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Ab initio analysis on metal ion catalysis in the enolization reactions of some acetylheterocycles: kinetics of the enolization reactions of 3-acetyl-5-methylisoxazole, 5-acetyl-3-methylisoxazole and 3(5)-acetylpyrazole

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epoc ABSTRACT: Kinetic data on the enolization reaction of 3-acetyl-5-methylisoxazole, 5-acetyl-3-methylisoxazole, 3(5)-acetylpyrazole and some previously studied acetylheterocycles have been the object of a comprehensive *ab initio* analysis. Enolization rate constants were measured spectrophotometrically by the halogen trapping technique at 25 °C and ionic strength of 0.3 mol dm^{-3} in water, in acetate buffers, in dilute hydrochloric acid, in dilute sodium hydroxide and in the presence of some metal ion salts. In the spontaneous (water) and base (acetate) catalysed reactions the ketones investigated are generally more reactive than acetophenone, according to the electron-withdrawing effect of the heterocyclic ring compared with the benzene ring. In particular, acetylisoxazoles, 3(5)-acetylpyrazole and acetylthiazoles are more reactive than acetylfurans, 2-acetylpyrrole and acetylthiophenes respectively, and this can be attributed to the additional effect of the second heteroatom in the heterocyclic moiety. On the other hand, the compounds investigated are generally less reactive than acetophenone in the H_3O^+-catalysed reaction. *Ab initio* calculations on the relative stability of the protonated and unprotonated forms of the substrates investigated have been compared with the kinetic results obtained in acid solutions. As far as the metal ion catalysis is concerned, an approach in terms of $\Delta\Delta E$ can give an estimate of the combined contributions of charge densities and frontier orbitals to the interaction of the substrate with the metal ion catalyst. A comparison of experimental metal activating factor values and *ab initio* calculations outlines the importance of charge density on the carbonyl oxygen atom of acetylheterocycles with one heteroatom. An analogous comparison for acetylheterocycles with two heteroatoms suggests the formation of a chelate complex or transition state, in which the metal ion coordinates both the carbonyl oxygen and the aza nitrogen, whenever these two atoms are suitably placed within the molecular structure of the acetylheterocycle. Copyright © 2002 John Wiley & Sons, Ltd.
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KEYWORDS: metal ion catalysis; *ab initio* calculations; Enolization reactions; acid–base catalysis

INTRODUCTION

Lewis acid catalysis by metal ions provides alternative pathways for specific acid-catalysed enolization reactions of ketones and comparisons of catalysis by metal ions and hydronium ion is a subject of considerable interest.[1] We have recently investigated[2] the effect of the addition of metal ions (e.g. Cu^{2+}, Zn^{2+}, Ni^{2+}) in the enolization reaction of acetophenone and a number of aromatic five-membered acetylheterocycles in aqueous solutions. The effectiveness of metal ion catalysis depends primarily upon 'hardness' and 'softness' of the carbonyl group and of the metal ion catalyst. With the use of a simple relative number, the metal activating factor (MAF) value, i.e. the ratio between the catalytic constants for metal ion catalysis k_M and that for proton catalysis k_H, we have defined as 'soft' the carbonyl groups of 3-acetyl-*N*-methylpyrrole[2b] (**3AP**) and 2-acetylpyrrole[2c] (**2APH**) as they enolize equally well (or faster) in the presence of the above-mentioned metal ions and in the presence of the hydronium ion. On the contrary, the carbonyl groups of acetophenone, 2- and 3-acetylthiophenes[2a] (**2AT** and **3AT**), 2-acetylfuran[2b] (**2AF**) and 5-acetylthiazole[2c] (**5ATZ**) can be defined 'hard', as the hydronium ion is a much more effective catalyst than any of the metal ions investigated in the enolization reaction. The formation of a chelate complex between the metal ion and the

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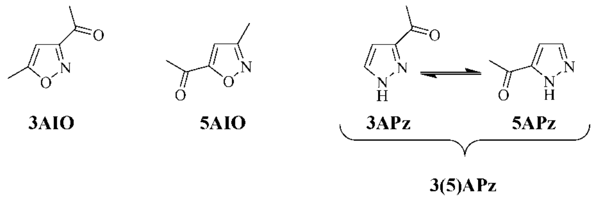


Scheme 1

acetylheterocycle, enolizing much faster than the uncomplexed substrate, was detected only for 2-acetylpyridine[3] and 2-acetylimidazole (**2AI**),[2d] probably due to the relatively high basicities of these substrates. On the other hand, the relatively high MAF values measured for the less basic 2- and 4-acetylthiazole (**2ATZ** and **4ATZ**) were attributed[2c] to a transition state in which the metal cation coordinates both the carbonyl oxygen and the aza nitrogen atoms. 3-Acetyl-5-methylisoxazole (**3AIO**), 5-acetyl-3-methylisoxazole (**5AIO**) and 3(5)-acetylpyrazole [**3(5)APz**] possess (Scheme 1), as 2-acetylpyridine, **2AI, 2ATZ** and **4ATZ** do, 'pyridine-like' nitrogen atoms. In two of them, i.e. **3AIO** and the tautomer **3APz**, this aza nitrogen atom is located in a position that could assist proton transfer by forming with the metal cation a chelate complex or transition state. Within this framework we have studied the enolization reaction of the title ketones in water, in dilute hydrochloric acid, in dilute sodium hydroxide, in acetate buffer solutions and in the presence of Zn^{2+}, Ni^{2+} and Cu^{2+} solutions, at 25.0 ± 0.1 °C and at a constant ionic strength of 0.3 mol dm^{-3} (KCl or $NaClO_4$).

Ab initio calculations on the same three and some previously investigated acetylheterocycles have been carried out: (i) to evaluate the influence of the thermodynamic contribution to the acid-catalysed enolizations; (ii) to correlate the calculated charge density on the carbonyl oxygen atoms and the energy of the substrate–metal ion interaction with the experimental rate constants for metal ion catalysis; (iii) to test further the validity of the previously suggested mechanisms[2c] for metal ion catalysis via the formation of a chelate complex (or transition state) in which the metal ion coordinates both the carbonyl oxygen and the aza nitrogen whenever these two atoms are suitably placed within the molecular structure of the acetylheterocycle; (iv) to estimate the relative stability of the two tautomeric forms of **3(5)APz** of Scheme 1.

