METAL ION CHELATES OF LIPOPHILIC ALKYL DIAZINYL KETOXIMES AS HYDROLYTIC CATALYSTS

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Dedicated to Professor Milan Kratochvíl on the occasion of his 75th birthday.

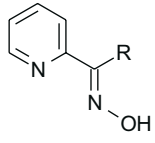
A series of lipophilic dodecyl hetaryl ketoximes (hetaryl = pyridin-2-yl, pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl as well as their methyl hetaryl homologues was synthesized and hydrolytic activity of their chelates with Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} in a micellar matrix of hexadecyltrimethylammonium bromide or in homogeneous aqueous solutions was investigated using 4-nitrophenyl acetate, 4-nitrophenyl hexanoate and 4-nitrophenyl diphenyl phosphate as model substrates. While Co^{2+} and Cu^{2+} chelates are almost inactive, those of Ni^{2+} and Zn^{2+} exhibit considerable activity. None of the studied chelates promotes hydrolysis of the used phosphate. The effective species are chelates of the metal : ligand stoichiometry 1 : 3 and 1 : 1 with Ni^{2+} and Zn^{2+}, respectively, when the ester cleavage proceeds in the micellar matrix. The 1 : 2 stoichiometry was found in aqueous solutions of Ni^{2+} and Zn^{2+} chelates of methyl ketoximes.

Key words: Ester cleavage; Micellar catalysis; Metallomicelles; Coordination chemistry; Diazines; Oximes; Pyridines; Chelates; Nickel; Zinc; Hydrolysis; Phosphates.

Transition metal ions play an important role in many types of enzymes[1a,1b]. Coordination to metal ions (most frequently Zn^{2+}) acidifies ionizable functions (*e.g.* covalently bound hydroxy group or coordinated water) in hydrolytic enzymes such as carboxypeptidase A[1a,1c], alkaline phosphatase[1a,1d] and carbonic anhydrase[1a] thus providing nucleophiles readily attacking electrophilic centres in substrates. A great number of simple models of hydrolytic metalloenzymes have been designed and studied over the years[2a–2d], many of them possessing hydrophobic moieties in their mole-

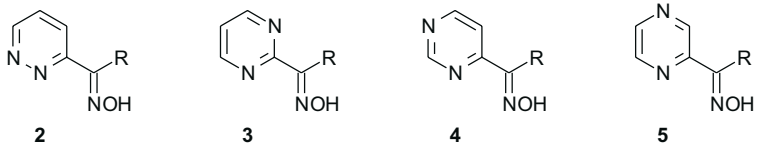
cules and utilizing the kinetic benefit of micellar catalysis[2e–2j]. Two main goals of these studies have been claimed: (i) better understanding the mechanism of the hydrolytic reactions catalyzed by metalloenzymes, (ii) practical applications as efficient destroying of organophosphorus pesticides and chemical warfare agents.

In our previous communications[3a,3b] we reported metallomicellar catalysts based on Ni^{2+} complexes of alkyl pyridin-2-yl ketoximes (**1c** and **1d**). Hydroxyimino groups of these oximes are acidified by coordination to the metal ion. Therefore high concentrations of ionized ligands (nucleophiles readily attacking the ester function) are present in aqueous solutions even in neutral conditions. Complexes of these ketoximes in comicelles with cationic surfactant hexadecyltrimethylammonium bromide (CTAB) exhibited considerable hydrolytic efficiency, surprisingly even at pH ranging from 4 up to 9.



	R
1a	CH_3
1b	$CH_3(CH_2)_{11}$
1c	$CH_3(CH_2)_7$
1d	$CH_3(CH_2)_{12}$

The obtained results stimulated the extension of our study. We speculated about the possibility of "tuning" the hydrolytic efficiency of the metallocatalyst by structural changes in the chelating subunit of the ligand and by employing different transition metal ions. For this reason, we decided to synthesize ligands **2**–**5**, aza analogues of the ligand **1**. We expected that the presence of another nitrogen in different positions of the



2 **3** **4** **5**

In the formulae **2-5**:
a, R = CH_3
b, R = $CH_3(CH_2)_{11}$

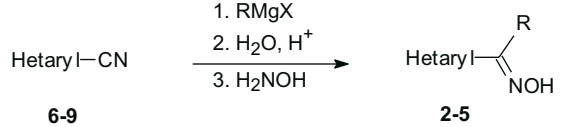
heteroaromatic ring should gently modify the coordination ability of the ligands and, consequently, also hydrolytic efficiency of their complexes with transition metal ions. In addition to lipophilic dodecyl diazinyl

ketoximes **2b**–**5b**, methyl diazinyl ketoximes **2a**–**5a** were included in this study. We expected the hydrolytic activity of metal ion complexes of the C_1 homologues should reflect the "intrinsic" reactivity of the metallocatalysts, excluding the contribution of the micellar catalysis. Since the length of the hydrophobic alkyl chain of the ligands **2a**–**5a** was not identical with that of the ligands **1** employed in our previous study[3a,3b] we also prepared dodecyl pyridin-2-yl ketoxime **1b** in order to be able to compare the reactivity of all metallomicellar catalysts based on ligands **1**–**5**.

RESULTS AND DISCUSSION

*Syntheses of the Ligands **1**–**5***

Ligands **2**–**5** were prepared by addition of a Grignard reagent to corresponding nitriles **6**–**10** followed by the reaction of the resulting ketones **11**–**16** with hydroxylamine (Scheme 1). In this way, lipophilic dodecyl pyridin-2-yl (**1b**), dodecyl pyridazin-3-yl (**2b**), dodecyl pyrimidin-2-yl (**3b**), dodecyl pyrimidin-4-yl (**4b**) and dodecyl pyrazin-2-yl (**5b**) ketoximes as well as methyl pyridazin-3-yl (**2a**), methyl pyrimidin-2-yl (**3a**), methyl pyrimidin-4-yl (**4a**) and methyl pyrazin-2-yl (**5a**) ketoximes were prepared.



6-9 **2-5**

	Hetaryl
6	pyridazin-3-yl
7	pyrimidin-2-yl
8	pyrimidin-4-yl
9	pyrazin-2-yl

	Hetaryl	R
2a	pyridazin-3-yl	CH_3
2b	pyridazin-3-yl	$CH_3(CH_2)_{11}$
3a	pyrimidin-2-yl	CH_3
3b	pyrimidin-2-yl	$CH_3(CH_2)_{11}$
4a	pyrimidin-4-yl	CH_3
4b	pyrimidin-4-yl	$CH_3(CH_2)_{11}$
5a	pyrazin-2-yl	CH_3
5b	pyrazin-2-yl	$CH_3(CH_2)_{11}$

SCHEME 1

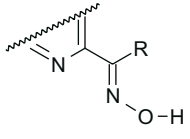
Only one set of resonances was observed in each of the ^1H and ^{13}C NMR spectra of the synthesized ligands **1**–**5** and therefore all these ketoximes were assumed to be single stereoisomers. We determined their configurations by means of IR spectroscopy. Dilution of tetrachloromethane solutions of ketoximes **1**, **2**, **4** and **5** decreased the intensity of the bridged O–H

bands (maximum at *ca* 3 250 cm^{-1}) while the intensity of the free O–H bands (*ca* 3 580 cm^{-1}) increased. This behaviour indicated the presence of intermolecular hydrogen bonds which could be expected rather in *E* than in *Z* isomers as shown in Fig. 1. On the other hand, dilution of tetrachloromethane solutions of alkyl pyrimidin-2-yl ketoximes **3a**, **3b** did not change the intensity of the bridged O–H bands (compared with other bands present in the spectrum) thus revealing the *Z* configuration. So far, we have had no idea of factors controlling the configuration of the arising ketoximes.

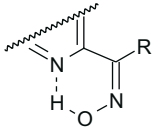
Preparation of Metallomicellar Catalysts

In several cases, solubilization of lipophilic ligands in water after addition of a proper transition metal ion has been reported[2e–2h]. Light scattering methods revealed the presence of colloidal particles (micelles and related aggregates) in the resulting solutions. The aggregation has been explained by formation of complexes, cationic "metallosurfactants". However, none of the ligands **1b**–**5b** (similarly to ligands **1c**, **1d**; refs[3a,3b]) was soluble in water in the presence of transition metal ions. Therefore we had to prepare aqueous solutions of their complexes in micellar matrix of the cationic surfactant CTAB.

