

## MICELLIZATION TRIGGERS PSEUDO-INTRAMOLECULAR TRANSACYLATION IN $\text{Cu}^{2+}$ COMPLEXES OF HYDROLYTIC METALLOMICELLES.

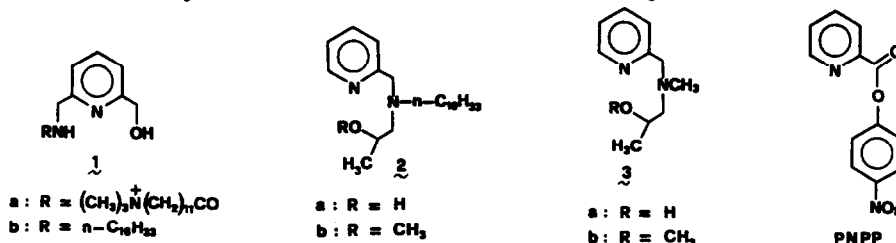
Giovanni De Santi, Paolo Scrimin\*, and Umberto Tonellato\*

Dipartimento di Chimica Organica and Centro CNR Meccanismi di Reazioni Organiche, Università di Padova, Via Marzolo, 1, 35131 Padova, Italy.

**Abstract** Micelles made up of lipophilic ligand 2a and  $\text{Cu}^{2+}$  or  $\text{Zn}^{2+}$  ions show catalytic properties in the cleavage of the *p*-nitrophenylester of picolinic acid (PNPP). In the case of the  $\text{Cu}^{2+}$  complex comparison with the non-micellar model 3a and the *O*-methylated siblings clearly shows how only the supramolecular assembly leads to catalysis with involvement of the hydroxyl as the nucleophile. A stereochemical modification of the complex in the aggregate is suggested as a likely explanation of the observed phenomena

Recent work from our<sup>1</sup> and other<sup>2</sup> laboratories demonstrated that the hydroxyls properly bound to a ligand structure may be activated by transition metal ions and act as effective nucleophiles in neutral aqueous media. Attention was focused, in particular, on ligands of Cu(II) or Zn(II), some of them hydrophobic in character and capable of forming micellar aggregates, as effective catalysts of the hydrolysis of activated esters of picolinic<sup>1b</sup> or other  $\alpha$ -amino acids<sup>3</sup>. From the study of ligands 1 the following relevant features of the catalytic process were apparent: i) Formation of a ternary complex<sup>4</sup> involving ligand/metal ion/substrate<sup>1b,2</sup> (see Figure 1A); ii) Pseudo-intramolecular attack of the metal ion-coordinated hydroxyl<sup>5</sup> to the bound ester; iii) Turn-over of the catalyst<sup>1b,c,2a</sup> ensuring a really catalytic process. Enhanced catalytic effects in micelles was attributed to concentration and local pH effects<sup>1b</sup>.

Here we add another feature to the already interesting picture of hydrolytic metallomicelles: kinetic evidence that the micellar aggregation may trigger catalytic effects as a likely consequence of changes in the coordination geometry of the complex. The ligands investigated were the lipophilic molecules 2, which, though insoluble in neutral water solution, in the presence of  $\text{Cu}^{2+}$  (pH=6.3) form micellar aggregates<sup>6</sup>. They may also be solubilized in an inert micellar matrix made of cetyltrimethylammonium bromide (CTABr) in the presence of  $\text{Zn}^{2+}$  or even without any added transition metal cation. Water soluble ligands 3, unable to form aggregates,



were also investigated. The cleavage of ester PNPP was the process studied as the rate of hydrolysis of this substrate is very sensitive to the nature and concentration of the added transition metal ions<sup>7</sup>.

Figures 2 and 3 show the results of a detailed kinetic investigation<sup>8</sup> carried out with micellar ligand 2a and its non micellar sibling 3a in the presence of a fixed amount of transition metal cation ( $\text{Cu}^{2+}$  or  $\text{Zn}^{2+}$ ). The effects of ligands 2b and 3b with the methylated hydroxyls are also reported: they are expected to give information on the involvement of the hydroxyl as the nucleophile<sup>9a</sup>. The following comments can be made on analyzing Figures 2 and 3.