RESULTS

Kinetics

The enolization reactions were followed spectrophotometrically by the well-established halogen-trapping procedure as described previously.[2] The iodination reactions (in hydrochloric acid, in acetate buffers and in salt solutions) were followed under pseudo-zero-order conditions[2] and the rate law had the form shown in Eqn. (1), where S refers to the substrate and $[I_2]_{tot}$ refers to the total concentration of iodine ($[I_2] + [I_3^-]$):

$$-d[I_2]_{tot}/dt = k_e[S] \qquad (1)$$

Under the experimental conditions adopted, the rate-determining step is the formation of the enol or enolate ion and there is no evidence of reversibility of the iodination reaction.

The bromination reactions (in dilute sodium hydroxide solution) were followed under pseudo-first-order conditions in solutions containing a slight excess of bromine as previously described[2a–c,e] and the rate law was given by:

$$-d[OBr^-]/dt = k_e[S] \qquad (2)$$

Enolization of 3AIO, 5AIO and 3(5)APz in dilute hydrochloric acid. Reaction rates were measured with a concentration of **3AIO** of about 1×10^{-2} mol dm^{-3}, **5AIO** of about 2×10^{-3} mol dm^{-3} and **3(5)APz** of about 5×10^{-3} mol dm^{-3}; [HCl] was in the range 0.0025–0.25 mol dm^{-3} and $[I^-] = 2$, 5 or 10×10^{-3} mol dm^{-3}. The observed rate law was given by Eqn. (3) with k_e being of the form shown in Eqn. (1):

$$k_e = k_{H_2O} + k_H[H^+] \qquad (3)$$

The intercepts, k_{H_2O}, of Eqn. (3) measure the 'water' rate constants, whereas k_H refers to the H_3O^+-catalysed rate constants. Values of k_e calculated from Eqn. (3) using evaluated k_{H_2O} and k_H values agree with experimental values to within 5% in an interval of H_3O^+ concentration at least of a factor of 100.

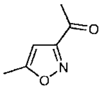
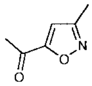
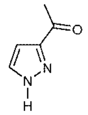
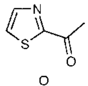
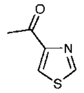
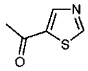
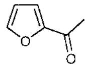
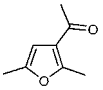
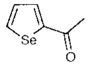
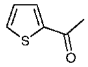
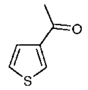
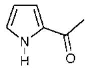
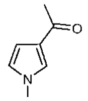
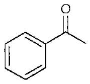
The results obtained are collected in Table 1, together with analogous results previously obtained for acetophenone and some other acetylheterocycles.

Enolization of 3AIO, 5AIO and 3(5)APz in acetate buffers. The observed rate constants k_e [Eqn. (1)] were of the form shown in Eqn. (4), where k_{AcO} represents the second-order rate constant for the acetate-catalysed reaction and the intercept k_o represents the rate constant for the water and the (very small) specific catalysis contributions.

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

Several sets of k_e values were measured for the three ketones at buffer ratios $r = [AcO^-]/[AcOH] = 0.5$, 1, 3 and 5 for **5AIO**, 1 and 5 for **3AIO** and 3 and 5 for **3(5)APz**, each set at four or more different concentrations of acetate, $[AcO^-]$, in a range of approximately a factor of ten. The values of k_e showed no evidence of general acid catalysis by the acidic component of the buffer, as

Table 1. Acid dissociation constants pK_{BH^+} and catalytic constants $k(\mathrm{dm^3\ mol^{-1}\ s^{-1}})$ for the enolization of acetophenone and some acetylheterocycles at 25 °C and ionic strength 0.3 mol dm^{-3} (NaCl or KClO$_4$)

	Substrate	k_{H_2O} $(10^{-9})/s^{-1}$	k_H (10^{-6})	k_{AcO} (10^{-7})	k_{OH} (10^{-1})	pK_{BH^+}	Ref.
3AIO		86.7	2.16	435	1.93	−3.79	this work
5AIO		193	1.29	1510	37.4	−3.58	this work
3(5)APz		16.5	5.97	30.9	–	0.09	this work
2ATZ		70.5	3.19	328	3.16	−0.69	2c
4ATZ		28.3	6.89	45.0	0.68	−0.45	2c
5ATZ		279	2.69	83.6	1.89	0.45	2c
2AF		6.72	11.8	10.7	4.08		2b
3AF		33.3	14.8	4.38	0.22		2c
2AS		36.0	2.99	6.41	2.00		2c
2AT		2.00	3.95	5.80	2.75	−4.14[a]	2a
3AT		2.20	11.8	6.60	2.46		2a
2APH		27.7	3.43	3.91	–		2c
3AP		154	10.6	250	1.59		2b
A		4.1	10.0[b]	8.40[b]	2.37[c]	−3.46[d]	2a

[a] Ref. 4.
[b] Ref. 5.
[c] Ref. 6.
[d] Ref. 7.

they were found to be independent of r. The correlation coefficient of the straight line of Eqn. (4) was, for each substrate, higher than 0.999 and the standard error of k_{AcO} was within 5%.

A slight linear dependence of k_e on the concentration of $[I_2]_{tot}$ was observed in the case of **3AIO** and k_{AcO} values for this ketone were extrapolated to zero $[I_2]_{tot}$ concentration. The reason of this dependence is not understood.

The results obtained for acetate catalysis are reported in Table 1.

Enolization of 3AIO, 5AIO in dilute sodium hydroxide. Ionization rates in dilute aqueous hydroxide [NaOH concentration in the range $(0.1\text{–}2.5) \times 10^{-2}$ mol dm^{-3}] were measured as rates of bromination using the rate law given by Eqn. (2).

The second-order rate constants k_{OH} obtained from Eqn. (5) are reported in Table 1.

$$k_e = k'_o + k_{OH}[OH^-] \qquad (5)$$

Values of k_e calculated from Eqn. (5) using experimental

k'_o and k_{OH} values agree with experimental values to within 5%. No OH^- catalysis was detected for **3(5)APz**, as this compound is probably acidic enough to be appreciably dissociated under the basic conditions adopted [pyrazole has pK_a 14.2[8a] and **3(5)APz** should be even more acidic].

Metal-ion-catalysed enolization of 3AIO, 5AIO and 3(5)APz. The effect of the presence of Zn^{2+}, Ni^{2+} and Cu^{2+} on the rates of enolization of the three substrates was studied in unbuffered solutions (pH 4–6). Substrate concentrations were *ca* $(2–5) \times 10^{-3}$ mol dm^{-3} and the concentrations of I_2 and I^- were the same as those for the reactions in the absence of metal ions. Rates were measured at several metal ion concentrations in the range $(2.5–75) \times 10^{-3}$ mol dm^{-3}. In the case of Cu^{2+} the concentration range $(0.25–7.5) \times 10^{-3}$ mol dm^{-3} was chosen instead, in order to avoid precipitation of CuI_2 (and/or Cu_2I_2).

