

Kinetics of the Enolisation Reactions of 2-Acetylpyrrole and of 2-, 4- and 5-Acetylthiazoles

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Kinetic results are reported on the rates of enolisation of title compounds in water, in acetate buffers, in dilute hydrochloric acid, in dilute sodium hydroxide solutions and in the presence of several metal-ion salts, as measured by their rates of halogenation at 25 °C. The results have been compared with those previously obtained from the corresponding reactions of acetophenone and a number of acetylheterocycles. It is shown that a suitable metal cation (*e.g.*, Cu²⁺) can be hundreds of times more effective than the proton in catalysing the enolisation process of an acetylheterocyclic compound. This can be due either to the 'soft' character of the acetyl group, as, for example, that of 2-acetylpyrrole, or to coordination of both the carbonyl oxygen and the heteroatom by the metal cation in the transition state of the reaction, as for 2- and 4-acetylthiazoles.

We have recently studied^{1,2} the enolisation reactions of acetophenone and a number of aromatic five-membered acetyl-heterocycles under a variety of experimental conditions. The ketones behave similarly with respect to their specific and general acid-base catalysed reactions; however, remarkable differences were observed in metal-ion catalysed reactions. The effects of the metal ions, which are conveniently expressed as metal activating factors (MAF), *i.e.*, the catalytic constant for metal-ion catalysis, k_M , relative to that for proton catalysis, k_H , are very sensitive to the nature of the substrate.

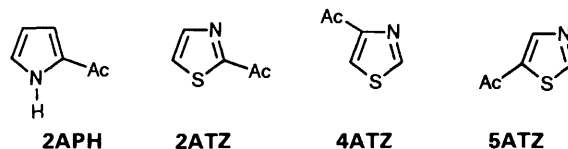
Metal-ion catalysis is probably due in all cases to coordination of the carbonyl-oxygen atom by the metal cation (Cu²⁺, Ni²⁺, Zn²⁺ or Cd²⁺) in the transition state of the reaction, but while MAF values are very low and fall within the range 0–0.08 for acetophenone (A), 2- and 3-acetylthiophenes (2AT and 3AT), and 2-acetylfuran (2AF), they are much larger for 2- and 3-acetyl-*N*-methylpyrroles (2AP and 3AP), with values ranging from 0.7 to 740. It appears, therefore, that it may be necessary to think in terms of 'hard' and 'soft' carbonyl groups, depending upon the observed metal-ion activating factor values.

In the present work we have studied the enolisation of 2-acetylpyrrole (2APH) under the same conditions² as previously adopted for 2AP and 3AP, in order to ascertain whether the 'soft' nature of the carbonyl group attached to the pyrrole ring was due to any special feature of the *N*-methyl groups of 2AP and 3AP.

In addition, we have considered the possibility that a 'two site' coordination could lead to particularly effective metal-ion catalysis, and in this context have studied the enolisation of 2- and 4-acetylthiazoles (2ATZ and 4ATZ) in comparison to that of 5-acetylthiazole (5ATZ). Indeed it has been shown³ by Cox that complex formation between 2-acetylpyridine and Zn²⁺, Ni²⁺ and Cu²⁺ leads to rates of enolisation which are up to 2×10^5 times larger than that of the uncomplexed substrate, with both nitrogen and oxygen atoms of 2-acetylpyridine being involved in coordination in the transition state. By contrast, no significant rate acceleration by these metal cations was observed for 4-acetylpyridine under the same conditions used for the 2-acetyl derivative. More recently More O'Ferrall and Murray⁴ have studied the enolisation of 2-acetyl-, 2-phenacyl- and 2-phenylacetyl-pyridines and -pyrazines. Metal catalysis

entails coordination at both nitrogen and oxygen atoms and 'appears to be most effective relative to acid catalysis when the metal bridges a weakly catalytic nitrogen coordination site and a strongly activating oxygen site. This occurs when the heterocyclic ring is attached to the carbonyl group of the ketone, rather than the carbon atom bearing the reacting hydrogen atom'.⁴

Both 2ATZ and 4ATZ possess 'pyridine-like' nitrogen atoms (albeit less basic than those of the previously studied³⁻⁵ six-membered heterocyclic systems) located in positions which should favour 'two-site' coordination. An additional point of interest is the different geometry of the potential coordinating sites relative to those of the substituted pyridines; molecular geometry is known^{6,7} to be an important factor in intramolecular catalysis. Finally, it should be noted that the 2-acetylthiazolium ion plays a key role in enzymatic acyl transfer reactions⁶ with nucleophilic reagents in which the expulsion of a thiazole ylide from tetrahedral addition compounds can give variously the free acid, thiol esters or acyl phosphates.



