

Kinetics of the Enolisation Reactions of 3-Acetyl-2,5-dimethylfuran and of 2-Acetylselenophene

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Rate constants for the enolisation reactions of title compounds have been measured by their rates of halogenation at 25 °C in water, in several buffers, in dilute hydrochloric acid, in dilute sodium hydroxide, and in the presence of some metal ion salts. The results have been compared with those previously obtained from the corresponding reactions of acetophenone and a number of other acetyl heterocycles. Electronegativity of the heteroatoms and the "π-excessive" nature of the heterocyclic rings appear to be the main factors determining the relative

reactivities in the acid-catalysed reactions. Brønsted β values and isotope effects, k_H/k_D , point to a more symmetrical transition state for the investigated acetyl heterocycles than that for acetophenone in the general base-catalysed reaction. Metal-activating factors (MAF), i.e. the catalytic constant for metal-ion (Cu^{2+} , Zn^{2+} , and Ni^{2+}) catalysis, k_M , relative to that for proton catalysis, k_H , are discussed as an empirical measure of the "hard or soft" character of the carbonyl groups in acyl heterocycles.

The occurrence of metal-ion (e.g. Cu^{2+} , Zn^{2+} , Ni^{2+}) catalysis in the enolisation reaction of particular carbonyl compounds in aqueous solutions is firmly established^{[1][2][3]}. The Brønsted and/or Lewis^[4] basicity of a ketone is an important factor in determining the relative effectiveness of acid- and metal-ion catalysis. Thus, for example, the less basic β-diketones display metal-ion catalysis because the additional carbonyl group acts as a second coordination site, but acid catalysis is either very weak or not observed at all^{[1b][5]}. The opposite situation applies to acetophenone and a number of five-membered acetyl heterocycles^{[3a][3b]}. However, high metal-activating factors (MAF), i.e. the catalytic constant for metal-ion catalysis, k_M , relative to that for proton catalysis, k_H , have been found for acetylpyrroles^{[3b][3c]} as well as for 2- and 4-acetylthiazoles^[3c]. The formation of a chelate complex preceding the enolisation step was detected for 2-acetylpyridine^[2] and 2-acetylimidazole^[3d] and this complex enolises much faster than the uncomplexed substrate. Within this framework we have studied the enolisation reaction of the title compounds in water, in dilute hydrochloric acid, in dilute sodium hydroxide, in several buffer solutions, and in the presence of Zn^{2+} , Ni^{2+} , and Cu^{2+} solutions at $25.0 \pm 0.1^\circ\text{C}$. The obtained results allow a comparison of the relative importance of the different factors governing the acid–base and metal-ion catalysed enolisation reactions of the present and the previously studied^{[3a][3b][3c]} acetyl heterocycles. Primary kinetic isotope effects (k_H/k_D) and Brønsted β values provide additional

information on the effect of the heterocyclic moiety on the structure of the reaction transition states.

Results

The rates of enolisation of 2-acetylselenophene (**2AS**) and 3-acetyl-2,5-dimethylfuran (**3AF**) were measured in water, in dilute aqueous hydrochloric acid and sodium hydroxide, in different buffers (chloroacetate, acetate, mandelate, hydrogen phosphate, and borate) and in the presence of Zn^{2+} , Ni^{2+} , and Cu^{2+} salts at $25.0 \pm 0.1^\circ\text{C}$ by trapping the enol with halogen (iodine or bromine). All reactions are strictly zero order with respect to halogen concentration, with the rate-determining step being the formation of the enol or enolate ion. There was no evidence of reversibility of the iodination reaction under the adopted experimental conditions. The iodination reactions were monitored under pseudo-zero-order conditions^{[3a][3b][3c]} and the rate law had the form shown in Eq. (1), where S refers to the substrate 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 rate constants for the OH^- -catalysed enolisation reaction of the title substrates and some $[\text{D}_3]$ acetyl heterocycles (2- $[\text{D}_3]$ acetylthiophene, 3- $[\text{D}_3]$ acetylthiophene, 2- $[\text{D}_3]$ acetylselenophene, and $[\text{D}_3]$ acetophenone) were measured by their bromination reactions under pseudo-first-order conditions^[3a].