Values of k_e for **3AIO** and **3(5)APz** showed a linear increase with increasing metal ion concentration according to:

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

where $[M^{2+}]$ represents the molar concentration of Zn^{2+}, Ni^{2+} or Cu^{2+} and k_M represents the second-order rate constant for the metal-ion-catalysed reaction. The correlation coefficients of the straight lines of Eqn. (6) were, in all cases, higher than 0.990 and the standard error of k_M was within 5%.

There was no evidence of saturation even at the highest metal ion concentration used, which is at variance with the behaviour previously observed with more basic substrates such as 2-acetylpyridine[3] and 2-acetylimidazole.[2d] On the other hand, no metal ion catalysis was observed for **5AIO**.

The results obtained are collected in Table 2.

***Ab initio* calculations.** As the accepted mechanism[9] for the acid-catalysed enolization reaction involves a pre-equilibrium proton transfer to the carbonyl group, with subsequent C—H ionization being assisted by the solvent or the conjugate base of the acid catalyst, the overall rate constant can be dissected into a kinetic term, k_v, and a thermodynamic term, $1/K_{BH^+}$ (where K_{BH^+} is the acid dissociation constant of the protonated acetylheterocycle), according to:

$$k_H = k_v / K_{BH^+} \qquad (7)$$

The relative stability of the unprotonated (B) and protonated (BH^+) forms of some 2-and 3-acetylheterocycles (pyrrole, thiophene and furan derivatives) can be evaluated by *ab initio* calculations according to the aqueous solvation model.[10] The results are collected in Table 3.

A similar mechanism could be proposed for the metal ion catalysis; however, no experimental evidence for the formation of a complex between the substrate and the metal ion has been found for a series of acetylheterocycles with one ring heteroatom[2] (with the notable exception of 2-acetylpyridine[3]). The observed metal ion catalysis can be interpreted according to the perturbation teory,[11] which provides semi-quantitative interpretation of relative reactivities in terms of the interactions of frontier orbitals [highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO)] and/or the electrostatic interactions between the species involved. *Ab initio* calculations on the acetylheterocycles investigated have been run and charge densities on their carbonyl oxygen atoms (and aza nitrogen atoms if appropriate) as well as the energies of their HOMOs have been derived. The results obtained are collected in Table 2.

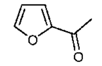
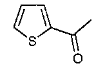
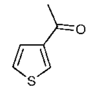
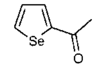
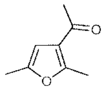
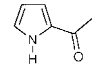
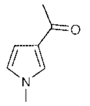
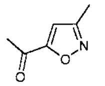
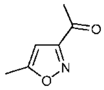
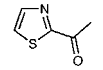
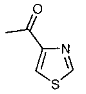
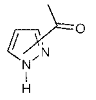
DISCUSSION

Inspection of the rate constants collected in Table 1 shows that **3(5)APz, 3AIO** and **5AIO** are more reactive than acetophenone in the 'water' and acetate-catalysed reactions. This fact can be easily accounted for by the electron-withdrawing effects of the heterocyclic rings, compared with the benzene ring, which should make the acetyl hydrogen atoms more easily removable by a base. This behaviour (with a few exceptions for the acetate reaction)[2b,c] appears to be quite general for acetylheterocycles compared with acetophenone. By the same token, the presence of the second ring heteroatom explains why **3(5)APz** is eight times more reactive than **2APH** in the acetate-catalysed reaction. Similarly **3AIO** and **5AIO** are respectively 40 and 140 times more reactive than **2AF**, and **2ATZ** and **4ATZ** are eight and 56 times more reactive than **2AT** in the same reaction. The prevalence of the inductive over the resonance effect in the protonation and the electrophilic substitution reactions of azoles compared with pyrrole, furan and thiophene has already been pointed out.[8]

The rate constant for the OH^--catalysed reaction of **5AIO** is about 20 times higher than that of **3AIO**, and this is in agreement with the strong inductive electron-withdrawing effect of the ring oxygen atom and the fact that k_{OH} of **2AF** is 19 times higher than k_{OH} of **3AF**.[2e] However, the k_{OH} values of the different acetylheterocycles are generally difficult to rationalize as they are rather insensitive[2] to the structure of the ketone. Indeed, for most of the substrates in Table 1 the k_{OH} values vary within a factor of about six (notable exceptions are the values of **5AIO** and **3AF** discussed above).

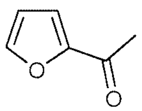
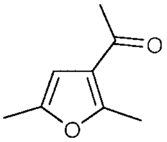
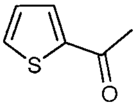
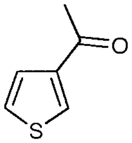
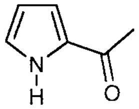
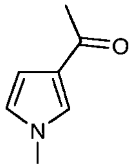
As expected, in the light of the accepted mechanism[9] for the acid-catalysed enolization reaction, **3(5)APz, 3AIO, 5AIO** and most acetylheterocycles are *vice versa* less reactive than acetophenone in the hydronium-

Table 2. Metal-ion-catalysed rate constants, MAF values, charge densities on the carbonyl oxygen and the aza nitrogen atoms and calculated HOMO energies for some acetylheterocycles with one ring heteroatom (a) and with two ring heteroatoms (b)