**Zn(II), (Figure 2).** Either the micellar<sup>9b</sup> system 2a and the non micellar 3a do accelerate the cleavage of PNPP. The far better efficiency of the aggregate may be ascribed (in line with previous findings<sup>1</sup>) to higher pH and PNPP concentration at the cationic micellar surface. In both systems the hydroxyls are involved in the nucleophilic process since, following their methylation, a remarkable decrease of the rate of release of *p*-nitrophenol is observed (factors of 100 and 6 in the micellar and non micellar systems respectively). With non micellar 3b inhibition occurs, likely due to a ternary complex less efficient than the  $\text{PNPP}\cdot\text{Zn}^{2+}$  complex.

**Cu(II), (Figure 3).** Contrary to what is observed with Zn(II) *only micellar<sup>9b</sup> 2a is catalytically active* with involvement of the hydroxyl: in fact, its methylation (2b) causes a 21 fold decrease of the rate constant. Non micellar 3a is an inhibitor of the cleavage of PNPP showing no evidence of the involvement of the hydroxyl in the process (kinetic effects of 3a and 3b are identical within the limit of the experimental error). Moreover, in 1:1 DMSO/water, *where aggregates are not formed*, ligands 2a,b behave exactly as non micellar 3a,b in water (see Figure 3, inset).

The conclusion suggested by these data is that the supramolecular assembly, in the case of Cu(II), imposes a change of the stereochemistry of the complex (with respect to the system unable to form micelles) such as to force the hydroxyl to play an active role in the cleavage process. Such a peculiar behavior was not present with ligands 1. In that case we demonstrated the existence of the nucleophilic attack by the hydroxyl with both metals either in micellar aggregates or not<sup>1b,c</sup>. Why such a striking difference?

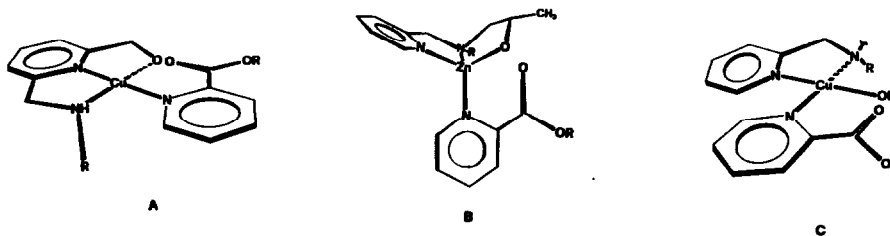


Figure 1

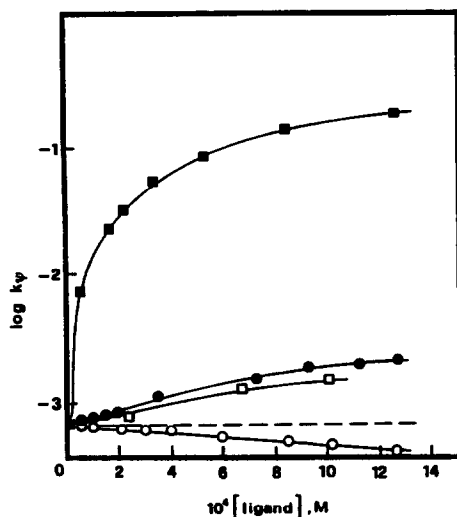


Figure 2. Rate vs. concentration profile for the cleavage of PNPP in the presence of ligands 2 and 3 and  $Zn^{2+}$ . ■ 2a; □ 2b; ● 3a; ○ 3b. Conditions: 2,6-lutidine buffer pH=7.3; 25°C;  $[Zn(NO_3)_2]=1.3 \times 10^{-3}$  M; ligands 2 were comicellized with CTABr ( $[CTABr]=10[ligand]$ ). Note the log scale in both Figures.