Enolisation of 2AS and 3AF in Dilute Hydrochloric Acid

Reaction rates were measured with concentration of the ketone in the range $5 \cdot 10^{-3}$ to $8 \cdot 10^{-3}$ mol dm $^{-3}$ and with HCl concentration in the range 0.25 – $60 \cdot 10^{-2}$ mol dm $^{-3}$ and $[I^-] = 2 \cdot 10^{-3}$ mol dm $^{-3}$. The observed rate law was given by Eq. (2) with k_e being of the form shown in Eq. (1).

$$k_e = k_o + k_H [H^+] \quad (2)$$

To obtain k_e values for **2AS** a gentle stream of nitrogen was bubbled in the cuvette in order to avoid oxidation of the substrate at the highest concentrations of acid. The following results were obtained:

$$\text{2AS } k_o = 16.6 (\pm 9.5) \cdot 10^{-9} \text{ s}^{-1}$$

$$k_H = 2.99 (\pm 0.08) \cdot 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

$$\text{3AF } k_o = 48.2 (\pm 9.4) \cdot 10^{-9} \text{ s}^{-1}$$

$$k_H = 14.8 (\pm 0.3) \cdot 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

As the above intercepts, k_o , obtained from k_e versus $[H^+]$ plots are subject to a large uncertainty, the "spontaneous" (water-catalysed) rate constants were preferably measured directly in water and are reported in Table 1 as k_{H_2O} .

Enolisation of 2AS and 3AF in Chloroacetate, Mandelate, and Acetate Buffers

Ketone concentrations were varied over the range 2 – $8 \cdot 10^{-3}$ mol dm $^{-3}$ and the observed rate constants, k_e [Eq. (1)], were of the form shown in Eq. (3), where B is the

basic component of the buffer and k represents the second-order rate constant of the general acid–base-catalysed reaction. The results are collected in Tables 2–4.

$$k_e = k_o + k[B] \quad (3)$$

Several sets of k_e values were measured for the two ketones at different buffer ratios, $r = [B]/[A]$ (where A is the acidic component of the buffer), each set at five or more different concentrations of base in a range of ca. a factor of ten. The values of k determined in chloroacetate buffer for **2AS** and **3AF** and in mandelate and acetate buffers for **3AF** showed evidence of general acid catalysis by the acidic component of the buffer as they were dependent of r . The separate contributions of buffer base, k_B , and buffer acid, k_A , to k_e (Eq. 4) were obtained by plotting the values of k , measured at the different r values, against $1/r$ and evaluating k_B as the intercept and k_A as the slope, according to Eq. (5).

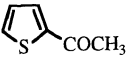
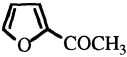
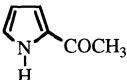
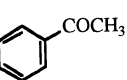
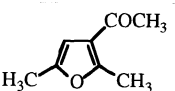
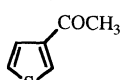
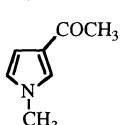
$$k_e = k_o + k_B[B] + k_A[A] \quad (4)$$

$$k = k_B + k_A/r \quad (5)$$

Enolisation of 2AS and 3AF in Hydrogen Phosphate and Borate Buffers

Ketone concentrations were varied over the range 2 – $8 \cdot 10^{-3}$ mol dm $^{-3}$ and the observed rate constants, k_e [Eq. (1)], were of the form shown in Eq. (3) where k is

Table 1. Catalytic constants ($k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) for the enolisation reaction of acetophenone and some 2- and 3-acetyl heterocycles at 25°C and ionic strength 0.3 mol dm $^{-3}$