	Substrate	$k_{Zn}/10^{-8}$ dm^3 mol^{-1} s^{-1} (MAF values)	$k_{Cu}/10^{-8}$ dm^3 mol^{-1} s^{-1} (MAF values)	$k_{Ni}/10^{-8}$ dm^3 mol^{-1} s^{-1} (MAF values)	Charge on oxygen (Charge on nitrogen)	HOMO/hartrees (kcal mol^{-1})	k_{Cu}/k_{Zn}
One ring heteroatom							
2AF		3.56 (0.011)	0.00	26.6 (0.079)	−0.348	−0.2193 (−137.6)	–
2AT		20.9 (0.059)	23.5 (0.059)	0.00	−0.359	−0.2226 (−139.7)	1.10
3AT		19.0 (0.016)	14.1 (0.012)	0.00	−0.354	−0.2183 (−136.9)	0.700
2AS		147 (0.49)	94.6 (0.32)	0.00	−0.362	−0.2238 (−140.4)	0.600
3AF		281 (0.19)	792 (0.54)	50.6 (0.03)	−0.370	−0.2101 (−131.8)	2.80
2APH		441 (1.30)	6790 (20:0)	1060 (3.09)	−0.391	−0.2128 (−133.5)	15.4
3AP		3200 (3.00)	788000 (740)	31800 (30)	−0.372	−0.2004 (−125.8)	246
Two ring heteroatoms							
5AIO		0.00	0.00	0.00	−0.330	−0.2345 (−147.1)	–
3AIO		3730 (17.3)	1090 (5.05)	261 (1.21)	−0.334 (−0.085)	−0.2266 (−142.2)	0.300
2ATZ		5510 (17.0)	131000 (410)	19600 (61.4)	−0.348 (−0.224)	−0.2318 (−145.5)	23.8
4ATZ		1530 (2.20)	299000 (430)	6470 (9.39)	−0.349 (−0.211)	−0.2226 (−139.7)	195
3(5)APz		1360 (2.28)	48800 (81.7)	1590 (2.66)	−0.350^{a} (−0.184)^{a,b} −0.364^{c} (−0.168)^{c,b}	−0.2145^{a} (−134.6)^{a} −0.2349^{c} (−147.4)^{c}	35.9

[a] Values calculated for the **3APz** tautomer.
[b] Charge on N–2.
[c] Values calculated for the **5APz** tautomer.

Table 3. Calculated energies [Density Functional Theory (DFT) + hydration; hartrees] for the most stable conformation of the protonated (BH^{+}) and unprotonated (B) forms of some acetylheterocycles

						
BH^{+}	−383.26169	−461.93115	−706.27506	−706.27558	−363.41189	−402.73025
B	−382.83673	−.461.50161	−705.85518	−705.84917	−362.98411	−402.29405
ΔE_{B-BH^+}	0.42496	0.42954	0.41988	0.42641	0.42778	0.43620
(kcal mol^{-1})	(266.67)	(269.54)	(263.48)	(267.58)	(268.44)	(273.72)

catalysed reaction, again due to the electron-withdrawing effect of the heterocyclic rings. In particular, in substrates with only one ring heteroatom, the more basic 3-acetyl derivatives react faster than their 2-acetyl isomers. This interpretation of the results for acid catalysis is supported by *ab initio* calculations, which show that the energy difference between the unprotonated and protonated forms of 3-acetyl heterocycles $\{\Delta\Delta E_{(\mathrm{B-BH^+})^3}\}$ is higher than that of the corresponding 2-acetyl isomers $\{\Delta\Delta E_{(\mathrm{B-BH^+})^2}\}$ [i.e. $\Delta\Delta E_{(\mathrm{B-BH^+})(3-2)}$ 2.87 kcal mol^{-1}, 4.10 kcal mol^{-1} and 5.28 kcal mol^{-1} for the acetylfurans, the acetylthiophenes and the acetylpyrroles respectively (see Table 3)]. However, for the acetylheterocycles with two ring heteroatoms, generally there is not a correspondence between thermodynamic and kinetic basicities, as for most of the substrates investigated the thermodynamic protonation site is the aza-nitrogen rather than the carbonyl oxygen atom. Therefore, similar $\Delta\Delta E_{(\mathrm{B-BH^+})}$ calculations were not performed for the latter compounds.

Interestingly for the substrates with an anomalously high (**5AIO**) or low (**3AF**) k_{OH} value, an anomalously low (**5AIO**) or high (**3AF**) k_{H} value has also been found. The overall variation of k_{H} for the investigated compounds so far (Table 1) is only a factor of 11, as expected from the well-known fact that the H_3O^+-catalysed enolization reaction of monocarbonyl compounds is not very sensitive[12] to the molecular structure of the substrate.

As for metal-ion catalysis, let us first discuss the acetylheterocycles with one ring heteroatom (Table 2). Rate enhancements for these substrates were previously[2a,b,e] attributed to coordination of the carbonyl oxygen atom by the metal cation in the transition state of the enolization reaction and the effectiveness of catalysis was related to the hardness and softness of their carbonyl groups.[2c,e]

Ab initio *calculations* on **2AF**, 3-acetylfuran (**3AF**), **2AT, 3AT**, 2-acetylselenphene (**2AS**) and **3AP** have highlighted the existence of a linear correlation ($n = 6$, $r = 0.954$) between the rate constant for the Zn^{2+}-catalysed reaction and the relative charge density on the carbonyl oxygen atom (Fig. 1). The rate constants for the Zn^{2+}-catalysed reaction have been conveniently expressed as the logarithm of the rate constant [$\ln(k_{\mathrm{Zn}\ i}/k_{\mathrm{Zn\ ref}})$] with reference to that of **3AP** ($k_{\mathrm{Zn\ ref}}$).

On the other hand, a comparison of the above catalytic effects of Zn^{2+} with those observed for Cu^{2+} points to an additional contribution arising from the interaction between frontier orbitals. According to Klopman[13] (based on the ionization potentials and the electronic affinities reported by Moore)[14] Cu^{2+} is a softer cation than Zn^{2+} or Ni^{2+} ($E_{\mathrm{n}} = -2.16$ eV, -1.57 eV and -0.24 eV respectively). In fact, catalysis by Cu^{2+} is more efficient than that by Zn^{2+} for **3AP** and **3AF**, in agreement with the higher energy values of the HOMOs of these substrates compared with the HOMOs of the other substrates containing one ring heteroatom in Table 2. A correlation between charge density and rate constants for the Cu^{2+}-catalysed reaction, similar to that discussed above for Zn^{2+} catalysis, shows a strong deviation from linearity for **3AP** (see Fig. 2). This is the substrate with the HOMO of highest energy and the contribution due to the interaction of the frontier orbitals clearly cannot be neglected for this acetylheterocycle.