The complex formation was confirmed by the appearance of new bands in UV spectra (Table I). As a consequence of their lower stability, all Zn^{2+} complexes were observed only if an excess of metal ion was added to a solution of the ligand. Ni^{2+} complexes of the lipophilic ligands **2b** and **4b** appeared only in an excess of the metal ion as well. The stoichiometry of Zn^{2+} and Ni^{2+} complexes was determined from kinetic measurements (see below). We did not determine stability constants of the complexes in any case. The rate of the complex formation was strongly dependent on the metal ion, similarly to lipophilic pyridin-2-yl ligands **1c**, **1d** (ref.[3b]) and ligand-surfactants[4a] we studied previously or to 7-(4-ethyl-1-methyloctyl)-quinolin-8-ol complexes mentioned by Tondre[4b]. Thus while Cu^{2+} com-



(*E*)-ketoxime



(*Z*)-ketoxime

FIG. 1
Structure of ketoxime isomers

plexes were formed immediately and Co^{2+} complexes in several minutes after an addition of the metal ion to buffered solutions of the ligands **1b**–**5b** in CTAB, formation of Ni^{2+} complexes was only completed in more than two hours at pH 6.5. This phenomenon was only observed in micellar solutions of the ligands **1b**–**5b**; in homogeneous solutions of the ligands **1a**–**5a**, the complexes were formed instantaneously after the addition of the metal ion.

Kinetic Measurements

Hydrolytic activity of the prepared micellar and metallomicellar catalysts was tested by measuring rate constants of the model substrate cleavage under pseudo-first-order conditions ($[c_{cat}] >> [c_{substr}]$). This approach has been generally used in the evaluation of the hydrolytic enzyme mimics efficiency[2,3].

In the first series of experiments, screen of the hydrolytic activity covering all the prepared lipophilic ketoximes **1b**–**5b** and their complexes with

TABLE I
UV absorption maxima of oximes **1**–**5** and their complexes

Oxime	λ_{max}, nm				
	–	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
1a[a]	232, 272	266, 340	292, 320 sh	318	272, 298 sh[c]
1b[b]	242, 270	278, 362 sh	278, 340	278, 340	270
2a[a]	240	252, 312 sh	254 sh	242, 268, 338 sh	240 sh, 300 sh[d]
2b[b]	246	256, 292	244, 310 sh[d]	284, 356 sh	244, 300 sh[d]
3a[a]	242	252, 370 sh	256	280, 316 sh	238, 300 sh[c]
3b[b]	248	256, 282, 400 sh	246, 310 sh	290, 334 sh	248, 300 sh[d]
4a[a]	268	268, 362	272, 316	328	268, 310 sh[d]
4b[b]	270	282, 394	272, 320 sh[d]	264 sh, 344	272, 310 sh[d]
5a[a]	232, 280	276, 392 sh	276, 312 sh	250, 346	280, 305 sh[d]
5b[b]	248, 280	280, 320 sh	280	256, 280, 358	280, 366 sh[d]

[a] [oxime] = [metal] = $1 \cdot 10^{-4}$ mol l^{-1}, pH 6.3 (0.05 M MES buffer); [b] [oxime] = [metal] = $1 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $8 \cdot 10^{-3}$ mol l^{-1}, pH 6.3 (0.05 M MES buffer); [c] [metal] = $4 \cdot 10^{-4}$ mol l^{-1}; [d] [metal] = $1.2 \cdot 10^{-3}$ mol l^{-1}.

several divalent metal ions (Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) was performed. The kinetic measurements were carried out in micellar matrix of CTAB at 25 °C and pH 6.3. 4-Nitrophenyl diphenyl phosphate (PNPDPP), 4-nitrophenyl hexanoate (PNPH) and 4-nitrophenyl acetate (PNPA) were used as model substrates. The conditions employed enable direct comparison of the results thus obtained with those reported previously[3]. In order to get more information about the "intrinsic" reactivity of the complexes, excluding the contribution of micellar catalysis, pseudo-first-order rate constants of the PNPA cleavage were measured in aqueous solutions of methyl azinyl ketoximes **1a**–**5a** and their complexes as well.

Similarly to the formerly studied pyridin-2-yl ligands **1a**–**1c** and their complexes[3b], neither oximes **2b**–**5b** nor their complexes exhibit apparent reactivity towards PNPDPP and relative rates k_Ψ/k_0 did not exceed the value of 3 in any case. k_Ψ and k_0 are pseudo-first-order rate constants of the catalyzed and uncatalyzed (*i.e.* in the presence of buffered CTAB only) reaction, respectively. Reactivity towards PNPH and PNPA strongly depends both on the type of the ligand and the metal ion as evident from the results summarized in Table II.

The data shown in Table II afford the following information: (i) When two nitrogens are present in the heteroaromatic nucleus of the ligand (ketoximes **2**–**5**), its reactivity towards esters somewhat increases, compared with pyridine ligand **1**. The rate enhancement of the ester hydrolysis corresponds to the increase in the hydroxyimino group acidity. (ii) When less lipophilic substrate PNPA is employed instead of PNPH, the order of the hydrolytic activity of the metallomicellar catalysts is virtually unchanged. Therefore, kinetic data obtained with both these substrates give the same qualitative information about the metallocatalyst reactivity. (iii) Similarly to pyridine ligands **1**, coordination to Co^{2+} and Cu^{2+} is without effect or even decreases the reactivity of the hydroxyimino group of ligands **2**–**5** and an accelerating effect on ester hydrolysis is shown only by some of their Ni^{2+} and Zn^{2+} complexes. Metal- and ligand-dependent differences in hydrolytic efficiency of the complexes are in accord with the hypothesis that the observed reactivity of the metallocatalyst is a result of two contradictory consequences of the coordination: an increase in the nucleophile concentration and a decrease in the nucleophilicity of the anion formed since both the effects depend on the nature of the coordination bonds[4a]. (iv) None of the complexes of diazinyl ligands **2**–**5** exhibits the efficiency of analogous complexes of pyridinyl ligands **1** which is really impressive, especially in the case of homogeneous solutions of Zn^{2+} complexes of **1a**. In dependence on hydrolytic activity of their Zn^{2+} and Ni^{2+} complexes, diazinyl

ligands **2**–**5** can be divided into two groups. In each of them, similar electron distribution in the heteroaromatic nucleus can be expected. In the first group, there are more reactive pyrimidinyl ligands **3** and **4** in which the second heteroatom is located in β-position to coordinated nitrogen and in α- or γ-position to carbon substituted with the hydroxyiminoalkyl group. In the other, there are less reactive pyridazin-3-yl **2** and pyrazin-2-yl **5** ligands in which the second heteroatom is located in α- or γ-position to coordinated nitrogen and in β-position to carbon substituted with the

TABLE II
Relative rates of the model substrate cleavage in the presence of ketoximes **1b**–**5b** and **1a**–**5a** and their metal ion chelates (25 °C, pH 6.3 (0.05 M MES buffer))

Substrate	Ligand	k_Φ/k_0				
		–	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
PNPH[a]	**1b**	1.6 · 10	2.1	$4.7 \cdot 10^2$	1.1 · 10	$1.8 \cdot 10^2$
	2b	3.4 · 10	6.9	9.7 · 10	1.2 · 10	3.3 · 10
	3b	3.3 · 10	2.4	$2.3 \cdot 10^2$	1.1 · 10	$2.0 \cdot 10^2$
	4b	8.9 · 10	9.3	$4.2 \cdot 10^2$	9.6	8.1 · 10
	5b	3.4 · 10	8.9	8.5 · 10	1.2 · 10	2.6 · 10
PNPA[b]	**1b**	2.2 · 10	3.7	$7.9 \cdot 10^2$	2.9 · 10	$1.8 \cdot 10^2$
	2b	6.4 · 10	1.2 · 10	$1.3 \cdot 10^2$	2.0 · 10	6.9 · 10
	3b	5.8 · 10	7.3	$1.6 \cdot 10^2$	1.1 · 10	$1.5 \cdot 10^2$
	4b	$1.5 \cdot 10^2$	1.0 · 10	$3.7 \cdot 10^2$	7.3	$1.4 \cdot 10^2$
	5b	6.5 · 10	1.3 · 10	$1.3 \cdot 10^2$	8.3	5.9 · 10
PNPA[c]	**1a**	3.3	3.0	$1.2 \cdot 10^3$	1.9 · 10	$9.6 \cdot 10^3$
	2a	5.0	2.3	$1.3 \cdot 10^2$	9.3	$1.1 \cdot 10^2$
	3a	3.7	1.9	$5.2 \cdot 10^2$	3.4	$1.8 \cdot 10^3$
	4a	8.5	1.6	$4.7 \cdot 10^2$	1.6	$3.8 \cdot 10^2$
	5a	3.8	3.4	$5.5 \cdot 10^2$	4.3	$1.9 \cdot 10^2$

[a] [ligand] = [metal] = $4.0 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $8.0 \cdot 10^{-3}$ mol l^{-1}, [PNPH] = $2.0 \cdot 10^{-5}$ mol l^{-1}, $k_0 = 3.75 \cdot 10^{-6}$ s^{-1} (rate constant of the PNPH cleavage in buffered CTAB solution); [b] [ligand] = [metal] = $4.0 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $8.0 \cdot 10^{-3}$ mol l^{-1}, [PNPA] = $2.0 \cdot 10^{-5}$ mol l^{-1}, $k_0 = 1.92 \cdot 10^{-6}$ s^{-1} (rate constant of the PNPA cleavage in buffered CTAB solution); [c] [ligand] = [metal] = $1.0 \cdot 10^{-3}$ mol l^{-1}, [PNPA] = $4.0 \cdot 10^{-5}$ mol l^{-1}, $k_0 = 1.29 \cdot 10^{-6}$ s^{-1} (rate constant of the PNPA cleavage in buffered aqueous solution).

hydroxyiminoalkyl group. Nevertheless, any unequivocal conclusions on the structure-activity relationships are premature since so far we have no exact information about the electron distribution in the conjugated system of the heteroaromatic ring and nucleophilic hydroxyimino group, modified by coordination with metal ions.