Substrate	Ref.	$k_{H_2O} / 10^{-9}[a]$	$k_H / 10^{-6}$	$k_{AcO} / 10^{-7}$	k_{OH}
 2AS	this work	36.0 (± 0.84)	2.99 (± 0.08)	6.41 (± 0.10)	0.200 (± 0.007)[b]
 2AT	[c]	2.00 (± 0.16)	3.95 (± 0.10)	5.81 (± 0.44)	0.275 (± 0.015)
 2AF	[d]	6.72 (± 0.42)	3.35 (± 0.10)	10.7 (± 0.9)	0.408 (± 0.008)
 2APH	[e]	27.7 (± 1.6)	3.43 (± 0.05)	3.91 (± 0.42)	–
 A	[c]	4.11 (± 0.20)	10.0	8.4 (± 0.3)	0.237 (± 0.004)
 3AF	this work	33.3 (± 0.31)	14.8 (± 0.3)	4.38 (± 0.08)	0.022 (± 0.001)
 3AT	[c]	2.22 (± 0.30)	11.8 (± 0.2)	6.58 (± 0.45)	0.246 (± 0.012)
 3AP	[d]	154 (± 6)	10.6 (± 0.5)	250 (± 19)	0.159 (± 0.006)

[a] Values measured directly in water. Units are s $^{-1}$. – [b] Ionic strength 0.5 mol dm $^{-3}$ at $[NaOH] = 0.4$ and 0.49 mol dm $^{-3}$. – [c] See ref. [3a]. – [d] See ref. [3b]. – [e] See ref. [3c].

Table 2. Slopes k and intercepts k_0 from the plot of the experimental pseudo-first-order rate constants (k_0/s^{-1}) of enolisation of **3AF** against concentration of buffer base in aqueous solution at 25°C and ionic strength 0.3 mol dm⁻³, buffer ratios and range of buffer concentration

Buffer base	r	pH	$k_0/10^{-8} s^{-1}$	$k/10^{-6} dm^3 mol^{-1} s^{-1}$	[B]/mol dm ⁻³
ClCH ₂ COO ^{-[a]}	0.6	2.51	7.54 (±1.14)	2.52 (±0.10)	0.012–0.203
	2	3.03	3.68 (±0.31)	0.80 (±0.03)	0.021–0.199
	3	3.20	4.25 (±0.25)	0.55 (±0.02)	0.026–0.251
	5	3.42	4.49 (±0.28)	0.32 (±0.02)	0.025–0.250
C ₆ H ₅ CH(OH)COO ^{-[a]}	0.5	2.91	3.59 (±0.70)	3.04 (±0.08)	0.020–0.150
	1	3.21	1.85 (±0.21)	1.74 (±0.02)	0.020–0.198
	3	3.68	2.71 (±0.02)	0.54 (±0.01)	0.015–0.100
	5	3.90	5.35 (±0.79)	0.44 (±0.06)	0.025–0.250
CH ₃ COO ⁻	0.25	4.01	5.28 (±0.17)	0.76 (±0.03)	0.008–0.100
	0.5	4.30	7.44 (±0.54)	0.62 (±0.06)	0.010–0.150
	1	4.61	3.33 (±0.18)	0.52 (±0.02)	0.020–0.198
	3	5.08	5.18 (±0.13)	0.47 (±0.01)	0.025–0.250
HPO ₄ ²⁻	5	5.30	4.44 (±0.31)	0.44 (±0.02)	0.025–0.250
	1	7.05	13.2 (±0.6)	21.5 (±0.46)	0.003–0.025

[a] Corrected for the dissociation of the buffer acid.

Table 3 Slopes k and intercepts k_0 from the plot of the experimental pseudo-first-order rate constants (k_0/s^{-1}) of enolisation of **2AS** against concentration of buffer base in aqueous solution at 25°C and ionic strength 0.3 mol dm⁻³, buffer ratios and range of buffer concentration