In conclusion, the linearity of the correlations of Figs 1 and 2 outlines the paramount importance of charge density on the carbonyl oxygen atom as a molecular

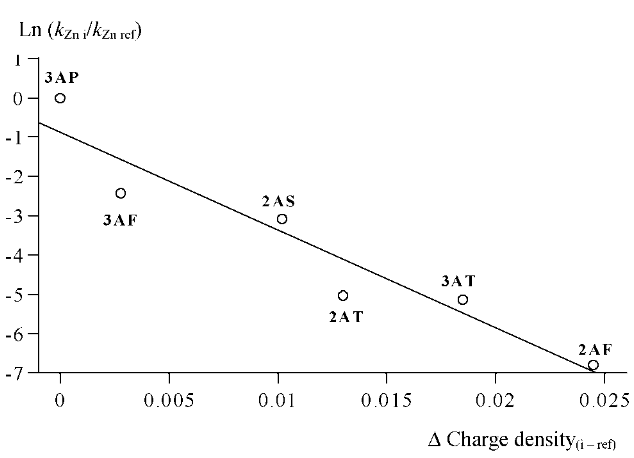


Figure 1. Linear correlation between rate constants for the Zn^{2+} -catalysed enolization reaction and differences in charge densities on the carbonyl oxygen atom, with reference to **3AP**, for some acetylheterocycles with one ring heteroatom

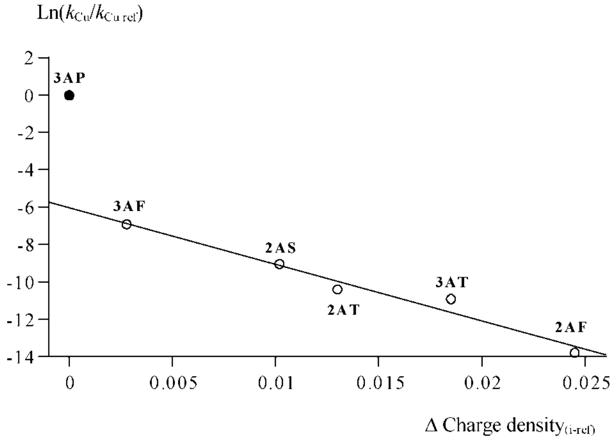


Figure 2. Linear correlation between rate constants for the Cu^{2+} -catalysed enolization reaction and differences in charge densities on the carbonyl oxygen atom, with reference to **3AP**, for some acetylheterocycles with one ring heteroatom. Open circles (○) refer to compounds used for drawing the line. **3AP** (●) has been excluded from the correlation

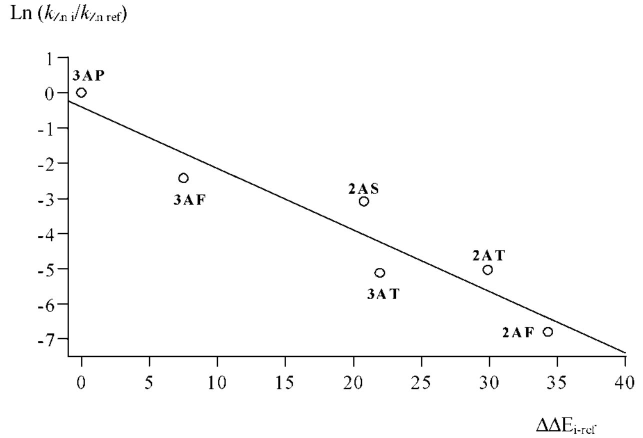


Figure 3. Linear correlation between rate constants for the Zn^{2+}-catalysed enolization reaction and thermodynamic stability of the substrate–metal ion complexes with reference to **3AP**

descriptor of the Lewis (but not Brønsted) basicity of the acetylheterocycles containing one ring heteroatom of Table 2 (with the exception of **3AP** toward Cu^{2+}).

A closer insight into the Zn^{2+} catalysis in the enolization reaction has been achieved from the linear correlation ($n = 6$, $r = 0.949$) obtained by plotting the relative reactivity, [$\ln(k_{Zn\ i}/k_{Zn\ ref})$], of the acetylheterocycles (containing one ring heteroatom) in Table 2 against the energy difference for the interaction of these substrates with the Zn^{2+} cation, calculated in the vacuum with reference to **3AP** (Fig. 3).

This approach in terms of $\Delta\Delta E$, unlike that in terms of charge density, can give an estimate of the combined contributions of charges and frontier orbitals to the interaction of the substrate with the metallic catalyst. The $\Delta\Delta E_{i-ref.}$ values were evaluated by neglecting the contribution due to solvation (responsible for the exoergonicity of the process), which should be similar for the different substrates and probably cancel out* in the calculation of $\Delta\Delta E_{i-ref.}$. It was also assumed that the $\Delta\Delta E$ values are proportional to the real $\Delta\Delta G^{\#}$ as the process under investigation occurs in a condensed phase ($PV = 0$, $\Delta U \approx \Delta H$) and it also seems reasonable to neglect both the perturbation induced by the coordinating metal ion on the vibrational motion ($\Delta\Delta E_{vibrational}$) and the entropy variation ($\Delta\Delta S$ about zero at room temperature).

2APH has been excluded from the correlations of Figs 1–3 because of the unique hydrogen-bonding properties of its N—H group with the solvent.

Let us now discuss the acetylheterocycles with two ring heteroatoms (Table 2). Calculations have been performed on **3AIO, 5AIO, 3(5)APz, 2ATZ** and **4ATZ**. Interestingly, the charge density on the carbonyl oxygen atoms of these substrates is lower (less negative values) than that calculated for the one ring heteroatom substrates in Table 2. Thus the present *ab initio* calculations support the previous[2c] interpretation that the exceptionally high metal ion catalysis for acetylheterocycles with two heteroatoms comes from the formation (where possible) of a chelate complex or transition state (the two pathways are kinetically indistinguishable) in which the Zn^{2+} ion coordinates both the carbonyl oxygen atom and the aza group. In particular, for **3(5)APz**, the tendency to form a chelate complex is so strong that the tautomeric equilibrium of Scheme 1 is completely shifted towards the 3-acetyl derivative, which, according to our calculations (see Table S1 available as supplementary material at www.wiley.com/epoc), *per se* is less stable than the 5-acetyl tautomer in the gas phase, and is only slightly more abundant at equilibrium in aqueous solution.

Our *ab initio* calculations also account for the absence of metal ion catalysis in the enolization reaction of **5AIO**. Indeed, the formation of the complex **5AIO**–Zn^{2+} would be characterized by the highest absolute value of $\Delta\Delta E_{i-ref}$ (calculated from data of Table S1 available as supplementary material at www.wiley.com/epoc) and the highest residual positive charge density on the zinc cation [Mulliken charges on Zn^{2+} in the substrate–Zn^{2+} complex are: **5AIO**, 1.224; **3AIO**, 1.131; **3(5)APz**, 1.112; **4ATZ**, 1.108; **2ATZ**, 1.111]. This is in agreement with a poor charge delocalization within the complex (due to the impossibility for the aza nitrogen atom to chelate the metal cation) as well as with the low energy value of the HOMO of **5AIO**.

Only a weak metal ion catalysis by Ni^{2+} was evidenced for the title substrates, as well as for some other acetylheterocycles (i.e. **2AT**,[2a] **3AT**,[2a] **2AS**,[2e] and **3AF**.[2e]) The lack of an exhaustive series of kinetic data did not allow a proper *ab initio* analysis of Ni^{2+} catalysis.