Further and more detailed investigation was focused on Ni^{2+} and Zn^{2+} complexes exhibiting appreciable hydrolytic activity. Being bidentate ligands, ketoximes **1**–**5** can form complexes of different metal ion : ligand ratios. In order to evaluate the "effective stoichiometry" (which is not a definition of the nature and quantity of the complexes present in solution but only the most effective metal : ligand ion ratio leading to the highest reactivity observed), we performed kinetic versions of Job's plots[3b] shown in Figs 2–5. These were obtained for solutions where [metal ion] + [ligand] = $4.0 \cdot 10^{-4}$ mol l^{-1} using PNPH as substrate (lipophilic ligands **1b**–**5b**) or [metal ion] + [ligand] = $2.0 \cdot 10^{-3}$ mol l^{-1} using PNPA as substrate (water soluble ligands **1a**–**5a**).

As evident from Job's plots in Fig. 2, Ni^{2+} complexes of lipophilic ketoximes **1b** and **3b** were of the 1 : 3 metal ion : ligand stoichiometry. This ratio means an improvement of our previous results[3] obtained with ligands **1c**, **1d**. We reported the 1 : 2 effective stoichiometry of Ni^{2+} complexes, although, with respect to the observed flat maxima, we also admitted existence of other stoichiometries[3b]. Job's plot of the pyrimidin-4-yl

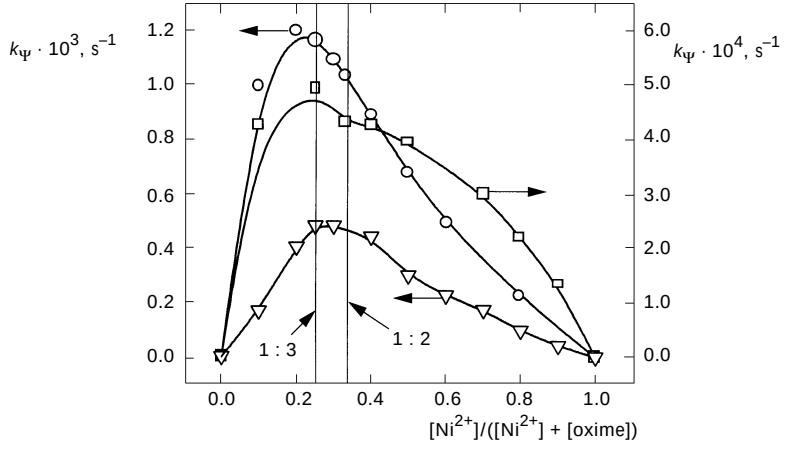


FIG. 2

Kinetic Job's plot for the PNPH cleavage by micellar solutions of **1b** (○), **3b** (□) and **4b** (▽) at pH 6.3 (0.05 M MES buffer) and 25 °C in the presence of Ni^{2+}; [Ni^{2+}] + [oxime] = $4 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $1 \cdot 10^{-2}$ mol l^{-1}

ligand **4b** is flat with the maximum located between the 1 : 2 and 1 : 3 stoichiometry. Surprisingly, different metal ion : ligand stoichiometries were found in homogeneous aqueous solutions. Job's plots shown in Fig. 3 give evidence that Ni^{2+} ions form the 1 : 2 complexes with ligands **1a**, **3a**–**5a**. This stoichiometry is in accord with our previous results[3b] and with those reported for similar types of ligands[5]. Since Ni^{2+} ion is hexavalent, forming mostly octahedral complexes, we assume coordination of two water molecules to reach the coordination number of six. One may only speculate which factors are responsible for different Ni^{2+} : ligand ratios in micellar and homogeneous solutions. Most probably, lipophilic alkyl chains of the ketoximes **1b**, **3b** and **4b** are a hydrophobic barrier for water to access the metal ion, thus preferring coordination of three ligand molecules.

Except for **3b**, hydrolytic acitivity of none of the lipophilic diazinyl ligands **2b**–**5b** is affected by Zn^{2+}. The reactivity and effective stoichiometry of the Zn^{2+} complex of pyrimidin-2-yl ketoxime **3b** is similar to that observed with lipophilic pyridin-2-yl ligand **1b** (Fig. 4). On the other hand, Zn^{2+} ion dramatically increases the reactivity of ketoximes **1a**–**5a** in homogeneous aqueous solutions (Table II and Fig. 5), the most active being 1 : 2 complexes of pyridin-2-yl **1a** and pyrimidin-2-yl **3a** ligands. The rates of the PNPA cleavage catalyzed by these complexes are really impressive. In all other cases (ketoximes **2a**, **4a** and **5a**), Zn^{2+} complexes are of 1 : 1

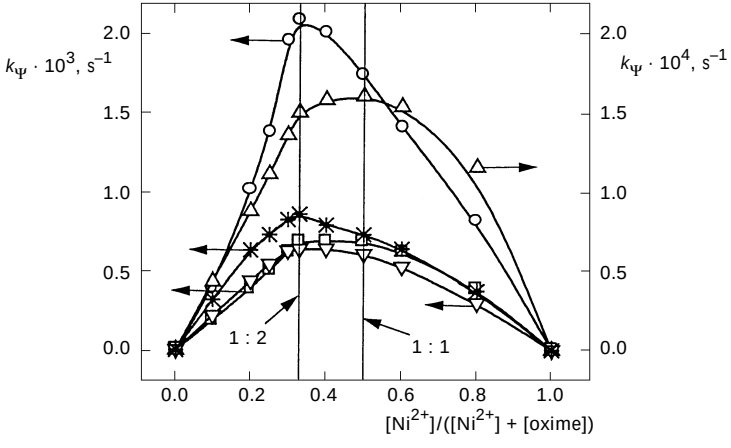


FIG. 3

Kinetic Job's plot for the PNPA cleavage by **1a** (○), **2a** (Δ), **3a** (□), **4a** (∇) and **5a** (*) at pH 6.3 (0.05 M MES buffer) and 25 °C in the presence of Ni^{2+}; $[Ni^{2+}] + [oxime] = 2 \cdot 10^{-3}$ mol l^{-1}

stoichiometry and their efficiency is lower approximately by one order of magnitude. Provided that the Zn^{2+} complexes of ligands **1**–**5** are of lower stability (see preparation of the metallomicellar catalysts), their stoichiometry could be influenced by the lipophilicity of the coordinated

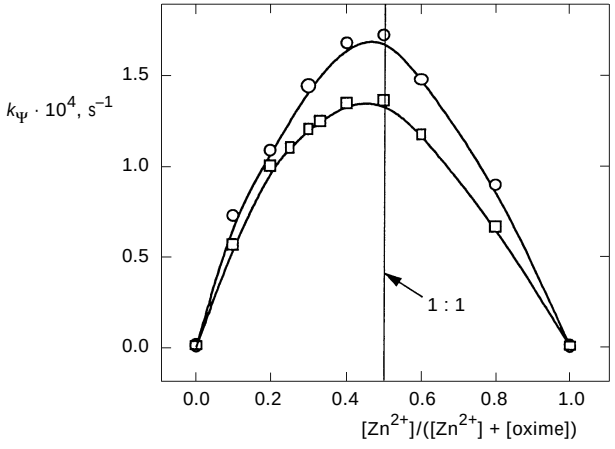


FIG. 4

Kinetic Job's plot for the PNPH cleavage by micellar solutions of **1b** (○) and **3b** (□) at pH 6.3 (0.05 M MES buffer) and 25 °C in the presence of Zn^{2+}; $[Zn^{2+}] + [oxime] = 4 \cdot 10^{-4}$ mol l^{-1}, $[CTAB] = 1 \cdot 10^{-2}$ mol l^{-1}