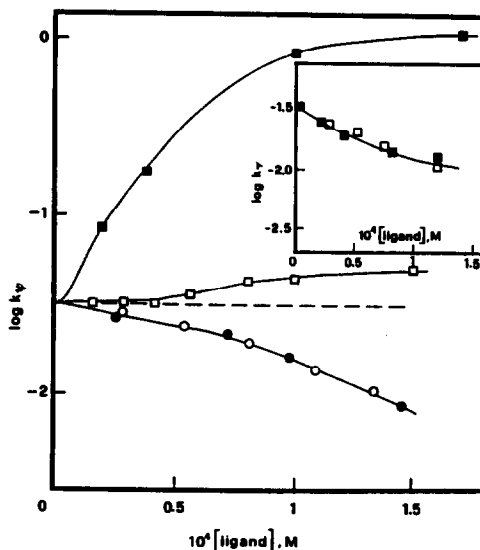


Figure 3. Rate vs. concentration profile for the cleavage of PNPP in the presence of ligands 2 and 3 and  $Cu^{2+}$ . ■ 2a; □ 2b; ● 3a; ○ 3b. Conditions: MES buffer pH=6.3; 25°C;  $[Cu(NO_3)_2]=1.3 \times 10^{-4}$  M; ligands 2 were comicellized with CTABr ( $[CTABr]=10[ligand]$ ). Inset: Same profile for ligands 2 in a 1:1 DMSO/buffer mixture. Conditions as above but CTABr was missing.

Inspection of molecular models suggests that in 2a, at variance with ligands 1, the pivotal position of the  $sp^3$  nitrogen leads to a preferential<sup>10</sup> tetrahedral geometry of the ternary complex. This is the preferred one by  $Zn(II)$ <sup>11</sup> and likely leads to a complex as the one depicted in Figure 1B. In the case of  $Cu(II)$ , since a planar coordination mode is preferred<sup>12</sup>, this may be reached by replacing the weakest donor of the ligand, the hydroxy group, with a competing ligand ( $H_2O$ , for instance). The formation of such a complex (Figure 1C) explains the non involvement of the hydroxyl in the process with non-micellar 3a in water and 2a in DMSO/water. The -OH would regain its role as the nucleophilic species in micellar aggregates of 2a likely through a stereochemical modification of the ligand subunit forced to assume a more planar and strained geometry. This is supported by preliminary e.s.r. data<sup>13</sup>. The origin of the phenomenon may be related to the packing of the complex in the aggregates and/or to lesser availability of competing ligands ( $H_2O$  or other anionic species) in the hydrophobic micellar surface. This latter point seems less probable as recent results<sup>14</sup> suggest that micelles are fully exposed to water molecules. Strained stereochemistry, the so-called entatic state<sup>15</sup>, has been claimed in the case of some metalloenzymes to explain their enhanced catalytic function.

While Tagaki and his coworkers<sup>16</sup> have recently demonstrated that the nature of the metal ion,  $Cu(II)$  or  $Zn(II)$ , may lead to the activation of differently located hydroxyls according to the geometrical requirements of the complexes, the modification of reactivity due to stereochemical changes imposed to the system by

the supramolecular assembly, as suggested by the present data, appears as a novel and attracting feature of these functionalized aggregates.

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### References and Footnotes

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5. The pKa of these hydroxyls decreases of several units. It has been reported in the range 6.5-8 (see ref. 2)
6. Micellization is clearly highlighted by the inflection observed in the rate vs concentration profiles at very low ligand concentration. The (R) isomers have been used throughout. New compounds gave correct elemental analyses (C,H,N) and spectra.
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8. **Experimental procedure:** kinetics were initiated by adding 20-40  $\mu\text{L}$  of  $1 \times 10^{-3}$  M solution of PNPP in  $\text{CH}_3\text{CN}$  to 2mL of the reaction mixture (see captions to Figures 1 and 2 for details). Release of *p*-nitrophenol was followed spectrophotometrically at 317 nm. Pseudo-first order rate constant were obtained with a PC computer by non-linear regression analysis of the absorbance vs time data.
9. Note that: a) The classical approach using excess substrate to detect turn-over suffers of complications with the PNPP substrate; b) The influence of the non functional surfactant CTABr on the rate of hydrolysis of PNPP
10. The models suggest some strain in the planar geometry where the two carbons connecting the amine nitrogen and the alcoholic oxygen are forced, by the presence of the pyridine moiety, on the same side of the coordination plane, as indicated in the Figure. This is in accord with the fact that such a conformation is rather rare in planar complexes. See: ref 11 p.56.
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13. A frozen sample of the micellized  $2a \cdot \text{Cu}^{2+}$  complex in water gave the following esr parameters:  $g_{\perp} = 2.066$ ,  $g_{\parallel} = 2.388$ ,  $A_{\parallel} = 127$ . Particularly the relatively small value of  $A_{\parallel}$  may suggest a compressed tetrahedral geometry. See: B. J. Hathaway in G. Wilkinson, R. D. Gillard, J. A. McCleverty (Eds) *Comprehensive Coordination Chemistry*, Vol. 5, Pergamon Press, Oxford 1987, p 667.
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