Studies on Biologically Active Acylhydrazones. Part 1. Acid–Base Equilibria and Acid Hydrolysis of Pyridoxal Aroylhydrazones and Related Compounds

Nicholas J. Lees-Gayed,* Maysa A. Abou-Taleb, Inas A. El-Bitash and Magdi F. Iskander*
Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt and University of Alexandria Research Center (UNARC)

A series of pyridoxal aroylhydrazones has been synthesized and their UV, IR and ^{1}H NMR spectra studied. In neutral methanol these hydrazones exist in the enolimine form, while in aqueous solution (pH *ca* 7.0) they exist predominantly in the zwitterionic form in which the phenolic proton is transferred to the pyridine nitrogen. Their aqueous acid–base equilibria show three successive steps for which protonation constants have been determined. The different acidity constants are correlated with Hammett substituent constants. The acid hydrolysis reactions of these hydrazones have also been investigated and the attack of a water molecule on the protonated azomethine seems to be the rate-controlling step. The hydrolysis reactions of *N*-salicylidene- and *N*-benzylidene-benzoylhydrazines have been studied for comparison.

Pyridoxal acyl- and aroyl-hydrazones are of considerable interest. It has been shown that pyridoxal isonicotinoylhydrazone and other acylhydrazones can remove iron from ferritin,[1] cells[2,3] and organisms.[4,5] Iron mobilization is vital in the treatment of diseases caused by iron overloading, such as thalassaemia.

As the start of an investigation into their complex formation reactions, the present work describes the synthesis, spectra and acid–base equilibria of a series of pyridoxal aroylhydrazones **1** (R = Ph, *p*-$CH_3C_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4 and *p*-$NO_2C_6H_4$). Also reported are the kinetics of acid hydrolysis of **1** (R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4 and *p*-$NO_2C_6H_4$) and related compounds. Knowledge of the acid hydrolysis is important when considering substances for possible use in oral iron deloading.[6]

Results and Discussion

Synthesis and Characterization.—The reaction of pyridoxal and pyridoxal hydrochloride with the appropriately substituted acylhydrazine afforded the corresponding pyridoxal aroylhydrazones **1** and pyridoxal hydrochloride aroylhydrazones **2** (R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4 and *p*-$NO_2C_6H_4$), respectively. As in the case of other pyridoxal Schiff bases,[7–14] pyridoxal aroylhydrazones can also exist in different tautomeric forms, with different degrees of protonation, as shown in Scheme 1.

The ^{1}H NMR spectra of the prepared aroylhydrazones in [$^2H_6$]DMSO show a well-resolved doublet at δ 4.62 ppm (J 5.0 Hz) besides a triplet at δ 5.38 ppm (J 5.0 Hz) due to the CH_2OH group. On deuteriation, the triplet disappears and the CH_2 signal appears as a singlet at δ 4.62 ppm. Both the CH=N and the α-H of the pyridine ring are quite deshielded and are located at δ 9.00 and 7.20 ppm, respectively. From such spectral patterns, the cyclic amino acetal form **1b** can be excluded and the hydrazone molecules exist predominantly as a single aldimine tautomer **1**.

Their IR spectra agree with this assignment. The spectra show series of bands at *ca.* 3200, 1660, 1610 and 1550 cm^{-1}, respectively, due to the ν_{NH}, amide I $\nu_{C=O}$, azomethine $\nu_{C=N}$ and amide II bands of the aroylhydrazone residues. In addition to these bands, the pyridoxal hydrochloride aroylhydrazones show a complex multiplet centred at 2880 cm^{-1} due to ν^+_{N-H}. We also observed that the amide I band in the spectra of pyridoxal aroylhydrazones is shifted to lower frequencies ($\Delta\nu$ = 20 ± 5 cm^{-1}) than those of the corresponding hydrochloride salts. This behaviour can be related to the contribution of **2a** to the ground state of these hydrochloride salts.