Buffer base	r	pH	$k_0/10^{-9} s^{-1}$	$k/10^{-7} dm^3 mol^{-1} s^{-1}$	[B]/mol dm ⁻³
ClCH ₂ COO ^{-[a]}	0.172	1.96	29.8 (±4.4)	19.8 (±0.5)	0.018–0.135
	0.5	2.42	23.4 (±4.7)	8.14 (±0.30)	0.028–0.254
	1	2.73	21.1 (±1.9)	4.48 (±0.13)	0.027–0.252
	3	3.20	12.0 (±2.5)	2.01 (±0.14)	0.031–0.296
	5	3.42	11.5 (±0.7)	1.58 (±0.05)	0.015–0.250
C ₆ H ₅ CH(OH)COO ^{-[a]}	0.333	2.73	13.5 (±1.2)	10.4 (±0.2)	0.013–0.126
	1	3.21	13.3 (±0.8)	4.07 (±0.06)	0.020–0.200
	3	3.68	9.26 (±0.93)	2.19 (±0.09)	0.015–0.180
	5	3.90	9.22 (±1.20)	1.67 (±0.08)	0.025–0.250
CH ₃ COO ⁻	0.5	4.30	7.58 (±1.15)	7.22 (±0.15)	0.013–0.125
	1	4.61	2.28 (±3.89)	6.64 (±0.32)	0.020–0.198
	3	5.08	21.3 (±4.6)	6.61 (±0.27)	0.030–0.300
	5	5.30	7.11 (±1.37)	6.50 (±0.09)	0.025–0.250
HPO ₄ ²⁻	1	7.05	41.2 (±4.0)	302 (±5)	0.001–0.015
H ₂ BO ₃ ⁻	1	9.08	6690 (±910)	1010 (±110)	0.013–0.150

[a] Corrected for the dissociation of the buffer acid.

Table 4. Rate constants (dm³ mol⁻¹ s⁻¹) for general base or acid catalysis, k_B or k_A , of enolisation of **2AS** and **3AF**, calculated from data reported in Tables 2 and 3

Buffer base	3AF		2AS	
	$k_B/10^{-7}$	$k_A/10^{-7}$	$k_B/10^{-7}$	$k_A/10^{-7}$
ClCH ₂ COO ^{-[a]}	0.254 (±0.111)	15.0 (±0.14)	1.15 (±0.22)	3.23 (±0.08)
C ₆ H ₅ CH(OH)COO ^{-[a]}	1.34 (±0.95)	14.8 (±0.8)	1.06 (±0.07)	3.11 (±0.04)
CH ₃ COO ⁻	4.38 (±0.08)	0.81 (±0.04)	6.41 (±0.10)	0.37 (±0.09)
HPO ₄ ²⁻	21.5 (±0.5)		302 (±5)	
H ₂ BO ₃ ⁻			1010 (±110)	

[a] Corrected for the dissociation of the buffer acid.

coincident with k_B as the two buffer acids are too weak to allow a general acid catalysis contribution to be detected. The values of k_e were measured at one buffer ratio, $r = 1$, and at five different concentrations of base in a range of ca. a factor of ten (See Tables 2 and 3). The k_B values for carboxylate, hydrogen phosphate and borate buffers fitted well a Brønsted plot with slopes $\beta = 0.52 (\pm 0.03)$ ($n = 6$, correlation coefficient = 0.995) and $\beta = 0.55 (\pm 0.02)$ ($n =$

5, correlation coefficient = 0.998), for **2AS** and **3AF** respectively.

Enolisation of **2AS**, **3AF** and the [D₃]Acetyl Heterocycles 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-order

conditions^{[3a][3b][3c]} as rates of bromination and the rate law was given by Eq. (6) where S refers to the substrate (2AS, 3AF, 2-[D₃]acetylthiophene, 3-[D₃]acetylthiophene, 2-[D₃]acetylselenophene, and [D₃]acetophenone).

$$-d[\text{OBr}^-]/dt = k_e[\text{S}] \quad (6)$$

The second-order rate constants, k_{OH} , obtained from Eq. (7) are reported in Table 1.

$$k_e = k_o + k_{\text{OH}}[\text{OH}^-] \quad (7)$$

Experimental k_e values were obtained in a range of hydroxide concentration $5\text{--}25 \cdot 10^{-2} \text{ mol dm}^{-3}$ for 2AS, 2-[D₃]acetylthiophene and 3-[D₃]acetylthiophene, $2.5\text{--}25 \cdot 10^{-2} \text{ mol dm}^{-3}$ for 3AF, $2.5\text{--}49 \cdot 10^{-2} \text{ mol dm}^{-3}$ for 2-[D₃]acetylselenophene and $5\text{--}20 \cdot 10^{-2} \text{ mol dm}^{-3}$ for [D₃]acetophenone. In the case of 2-[D₃]acetylselenophene the ionic strength at [NaOH] = 0.40 and 0.49 was 0.50 mol dm^{-3} . Experimental k_e values agree with k_e values calculated from Eq. (7) to within 5%.