Experimental

General.—All inorganic salts [LiCl, KCl, NaClO₄, KI, NaBr, ZnCl₂, CdCl₂, NiCl₂, Cu(NO₃)₂] and halogens (I₂ and Br₂) were samples of AnalaR grade (Aldrich, Merck or Carlo Erba) and were used without further purification. Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminium hydride. Acetyl chloride was freshly distilled over molecular sieves (Union Carbide, type 13X and 4 Å). Solvents were removed under reduced pressure by rotary evaporation.

Materials.—2APH and 2ATZ were commercial samples (Aldrich), purified by crystallization and distillation under reduced pressure, respectively. 5ATZ was prepared according to a literature procedure.⁸

Table 1 Rate measurements for **2APH** and **2-, 4-** and **5-ATZ**

Substrate	$k_o/10^{-8} \text{ s}^{-1}$	$k_H/10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
2APH	3.07 ± 0.15	3.43 ± 0.05
2ATZ	6.49 ± 0.38	3.19 ± 0.12
4ATZ	9.84 ± 0.82	6.89 ± 0.28
5ATZ	16.2 ± 0.6	2.68 ± 0.15

4-Acetylthiazole.—A previously described⁹ synthesis of this compound was modified in order to obtain a higher yield in the following way. Hydroxylamine hydrochloride (9.32 g, 0.134 mol) in water (50 cm³) containing Na₂CO₃ (5.8 g) was added dropwise with cooling at 0–10 °C to a solution of 1-bromobutane-2,3-dione¹⁰ (22.1 g, 0.134 mol) in water (36 cm³), to give the corresponding 3-oxime derivative¹⁰ (21.25 g, 88.1%). Phosphorus pentasulfide (2.81 g) was added in portions to a solution of the oxime (6.75 g, 0.038 mol) in THF (40 cm³) containing formamide (2.81 g, 0.062 mol) and stirred for 6 h. The reaction was performed with rigorous exclusion of moisture under a dry nitrogen atmosphere. The separated solid was filtered and washed with THF to give 4-acetylthiazole oxime (98%); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}; 200 \text{ MHz}]$ 2.20 (3 H, s, Me), 7.20 (1 H, v br, OH), 7.92 (1 H, d, $J_{2,5}$ 2.0, 5-H) and 9.19 (1 H, d, $J_{2,5}$ 2.0, 2-H). Formaldehyde (40% w/v, 1.65 cm³) was added to a solution of the oxime (3 g, 0.021 mol) in water (150 cm³) and the mixture stirred at room temperature for 15 h and then at 50 °C for 1 h. Exhaustive extraction with chloroform gave 4-acetylthiazole (2.28 g, 85%) which was purified by flash chromatography (ethyl acetate–light petroleum 1:3), m.p. 57.5–58.5 °C (Found: C, 47.3; H, 3.8; N, 11.1. C₅H₅NOS requires C, 47.23; H, 3.96; N, 11.01%); $\delta_{\text{H}}(\text{CDCl}_3; 200 \text{ MHz})$ 2.69 (3 H, s, COMe), 8.20 (1 H, d, $J_{2,5}$ 2.1, 5-H) and 8.82 (1 H, d, $J_{2,5}$ 2.21, 2-H); m/z 127 (M⁺, 68%), 112 (100), 84 (42), 57 (29) and 43 (38).

Kinetic Measurements.—The enolisations were followed by monitoring spectrophotometrically the rate of halogenation of the different substrates as previously described^{1,2} by using a Kontron Uvikon 860 spectrophotometer equipped with a Hittech rapid kinetic accessory for the faster reactions. All kinetic measurements were made at 25.0 ± 0.1 °C and with an ionic strength of 0.3 mol dm^{-3} (KCl or NaClO₄).