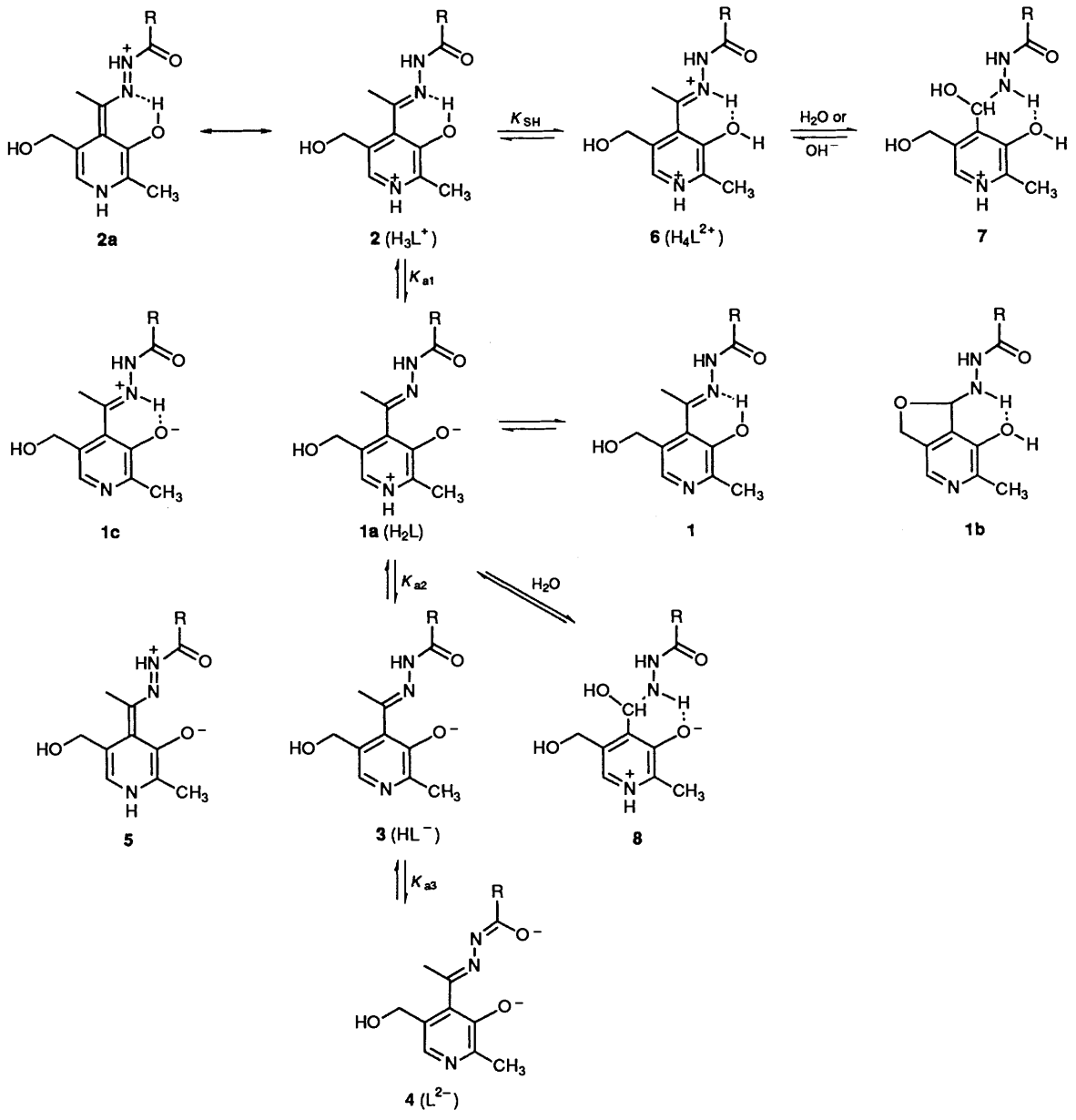
Absorption Spectra and Acid–Base Equilibria.—The electronic absorption spectra of the neutral pyridoxal aroylhydrazones in absolute methanol show absorption maxima at 230, 295 and 338 nm, mainly due to the neutral aldimine species **1**. A slight red shift is observed in the spectra of the corresponding hydrochloride salts **2**, due to the protonation of the pyridine nitrogen. Similar behaviour was previously reported for the protonation of the 2- and 4-hydroxymethyl-3-hydroxypyridines.[15] Furthermore, gradual addition of water to the methanol solution of the neutral hydrazones results in the gradual development of new bands at 300 and 380 nm with a simultaneous decrease in the intensity of the bands at 250 and 338 nm; these changes can be related to the formation of more zwitterionic tautomer (**1a**). In aqueous solutions the equilibrium **1** ⇌ **1a** is greatly shifted towards the formation of the zwitterion **1a**, rather than the previously proposed[13] ketoenamine **1c** tautomer. The dipolar species **1a** is stabilized by intermolecular hydrogen bonding with water molecules. In methanol, however, the neutral aldimine form dominates and is stabilized by intramolecular hydrogen bonding.