Metal Ion Catalysed Enolisation of 2AS and 3AF

The effect of Zn^{2+} , Ni^{2+} , and Cu^{2+} on the rates of enolisation of the two ketones was studied in unbuffered solutions (pH in the range 4–6). Substrate concentrations were ca. $10^{-2} \text{ mol dm}^{-3}$ and the concentrations of I_2 and I^- were the same^{[3a][3b][3c]} as those for reactions carried out in the absence of metal ions. Ionic strength was 0.3 mol dm^{-3} for all reactions (KCl). Rates were measured at several metal ion concentrations in the range $2.5\text{--}75 \cdot 10^{-3} \text{ mol dm}^{-3}$. In the case of Cu^{2+} the concentration range $0.25\text{--}7.5 \cdot 10^{-3} \text{ mol dm}^{-3}$ was chosen instead, in order to avoid precipitation of CuI_2 . Values of k_e showed a linear increase with increasing metal ion concentration according to Eq. (8), where $[\text{M}^{2+}]$ represents the molar concentration of Zn^{2+} , Ni^{2+} , or Cu^{2+} .

$$k_e = k_o + k_{\text{M}}[\text{M}^{2+}] \quad (8)$$

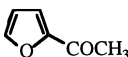
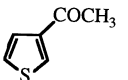
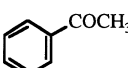
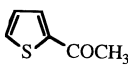
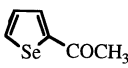
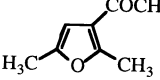
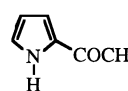
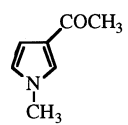
There was no evidence of saturation even at the highest used metal ion concentration, at variance with the behaviour previously observed with more basic substrates^{[2][3d]}. The results are collected in Table 5.

Discussion

Kinetic results for the “spontaneous” and acid–base-catalysed enolisation reactions of some 2- and 3-acetyl-substituted five-membered heterocycles and acetophenone are summarized in Table 1 (where acetate ion is taken as a typical general base useful for comparison).

It can be seen that in the H_3O^+ -catalysed reaction (k_{H}) 2-acetyl heterocycles are less reactive than acetophenone and this can probably be simply accounted for in terms of the electronegativity of the heteroatoms, as the accepted enolisation mechanism^[6] involves, in its first step, a fast protonation of the carbonyl oxygen atom with subsequent rate-determining C–H ionisation being assisted by water or the conjugate base of the acid catalyst. In fact positive σ values are reported for the 2-furyl ($\sigma = 1.10^{[7]}$), 2-thienyl ($\sigma = 0.66^{[7]}$), and 2-selenyl ($\sigma = 0.60^{[7]}$) groups. A reliable σ value for the 2-pyrrolyl group cannot be taken, as the re-

Table 5. Metal-ion catalysed enolisation of some acetyl heterocycles and acetophenone

Substrate		$k_{\text{M}}/10^{-8} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	Ref.
	Zn^{2+}	3.56 (± 0.28)	[a]
	Ni^{2+}	26.6 (± 1.3)	[a]
	Cu^{2+}	14.1 (± 1.0)	[b]
	Zn^{2+}	19.0 (± 2.5)	[b]
	Cu^{2+}	28.4 (± 3.8)	[b]
	Zn^{2+}	31.8 (± 3.4)	[b]
	Cu^{2+}	23.5 (± 1.0)	[b]
	Zn^{2+}	20.9 (± 1.7)	[b]
	Cu^{2+}	94.6 (± 9.9)	this work
	Zn^{2+}	147 (± 4)	
	Cu^{2+}	792 (± 46)	this work
	Zn^{2+}	281 (± 16)	
	Ni^{2+}	50.6 (± 3.9)	
	Cu^{2+}	6790 (± 320)	[c]
	Zn^{2+}	441 (± 41)	[c]
	Ni^{2+}	1060 (± 40)	[c]
	Cu^{2+}	788000 (± 64000)	[a]
	Zn^{2+}	3200 (± 100)	[a]
	Ni^{2+}	31800 (± 1000)	[a]