The iodination reactions were followed under pseudo-zero-order conditions^{1,2} where there was no evidence of reversibility.¹ The rate law had the form shown in eqn. (1) where S refers to the substrate (**2APH**, **2ATZ**, **4ATZ** or **5ATZ**) and $[\text{I}_2]_{\text{tot}}$ refers to the total concentration of iodine ($[\text{I}_2] + [\text{I}_3^-]$).

$$-d[\text{I}_2]_{\text{tot}}/dt = k_e[\text{S}] \quad (1)$$

The bromination reactions in dilute hydroxide solutions were followed under pseudo-first-order conditions^{1,2} and the rate law was similarly given by eqn. (2).

$$-d[\text{OBr}^-]/dt = k_e[\text{S}] \quad (2)$$

pK_{BH}⁺ Measurements.—The thermodynamic acid dissociation constants of the acetylthiazoles were determined both potentiometrically and spectrophotometrically according to previously described¹¹ procedures. Average values obtained from the two methods were the following.

$$\begin{aligned} \text{p}K_{\text{BH}^+}(\text{2ATZ}) &= 0.69 \pm 0.05; m \text{ 1.05} \\ \text{p}K_{\text{BH}^+}(\text{4ATZ}) &= 0.45 \pm 0.07; m \text{ 1.03} \\ \text{p}K_{\text{BH}^+}(\text{5ATZ}) &= 0.43 \pm 0.12; m \text{ 0.99} \end{aligned}$$

The above values for **2ATZ** and **5ATZ** compare quite reasonably with the values of -0.66 and $+0.35$, respectively, interpolated from previously established¹¹ Hammett-type relationships for 2- and 5-substituted thiazoles.

Results

The rates of halogenation (iodination or bromination) of **2APH**, **2ATZ**, **4ATZ**, and **5ATZ** were measured in water, in dilute aqueous hydrochloric acid and sodium hydroxide, in acetate buffers and in the presence of several metal-ion salts at 25.0 ± 0.1 °C. All reactions are zero-order with respect to halogen concentration, with the rate-determining step being the formation of the enol or enolate ion.

Enolisation of 2APH, 2ATZ, 4ATZ and 5ATZ in Dilute Hydrochloric Acid.—Reaction rates were measured with the concentration of the ketone in the range $(1-3) \times 10^{-2} \text{ mol dm}^{-3}$ and HCl concentration in the range $(2-60) \times 10^{-3} \text{ mol dm}^{-3}$. The observed rate law was given by eqn. (3) with k_e being of the form shown in eqn. (1). It was found that k_e of eqn. (3) decreases

$$k_e = k_o + k_H[\text{H}^+] \quad (3)$$

slightly upon successive additions of I₂ to a given solution of **4ATZ** at relatively high concentration of HCl, probably due to some slow side reactions of the substrate. Therefore rate measurements for **4ATZ** were simply obtained by the first addition of I₂ to a fresh solution of **4ATZ** in a narrower HCl range of $(2-50) \times 10^{-3} \text{ mol dm}^{-3}$.

The results obtained for the different substrates are given in Table 1.

The slope values, k_H , represent the specific-acid-catalysed rate constants of enolisation of the free substrates. For **2ATZ**, **4ATZ** and **5ATZ** an alternative interpretation in terms of a kinetically equivalent 'water'-catalysed reaction of the *N*-protonated acetylthiazole seems very unlikely in view¹² of the fact that the present k_H values are of the same order of magnitude as that found for the related ketones (Table 2) not containing basic nitrogen atoms.

As the intercepts, k_o , of eqn. (3) are subjected to some uncertainty, the 'spontaneous' (water-catalysed) rate constants, $k_{\text{H}_2\text{O}}$, were measured directly in water. The results obtained are reported in Table 2.

Enolisation of 2APH, 2ATZ, 4ATZ and 5ATZ in Acetate Buffers.—Ketone concentrations were varied over a wide range $[(7.5-25) \times 10^{-3} \text{ mol dm}^{-3}]$ and the observed rate constants, k_e [eqn. (1)], were of the form shown in eqn. (4). Two sets of k_e

$$k_e = k_o + k_{\text{AcO}^-}[\text{AcO}^-] \quad (4)$$

values were measured for the four ketones at $r = [\text{AcO}^-]/[\text{AcOH}] = 1$ and 3, each set at five or more different concentrations of AcO⁻ over a range of ca. a factor of ten. The value of k_{AcO^-} is independent of the buffer ratio r , to within experimental error, and represents the second-order rate constant of the acetate-anion-catalysed reaction (Table 2). There is no evidence of general-acid catalysis by acetic acid.