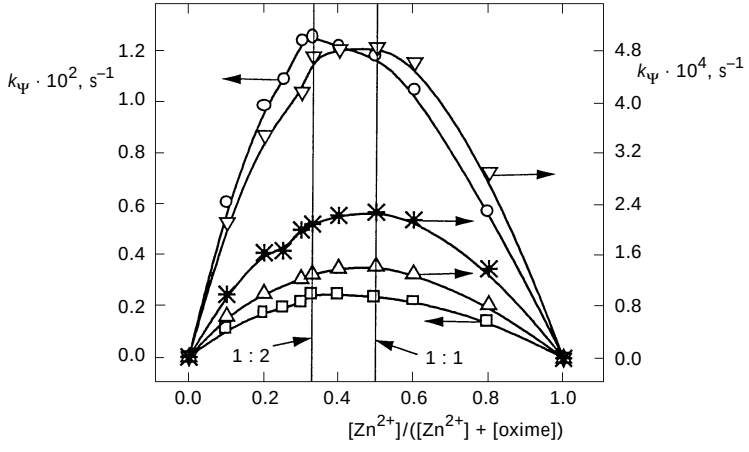


FIG. 5

Kinetic Job's plot for the PNPA cleavage by **1a** (○), **2a** (Δ), **3a** (□), **4a** (∇) and **5a** (*) at pH 6.3 (0.05 M MES buffer) and 25 °C in the presence of Zn^{2+}; $[Zn^{2+}] + [oxime] = 2 \cdot 10^{-3}$ mol l^{-1}

ligand. If the tetrahedral 1 : 2 Zn^{2+} complex with lipophilic dodecyl ligand is formed in micellar matrix, hydrophobic alkyl chain of one of the ligands coordinated should be oriented into bulk aqueous phase and the surface free energy increase might be higher than the energy released by the second ligand coordination, thus discriminating the 1 : 2 complex formation.

A question may appear about the structure of pyridin-2-yl **1** and pyrimidin-2-yl **3** complexes. In the former case, the ketoxime is of *E* configuration while in the latter one *Z* configuration was found (Fig. 1). N,N′-Chelates can be expected when an (*E*)-ketoxime coordinates to metal ion. Coordination of (*Z*)-ketoximes should lead to less stable N,O-chelates of quite different reactivity[2b] (Fig. 6). Surprisingly, the reactivity of Ni^{2+} and Zn^{2+} complexes of both these ligands, **1** and **3**, was similar (Table II, Figs 2–5) thus indicating the same type coordination. We assume that coordination to metal ion induced equilibration of the ligand **3** configuration.

Using the optimum metal ion : ligand ratio (see above) we studied the influence of pH on the hydrolytic activity of the complexes of lipophilic ketoximes **1b** and **3b**. As shown in Figs 7 and 8, corresponding complexes of both ligands exhibit similar rate *vs* pH profiles of the PNPH cleavage. In the case of Zn^{2+} complexes, on going from lower to higher pH values, the rate (log k_Ψ) linearly increases, reaching a plateau indicating complete ionization of the hydroxyimino group (at pH > 8). Coordination to Ni^{2+} ions acidifies hydroxyimino groups of ketoximes **1b** and **3b** much more than coordination to Zn^{2+} since the rate *vs* pH profiles of Ni^{2+} complexes already reach a "waving" plateau already at pH 5. Above this value, the rate of PNPH hydrolysis is almost insensitive to pH in the range of several pH units (5–11), the changes in the rate constants being only within one order of magnitude. A discontinuity observed in almost all profiles around pH 5 is a consequence of changing type of the buffer (acetate and biological below and above pH 5). The rate constants of the PNPH hydrolysis by fully ionized complexes (above pH 5 and 8 for Ni^{2+} and Zn^{2+}, respectively) give evi-

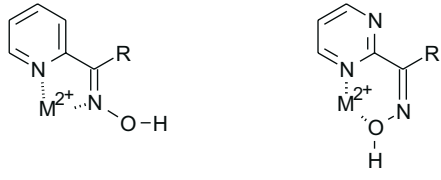


FIG. 6
Structure of N,N′- and N,O-chelates

dence that the nucleophilicity of the oximate anion in Zn^{2+} complexes is higher than that in Ni^{2+} complexes. This observation again illustrates the fact that the more the Nu–H group of the ligand of any hydrolytic

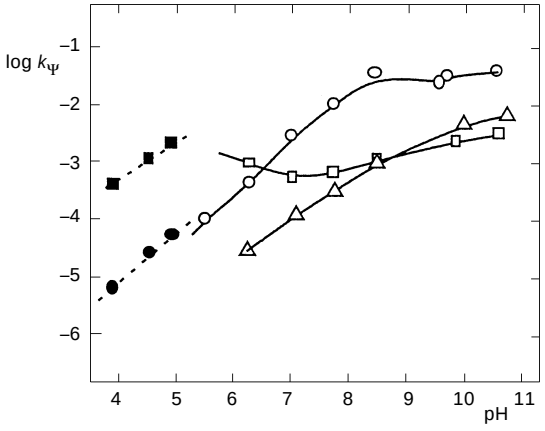


FIG. 7

pH dependence of the rate constant for the PNPH cleavage by **1b** (Δ), **1b**/Ni^{2+} (❒, 3 : 1) and **1b**/Zn^{2+} (○, 1 : 1). Filled and empty symbols indicate the use of acetate and biological buffers, respectively. Conditions: [**1b**] = $3.6 \cdot 10^{-4}$ mol l^{-1}, [Ni^{2+}] = $1.2 \cdot 10^{-4}$ mol l^{-1}, [Zn^{2+}] = $3.6 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $1.2 \cdot 10^{-2}$ mol l^{-1}, [buffer] = 0.05 mol l^{-1}, 25 °C

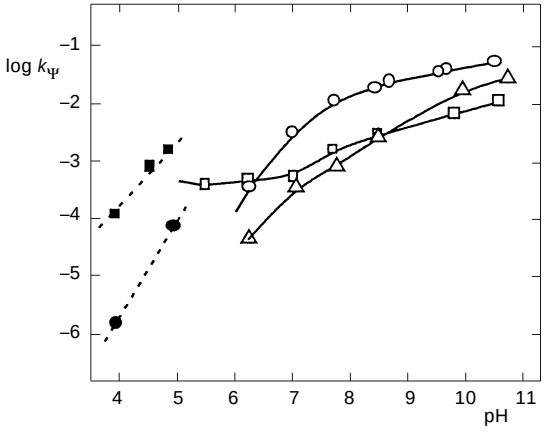


FIG. 8

pH dependence of the rate constant for the PNPH cleavage by **3b** (Δ), **3b**/Ni^{2+} (❒, 3 : 1) and **3b**/Zn^{2+} (○, 1 : 1). Filled and empty symbols indicate the use of acetate and biological buffers, respectively. Conditions: [**3b**] = $3.6 \cdot 10^{-4}$ mol l^{-1}, [Ni^{2+}] = $1.2 \cdot 10^{-4}$ mol l^{-1}, [Zn^{2+}] = $3.6 \cdot 10^{-4}$ mol l^{-1}, [CTAB] = $1.2 \cdot 10^{-2}$ mol l^{-1}, [buffer] = 0.05 mol l^{-1}, 25 °C

metallocatalyst is acidified by coordination to metal ion, the less nucleophilic anion Nu^- is formed.

As shown in Fig. 9, pH rate profiles of the PNPA hydrolysis in homogeneous solutions of Zn^{2+} complexes of ligands **1a**–**5a** follow the same trend as was observed in the above-mentioned micellar systems. The nucleophilicity of the Zn^{2+} coordinated deprotonated ketoximes decreases in the following order: pyridin-2-yl **1a**, pyrimidin-2-yl **3a**, pyrimidin-4-yl **4a**, pyrazin-2-yl **5a** and pyridazin-3-yl **2a**. In the case of Zn^{2+} complex of pyridazin-3-yl ligand **2a**, the profile is not monotonic as it is in all other cases. Most probably, decomposition of this complex (by concurrent hydroxo complexes formation) begins under weakly basic conditions (above pH 8) since above pH 10, there is an apparent convergence to the profile of the free ligand. pH rate profiles of the Ni^{2+} complexes of ligands **1a**–**5a** are given in Fig. 10. Compared with Zn^{2+} complexes, the reactivity of Ni^{2+} complexes is moderately influenced by the type of ligand employed, except for the pyridazinyl ketoxime **2a**. Profiles of pyrimidin-2-yl **3a**, pyrimidin-4-yl **4a** and pyrazin-2-yl **5a** complexes are almost indistinguishable thus giving evidence of the same acidity of their hydroxyimino groups as well as nucleophilicity of their anions. The Ni^{2+} complex of the pyridazin-3-yl ligand **2a** is stable even in strongly basic media and the drift