[a] See ref.^[3b]. — [b] See ref.^[3a]. — [c] See ref.^[3c].

ported values vary from -0.51 to $+0.20$ over the substituent range examined, probably due to the different possibility of H-bonding interaction in the neutral or the anionic form of substituted pyrrole-2-carboxylic acids^[7].

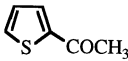
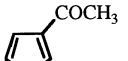
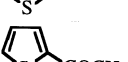
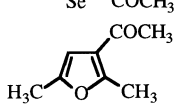
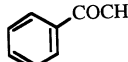
For 3-acetylheterocycles this electronegativity effect on k_{H} is apparently more than offset by the fact that five-membered acetyl heterocycles possess π -excessive rings; thus, they are more reactive than acetophenone in the H_3O^+ -catalysed reaction. As an average k_{H} values for 3-acetyl heterocycles are about a factor of four higher than those for the corresponding 2-acetyl heterocycles.

On the other hand the results for the “spontaneous” and the base-catalysed reactions can hardly be explained simply in terms of either effect, as previously pointed out^[3c].

Brønsted β values and isotope effects for the OH^- -catalysed reaction of 2- and 3-acetylthiophene, 2-acetylselenophene, 3-acetyl-2,5-dimethylfuran, and acetophenone are reported in Table 6. In spite of the similar reactivity of acetophenone and acetyl heterocycles (Table 1 and 4) it appears that the structures of the corresponding transition states in base-catalysed reactions are quite different. Both β values and isotope effects point to a considerably more symmetrical^[6] transition state for the investigated acetyl heterocycles than that for acetophenone. The different ρ values^[8] for the OH^- -catalysed reaction of 4- and 5-substituted 2-acetylthiophenes ($\rho = 1.61$) and of *m*- and *p*-substi-

tuted acetophenones ($\rho = 1.03$), was attributed to a superior capability of the former to transmit the substituent effects.

Table 6. Brønsted β coefficients and deuterium isotope effects in the base-catalysed reaction of some acetyl heterocycles and acetophenone

	β	k_H/k_D
	0.55	4.52
	0.51	5.10
	0.52	5.03
	0.55	-
	0.71[a]	3.70

[a] M. Aurelly, G. Lamaty, *Bull. Soc. Chim. Fr.* **1980**, 385–388.

The efficiency of metal-ion catalysis in the enolisation reaction can probably be rationalised in terms of “hard and soft”^[9] carbonyl groups. Hardness and softness are not as precisely defined as the strenghts of acids and bases and there is no convenient measurement in common use analogous to pK_a . However, the development of frontier orbital theory has allowed hardness and softness to be described more satisfactorily. Soft bases have high-energy HOMOs and soft acids have low-energy LUMOs and this explains why soft acids and soft bases have an affinity with each other. On the other hand what is important in the interaction of a hard base with a hard acid is the electrostatic attraction between the two species. MAF values can be taken as an empirical probe of hard-soft interactions in the reaction under examination. The investigated ketones can therefore be distinguished^[3d] depending upon their experimental MAFs. Accordingly, the carbonyl groups of ketones with MAF values < 1 can be defined “hard” while those with MAF values ≥ 1 can be defined “soft” with respect to some specified “borderline” (Cu^{2+} , Ni^{2+} , Zn^{2+})^[10] Lewis acids.