In general, the stabilities of the complexes between the acetylheterocycles with two ring heteroatoms in Table 2 and metal ions depend on the Lewis basicities of both the pyridine-like nitrogen and the oxygen carbonyl atoms. Consequently, the complex can be qualitatively analysed in terms of electrostatic interactions and of overlapping of frontier orbitals. The presence of a significant negative charge density on both the carbonyl oxygen and the aza nitrogen atoms is an essential factor in determining the existence of a chelate metal catalysis, whereas a high value of the HOMO energy suggests an effective overlapping of the frontier orbitals and a considerable reduction of the ion–substrate distance in the chelate complex. Thus **2ATZ**, which is the most sensitive substrate to Zn^{2+} catalysis among the acetylheterocycles with two ring heteroatoms, is characterized by the highest values of charge density on the aza nitrogen atom (Table

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*Additional calculations [suggested by one reviewer and performed using a more recent program (GAMESS)] that take into account differential solvation effects give a very similar linear plot, albeit with a worse correlation coefficient ($r = 0.88$).

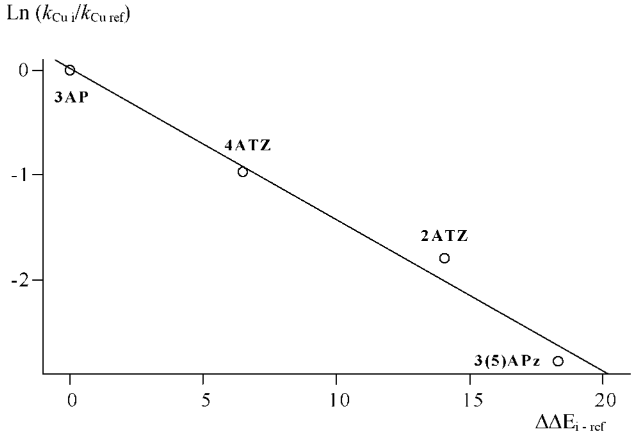


Figure 4. Linear correlation between rate constant for the Cu^{2+}-catalysed enolization reaction and thermodynamic stability of the substrate–metal ion complexes of **3AP, 2ATZ, 4ATZ** and **3(5)APz**, with reference to **3AP**

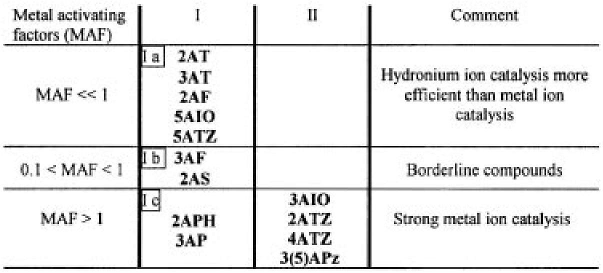
2). On the other hand, **4ATZ**, which is the most sensitive substrate to Cu^{2+} catalysis among the acetylheterocycles with two ring heteroatoms, has a high value for its HOMO energy (Table 2).

Finally, the good correlation coefficient ($r = 0.991$) of the linear plot of $\ln(k_{Cu\ i}/k_{Cu\ ref})$ against $\Delta\Delta E_{i-ref.}$ (Fig. 4) for **3AP, 2ATZ, 4ATZ** and **3(5)APz** (i.e. for the most sensitive substrates to Cu^{2+} catalysis) highlights the importance of the proposed approach in terms of $\Delta\Delta E$ to estimate the combined contributions of charges and frontier orbitals to the interaction of the acetylheterocycles with the Cu^{2+} cation.

CONCLUSIONS

The efficiency of metal ion catalysis in the enolization reaction of acetophenone and a number of acetylheterocycles was previously[2c,e] rationalized in terms of 'hard' and 'soft'[15] carbonyl groups. In this paper we have shown that *ab initio* calculations can improve the understanding of the influence of the factors affecting relative reactivity. The substrates investigated can consequently be divided in two groups: group I acetylheterocycles, which form transition states or intermediate complexes by interaction of the metal cation with the oxygen carbonyl atom, and group II acetylheterocycles, which form a chelate complex or transition state with the metal ion.

In turn, compounds of group I can be subdivided in three sub-groups: group Ia contains less reactive substrates (**2AT, 3AT, 2AF, 5AIO, 5ATZ**), characterized by 'hard' carbonyl groups, with MAF $\ll 1$; group Ib substrates (**2AS, 3AF**) characterized by 'borderline' carbonyl groups, for which $0.1 < \text{MAF} < 1$; group Ic contains more reactive substrates bearing a 'soft' carbonyl group (**2APH**,[2c] **3AP**), with $\text{MAF} > 1$. In particular, for **3AP** the high metal ion catalysis appears to be due to a dominant contribution from the overlapping of frontier orbitals.



Metal activating factors (MAF)	I	II	Comment
MAF << 1	I a 2AT 3AT 2AF 5AIO 5ATZ		Hydronium ion catalysis more efficient than metal ion catalysis
0.1 < MAF < 1	I b 3AF 2AS		Borderline compounds
MAF > 1	I c 2APH 3AP	3AIO 2ATZ 4ATZ 3(5)APz	Strong metal ion catalysis

Scheme 2. Classification of substrates with reference to metal ion caralysis

The substrates of group II, characterized by relatively high MAF values ($2 \leq \text{MAF} \leq 430$), display high charge densities on both the aza nitrogen and the oxygen carbonyl atom. The proposed classification is summarized in Scheme 2.

Finally, the ratio of the rate constants for Cu^{2+}- and Zn^{2+}-catalyses can be taken as an indication of the importance of the overlapping of frontier orbitals in the interaction of the substrate with the metal cation in the enolization reaction. High energies of the frontier orbital (e.g. those of **3AP, 3(5)APz** and **4ATZ**) are generally associated with a large (i.e. >30) ratio of the two experimental rate constants [k_{Cu}/k_{Zn} are 246, 35.9 and 195, for **3AP, 3(5)APz** and **4ATZ** respectively].

EXPERIMENTAL

Instruments

The kinetic experiments were carried out with a Jasco V-550 UV–Vis spectrophotometer equipped with a Hi-tech rapid kinetic accessory for the faster reactions or with a Varian Cary 1E spectrophotometer. A 93 Radiometer pH-meter was used for the pH measurements. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 300-MHz.