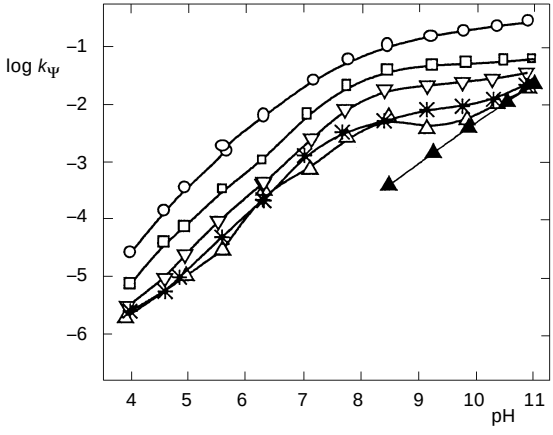


FIG. 9

pH dependence of the rate constant for the PNPA cleavage by **1a**/Zn^{2+} (○, 2 : 1), **2a**/Zn^{2+} (△, 1 : 1), **3a**/Zn^{2+} (□, 2 : 1), **4a**/Zn^{2+} (▽, 1 : 1), **5a**/Zn^{2+} (∗, 1 : 1) and **2a** (▲). Conditions: [oxime] = $1.0 \cdot 10^{-3}$ mol l^{-1}, [Zn^{2+}] = $5.0 \cdot 10^{-4}$ mol l^{-1} (in the case of **1a**/Zn^{2+} and **3a**/Zn^{2+}) or $1.0 \cdot 10^{-3}$ mol l^{-1} (in the case of **2a**/Zn^{2+}, **4a**/Zn^{2+} and **5a**/Zn^{2+}), [buffer] = 0.05 mol l^{-1}, 25 °C

of its pH rate profile at pH > 10 is a contribution of the PNPA hydrolysis with OH^- ions.

CONCLUSIONS

Detailed kinetic studies focused on hydrolytic activity of alkyl hetaryl ketoximes **1**–**5** and their complexes both in micellar and in homogeneous systems has brought many interesting pieces of information. However, at the present stage of knowledge, their interpretation is speculative in several cases and further investigation will be necessary. Compared with previously studied[3] complexes of alkyl pyridin-2-yl ketoximes **1**, the presence of the second nitrogen in the heteroaromatic ring of the diazinyl ketoximes **2**–**5** rather decreases hydrolytic activity of their complexes with metal ions. There exist unequivocal relationships between the position of the non-coordinating nitrogen in the heteroaromatic rings of diazinyl ligands **2**–**5** and hydrolytic activity of their Zn^{2+} and Ni^{2+} complexes. Nevertheless, general conclusions in term of structure–activity relationships are still premature and correlations of the calculated electron distributions in free and coordinated ligands with hydrolytic activities of their transition metal ion complexes will have to be performed. The observed influence of the ligand lipophilicity on the effective complex stoichiometry and, consequently,

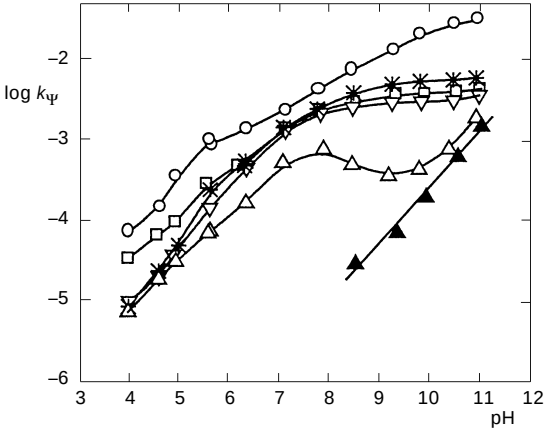


FIG. 10

pH dependence of the rate constant for the PNPA cleavage by **1a**/Ni^{2+} (○, 2 : 1), **2a**/Ni^{2+} (Δ, 1 : 1), **3a**/Ni^{2+} (□, 2 : 1), **4a**/Ni^{2+} (▽, 2 : 1), **5a**/Ni^{2+} (*, 2 : 1) and OH^- (▲). Conditions: [oxime] = $1.0 \cdot 10^{-3}$ mol l^{-1}, [Ni^{2+}] = $5.0 \cdot 10^{-4}$ mol l^{-1} (in the case of **1a**/Ni^{2+}, **3a**/Ni^{2+}, **4a**/Ni^{2+} and **5a**/Ni^{2+}) or $1.0 \cdot 10^{-3}$ mol l^{-1} (in the case of **2a**/Ni^{2+}), [buffer] = 0.05 mol l^{-1}, 25 °C

also on its reactivity is another interesting phenomenon. Most probably, determination of binding constants of the complexes both in homogeneous and in micellar solutions is the key to its explanation.

EXPERIMENTAL

Temperature data were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX3 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard, coupling constants *J* in Hz. Elemental analyses were performed on a Perkin–Elmer 240 analyser. IR spectra were taken on a FTIR spectrometer Nicolet 740. TLC analyses were carried out on DC Alufolien Kieselgel 60H F254 (Merck).

Chemicals: Pyridazine-3-carbonitrile[6] (**6**), pyrimidine-2-carbonitrile[7] (**7**) and pyrimidine-4-carbonitrile[7b,8] (**8**) were synthesized and purified by literature methods from furan-2-carbaldehyde (purum, Lachema), 2-chloropyrimidine (purum, Aldrich) and 4-methylpyrimidine (purum, Aldrich), respectively. All the prepared compounds gave correct elemental analyses and ^{1}H NMR spectra. Pyrazine-2-carbonitrile (**9**) and pyridine-2-carbonitrile (**10**) were obtained from Aldrich and methyl pyridin-2-yl ketone (**11a**) from Fluka (all purum). A stock solution of methylmagnesium iodide was prepared from magnesium and methyl iodide in ether and stored under argon atmosphere. Its concentration (1.7 mol l^{-1}) remained unchanged for several weeks as proved by titration with butan-2-ol using *N*-phenyl-1-naphthylamine as indicator[9]. Dodecylmagnesium bromide (1 M ethereal solution) was the product of Aldrich. 4-Nitrophenyl hexanoate (PNPH) (analytical grade) was purchased from Sigma. 4-Nitrophenyl acetate[10a] (PNPA) and 4-nitrophenyl diphenyl phosphate[10b] (PNPDPP) were synthesized and purified according to described methods. Hexadecyltrimethylammonium bromide (CTAB) (analytical grade) was the product of Merck. Biological buffers, 2-(morpholin-4-yl)ethane-1-sulfonic acid (MES), 2-[4-(2-hydroxyethyl)-piperazin-1-yl]ethane-1-sulfonic acid (HEPES), 3-[4-(2-hydroxyethyl)piperazin-1-yl]propane-1-sulfonic acid (EPPS), 2-cyclohexylaminoethane-1-sulfonic acid (CHES), 3-cyclohexylamino-propane-1-sulfonic acid (CAPS) (analytical grade) were purchased from Sigma. Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} nitrates (analytical grade) were products of Lachema Brno; their concentrations in stock solutions were determined by EDTA titrations following standard procedures[11].

Alkyl Diazinyl Ketones **11**–**15**. General Procedure

Ethereal solution of methylmagnesium iodide or dodecylmagnesium bromide (20% excess) was added dropwise during 1 h to stirred solution of diazinecarbonitrile **6**–**9** in dry ether (*ca* 0.2 mol l^{-1}) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h, quenched with water and neutralized with dilute hydrochloric acid (1 : 1) to adjust pH 8 in aqueous phase. The ethereal layer was separated and the aqueous phase was several times extracted with ether. The combined organic layers were dried with anhydrous sodium sulfate (ketones **12a**–**15a**) or potassium carbonate (ketones **11b**–**15b**). Evaporation of the solvent under reduced pressure afforded crude product which was purified by column chromatography. Analytical samples were obtained by sublimation under reduced pressure or by distillation (ketone **11b**).

Methyl pyridazin-3-yl ketone (**12a**). Ketone **12a** was prepared from nitrile **6** (1.0 g, 9.5 mmol). Eluent: dichloromethane–methanol 100 : 3. Sublimation: 75 °C/0.8 kPa. Yield 0.65 g (56%), m.p. 85–87 °C (reported[12] 87–88 °C). ^{1}H NMR ($CDCl_3$): 2.90 s, 3 H (CH_3); 7.66 dd, 1 H, *J*(5,4) = 8.8, *J*(5,6) = 5.0 (H-5); 8.15 dd, 1 H, *J*(4,5) = 8.8, *J*(4,6) = 1.7 (H-4); 9.34 dd, 1 H, *J*(6,5) = 5.0, *J*(6,4) = 1.7 (H-6).