In aqueous solution, the electronic absorption spectra were found to be sensitive to pH variation. Three series of absorption curves, depending on the pH range, were obtained and are shown in Fig. 1. The equilibria which occur are shown in Scheme 1. The predominance of the zwitterion **1a** over the neutral uncharged form **1** has been mentioned above and is also observed with 3-hydroxypyridinium salts.[15,16] At lower pH values (pH < 3.0) the spectra were found to be time dependent owing to the hydrolysis of the C=N linkage, and the acid–base equilibria were studied at pH values above 3.0 where the pyridoxal aroylhydrazones withstand hydrolytic fission.

From the observed variation of the spectra of pyridoxal aroylhydrazones in aqueous solutions at different pH values, the following three equilibria can be suggested:

$$H^+ + L^{2-} \rightleftharpoons HL^- \qquad \beta_1^H = \frac{[HL^-]}{[H^+][L^{2-}]}$$

$$2H^+ + L^{2-} \rightleftharpoons H_2L \qquad \beta_2^H = \frac{[H_2L]}{[H^+]^2[L^{2-}]}$$



Scheme 1

Table 1 Overall protonation constants of the pyridoxal aroylhydrazones[a]

R	$\log \beta_1^H$	$\log \beta_2^H$	$\log \beta_3^H$
Ph	11.5 ± 0.03	19.6 ± 0.1	24.1 ± 0.1
p-ClC_6H_4	11.1 ± 0.03	18.8 ± 0.1	23.2 ± 0.1
p-BrC_6H_4	11.0 ± 0.04	19.1 ± 0.1	23.6 ± 0.1
p-IC_6H_4	11.0 ± 0.01	18.8 ± 0.1	23.3 ± 0.2
p-MeC_6H_4	11.6 ± 0.04	19.7 ± 0.1	24.2 ± 0.1
p-$MeOC_6H_4$	11.5 ± 0.1	19.7 ± 0.1	24.2 ± 0.2
p-$NO_2C_6H_4$	10.7 ± 0.1	18.2 ± 0.1	22.6 ± 0.1

[a] Errors are estimated standard deviations.

$$3H^+ + L^{2-} \rightleftharpoons H_3L^+ \qquad \beta_3^H = \frac{[H_3L^+]}{[H^+]^3[L^{2-}]}$$

where H_3L^+, H_2L, HL^-, and L^{2-} refer, respectively, to **2**, **1a**, **3** and **4**. β_j^H refers to the jth overall protonation constant.

The protonation constants were calculated by fitting the absorbance values at 380 nm (A_{380}) measured at different pH values to eqn. (1) using a non-linear least-squares procedure. In eqn. (1),[17] $\beta_0^H = 1$, ε_j are the molar absorptivities of the species

$$A_{380} = bC\frac{\sum_{j=0}^{j=3} \varepsilon_j \beta_j^H [H^+]^j}{\sum_{j=0}^{j=3} \beta_j^H [H^+]^j} \qquad (1)$$

H_jL, b is the optical path length, and C represents the analytical concentrations of the pyridoxal aroylhydrazones (mol dm^{-3}) in the solutions studied. The logarithms of the calculated overall protonation constants are listed in Table 1.

From the data given in Table 1, it is apparent that the protonation constants depend on the nature of the substituent R of the aroylhydrazone molecule. The negative logarithms of the acidity constants ($pK_{\alpha j}$) were calculated from the protonation constants and were related to the Hammett substituent constants σ (using a weighted least-squares method) as shown in Fig. 2. Thus it is seen that the effect of the substituent R on $pK_{\alpha 3}$ is higher than that on $pK_{\alpha 2}$, while the least effect is

