Letter

Micellar nickel(II)-2-pyridineketoxime complexes as powerful catalysts of the cleavage of carboxylic acid esters in weakly acidic conditions

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Abstract

Metallomicelles made of Ni(II) complexes of lipophilic 2-pyridineketoximes such as 2 or 3a and CTABr, in water at pH 4, accelerate the cleavage of p-nitrophenyl hexanoate over a half million fold.

Keywords: Nickel; Pyridine derivatives; Ketoxime derivatives; Ester; Metallomicelle

Transition metal ions play an essential role in the catalytic activity in the active site of a variety of hydrolytic enzymes [1]. Over the years, the study of simple models led to the realization of effective metallocatalysts [2]. More recently, attention has been focused on micellar or vesicular systems, thus providing a suitable microenvironment which can bring together the reacting species and modify binding and dissociation equilibria, relative to the aqueous solution, with relevant kinetic benefits [3]. The metalloaggregates so far investigated in our [4], as well in other laboratories [5], relied on hydroxy functions or metal-bound water molecules which act as nucleophiles. The pK_a of the bound hydroxyl or water is typically

close to or greater than 6–7 [4,5]. The efficiency of these systems is confined to solutions in the pH range 7–10 and to substrate capable of binding to the metal ion, such as amino acid or phosphoric acid esters [2]c. Carboxylate esters appear much less reactive and the rate accelerations are much lower.

In search for more powerful systems for these substrates we turned our attention to 2-pyridineketoxime derivatives which effectively chelate transition metal ions and provide the system with the oxime group, an alpha nucleophile. The reactivity of such functions in the cleavage of esters is exploited in the case of PAM, a methylpyridium aldoxime, employed as a dephosphorylating agent for poisoned acetylcholinesterase [6]. Some examples of activation of 2-pyridinealdoximes

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upon complexation of a transition metal ion are also known [2]d[7]. We synthesized the 2-pyridineketoximes 1–3 with different degrees of hydrophobic character and tested their catalytic activity in the cleavage of p-nitrophenyl esters of carboxylic acids (mainly hexanoic acid, PNPH) in cationic micelles.
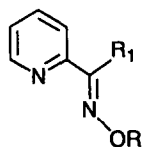
1a: R = H; R$_1$ = CH$_3$
1b: R = CH$_3$; R$_1$ = CH$_3$
2 : R = H; R$_1$ = n-C$_8$H$_{17}$
3a: R = H; R$_1$ = n-C$_{13}$H$_{27}$
3b: R = CH$_3$; R$_1$ = n-C$_{13}$H$_{27}$

Ligands 1–3 [1] were readily synthesized from the corresponding ketones and hydroxylamine hydrochloride or O-methoxyhydroxylamine hydrochloride. The ketones, except for the commercially available 2-acetylpyridine, were obtained by the addition of the proper Grignard reagent to 2-pyridinecarbonitrile (R$_1$ = n-C$_8$H$_{17}$) or by the ketonic fission of the product of alkylation of ethyl 3-(2-pyridinyl)-3-oxobutanoate (R$_1$ = n-C$_{13}$H$_{27}$). While oximes 1a, 1b are moderately soluble in water at any pH, the more hydrophobic analogues 2 and 3 are practically not dispersible even in acidic water or in the presence of transition metal ions; they are soluble in a solution of micellar hexadecyltrimethylammonium bromide (CTABr) at a minimum ratio [CTABr]/ [Ligand] of 5 (ligand 2) or 20 (ligand 3).

In preliminary kinetic experiments, the hydrolysis of PNPH [2] was carried out in an aqueous solution of micellar CTABr and 3a (in the ratio 20:1) employing divalent cations of Cu, Ni, Zn, and Co. Ni(II) was singled out as the most effective and unusual among them. The formation of Ni(II)–ketoxime complexes, as monitored spectrophotometrically, is a slow process [8] and

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[1] All new compounds gave correct elemental analyses (C, H, N) and the expected ^{1}H-NMR spectra.

[2] The hydrolysis of PNPH was followed by UV–Vis monitoring the release of p-nitrophenol at 317 nm or of p-nitrophenoxide at 400 nm depending on the operational pH. All the kinetic experiments were performed under pseudo-first-order condition with [ligand] > > [PNPH]. In each case, the reaction temperature was 25.0°C.
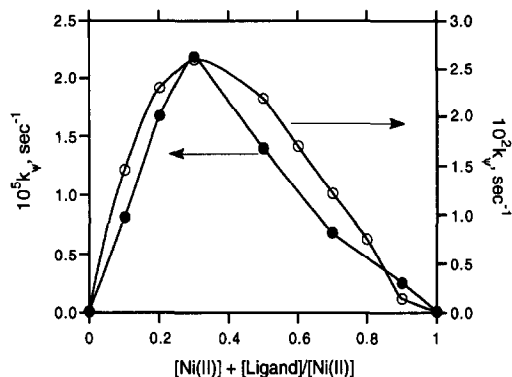

Fig. 1. Kinetic Job plot for the cleavage of PNPH by (●) 1a, (○) 2/CTABr 1:5 and Ni(II) at pH 4.0 (acetate buffer 5 mM). The sum of the concentrations of ligand and metal ion was kept constant at 0.6 mM for 1a and 0.8 mM for 2.

before starting any kinetic experiments it was ascertained that the equilibrium was attained. Moreover, it was established by means of the kinetic version of the Job plot [9] (see Fig. 1) using either 1a or 2 as ligands, that the most active complex in slightly acidic or neutral solutions is obtained when the ligand/Ni(II) ratio is close to 2:1 and this ratio was then used in the kinetic study here reported. Table 1 shows significant pseudo-first-order rate constants (k_ψ) for the hydrolysis of PNPH measured at different pH values in the absence and presence of Ni(II) and of 1a or 3a/ CTABr.