Each k_{AcO^-} value of Table 2 is an average of individual values determined in the two buffers systems ($r = 1$ and 3). Values of k_e calculated from eqn. (4) using experimental k_o and k_{AcO^-} values agree with experimental values to within 4%.

Enolisation of 2ATZ, 4ATZ and 5ATZ in Dilute Sodium Hydroxide.—Ionisation rates in dilute aqueous hydroxide were too fast to measure using zero-order iodination conditions as above. The rates were measured instead under pseudo-first-

Table 2 Catalytic constants ($k/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$) for the enolisation of 2-acetylpyrrole (**2APH**), 2-acetylthiazole (**2ATZ**), 4-acetylthiazole (**4ATZ**), 5-acetylthiazole (**5ATZ**), 2-acetyl-*N*-methylpyrrole (**2AP**), 3-acetyl-*N*-methylpyrrole (**3AP**), 2-acetylthiophene (**2AT**), 3-acetylthiophene (**3AT**), 2-acetylfuran (**2AF**) and acetophenone (**A**) at 25 °C and ionic strength 0.3 mol dm⁻³ (KCl or NaClO₄)

Acid or base (factor)	2APH	2ATZ	4ATZ	5ATZ	2AP^a	3AP^a	2AT^a	3AT^a	2AF^a	A^a
H ₂ O ^b (10 ⁻⁸)	2.77 ± 0.16	7.05 ± 0.11	2.83 ± 1.23	27.9 ± 0.3	7.22	15.4	0.20	0.22	0.67	0.41
Hydronium ion (10 ⁻⁶)	3.43 ± 0.05	3.19 ± 0.12	6.89 ± 0.28	2.69 ± 0.15	1.48	10.6	3.95	11.8	3.35	10.0
Acetate (10 ⁻⁶)	0.391 ± 0.042	32.8 ± 2.8	4.50 ± 0.13	8.36 ± 0.59	0.64	25.0	0.58	0.66	1.07	0.84
Hydroxide ion (10 ⁻¹)	—	3.16 ± 0.17	0.68 ± 0.03	1.89 ± 0.05	9.31	1.59	2.75	2.46	4.08	2.37

^a Data from ref. 2. ^b Units are s⁻¹.

Table 3 Metal-ion-catalysed enolisation of **2APH**, **2ATZ**, **4ATZ** and **5ATZ** at 25 °C and ionic strength 0.3 mol dm⁻³ (KCl)

Substrate	Catalyst	$k_o/10^{-8} \text{s}^{-1}$	$k_M/10^{-6} \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$
2APH	Cu ²⁺	33.3 ± 1.5	67.9 ± 3.2
	Ni ²⁺	7.41 ± 0.96	10.6 ± 0.4
	Zn ²⁺	14.5 ± 1.8	4.41 ± 0.41
	Cd ²⁺	4.71 ± 1.33	4.28 ± 0.30
2ATZ	Cu ²⁺	46.8 ± 23.0	1310 ± 90
	Ni ²⁺	22.5 ± 18.8	196 ± 7
	Zn ²⁺	-14.7 ± 16.5 ^a	55.1 ± 4.0
	Cd ²⁺	12.8 ± 2.4	10.7 ± 0.6
	Li ⁺ ^b	10.3 ± 0.3	— ^c
4ATZ	Cu ²⁺	15.0 ± 2.6	2990 ± 20
	Ni ²⁺	83.2 ± 23.4	64.7 ± 5.0
	Zn ²⁺	2.21 ± 0.98	15.3 ± 0.3
	Cd ²⁺	4.04 ± 0.50	1.99 ± 0.09
5ATZ	Cu ²⁺	43.3 ± 1.8	— ^c
	Ni ²⁺	17.9 ± 4.0	— ^c
	Zn ²⁺	28.6 ± 4.7	— ^c