Materials

All inorganic salts [KCl, $NaClO_4$, KI, NaBr, $ZnCl_2$, $NiCl_2$, $Cu(NO_3)_2$] and halogens (I_2 and Br_2) were samples of AnalaR grade (Aldrich, Merck or Carlo Erba) and were used without further purification.

3-Acetyl-5-methylisoxazole (3AIO)

3AIO was prepared by essentially the same procedure described in Ref. 16. Acetonylacetone (Aldrich; 2 ml), HNO_3 ($d = 1.40\ \text{g dm}^{-3}$; 4 g) and water (6 ml) were heated to boiling. The reaction mixture was then allowed to cool at room temperature. After the addition of 6 ml of water the compound was extracted with diethyl ether, dried and distilled under reduced pressure (b.p. 68–69 °C at 20 mmHg; lit.[16] 65–70 °C at 20 mmHg). The identity of the product was confirmed from its ^{1}H NMR spectrum.

5-Acetyl-3-methylisoxazole (5AIO)

5AIO was prepared following the procedure described in Ref. 17 A solution of nitroethane (Aldrich; 7.2 g, 96 mmol) and triethylamine (Aldrich; 20 drops) in dry benzene was added dropwise to a solution of phenyl isocyanate (Aldrich; 20.7 g, 174 mmol) and 3-buten-2-one (Aldrich; 6.7 g, 95 mmol) in dry benzene (35 ml). After stirring for 1 h, the reaction mixture was refluxed for one additional hour and cooled. The solid was filtered off and the filtrate was concentrated to give a yellow oil which was distilled to afford 5-acetyl-3-methyl-4,5-dihydroisoxazole (**i**). Compound **i** (2.0 g, 15.7 mmol) in dry benzene (50 ml) and active γ-manganese dioxide (5.0 g) were refluxed for 3 h, while the water produced was removed by means of a Dean–Stark trap. The solid was filtered through Celite and washed with dry benzene. Evaporation of the filtrate gave 5-acetyl-3-methylisoxazole, which was then purified by sublimation at 40 °C/ 20 mmHg: m.p. 72–74 °C (lit. m.p. 73–74 °C).[17] The identity of the product was confirmed by its ^{1}H and ^{13}C NMR spectra.

3(5)-Acetylpyrazole [3(5)APz]

3(5)APz was prepared according to a literature procedure.[18] An ethereal solution of diazomethane was added dropwise to an ethereal solution of methylethynylketone at 0 °C. After 12 h, evaporation of the solution gave a pale yellow solid, which on crystallization from petroleum ether yielded needles of 3(5)-acetylpyrazole: m.p. 100 °C (lit. m.p. 100–101 °C).[19] The identity of the product was confirmed by its ^{1}H NMR spectrum.

p$K_{\mathrm{BH^+}}$ measurements

The thermodynamic acid dissociation constants of **3AIO** and **5AIO** were determined spectrophotometrically. Acid solutions of appropriate concentrations were made up by diluting concentrated perchloric acid (*ca* 11 mol dm^{-3}). The absorbances D of equivalent amounts of substrate in aqueous $\mathrm{HClO_4}$ of different molarities were measured at appropriate wavelengths, near $\lambda_{\max}$ of the free base B. The spectra were recorded against blank $\mathrm{HClO_4}$ solutions of the same molarity and the absorbance values D were taken immediately after the addition of the substrate. Ionization ratios I were calculated from Eqn. (8), where D_{B} is the absorbance of the unprotonated substrate, $D_{\mathrm{BH^+}}$ that of the conjugate acid and C are molar concentrations of the specified species.

$$I = C_{\mathrm{BH^+}}/C_{\mathrm{B}} = (D_{\mathrm{B}} - D)/(D - D_{\mathrm{BH^+}}) \qquad (8)$$

The data were analysed by both the Hammett[20a] and the Cox and Yates 'excess acidity'[20b] methods. With the former method, p$K_{\mathrm{BH^+}}$ was obtained by plotting log I against the acidity function $\mathrm{H_A}$[20a] according to:

$$\log I = \log(C_{\mathrm{BH^+}}/C_{\mathrm{B}}) = -m\mathrm{H_A} + \mathrm{p}K_{\mathrm{BH^+}} \qquad (9)$$

With the latter method, p$K_{\mathrm{BH^+}}$ was obtained as the intercept by plotting the left-hand side of Eqn. (10) against excess acidity values X[20b] of the $\mathrm{HClO_4}$ solutions:

$$\log I - \log C_{\mathrm{H^+}} = m^*X + \mathrm{p}K_{\mathrm{BH^+}} \qquad (10)$$

The average values obtained by the two methods were as follows:

p$K_{\mathrm{BH^+}}$ (**3AIO**) – 3.79(±0.11); (*m* 1.12, *m** 0.55)
p$K_{\mathrm{BH^+}}$ (**5AIO**) – 3.58(±0.34); (*m* 0.93, *m** 0.50)

A p$K_{\mathrm{BH^+}}$ of 0.09 for **3(5)APz** was interpolated from a Hammett correlation reported for a series of monosubstituted pyrazoles.[21]

Though the site of protonation of **3(5)APz** is the aza nitrogen,[21] it is not quite clear which is the site of protonation of **3AIO** and **5AIO**. However, the following pieces of evidence point to a carbonyl oxygen rather than nitrogen protonation: (1) the absorbance of the substrate increases upon protonation, and this is typical of α,β-unsaturated carbonyl compounds,[22a] whereas the absorbance of thiazoles, which are protonated on the aza nitrogen atom, decreases upon protonation;[22b] (2) the present acetylisoxazoles, like most α,β-unsaturated carbonyl compounds,[22a] follow the $\mathrm{H_A}$ acidity function (whereas thiazoles[22b] and pyridines[22c] follow the $\mathrm{H_0}$ acidity function); (3) by comparing the values of p$K_{\mathrm{BH^+}}$ of different heterocyclic compounds for which the aza nitrogen atom is the site of protonation, it transpires that the p$K_{\mathrm{BH^+}}$ of the acetyl-substituted derivative is much lower (from 2.5 to 4 logarithmic units) than that of the parent compound [e.g. p$K_{\mathrm{BH^+}}$ (2-acetylpyridine) 2.64[3] *versus* p$K_{\mathrm{BH^+}}$ (pyridine) 5.2;[8a] p$K_{\mathrm{BH^+}}$ (**4ATZ**) – 0.45[2c] *versus* p$K_{\mathrm{BH^+}}$ (thiazole) 2.5;[23] p$K_{\mathrm{BH^+}}$ (**2AI**) 3.12[2d] *versus* p$K_{\mathrm{BH^+}}$ (imidazole) 7.1;[23] p$K_{\mathrm{BH^+}}$ (**3(5)APz**) 0.09 *versus* p$K_{\mathrm{BH^+}}$ (pyrazole) 2.52[24]]. The p$K_{\mathrm{BH^+}}$ of 5-methyl-(-2.01)[25] and 3-methyl-isoxazole (-1.62)[25] are only 2.17 and 1.57 units higher than those of **3AIO** and **5AIO** respectively; nevertheless, both heterocycles behave as Hammet bases (i.e. follow the $\mathrm{H_0}$ acidity function); (4) the p$K_{\mathrm{BH^+}}$ values obtained of **3AIO** and **5AIO** fall within the 'sensible pattern'[7] of p$K_{\mathrm{BH^+}}$ values of ketones (i.e. from -3.1 for acetone to -4.7 for benzophenone) and the