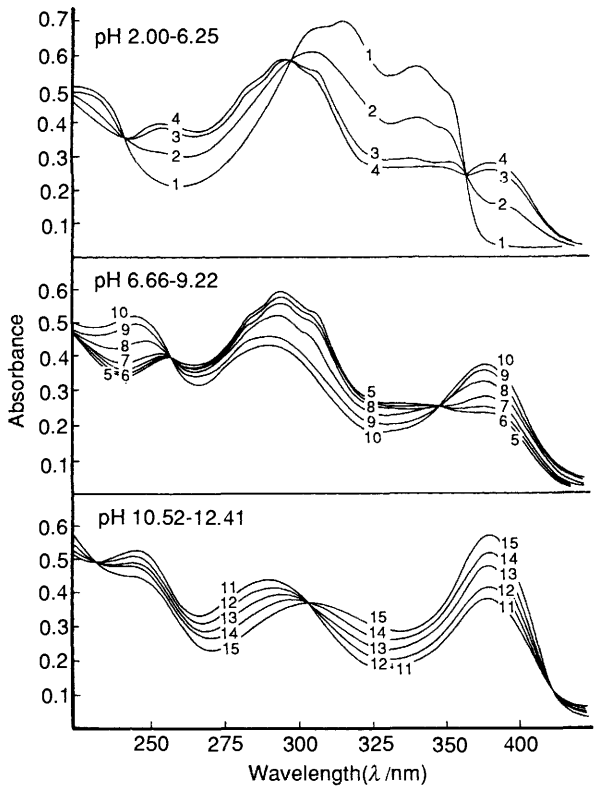


Fig. 1 Electronic absorption spectra of pyridoxal *p*-toluoylhydrazone (2.64×10^{-4} mol dm^{-3}) in aqueous solutions of different pH values: 1, 2.00; 2, 4.68; 3, 5.67; 4, 6.25; 5, 6.66; 6, 7.02; 7, 7.35; 8, 7.70; 9, 8.31; 10, 9.22; 11, 10.52; 12, 11.05; 13, 11.43; 14, 11.76; 15, 12.41

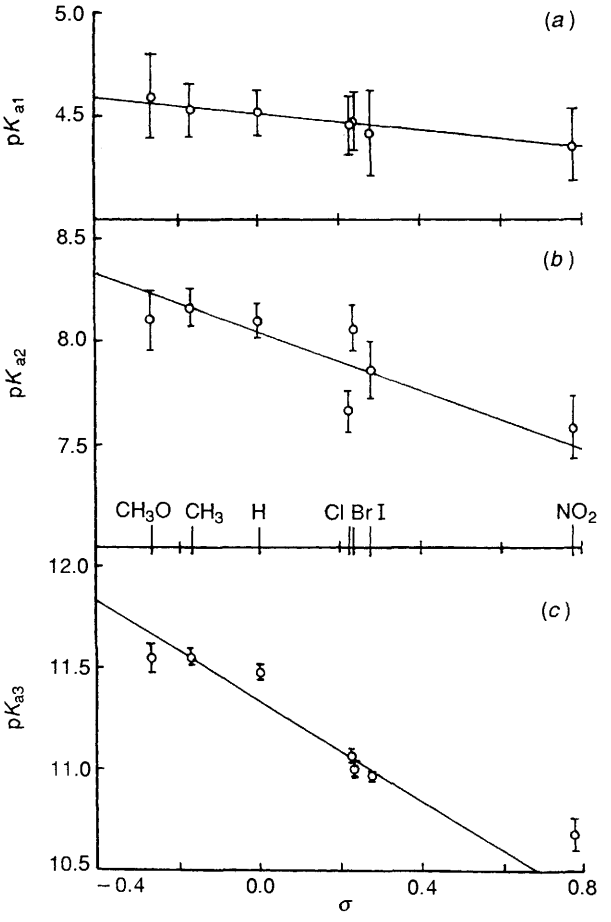


Fig. 2 Correlation of $pK_{\alpha 1}$, $pK_{\alpha 2}$ and $pK_{\alpha 3}$ with Hammett σ constants: (*a*) $pK_{\alpha 1} = 4.52 - 0.200\ \sigma$; (*b*) $pK_{\alpha 2} = 8.04 - 0.703\ \sigma$; (*c*) $pK_{\alpha 3} = 11.3 - 1.23\ \sigma$

observed for $pK_{\alpha 1}$. The highest effect (for $pK_{\alpha 3}$) is in accordance with the deprotonation of the highly conjugated enolized anion **4**, where R strongly affects both enolization and deprotonation of the amide moiety. It is also apparent that the substituent R can affect the acidity of the protonated pyridine nitrogen of the zwitterion **1a** *via* the large contribution of the conjugated form **5**. Finally, the least effect observed for $pK_{\alpha 1}$ is also in agreement with the deprotonation of the phenolic oxygen rather than the pyridine nitrogen.