In the absence of Ni(II), 3a/CTABr is moderately effective as expected for a species bearing an oxime function with a pK_a of ca. 11 [10]: the observed rate is about 80 times faster on going

Table 1
Observed rate constant (k_ψ, s^{-1}) for the cleavage of PNPH at different pH [a] at 25°C

Entry	Ligand	Additive	Metal ion	k_ψ, s^{-1} pH = 4	pH = 6.5	pH = 8.5
1	3a	CTABr	Ni(II)	4.1×10^{-3}	1.4×10^{-3}	4.5×10^{-3}
2	3a	CTABr	none	5.6×10^{-6}	1.0×10^{-4}	8.2×10^{-3}
3	1a	none	Ni(II)	6.2×10^{-5}	4.9×10^{-4}	4.5×10^{-3}
4	none	CTABr	none	1.9×10^{-7}	1.0×10^{-5}	5.8×10^{-4}

[a] Conditions. Buffers (5 mM): acetate, pH = 4; 2-morpholinoethanesulfonic acid (MES), pH = 6.5; 4-(2-hydroxyethyl)piperazine-1-propanesulfonic acid (EPPS), pH = 8.5. When present: [ligand] = 0.8 mM; [CTABr] = 0.016 M, [Ni(II)] = 0.4 mM.

Table 2
Observed (k_ψ) and extrapolated (k_{lim}) rate constants for the cleavage of PNPH at pH = 4 [a]

Entry	Ligand	[CTABr]/ [ligand]	k_ψ, s^{-1}	k_ψ/k_0 [b]	k_{lim}, s^{-1}	k_{lim}/ k_0 [b]
1	1a	–	7.6×10^{-5}	260	–	–
2	1b	–	9.5×10^{-7}	3	–	–
3	2	20	0.014	47,400	0.025	84,700
4	2	10	0.049	166,100	0.077	261,000
5	2	5	0.12	406,800	0.15	508,500
6	2 [c]	5	1.1×10^{-5}	37	–	–
7	3a	20	0.008	27,100	0.010	33,900
8	3b [d]	20	5.3×10^{-7}	2	–	–

[a] [ligand] = 1.1 mM, [Ni(II)] = 5.5 mM, acetate buffer pH 4, 25°C.
[b] k_0 = rate constant in pure buffer.
[c] Without Ni(II).
[d] [3b] = 0.8 mM, [Ni(II)] = 1.6 mM.

from pH 6.5 to pH 8.5 (entry 2). On the other hand, *in the presence of Ni(II)*, the observed rate constant obtained for the same ligand is virtually constant in the pH range explored (entry 1). This behaviour is observed only in presence of micellar aggregates. In fact, in the case of the complex 1a·Ni(II) (entry 3), in absence of CTABr and any aggregate, the rate increases as a function of the pH: a plot of logk_ψ vs. pH shows a change in the slope around pH 5 as expected for a nucleophile with a pK_a of ca. 5, quite likely the oxime hydroxyl activated by the metal ion [11]. The striking observation from the data of Table 1 is that metallomicelles made of 3a/Ni(II)/CTABr are still very active at pH 4 where the oxime alone or its Ni(II) complex outside micelles are very poor catalysts of PNPH cleavage.

Table 2 shows the kinetic data collected for the different ligands at pH 4. For the micellar systems the maximum rate attainable (k_{lim}) under these conditions was obtained from the rate–concentration profiles using the proper treatment [12].

The data of Table 2 consolidate the evidence that large rate accelerations are obtained when the Ni(II) complexes of the oxime are included in the micellar aggregate. In fact the monomeric complex 1a/Ni(II) accelerates the reaction 260 fold (entry 1) while 2, in aggregate devoid of Ni(II), increases the rate by a factor of 37 only (entry 6). Moreover the hydroxyl of the oxime has to be

available for the reaction: both the methylated compounds 1b or 3b are virtually inert (compare entries 1, 2 and 7, 8). Also very important is the ratio [CTABr]/[ligand] i.e. the concentration of the complex in the aggregate. A four fold decrease in such ratio leads to a rate increase of about one order of magnitude (entries 3, 4 and 5), so that the best result ($k_{lim}/k_0 = 5 \times 10^5$) is obtained when [CTABr]/[2] = 5.

The results of the preliminary study of these metalloaggregates indicate the following: (i) The substrate is brought into the proximity of the Ni(II) complex of the lipophilic oximes in the cationic micelle. Hydrophobic forces are at play and, as a result, relatively high concentrations of the reactants are achieved in the small micellar volume. (ii) Inside this aggregate, the oximic function attacks the ester cleaving it. The oximic hydroxyl is likely to be in the oximate form even at pH = 4, due to lowering of its pK_a to a value presumably below 4, as a consequence of its complexation with Ni(II) [11] and of the interaction of the complex with the cationic aggregates [13].

In conclusion, we have shown that using very simple oxime-based metalloaggregates it is possible to realize a catalyst which accelerates the rate of cleavage of a simple carboxylic acid ester over a half million fold at a moderately acidic pH. This is imprecedent for any kind of substrate. Studies are in progress to better define the mechanism of this reaction and the source of the unique properties of Ni(II) among other transition metal complexes.

Acknowledgements

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