Methyl pyrimidin-2-yl ketone (**13a**). Ketone **13a** was prepared from nitrile **7** (1.3 g, 12.4 mmol). Eluent: chloroform–methanol 100 : 5. Sublimation: 80 °C/0.9 kPa. Yield 0.46 g (30%), m.p. 49–52 °C (reported[13] 52 °C). ^{1}H NMR ($CDCl_3$): 2.78 s, 3 H (CH_3); 7.46 t, 1 H, *J*(5,4) = *J*(5,6) = 4.9 (H-5); 8.93 d, 2 H, *J*(4,5) = *J*(6,5) = 4.9 (H-4, H-6).

Methyl pyrimidin-4-yl ketone (**14a**). Ketone **14a** was prepared from nitrile **8** (0.3 g, 2.9 mmol). Eluent: dichloromethane–methanol 100 : 4. Sublimation: 70 °C/0.7 kPa. Yield 0.13 g (37%), m.p. 64–67 °C (reported[13] 66–67 °C). ^{1}H NMR ($CDCl_3$): 2.74 s, 3 H (CH_3); 7.90 d, 1 H, *J*(5,6) = 5.5 (H-5); 8.99 d, 1 H, *J*(6,5) = 5.0 (H-6); 9.38 s, 1 H (H-2).

Methyl pyrazin-2-yl ketone (**15a**). Ketone **15a** was prepared from nitrile **9** (0.37 g, 3.5 mmol). Eluent: dichloromethane–methanol 100 : 2. Yield 0.18 g (42%), m.p. 76–77 °C (reported[14] 76–78 °C). ^{1}H NMR ($CDCl_3$): 2.74 s, 3 H (CH_3); 8.67 dd, 1 H, *J*(6,5) = 2.2, *J*(6,3) = 1.7 (H-6); 8.77 d, 1 H, *J*(5,6) = 2.2 (H-5); 9.25 d, 1 H, *J*(3,6) = 1.7 (H-3).

Dodecyl pyridin-2-yl ketone (**11b**). Ketone **11b** was prepared from nitrile **10** (3.0 g, 28.8 mmol). Crude product was purified by column chromatography (chloroform–methanol 100 : 1) and by distillation (b.p. 125 °C/27 Pa). Yield 2.63 g (33%). For $C_{18}H_{29}NO$ (275.3) calculated: 78.49% C, 10.61% H, 5.08% N; found: 79.10% C, 10.78% H, 5.02% N. ^{1}H NMR ($CDCl_3$): 0.87 t, 3 H, *J*(12′,11′) = 6.6 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.72 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.2 (H-2′); 3.21 t, 2 H, *J*(1′,2′) = 7.3 (CH_2C=O); 7.46 ddd, 1H, *J*(5,4) = 7.7, *J*(5,6) = 5.0, *J*(5,3) = 1.1 (H-5); 7.83 td, 1 H, *J*(4,5) = *J*(4,3) = 7.7, *J*(4,6) = 1.7 (H-4); 8.04 d, 1 H, *J*(3,4) = 7.7 (H-3); 8.68 dd, 1 H, *J*(6,5) = 5.0, *J*(6,4) = 1.1 (H-6). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 24.7 s (C-10′); 28.0 s (C-9′); 30.1 s (C-8′); 30.21 s (C-7′); 30.25 s (C-6′); 30.35 s (C-5′); 30.38 s (C-4′); 30.4 s (C-3′); 32.6 s (C-2′); 38.4 s (C-1′); 122.5 s (C-3); 127.6 s (C-5); 137.5 s (C-4); 149.6 s (C-6); 154.3 s (C-2); 202.9 s (C=O).

Dodecyl pyridazin-3-yl ketone (**12b**). Ketone **12b** was prepared from nitrile **6** (0.3 g, 2.9 mmol). Eluent: chloroform–methanol 100 : 3. Sublimation: 120 °C/0.04 kPa. Yield 0.27 g (34%), m.p. 68–70 °C. For $C_{17}H_{28}N_2O$ (276.4) calculated: 73.86% C, 10.21% H, 10.13% N; found: 73.82% C, 9.98% H, 10.12% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 6.8 (CH_3); 1.26 m, 18 H (H-3′–H-11′); 1.78 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.4 (H-2′); 3.40 t, *J*(1′,2′) = 7.4 (CH_2C=O); 7.64 dd, 1 H, *J*(5,4) = 8.4, *J*(5,6) = 5.1 (H-5); 8.13 dd, 1 H, *J*(4,5) = 8.4, *J*(4,6) = 1.7 (H-4); 9.33 dd, 1 H, *J*(6,5) = 5.1, *J*(6,4) = 1.7 (H-6). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 24.6 s (C-10′); 26.5 s (C-9′); 30.0–30.3 m (C-8′–C-4′); 31.1 s (C-3′); 32.6 s (C-2′); 38.9 s (C-1′); 125.4 s (C-5); 127.9 s (C-4); 153.9 s (C-6); 156.2 s (C-3); 201.5 s (C=O).

Dodecyl pyrimidin-2-yl ketone (**13b**). Ketone **13b** was prepared from nitrile **7** (0.5 g, 4.7 mmol). Eluent: dichloromethane–methanol 100 : 1. Sublimation: 140 °C/0.08 kPa. Yield 0.38 g (29%), m.p. 52–56 °C. For $C_{17}H_{28}N_2O$ (276.4) calculated: 73.86% C, 10.21% H, 10.13% N; found: 74.17% C, 10.25% H, 9.88% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 6.8 (CH_3); 1.28 m, 18 H (H-3′–H-11′); 1.77 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.4 (H-2′); 3.22 t, *J*(1′,2′) = 7.5 (CH_2C=O); 7.44 t, 1 H, *J*(5,4) = *J*(5,6) = 4.8 (H-5); 8.93 d, 2 H, *J*(4,5) = *J*(6,5) = 4.8 (H-4, H-6). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 24.7 s (C-10′); 28.1 s (C-9′); 29.98 s (C-8′); 30.02 s (C-7′); 30.11 s (C-6′); 30.18 s (C-5′); 30.31 s (C-4′); 30.34 s (C-3′); 32.6 s (C-2′); 39.8 s (C-1′); 123.4 s (C-5); 158.3 s (C-4, C-6); 161.0 s (C-2); 200.6 s (C=O).

Dodecyl pyrimidin-4-yl ketone (**14b**). Ketone **14b** was prepared from nitrile **8** (0.3 g, 2.9 mmol). Eluent: chloroform–methanol 100 : 3. Sublimation: 120 °C/0.04 kPa. Yield 0.29 g (37%), m.p. 50–52 °C. For $C_{17}H_{28}N_2O$ (276.4) calculated: 73.86% C, 10.21% H, 10.13% N; found: 74.11% C, 9.81% H, 9.86% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 6.6 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.72 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.2 (H-2′); 3.19 t, *J*(1′,2′) = 7.4 (CH_2C=O); 7.89 dd, 1 H, *J*(5,6) = 5.0, *J*(5,2) = 1.1 (H-5); 8.98 d, 1 H, *J*(6,5) = 5.0 (H-6); 9.37 d, 1 H, *J*(2,5) = 1.7 (H-2). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 24.3 s (C-10′); 29.9 s (C-9′); 30.03 s (C-8′); 30.11 s (C-7′); 30.2–30.3 m (C-6′–C-3′); 32.6 s (C-2′); 38.4 s (C-1′); 118.0 s (C-5); 159.3 s (C-4); 159.6 s (C-6); 159.7 s (C-2); 202.3 s (C=O).

Dodecyl pyrazin-2-yl ketone (**15b**). Ketone **15b** was prepared from nitrile **9** (0.41 g, 3.9 mmol). Eluent: chloroform-methanol 100 : 1. Sublimation: 120 °C/0.04 kPa. Yield 0.27 g (25%), m.p. 61–62.5 °C. For $C_{17}H_{28}N_2O$ (276.4) calculated: 73.86% C, 10.21% H, 10.13% N; found: 73.95% C, 10.28% H, 10.11% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 6.8 (CH_3); 1.26 m, 18 H (H-3′–H-11′); 1.74 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.2 (H-2′); 3.18 t, *J*(1′,2′) = 7.4 (CH_2C=O); 8.65 dd, 1 H, *J*(6,5) = 2.3, *J*(6,3) = 1.6 (H-6); 8.75 d, 1 H, *J*(5,6) = 2.5 (H-5); 9.23 d, 1 H, *J*(3,6) = 1.4 (H-3). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 24.5 s (C-10′); 30.0–30.6 m (C-9′–C-3′); 32.6 s (C-2′); 38.6 s (C-1′); 144.2 s (C-5); 144.4 s (C-6); 148.4 s (C-3); 168.3 s (C-2); 202.2 s (C=O).