The Acid Hydrolysis Reactions.—In acidic solutions (0.05–0.25 mol dm^{-3} hydrochloric acid), the electronic absorption spectra of **1** (R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4 and *p*-$NO_2C_6H_4$) were found to be time dependent due to the hydrolysis of the azomethine linkage. From the change of absorbance with time, the observed first-order rate constants (k_{obs}/s^{-1}) were calculated. The dependence of k_{obs} on [H$^+$] can be expressed by eqn. (2), and plots of k_{obs} *vs.* [H$^+$] give straight

$$k_{obs} = k' + k''[H^+] \quad (2)$$

lines. The intercepts (k'/s^{-1}) and the slopes (k''/dm^3 mol^{-1} s^{-1}) of these lines (computed using a weighted least-squares procedure[17]) at different temperatures are listed in Table 2. For the sake of comparison, the acid hydrolysis of *N*-salicylidenebenzoylhydrazine (**9a**) and *N*-benzylidenebenzoylhydrazine (**10**) has been studied similarly. The variation of k_{obs} measured for both **9a** and **10** as a function of [H$^+$] can also be expressed by eqn. (2).

The kinetics of hydrolysis of both aliphatic and aromatic Schiff bases have been extensively studied and the general features of these complex reactions are well established.[18–21]

In acidic solutions ($0.5 < pH < 3.0$) the azomethine nitrogen of the pyridoxal aroylhydrazone molecule can be protonated giving rise to the dipositive cation **6** (H_4L^{2+}) in equilibrium with the monopositive cation **2**. Addition of H_2O or OH^- to the protonated azomethine group gives rise to intermediate **7**, while the attack of H_2O on the azomethine group of **1a** gives the intermediate **8**. Apart from any mechanistic details reported for other Schiff bases,[22–25] the acid hydrolysis of the pyridoxal aroylhydrazones involves the following paths:

$$H_4L^{2+} \overset{K_{SH}}{\rightleftharpoons} H_3L^+ + H^+$$

$$H_4L^{2+} + H_2O \xrightarrow{k'_{H_2O}} \text{products}$$

$$H_4L^{2+} + OH^- \xrightarrow{k'_{OH^-}} \text{products}$$

$$H_3L^+ + H_2O \xrightarrow{k''_{H_2O}} \text{products}$$

where $K_{SH} = [H_3L^+][H^+]/[H_4L^{2+}]$. Similar to that reported for *N*-(2-pyridylmethylidene)aniline,[26] the rate equation for the acid hydrolysis reaction can be expressed by eqn. (3), and the

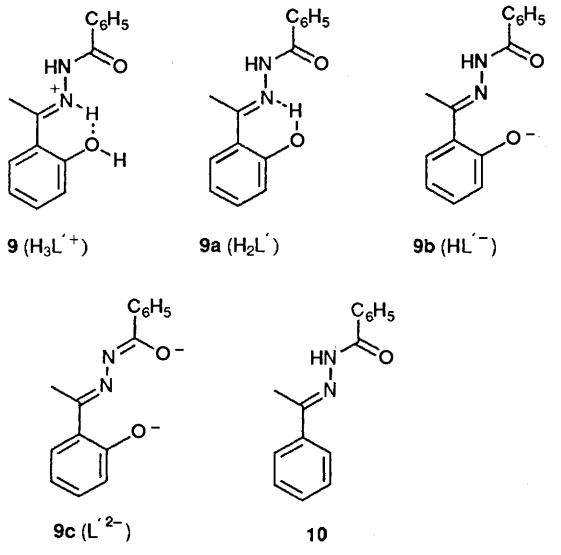
$$\text{rate} = k'_{H_2O}[H_4L^{2+}] + k'_{OH^-}[H_4L^{2+}][OH^-] + k''_{H_2O}[H_3L^+] \quad (3)$$

observed rate constant is given by eqn. (4).