^a The negative value of the intercept with a large uncertainty must be a reflection of experimental error as it has no physical meaning. ^b The effect of the addition of Li⁺ on the k_e was also measured, for comparison, for **2AT** ($k_o = 0.678 \pm 0.044 \times 10^{-8} \text{s}^{-1}$) and for **3AP** ($k_o = 15.5 \pm 2.5 \times 10^{-8} \text{s}^{-1}$). ^c The obtained values are zero or slightly negative indicating the absence of metal-ion catalysis.

order conditions as rates of bromination [eqn. (2)] in solutions containing a slight excess of bromine as previously described.^{1,2} The second-order rate constants, k_{OH} , obtained from eqn. (5) are reported in Table 2. Values of k_e calculated from eqn. (5)

$$k_e = k_o + k_{\text{OH}}[\text{OH}^-] \quad (5)$$

using experimental k_o and k_{OH} values agree with experimental values to within 5% in a range of hydroxide concentration (7.5–50) × 10⁻³ mol dm⁻³.

Metal-ion-catalysed Enolisation of 2APH, 2ATZ, 4ATZ and 5ATZ.—The effect of Cd²⁺, Zn²⁺, Ni²⁺ and Cu²⁺ on the rates of enolisation of the four ketones was studied in unbuffered solutions (pH range 4–6). Substrate concentrations were ca. 10⁻² mol dm⁻³ and the concentrations of I₂ and I⁻ were the same^{1,2} as those for reactions in the absence of metal ions. The ionic strength was 0.3 mol dm⁻³ for all reactions (KCl). Rates were measured at several metal-ion concentrations in the range (2.5–75) × 10⁻³ mol dm⁻³. In the case of Cu²⁺ the concentration range (0.25–7.5) × 10⁻³ mol dm⁻³ was chosen instead, in order to avoid precipitation of CuI₂.

The observed rate constants, k_e [eqn. (1)], in the presence of Zn²⁺, Ni²⁺ and Cu²⁺ were, for **5ATZ** (in the above range of metal-ion concentration), essentially coincident, to within experimental error, with the 'spontaneous' rate constant, $k_{\text{H}_2\text{O}}$ (see Table 2).

For the remaining ketones, k_e showed a linear increase with

increasing metal-ion concentration according to eqn. (6), where

$$k_e = k_o + k_M[\text{M}^{2+}] \quad (6)$$

[M²⁺] represents the molar concentration of Cd²⁺, Zn²⁺, Ni²⁺ or Cu²⁺. The behaviour shows that saturation does not occur even at the highest metal-ion concentration used in contrast with the behaviour previously³ observed for more basic substrates. The results obtained are reported in Table 3.

It is well documented^{13,14} that Li⁺ has a strong affinity for the oxygen atom of carbonyl compounds. Therefore an attempt was made to determine the effect of the addition of LiCl on the k_e (unbuffered solutions, pH 5.8–6.0) of **2ATZ**, **2AT** and **3AP**. The observed rate constants remained essentially unchanged [in the LiCl concentration range (1.25–12.5) × 10⁻² mol dm⁻³] and coincident, to within experimental error, with the corresponding 'spontaneous' rate constants $k_{\text{H}_2\text{O}}$ (Table 2) of the three ketones. This suggests that the strong hydration¹⁵ of Li⁺ ions inhibits replacement of water molecules on the metal ion by ketone molecules in the transition state of the enolisation process. Indeed the interaction between Li⁺ and the carbonyl oxygen atom appears particularly strong¹⁴ in non-aqueous solvents, such as dioxane.

Ni²⁺- and Cu²⁺-catalysed Enolisation of 2ATZ in Acetate Buffers.—The effect of Ni²⁺ and Cu²⁺ addition on the rate of the acetate-catalysed enolisation of **2ATZ** was also investigated. Acetate ion concentrations were varied in the range 0.001–0.1 mol dm⁻³ ($r = 1$) at fixed metal-ion concentrations.

