OH}$ groups and their acid-strengthening effects calculated from their σ^* values (0.25 ¹⁴ and 1.34 ¹⁴) are -0.22 and -0.90 log units, respectively. Then the acid pK_a of the intermediate is $9.15 + 3.61 - 0.90 = 11.64$. Even accepting an error of one pK unit in the calculation, it is clear that this pK_a is smaller than that of hydroxide ion. Since, according to Jencks,¹⁵ the pK_a of a general catalyst must be between those of the initial and final substrate sites, where the proton transfer occurs, it is evident that in this case the hydroxide ion cannot be a general catalyst.

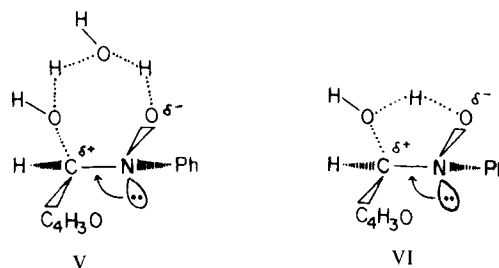
The value of the hydronium ion catalytic rate constant is four times larger than that predicted by the Brønsted line for general acid catalysis. The reasons for this behaviour are not clear, but it could be due to the catalyst being another species of solvated proton or to specific-acid catalysis by hydronium ion, although the coexistence of general and specific acid catalysis is rare.¹⁶

pH-independent reaction

If the reaction in the pH-independent region (from pH 5.5 to 9 for the reaction of furfural and phenylhydroxylamine) is considered to be water catalysed, the

third-order rate constant is approximately 400 times larger than that predicted by the Brønsted relationship (Figure 3). Some form of bifunctional catalysis^{17,18} in the transition state is usually invoked to explain this behaviour. Thus, for general base catalysis of the methoxyaminolysis of phenyl acetate,¹⁹ the catalytic rate constant for water is 100 times larger than that predicted by the Brønsted relationship, which was attributed to the fact that water acts as a bifunctional catalyst, for proton transfer, through an eight-membered ring. Transfer of a proton between oxygen atoms probably occurs through rings that vary in size from five- to ten-membered, which may include one or two water molecules.²⁰ In the reaction between furfural and phenylhydroxylamine, water could act as a bifunctional catalyst for proton transfer through a seven-membered ring (structure V) in a stepwise mechanism, where initially cleavage of the carbon-oxygen bond is concerted with proton transfer from water to the leaving hydroxide group. In a second step the proton from the hydroxyl group, bonded to the nitrogen, could be transferred. A concerted mechanism is improbable considering the requirements for the proton transfer and the unfavourable pK_a values of the reacting groups.

However, the absence of bifunctional catalysis by phosphate monoanion, the nature of the transition state, the solvent effect that will be discussed below and the non-occurrence of this kind of catalysis in the similar reaction of azoxybenzene formation²¹ suggest that intramolecular catalysis provides a more satisfactory explanation of the results. The existence and importance of hydrogen bonds were shown in cyclic systems, including five-membered rings, in which the hydrogen bond is almost certainly non-linear.^{6b,22} Then, the initial and fundamental process of carbon-oxygen cleavage is favoured by the high anion-solvating tendency of water but the posterior departure of the hydroxide ion in the transition state is catalysed by intramolecular proton transfer to it from the hydroxyl group bonded to the nitrogen atom (structure VI).



Important support for this mechanism is that this hydroxyl group is more acid than water ($pK_{a1} = 11.64$, $pK_{aH_2O} = 15.7$) and that intramolecular proton transfer will reduce the repulsion between the negative charges in the oxygen atoms.

Solvent effect

Reaction between furfural and phenylhydroxylamine occurs in water, methanol and benzene, but strikingly does not occur in dimethyl sulphoxide (DMSO) and tetrahydrofuran (THF) (Table 5). It is evident that this behaviour is not caused by bulk properties of the solvents. This dramatic solvent effect can be explained by considering the nature of the dehydration process where the initial carbon—oxygen cleavage in DMSO and THF is not possible owing to their very poor anion-solvating ability.²³ However, reaction occurs in benzene despite its poor anion-solvating ability.²³ The dihydroxy intermediate of the reaction should be stabilized in DMSO and THF by hydrogen bonding between its hydroxyl groups and the solvent, but in benzene, where this is not possible, the intermediate should be stabilized only by hydrogen bonding between its hydroxyl groups, that is, by intramolecular hydrogen bonding. The internuclear distance between oxygens, for this hydrogen bonding, should be between 2.70 and 2.90 Å.²⁴ The internuclear distances between the oxygen atoms in the intermediate, and also in the transition state of the antiperiplanar elimination, calculated from bond lengths²⁵ and angles, are consistent with this value. In this way the initial carbon—oxygen cleavage with stabilization of the incipient hydroxide ion by hydrogen bonding and intramolecular proton transfer in the transition state are possible in benzene. From molecular models it is possible to see that the more stable conformation of the intermediate in DMSO and THF does not leave the lone pair of electrons on nitrogen in an anti position of the leaving group, making the reaction difficult.

The reaction occurs in DMSO when a small quantity of acetic acid or water is added (0.05 and 0.1 M acetic acid and 10% v/v of water, Table 5). The small quantity of acetic acid and water should not affect substantially the bulk properties of the solvent but will facilitate the initial carbon—oxygen bond cleavage by stabilization of the hydroxide ion that is formed, making the reaction possible. This fact confirms the mechanism suggested.

Table 5. Solvent effects on second order-rate constants for formation of nitrone from furfural

Solvent	k_2 (l mol ⁻¹ s ⁻¹)
Water	2.8×10^{-3}
Benzene	1.17×10^{-3}
Methanol	1.68×10^{-3}
Dimethyl sulphoxide (DMSO)	No reaction
Tetrahydrofuran (THF)	No reaction
DMSO, 0.05 M AcOH	1.32×10^{-3}
DMSO, 0.1 M AcOH	5.00×10^{-3}
DMSO, 10% E(v/v) H ₂ O	4.82×10^{-4}

EXPERIMENTAL

Materials. 5-Nitrofurfural and phenylhydroxylamine were prepared and purified according to methods in the literature.^{26,27} All other reagents were obtained commercially and, with the exception of reagent-grade inorganic salts, were either recrystallized or redistilled prior to use.

Kinetic measurements. The reactions were followed spectrophotometrically at 25 °C by monitoring formation of the nitrone at 360 nm in solutions of the aldehydes, 0.5×10^{-3} – 1×10^{-3} M, and of the phenylhydroxylamine, 3.33×10^{-4} – 1×10^{-4} M, which gave first-order kinetics. Reactions were followed in water at an ionic strength of 1.0 (KCl) and 2×10^{-4} M EDTA for three half-lives and first-order rate constants were calculated with a computer. Second-order rate constants were calculated by dividing the first-order rate constants, k_{obs} , by the concentration of the aldehyde multiplied by f_c , where $f_c = K_a / (K_a + [H^+])$ and K_a is the acid dissociation constant of phenylhydroxylamine.

pK_a determination. The pK_a of phenylhydroxylamine under the reaction conditions [water, 25 °C, $\mu = 1.0$ (KCl)] and at different temperatures were determined following the spectrometric method of Albert and Serjeant.²⁸ The values obtained were: 1.96 (25 °C), 1.88 (30 °C) and 1.82 (35 °C).

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