As far as the presently investigated acetyl heterocycles, **2AS** and **3AF**, are concerned it is interesting to note that they both display substantial catalysis by the above-mentioned metal ions. An examination of k_M values (Table 5) shows that, for example, the enolisation of **3AF** is much more effectively promoted by Cu^{2+} and Zn^{2+} than that of the structurally related **2AF**^[3b].

k_{Cu} (**2AF**) no catalysis observed k_{Cu} (**3AF**) = $7.92 \cdot 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$

k_{Zn} (**2AF**) = $3.56 \cdot 10^{-8}$ k_{Zn} (**3AF**) = $2.81 \cdot 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$

Metal-ion catalysis is somewhat more effective on **2AS** than on its sulfur analogue **2AT**.

k_{Cu} (**2AT**) = $2.35 \cdot 10^{-7}$ k_{Cu} (**2AS**) = $9.46 \cdot 10^{-7} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$

k_{Zn} (**2AT**) = $2.09 \cdot 10^{-7}$ k_{Zn} (**2AS**) = $14.7 \cdot 10^{-7} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$

However, MAF values are probably a better indication than k_M of the “hard and soft” character of the carbonyl groups of the substrates under discussion and the related effectiveness of metal-ion catalysis, as mentioned in the Introduction. From the present and the previously obtained results acetophenone and the so far investigated acetyl heterocycles can be ranked in the group shown in Scheme 1, according to their MAF values (See Table 7).

Scheme 1



Table 7. MAF values for some acetyl heterocycles and acetophenone

	2AF	3AT	A	2AT	2AS	3AF	2APH	3AP
Cu^{2+}	0.0	0.012	0.028	0.059	0.32	0.54	20	740
Zn^{2+}	0.011	0.016	0.032	0.053	0.49	0.19	1.3	3.0
Ref.	[a]	[b]	[b]	[b]	this work	this work	[c]	[a]

[a] See ref.^[3b], — [b] See ref.^[3a], — [c] See ref.^[3c].

It can be concluded that the acetyl groups of **2AS** and **3AF** behave quite similarly towards metal-ion catalysis, due to a similar “borderline” character of their carbonyl groups.

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Experimental Section

General: UV/Vis: Varian Cary 1E, Kontron Uvikon 860 spectrophotometer equipped with a Hi-tech rapid kinetic accessory for the faster reactions. — NMR: Varian Gemini 300 MHz. TMS was used as internal standard, CD_3CN and CDCl_3 as solvents.

Materials: All inorganic salts [KCl , NaClO_4 , KI , NaBr , ZnCl_2 , CdCl_2 , NiCl_2 , $\text{Cu}(\text{NO}_3)_2$] 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-2,5-dimethylfuran (3AF): This was a commercial sample (Aldrich), purified by distillation under reduced pressure.

2-Acetylselenophene (2AS): This compound was prepared by essentially the same procedure described in ref.^[11a] for the synthesis of 2-acetylthiophene. The procedure was slightly modified in order to use a smaller quantity of the expensive selenophene (Aldrich). Selenophene (5 g, 0.038 mol) and acetic anhydride (4.36 g, 0.043 mol) were stirred together and heated to 50°C . Orthophosphoric acid (0.18 g, 0.0018 mol) was added in one portion and the mixture warmed at 80 – 90°C for 2 h. The mixture was then cooled to room temperature and washed three times with water and then with aqueous Na_2CO_3 (10%, w/w). Diethyl ether (few milliliters) was added to the water-insoluble organic material. The ethereal layer was dried with sodium sulphate and the recovered oil distilled under reduced pressure. — ^1H NMR (CD_3CN): δ = 8.52 (1 H, dd, $J_{3,5} = 1.07 \text{ Hz}$, $J_{4,5} = 5.47 \text{ Hz}$, 5-H), 8.05 (1 H, dd, $J_{3,5} = 1.07$, $J_{3,4} = 4.00$, 3-H), 7.49 (1 H, dd, $J_{3,4} = 3.93$, $J_{4,5} = 5.47$, 4-H), 2.59

(3 H, s, CH₃). – ¹H NMR (CDCl₃): δ = 8.38 (1 H, dd, *J*_{3,5} 1.06, *J*_{4,5} 5.60, 5-H), 7.91 (1 H, dd, *J*_{3,5} 1.06, *J*_{3,4} 3.97, 3-H), 7.40 (1 H, dd, *J*_{3,4} 4.03, *J*_{4,5} 5.49, 4-H), 2.59 (3 H, s, CH₃). – ¹³C NMR (CD₃CN): δ = 191.89 (C=O), 151.28 (C-2), 140.08 (C-5), 135.58 (C-3), 131.07 (C-4), 25.33 (CH₃). – The identity of the product was confirmed by the fact that the recorded ¹H- and ¹³C-NMR spectra are essentially coincident with those reported^[11b] in [D₆]-acetone.