The following results were obtained.

$$\begin{aligned} [\text{Ni}^{2+}] &= 25.0 \times 10^{-3} \text{mol dm}^{-3} \\ k_e &= (7.87 \pm 2.12) \times 10^{-6} + (3.89 \pm 0.08) \times 10^{-3}[\text{AcO}^-] \\ [\text{Cu}^{2+}] &= 1.88 \times 10^{-3} \text{mol dm}^{-3} \\ k_e &= (9.99 \pm 2.56) \times 10^{-6} + (0.922 \pm 0.046) \times 10^{-3}[\text{AcO}^-] \\ [\text{Cu}^{2+}] &= 3.75 \times 10^{-3} \text{mol dm}^{-3} \\ k_e &= (45.8 \pm 4.9) \times 10^{-6} + (1.71 \pm 0.08) \times 10^{-3}[\text{AcO}^-] \end{aligned}$$

Acetate concentrations were kept lower than those adopted in the absence of Ni²⁺ or Cu²⁺ in order to avoid complexation¹⁶ between the carboxylate ion and the metal cations. Concentrations of Cu²⁺ lower than those of Ni²⁺ were chosen in order to avoid very fast reactions.

The above slope values can be compared with the value of $k_{\text{AcO}} = 0.0328 \times 10^{-3} \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ for **2ATZ** (Table 2), showing the strong effect exerted by the metal ions under consideration on the acetate-catalysed process. A slope value of $10.6 \times 10^{-3} \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ can be extrapolated from the above results at [Cu²⁺] = 25.0 × 10⁻³ mol dm⁻³ showing that the relative effectiveness of Cu²⁺ and Ni²⁺ is approximately the same in the acetate and 'water' (Table 3) reactions of **2ATZ**.

It is noteworthy that the present metal-ion effect on the acetate-catalysed process is probably due to concerted participation of both the acetate anion and the metal cation in the transition state of the reaction. This effect is formally similar to

Table 4 Metal-ion activating factors (MAF) with reference to the proton (k_M/k_H) for **2APH**, **2ATZ** and **4ATZ**

Substrate	Catalyst			
	Cu ²⁺	Ni ²⁺	Zn ²⁺	Cd ²⁺
2APH	20	3.1	1.3	1.3
2ATZ	410	61	17	3.4
4ATZ	430	9.4	2.2	0.29

a 'third order' term long sought, but rarely found in the general acid-base catalysed enolisation of ketones.^{17,18}

¹H NMR and UV Spectra of **2ATZ** in the Presence of Ni²⁺ and Cu²⁺ Ions.—Addition of NiCl₂ (ca. 0.09 mol dm⁻³) to a deuterium oxide solution of **2ATZ** (ca. 0.03 mol dm⁻³) did not affect the chemical shifts of the ring proton H-4 (7.82 ppm) and H-5 (7.89 ppm) or that of the methyl protons (2.54 ppm). The paramagnetic properties of Cu²⁺ did not allow an analogous analysis of the proton chemical shifts. However inspection of the UV spectrum of **2ATZ** in the presence of the maximum concentration of Cu(NO₃)₂ used in the kinetic experiments did not show evidence of complexation between Cu²⁺ (for which metal-ion catalysis was found to be most effective) and **2ATZ**. The NMR spectra were recorded on a Varian Gemini 300 MHz instrument.

No evidence of complexation of **2AT** and **3AT** by Zn²⁺ and Cd²⁺ and of **3AP** by Cu²⁺ was previously^{1,2} found by different spectroscopic techniques.

Discussion

Inspection of the results reported in Table 2 allows some conclusions to be drawn about the relative reactivities of acetophenone and the different acetylthiazoles in the acid-base catalysed and the 'spontaneous' or 'water' enolisation reactions.

Acetylpyrroles and acetylthiazoles are from four to about one hundred times more reactive than acetophenone, 2-acetylfuran, or the acetylthiophenes in the water reaction. The presence of an *N*-methyl group in **2AP** confers only a slight increase in reactivity compared with **2APH**. A similarly high reactivity of acetylthiazoles (as well as that of **3AP** and acetylpyridines³) relative to the remaining ketones is also apparent in the acetate-catalysed enolisations. Rate constants for the hydroxide-catalysed reactions are quite insensitive to the structure of the ketone. The total variation among the k_{OH} values for the different substrates (excluding **4ATZ** and **2AP**) covers less than a factor of three, providing further confirmation of the well-known^{1,2} 'levelling-off' effect characteristic of the hydroxide-catalysed reaction.