Methyl Azinyl Ketoximes **1a**–**5a**. General Procedure

Ketone **11a**–**15a** was stirred with aqueous hydroxylamine (prepared by mixing saturated aqueous solutions of hydroxylamine hydrochloride and potassium carbonate in a stoichiometric ratio) until the ketone was completely converted to oxime (TLC, dichloromethane–methanol 100 : 3). The resulting crystals of the crude product were purified by column chromatography (dichloromethane–methanol 100 : 2) and/or crystallization.

(E)-Methyl pyridin-2-yl ketoxime (**1a**). Oxime **1a** was prepared by heating ketone **11a** (4.1 g, 33.9 mmol) and aqueous hydroxylamine (38.8 mmol) at 60 °C for 1 h. Pure product was obtained by crystallization from ethanol–water (1 : 1). Yield 3.0 g (65%), m.p. 120–122 °C (reported[15] 121 °C). For $C_7H_8N_2O$ (136.2) calculated: 61.75% C, 5.92% H, 20.58% N; found: 61.57% C, 6.02% H, 20.61% N. ^{1}H NMR (DMSO-d_6): 2.22 s, 3 H (CH_3); 7.36 ddd, 1 H, *J*(5,4) = 7.3, *J*(5,6) = 4.9, *J*(5,3) = 1.1 (H-5); 7.79 td, 1 H, *J*(4,3) = *J*(4,5) = 7.9, *J*(4,6) = 1.7 (H-4); 7.86 d, 1 H, *J*(3,4) = 8.1 (H-3); 8.58 dd, 1 H, *J*(6,5) = 6.5, *J*(6,4) = 1.1 (H-6); 11.48 s, 1 H (OH). ^{13}C NMR (DMSO-d_6): 10.3 (CH_3); 119.7 (C-4); 123.6 (C-5); 136.5 (C-3); 148.7 (C-6); 154.4 (C=NOH); 154.5 (C-2). IR ($CHCl_3$): 3 580, 3 241 (O–H); 1 616 (C=N). pK_a = 11.1 (reported[16] 10.87).

(E)-Methyl pyridazin-3-yl ketoxime (**2a**). Oxime **2a** was prepared from ketone **12a** (0.3 g, 2.5 mmol) and aqueous hydroxylamine (4.9 mmol). The reaction was completed in 0.5 h at room temperature. Pure product was obtained by column chromatography and crystallization from ethanol. Yield 0.2 g (60%), m.p. 204–206 °C. For $C_6H_7N_3O$ (137.1) calculated: 52.55% C, 5.15% H, 30.64% N; found: 52.83% C, 5.16% H, 31.05% N. ^{1}H NMR spectrum (DMSO-d_6): 2.33 s, 3 H (CH_3); 7.69 dd, 1 H, *J*(5,4) = 8.5, *J*(5,6) = 5.0 (H-5); 8.06 dd, 1 H, *J*(4,5) = 8.5, *J*(4,6) = 1.7 (H-4); 9.21 dd, 1 H, *J*(6,5) = 5.0, *J*(6,4) = 1.7 (H-6); 11.93 s, 1 H (OH). ^{13}C NMR (DMSO-d_6): 10.1 (CH_3); 123.3 (C-5); 127.0 (C-4); 151.6 (C-6); 152.7 (C-3); 156.8 (C=NOH). pK_a = 10.6.

(Z)-Methyl pyrimidin-2-yl ketoxime (**3a**). Oxime **3a** was prepared from ketone **13a** (0.45 g, 3.7 mmol) and aqueous hydroxylamine (7.3 mmol). The reaction was completed in 2 h at

room temperature. Pure product was obtained by crystallization from ethanol. Yield 0.29 g (58%), m.p. 195–198 °C. For $C_6H_7N_3O$ (137.1) calculated: 52.55% C, 5.15% H, 30.64% N; found: 52.32% C, 4.93% H, 30.52% N. ^{1}H NMR (DMSO-d_6): 2.22 s, 3 H (CH_3); 7.47 t, 1 H, J(5,4) = J(5,6) = 4.9 (H-5); 8.84 d, 2 H, J(4,5) = J(6,5) = 4.9 (H-4, H-6); 11.79 s, 1 H (OH). ^{13}C NMR (DMSO-d_6): 11.2 (CH_3); 120.6 (C-5); 153.3 (C-2); 157.2 (C-4, C-6); 162.2 (C=NOH). pK_a = 10.8.

(E)-Methyl pyrimidin-4-yl ketoxime (**4a**). Oxime **4a** was prepared from ketone **14a** (0.14 g, 1.1 mmol) and aqueous hydroxylamine (2.3 mmol). The reaction was completed in 0.5 h at room temperature. Pure product was obtained by crystallization from methanol. Yield 0.11 g (70%), m.p. 182–183 °C (reported[17] 184–185 °C). For $C_6H_7N_3O$ (137.1) calculated: 52.55% C, 5.15% H, 30.64% N; found: 52.31% C, 5.16% H, 30.56% N. ^{1}H NMR (DMSO-d_6): 2.19 s, 3 H (CH_3); 7.86 dd, 1 H, J(5,6) = 5.5, J(5,2) = 1.6 (H-5); 8.76 d, 1 H, J(6,5) = 5.5 (H-6); 9.21 d, 1 H, J(2,5) = 1.6 (H-2); 12.10 s, 1 H (OH).^{13}C NMR (DMSO-d_6): 9.5 (CH_3); 116.3 (C-5); 153.2 (C-4); 156.9 (C-6); 158.4 (C-2); 161.2 (C=NOH). pK_a = 10.3.

(E)-Methyl pyrazin-2-yl ketoxime (**5a**). Oxime **5a** was prepared from ketone **15a** (0.18 g, 1.5 mmol) and aqueous hydroxylamine (2.2 mmol). The reaction was completed in 2 h at room temperature. Pure product was obtained by sublimation at 80 °C/2.7 Pa. Yield 0.14 g (72%), m.p. 113–115 °C (reported[14] 113–115 °C). For $C_6H_7N_3O$ (137.1) calculated: 52.55% C, 5.15% H, 30.64% N; found: 52.07% C, 5.32% H, 30.36% N. ^{1}H NMR (DMSO-d_6): 2.20 s, 3 H (CH_3); 8.61 dd, 1 H, J(6,5) = 2.2, J(6,3) = 1.7 (H-6); 8.63 d, 1 H, J(5,6) = 2.2 (H-5); 9.07 d, 1 H, J(3,6) = 1.7 (H-3); 11.89 s, 1 H (OH).^{13}C NMR (DMSO-d_6): 9.9 (CH_3); 141.6 (C-3); 143.5 (C-6); 143.8 (C-5); 149.9 (C-2); 153.0 (C=NOH). pK_a = 10.9.

Dodecyl Azinyl Ketoximes **1b**–**5b**. General Procedure

Aqueous hydroxylamine (prepared by mixing saturated solutions of hydroxylamine hydrochloride and potassium carbonate in a stoichiometric ratio) was added in three portions during 2 h to solution of ketone **11b**–**15b** in ethanol at 60 °C. Then, the reaction mixture was stirred at 60 °C until the ketone was completely converted to oxime (TLC, chloroform–methanol 100 : 3). Formed potassium chloride was filtered off and water was added to precipitate the crude product which was purified by crystallization from methanol. Analytical samples were obtained by sublimation.

(E)-Dodecyl pyridin-2-yl ketoxime (**1b**). Oxime **1b** was prepared from ketone **11b** (2.45 g, 9.1 mmol) in ethanol (37 ml) and aqueous hydroxylamine (14.4 mmol). Pure product was obtained by crystallization from ethanol-water and sublimation at 120 °C/1.3 Pa. Yield 1.88 g (73%), m.p. 58–63 °C. For $C_{18}H_{30}N_2O$ (290.5) calculated: 74.44% C, 10.41% H, 9.64% N; found: 74.58% C, 10.23% H, 9.63% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 7.2 (CH_3); 1.24 m, 18 H (H-3′–H-11′); 1.59 qi, 2 H, J(2′,3′) = J(2′,1′) = 7.2 (H-2′); 2.99 t, 2 H, J(1′,2′) = 7.6 (CH_2C=O); 7.27 m, 1 H (H-5); 7.69 td, 1 H, J(4,5) = J(4,3) = 7.6, J(4,6) = 1.6 (H-4); 8.04 d, 1 H, J(3,4) = 8.0 (H-3); 8.64 d, 1 H, J(6,5) = 4.4 (H-6); 8.82 s, 1 H (OH). ^{13}C NMR ($CDCl_3$): 14.9 s (CH_3); 23.5 s (C-11′); 25.4 s (C-10′); 27.0 s (C-9′); 30.1 s (C-8′); 30.2–30.7 m (C-7′–C-2′); 32.7 s (C-1′); 121.7 s (C-3); 124.3 s (C-5); 137.1 s (C-4); 149.8 s (C-6); 154.8 s (C-2); 161.6 s (C=NOH). pK_a = 10.9.