Table 2 Rate constants for the acid hydrolysis of pyridoxal aroylhydrazones and related compounds[a]

Compound	$[H^+]$/mol dm^{-3}	T/°C	No. of runs	$k'/10^{-5}$ s^{-1}	$k''/10^{-3}$ dm^3 mol^{-1} s^{-1}
Pyridoxal aroylhydrazones (**1**)					
R = Ph	0.067–0.236	30.0	7	2.0 ± 0.6	1.2 ± 0.05
	0.006–0.213	35.0	7	3.8 ± 0.5	1.8 ± 0.2
	0.056–0.207	40.0	8	7.6 ± 1.4	2.6 ± 0.1
	0.056–0.207	45.0	6	10.4 ± 1.6	3.8 ± 0.2
R = *p*-ClC$_6$H$_4$	0.056–0.207	30.0	6	1.2 ± 0.3	1.1 ± 0.1
	0.001–0.213	35.0	8	4.6 ± 0.2	1.8 ± 0.1
	0.056–0.213	40.0	6	8.1 ± 0.4	2.3 ± 0.04
	0.056–0.213	45.0	5	13.1 ± 0.5	3.3 ± 0.05
R = *p*-MeC$_6$H$_4$	0.078–0.207	30.0	6	1.2 ± 0.6	1.2 ± 0.04
	0.079–0.251	35.0	4	<0	1.6 ± 0.2
	0.056–0.207	40.0	6	8.6 ± 0.3	2.1 ± 0.03
	0.056–0.207	45.0	6	16.9 ± 0.2	2.7 ± 0.2
R = *p*-MeOC$_6$H$_4$	0.080–0.320	30.0	5	2.2 ± 0.2	0.73 ± 0.11
	0.056–0.213	35.0	8	2.3 ± 0.3	1.5 ± 0.1
	0.056–0.207	40.0	6	5.3 ± 0.7	2.2 ± 0.1
	0.078–0.207	45.0	7	10.8 ± 0.4	2.8 ± 0.3
R = *p*-NO$_2$C$_6$H$_4$	0.056–0.207	30.0	5	0.55 ± 0.10	1.2 ± 0.01
	0.056–0.213	35.0	8	2.6 ± 0.3	1.8 ± 0.1
	0.078–0.207	40.0	5	8.8 ± 0.5	2.3 ± 0.04
	0.056–0.207	45.0	6	15.9 ± 1.8	3.3 ± 0.2
Salicylaldehyde benzoylhydrazone **9a**					
	0.004–0.063	26.0	10	152 ± 3	134 ± 21
	0.002–0.050	30.0	6	107 ± 14	194 ± 19
	0.001–0.040	35.0	6	138 ± 25	265 ± 38
	0.001–0.070	40.0	6	383 ± 35	348 ± 15
Benzaldehyde benzoylhydrazone **10**					
	0.006–0.050	25.0	5	40.1 ± 8.8	97.7 ± 5.6
	0.0005–0.05	30.0	7	47.6 ± 2.7	121 ± 5
	0.001–0.050	35.0	6	50.9 ± 1.7	230 ± 3
	0.006–0.040	40.0	5	94.6 ± 1.4	294 ± 9

[a] Errors are estimated standard deviations.



Scheme 2

$$k_{obs} = \frac{k'_{H_2O}[H^+] + k'_{OH^-}K_w + k''_{H_2O}K_{SH}}{K_{SH} + [H^+]} \quad (4)$$

Similarly, *N*-salicylidenebenzoylhydrazine (**9a**) can be considered as a dibasic acid H_2L', as shown in Scheme 2, and in acidic solutions (1.0 < pH < 3.0) the protonated species **9** ($H_3L'^+$) exists in equilibrium with the neutral aldimine form **9a**. The rate expression for the acid hydrolysis of **9a** would be expected to take the form of eqn. (3) so that k_{obs} is given by eqn. (4). In this case k'_{H_2O} and k'_{OH^-} are the rate constants for the hydrolysis of $H_3L'^+$ with H_2O and OH^-, respectively, while k''_{H_2O} is the rate constant for the hydrolysis of the aldimine species **9a** with H_2O.

The presence of strong intramolecular hydrogen bonding in both **1** and **9a** as well as the presence of the protonated pyridine nitrogen in **1a** will decrease the basicity of the azomethine nitrogen thus reducing the concentration of both **6** (H_4L^{2+}) and **9** ($H_3L'^+$). Accordingly, it seems reasonable to assume that $K_{SH} \gg [H^+]$ so that eqn. (4) can be simplified to eqn. (5).

$$k_{obs} = \frac{k'_{H_2O}}{K_{SH}}[H^+] + \frac{k'_{OH^-}K_w + k''_{H_2O}K_{SH}}{K_{SH}} \quad (5)$$

Comparison with eqn. (2) leads to eqns. (6) and (7).