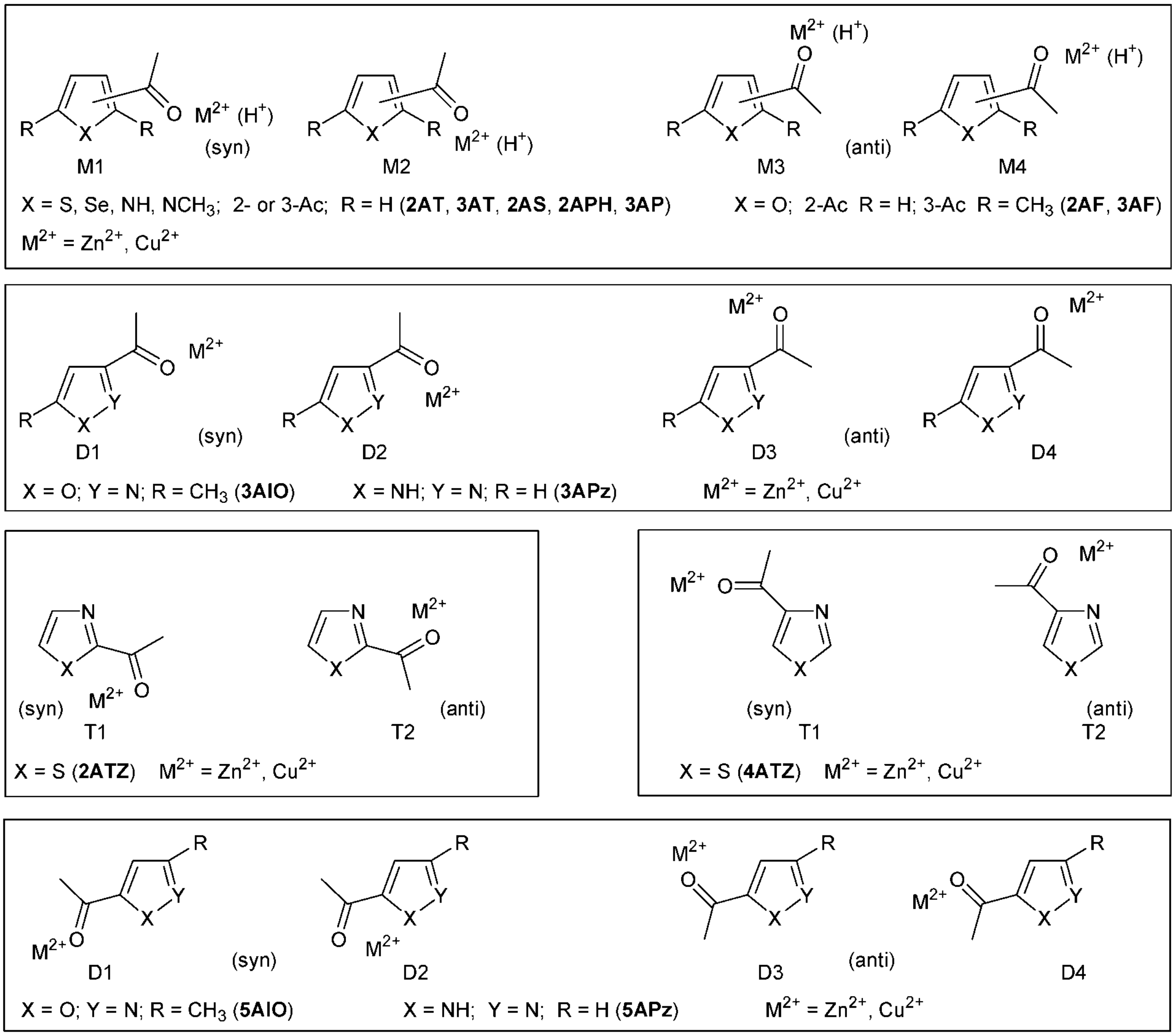


Figure 5. Structures and conformations (syn/anti) of some acetylheterocyles and their adducts with metal (M^{2+}) or proton (H^+) ions considered for DFT calculations

observed m^* values are only slightly higher than that found for acetophenone (i.e. 0.46).

As expected the pK_{BH^+} values of the two isoxazole isomers are quite similar, as the aza nitrogen is either in position ortho-like or para-like with respect to the carbonyl group.

Ab initio calculations

The DFT *ab initio* method (non-local density calculations using the BP86 functional), as implemented in the PC Spartan Pro v.1.0.3 package, was used throughout this work. Structures and energies of all acetylheterocycles and their adducts with the proton and metal ions were optimized at the SCF level with the pBP/DN** numerical polarization basis set (equivalent in size to the 6-31G** Gaussian basis set). Both syn and anti conformations (see Fig. 5) for all the acetylheterocycles were considered and the most stable one was selected.

Some molecular and atomic properties of the structures of minimal energy were evaluated (Mulliken atomic charge and HOMO OM energies). The lowest energy structure among the four possible structures of acetylheterocycle–Zn^{2+} adducts, as depicted in Fig. 5, was selected and used in the $\Delta\Delta E_{i-ref}$ calculations (see Discussion section). The structures of the acetylheterocycle–Cu^{2+} adducts have been obtained by replacing Cu^{2+} for Zn^{2+} ion in each lowest-energy complex previously selected and the geometries and energies of the adducts were re-optimized. All lowest-energy structures of acetylheterocycles and their proton or metal ion adducts were identified as minima points by calculating harmonic vibrational frequencies at the DFT pBP/DN** level. For the basicity comparison of the 3- and 2-acetylheterocycles (see Results and Discussion sections) the hydration energy has also been estimated for the protonated and the unprotonated forms, using the SM5.4 procedure of Cramer and co-workers.[10]

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