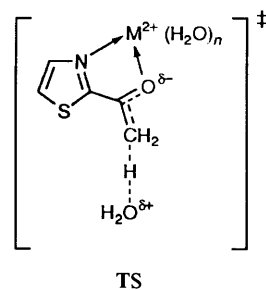
It is difficult to provide a simple explanation for the relative reactivities of the substrates in their water- or base-catalysed reactions. Indeed it is apparent from the data in Table 2 that there is no correlation of the reactivities, within this series of compounds, with known electronic effects such as the electron-withdrawing properties of the heteroatoms of the different heterocycles or the 'π-excess' in five-membered heterocycles compared with the benzene ring.

A somewhat clearer picture emerges for the specific acid-catalysed enolisation pathway. The accepted mechanism¹⁷ for specific-acid catalysis involves a pre-equilibrium proton transfer to the carbonyl group, with a subsequent water-assisted C-H ionisation. This would suggest a relationship between substrate basicity and reactivity, and in accord with this it has been observed previously^{1,2} that 3-acetyl derivatives of single-heteroatom heterocycles (and acetophenone) are significantly

more reactive than their less basic 2-acetyl counterparts. Similarly, **2APH** shows the low reactivity typical of 2-acetylthiazoles. The reactivities of the three isomeric acetylthiazoles in Table 2 do not parallel their thermodynamic basicities, but the total spread of the k_H values is only a factor of 2.6.

The metal-ion effects on the rates of enolisation of **2APH** reported in Table 3 are intermediate between those previously² observed for **2AP** and **3AP**. The biggest difference between **2APH** and **2AP** is seen for the cations Ni²⁺ and Zn²⁺ as no catalysis was observed for the latter. This suggests the presence of a considerable steric retardation caused by the *N*-methyl group in **2AP**. The MAF values measured for **2APH** (see Table 4) are in all cases ≥ 1. This clearly emphasises the 'soft' character of a carbonyl bonded directly to a pyrrole ring as opposed to the 'hard' character of carbonyl groups bonded to benzene, thiophene and furan rings (MAF values ≤ 1).²

With respect to acetylthiazoles, no catalytic effects by Cu²⁺, Ni²⁺ and Zn²⁺ were observed for **5ATZ**, suggesting an intrinsically 'hard' carbonyl group similar to that of the acetylthiophenes. In the absence of any additional factor parallel behaviour would be expected for the other acetylthiazoles. However, strong metal-ion activation occurs for both **2ATZ** and **4ATZ** with MAF values generally > 1. This is therefore best interpreted in terms of bidentate coordination of the metal cations (M²⁺), involving both the nitrogen and oxygen atoms of the substrate, in a transition state (TS) which could be depicted by the following structure (for **2ATZ**).



The effect is particularly marked in the cases of Cu²⁺, which is some 410 and 430 times more effective than the proton in promoting the enolisation of **2ATZ** and **4ATZ**, respectively. Bidentate coordination of the type shown in the TS, which is well established in the acylpyridines discussed above,^{3,4} is of course not possible for **5ATZ**.

Finally, a comparison of the present results on metal-ion catalysis for **2ATZ** and **4ATZ** with those for 2-acetylpyridine³ seems interesting. Such a comparison in terms of MAFs is not straightforward, owing to the difference in the reaction mechanisms. A discrete complex is formed³ between 2-acetylpyridine and the metal cation and it is this complex that enolises much faster than the uncomplexed substrate. In addition the conjugate acid of 2-acetylpyridine is the reacting species in water (and, *a fortiori*, in dilute acids) rather than the free base. However, k_M and k_H values for 2-acetylpyridine formally identical with those measured for **2ATZ** and **4ATZ** can easily be calculated from reported³ rate constants for the 'water'- and metal-ion-catalysed reactions and from protonation and complex formation equilibrium constants. The calculated MAF values for 2-acetylpyridine are 1800, 38.5 and 1.93 for Cu²⁺, Ni²⁺ and Zn²⁺, respectively. It appears that the MAF values for 2-acetylpyridine and for **2ATZ** and **4ATZ** (Table 4) are similar, however, it should be considered that the Brønsted basicities of the acetylthiazoles are some three pK units lower than that³ of 2-acetylpyridine, once again showing the high efficiency of metal-ion catalysis in promoting the enolisation reaction of **2ATZ** and **4ATZ**.

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Paper 3/06640A

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