$$k' = \frac{k'_{OH^-}K_w + k''_{H_2O}K_{SH}}{K_{SH}} \quad (6)$$

$$k'' = \frac{k'_{H_2O}}{K_{SH}} \quad (7)$$

A similar increase in k_{obs} on increasing $[H^+]$ was also

reported for the hydrolysis of *N*-benzylidene-(2-hydroxybenzoyl)hydrazine.[27] This behaviour, however, is quite different from that usually observed for the acid hydrolysis of other Schiff bases where, below pH 4, k_{obs} was found to decrease with increasing acidity. Such a decrease in k_{obs} was attributed to the reversible attack of a water molecule on the protonated azomethine nitrogen, and the decomposition of the carbinolamine intermediate was assigned as the rate-determining step.[22] However, the observed dependence of k_{obs} on $[H^+]$ suggests that the attack of a water molecule (k'_{H_2O}) on the protonated species **6** or **9**, rather than the decomposition of the formed carbinolamine, is the rate-controlling step. It is also apparent, Table 2, that substitution in the hydrazide residue of **1** has almost no effect on either k' or k''. The activation parameters pertaining to k'' are composites, and range from 45 ± 2 to 62 ± 13 kJ mol^{-1} for $\Delta H^{\ddagger}$ and from −154 ± 7 to −32 ± 19 J mol^{-1} K^{-1} for $\Delta S^{\ddagger}$. These values are within the range reported for the attack of H_2O on protonated azomethine nitrogen.[19] However, for k', which is the intercept of eqn. (2), the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ suffer from large errors, and no reliable values could be obtained.

The value of k'' measured for *N*-salicylidenebenzoylhydrazine **9a** at 30 °C is *ca.* 100 times greater than the corresponding pyridoxal derivative. This can be attributed to the presence of the strongly electron-withdrawing protonated nitrogen in **1a**, which greatly decreases the basicity of the azomethine nitrogen. Furthermore, *N*-salicylidenebenzoylhydrazine shows more or less the same k'' values as the corresponding *N*-benzylidene derivatives, indicating that the *ortho* phenolic group in **9a** has no effect on the acid hydrolysis rate of these aroylhydrazones. These results are in agreement with the previously reported results on the hydrolysis of hydroxy derivatives of *N*-benzylidenepropan-2-ylamine.[24]

Experimental

Materials.—Analytical grade reagents were used and methanol was purified according to the published procedure. Pyridoxal hydrochloride was a gift from E. Merck (Darmstadt) and was used without further purification. The pyridoxal acylhydrazones were prepared according to the method previously described.[28]

Spectroscopic Measurements.—IR spectra were recorded using a Pye–Unicam SP 2000 spectrophotometer equipped with a sodium chloride prism. Frequency calibration was done with a polystyrene film. Solid samples were examined as KBr disks.

^{1}H NMR spectra were recorded on a Varian 400 spectrometer at the Chemistry Department, Boston University, USA.

The UV and visible spectra of the various solutions were recorded using a Pye–Unicam SP 1800 spectrophotometer equipped with 1 cm cuvettes in a constant temperature holder connected to a Neslab RTE-8 cooled bath with water circulating.

Equilibrium and Kinetic Measurements.—For the measurement of the protonation constants, the solutions were prepared by adding 1 cm^3 of pyridoxal aroylhydrazone solution (9.14×10^{-4} – 1.37×10^{-3} mol dm^{-3}) to 20 cm^3 of a buffer solution containing dipotassium hydrogen phosphate, and either hydrochloric acid or sodium hydroxide. The ionic strength was maintained constant at $I = 0.5$ mol dm^{-3} using potassium chloride. The pH values of the solutions were measured using an Orion model 811 pH meter. The temperature was kept at 25.0 ± 0.2 °C.

For the kinetic measurements, the rate of hydrolysis was followed spectrophotometrically as previously described.[29] In most cases, the kinetic data were analysed over 4–5 half-lives. The k_{obs} values are the means of at least three replicates. From the temperature variation of the rate constants, the enthalpies and entropies of activation were obtained using a non-linear least-squares fit[17] of the Eyring equation in a logarithmic form. The temperature of the measurements was varied from 25–45 °C.

Acknowledgements

The authors would like to thank E. Merck (Darmstadt) for a gift of pyridoxal hydrochloride.

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Paper 1/02437J
Received 23rd *May* 1991
Accepted 3rd *October* 1991