(E)-Dodecyl pyridazin-3-yl ketoxime (**2b**). Oxime **2b** was prepared from ketone **12b** (0.15 g, 0.54 mmol) in ethanol (8 ml) and aqueous hydroxylamine (2.7 mmol). Pure product was obtained by crystallization from methanol and sublimation at 130 °C/2.7 Pa. Yield 0.083 g (53%), m.p. 101–103 °C. For $C_{18}H_{30}N_2O$ (291.3) calculated: 70.06% C, 10.03% H, 14.42% N;

found: 69.88% C, 10.03% H, 14.21% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 6.8 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.64 qi, 2 H, J(2′,3′) = J(2′,1′) = 7.6 (H-2′); 3.13 t, J(1′,2′) = 7.6 (CH_2C=O); 7.47 dd, 1 H, J(5,4) = 8.5, J(5,6) = 4.8 (H-5); 8.03 d, 1 H, J(4,5) = 8.4 (H-4); 8.44 s, 1 H (OH); 9.16 d, 1 H, J(6,5) = 4.0 (H-6). ^{13}C NMR ($CDCl_3$): 14.5 s (CH_3); 23.1 s (C-11′); 24.7 s (C-10′); 26.7 s (C-9′); 29.8–30.1 m (C-8′–C-3′); 30.3 s (C-2′); 32.3 s (C-1′); 124.6 s (C-5); 126.7 s (C-4); 151.7 s (C-6); 157.0 s (C-3); 159.6 s (C=NOH). pK_a = 10.4.

(Z)-Dodecyl pyrimidin-2-yl ketoxime (**3b**). Oxime **3b** was prepared from ketone **13b** (1.35 g, 4.9 mmol) in ethanol (20 ml) and aqueous hydroxylamine (24.4 mmol). Pure product was obtained by crystallization from ethanol–water and sublimation at 130 °C/2.7 Pa. Yield 0.25 g (18%), m.p. 89–91 °C. For $C_{18}H_{30}N_2O$ (291.3) calculated: 70.06% C, 10.03% H, 14.42% N; found: 69.83% C, 9.78% H, 14.09% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 7.0 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.63 qi, 2 H, J(2′,3′) = J(2′,1′) = 7.6 (H-2′); 2.99 t, J(1′,2′) = 7.6 (CH_2C=O); 7.27 m, 1 H (H-5); 8.81 d, 2 H, J(4,5) = J(6,5) = 4.8 (H-4, H-6); 9.54 s, 1 H (OH). ^{13}C NMR ($CDCl_3$): 14.8 s (CH_3); 23.4 s (C-11′); 25.5 s (C-10′); 27.0 s, (C-9′); 30.1–30.4 m (C-8′–C-3′); 30.6 s (C-2′); 32.7 s (C-1′); 121.0 s (C-5); 157.9 s (C-4, C-6); 159.2 s (C-2); 162.8 s (C=NOH). pK_a = 10.5.

(E)-Dodecyl pyrimidin-4-yl ketoxime (**4b**). Oxime **4b** was prepared from ketone **14b** (0.15 g, 0.54 mmol) in ethanol (15 ml) and aqueous hydroxylamine (2.7 mmol). Pure product was obtained by crystallization from methanol and sublimation at 130 °C/1.3 Pa. Yield 0.98 g (62%), m.p. 87–88 °C. For $C_{18}H_{30}N_2O$ (291.3) calculated: 70.06% C, 10.03% H, 14.42% N; found: 70.44% C, 9.42% H, 14.30% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 7.0 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.56 qi, 2 H, J(2′,3′) = J(2′,1′) = 7.7 (H-2′); 2.94 t, J(1′,2′) = 7.7 (CH_2C=O); 7.82 dd, 1 H, J(5,6) = 5.3, J(5,2) = 1.1 (H-5); 8.71 d, 1 H, J(6,5) = 5.4 (H-6); 9.12 s, 1 H (OH); 9.26 s, 1 H (H-2). ^{13}C NMR ($CDCl_3$): 14.7 s (CH_3); 23.4 s (C-11′); 24.6 s (C-10′); 26.9 s (C-9′); 30.0–30.3 m (C-8′–C-3′); 30.5 s (C-2′); 32.6 s (C-1′); 118.0 s (C-5); 157.4 s (C-6); 159.4 s (C-2); 160.3 s (C-4); 162.0 s (C=NOH). pK_a = 10.1.

(E)-Dodecyl-pyrazin-2-yl ketoxime (**5b**). Oxime **5b** was prepared from ketone **15b** (0.3 g, 1.1 mmol) in ethanol (10 ml) and aqueous hydroxylamine (5.3 mmol). Pure product was obtained by crystallization from methanol and sublimation at 130 °C/2.7 Pa. Yield 0.11 g (35%), m.p. 80–81 °C. For $C_{18}H_{30}N_2O$ (291.3) calculated: 70.06% C, 10.03% H, 14.42% N; found: 69.55% C, 10.02% H, 14.18% N. ^{1}H NMR ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 6.7 (CH_3); 1.25 m, 18 H (H-3′–H-11′); 1.58 qi, 2 H, J(2′,3′) = J(2′,1′) = 7.5 (H-2′); 2.94 t, J(1′,2′) = 7.8 (CH_2C=O); 8.50 s, 1 H (OH); 8.53 d, 1 H, J(6,5) = 2.5 (H-6); 8.57 m, 1 H (H-5); 9.15 s, 1 H (H-3). ^{13}C NMR ($CDCl_3$): 14.7 s (CH_3); 23.3 s (C-11′); 24.8 s (C-10′); 26.7 s (C-9′); 30.0–30.2 m (C-8′–C-3′); 30.5 s (C-2′); 32.5 s (C-1′); 143.6 s (C-5); 144.0 s (C-6); 144.3 s (C-3); 150.4 s (C–2); 159.9 s (C=NOH). pK_a = 10.4.

Determination of pK_a

Values of pK_a of the ketoximes were obtained as the averages of the values calculated from the absorbance *vs* pH plots at two wavelengths (maxima of the =NOH and =NO$^-$ forms) using the software package Enzfitter[18]. Aqueous sodium hydroxide was used to adjust pH of aqueous solution of ketoximes **1a**–**5a** (70 ml, $8.0 \cdot 10^{-5}$ mol l^{-1}) or micellar solution of ketoximes **1b**–**5b** (70 ml, $8.0 \cdot 10^{-5}$ mol l^{-1}) in $1.0 \cdot 10^{-2}$ M CTAB. Total volume of the NaOH solution added did not exceed 0.3 ml in any case.

Kinetic Measurements

Solutions of the complexes were prepared directly in spectrophotometric cells by addition of an appropriate amount of aqueous solution of the metal ion to a buffered homogeneous aqueous solution of the ligand (ligands **1a**–**5a**) or to a micellar solution of the ligand in CTAB (ligands **1b**–**5b**). The cells were standing overnight to assure the complex formation reached the equilibrium. 2-(Morpholin-4-yl)ethane-1-sulfonic acid (MES), 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethane-1-sulfonic acid (HEPES), 3-[4-(2-hydroxyethyl)piperazin-1-yl]propane-1-sulfonic acid (EPPS), 2-cyclohexylaminoethane-1-sulfonic acid (CHES), 3-cyclohexylaminopropane-1-sulfonic acid (CAPS) and acetate buffers (0.05 mol l^{-1}) were used to maintain the desired pH. No changes in pH were observed during the kinetic runs. The reactions were followed on a spectrophotometer Hewlett–Packard HP8452 equipped with a thermostatted multicell transport cell holder HP89075C maintaining the reaction temperature at 25.0 ± 0.1 °C. The reactions were initiated by injection of a substrate solution in acetonitrile (20 μl) into the spectrophotometric cell containing a buffered solution of catalyst, the resulting concentration of the substrate being $4.0 \cdot 10^{-5}$ and $2.0 \cdot 10^{-5}$ mol l^{-1} in the case of ligands **1a**–**5a** and **1b**–**5b**, respectively. The reactions were monitored at the wavelengths 400 nm (maximum of the 4-nitrophenoxide absorption) or at 318 nm (maximum of the 4-nitrophenol absorption) when pH of the catalytic system was below 6. The kinetics followed a first-order law in each case at least up to 95% conversion. The pseudo-first-order rate constants k_Ψ were obtained by non-linear regression analysis of the absorbance *vs* time data using software package Enzfitter[18]. The fit error of the rate constant did not exceed 5%.

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