Deuteration Procedure: 2-Acetylselenophene (**2AS**) (1 g, 0.0058 mol), 2-acetylthiophene (**2AT**) (2 g, 0.0159 mol), 3-acetylthiophene (**3AT**) (2 g, 0.0159 mol), and acetophenone (**A**) (2 g, 0.0167 mol) were separately dissolved in a small volume (ca. 2 ml) of dioxane, a pellet of NaOH was added to each ketone followed by deuterium oxide (5 ml), and each mixture was kept in a sealed tube for up to 24 h at room temperature. Extraction with diethyl ether gave the deuterated products that were purified by distillation under reduced pressure. ¹H-NMR spectra of the deuterated compounds were recorded and the acetyl group turned out to be more than 98% deuterated in all cases.

Kinetic Measurements: The enolisation reactions were monitored by measuring spectrophotometrically the rate of halogenation of the substrates as previously described^{[3a][3b][3c]}. 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) unless otherwise stated.

- [1] [1a] K. J. Pedersen, *Acta Chem. Scand.* **1948**, 2, 252–263. – [1b] K. J. Pedersen, *Acta Chem. Scand.* **1948**, 2, 385–399.
 [2] B. G. Cox, *J. Am. Chem. Soc.* **1974**, 96, 6823–6828.
 [3] [3a] P. De Maria, A. Fontana, D. Spinelli, *J. Chem. Soc., Perkin Trans. 2* **1991**, 1067–1070. – [3b] P. De Maria, A. Fontana, S. Frascari, F. Ferroni, D. Spinelli, *J. Chem. Soc., Perkin Trans. 2* **1992**, 825–828. – [3c] P. De Maria, A. Fontana, M. Arlotta, S. Chimichi, D. Spinelli, *J. Chem. Soc., Perkin Trans. 2* **1994**, 415–419. – [3d] P. De Maria, A. Fontana, D. Spinelli, G. Macaluso, *Gazz. Chim. Ital.* **1996**, 126, 1996, 45–51.
 [4] S. Shambayati, S. L. Schreiber, in *Comprehensive Organic Synthesis* (Eds.: B. Trost, J. Fleming), Pergamon Press, Cambridge, **1991**, part 1, vol. 1, pp. 283–324.
 [5] M. J. Hynes, C. A. Blanco, M. T. Mooney, *J. Chem. Soc., Perkin Trans. 2* **1991**, 2055–2059 and refs. cited herein.
 [6] R. P. Bell, *The Proton in Chemistry*, 2nd ed., Chapman and Hall, London, **1973**.
 [7] P. Tomasik, C. D. Johnson, *Adv. Heterocycl. Chem.* **1976**, 20, 1–64 and refs. cited herein.
 [8] J. R. Jones, G. Pearson, D. Spinelli, G. Consiglio, C. Arnone, *J. Chem. Soc., Perkin Trans. 2* **1985**, 557–558.
 [9] G. Pearson, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, **1977**.
 [10] A. Jacobs, *Understanding Organic Reaction Mechanisms*, Cambridge University Press, Cambridge, **1997**, chapter 2, p. 39.
 [11] [11a] H. D. Hartough, A. I. Kosak, *J. Amer. Chem. Soc.* **1947**, 69, 3093–3096. – [11b] F. Fringuelli, S. Gronowitz, A.-B. Hornfeldt, I. Johnson, A. Taticchi, *Acta Chem. Scand., Ser. B* **1974**, 28, 175–184.

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