Micellar catalysis of organic reactions. Part 37.[1] A comparison of the catalysis of ester and amide hydrolysis by copper-containing micelles

Trevor J. Broxton and Abdulla Nasser

Abstract: The hydrolysis of a number of nitroactivated esters and amides has been studied in the presence of copper-containing metallomicelles at neutral pH. The relative rates of hydrolysis in the pure metallomicelle and in co-micelles with either cetyltrimethylammonium bromide (ctab) or Triton X-100 depends on the hydrophobicity of the substrate and whether it is completely solubilized by the copper micelle. Thus it depends on the concentration of the copper micelle. At low concentrations of copper micelle (0.2 mM) where the substrate is incompletely solubilized, the reaction is faster when 2 mM ctab is added. At higher concentrations (>0.6 mM) where the substrate may be almost completely solubilized by the copper micelle, the reaction is slower when 2 mM ctab is added. For ester hydrolysis the presence of either a carboxylic acid group or a heterocyclic nitrogen atom close to the reaction centre resulted in much larger catalysis by the metallomicelle than for model compounds without these additional groups. It is postulated that these groups coordinate with the metal ion and thus present the reaction centre close to a metal-bound hydroxyl resulting in a significant increase in the rate of bond formation, which is the rate-determining step for ester hydrolysis. For amide hydrolysis the presence of a carboxyl group *ortho* to the reaction centre did not lead to larger catalysis by the copper micelle than for the compound without this group. This difference is attributed to the different rate-determining steps for amide and for ester hydrolysis.

Key words: metallomicelles, ester and amide hydrolysis.

Résumé : Opérant à un pH neutre, en présence de métallomicelles contenant du cuivre, on a étudié l'hydrolyse d'un certain nombre d'esters et d'amides activés par des groupes nitro. Les vitesses relatives d'hydrolyse dans la métallomicelle pure et dans des comicelles comportant soit du bromure de cétyltriméthylammonium («ctab») soit du Triton X-100 dépend du caractère hydrophobe du substrat et de sa solubilité dans la micelle de cuivre. Elles dépendent donc de la concentration de micelle de cuivre. À de faibles concentrations de micelle de cuivre (0,2 mM), alors que le substrat ne se solubilise pas complètement, la vitesse de la réaction est accélérée par l'addition de 2 mM de «ctab». À des concentrations plus élevées (>0,6 mM), alors que le substrat est pratiquement solubilisé par la micelle de cuivre, la réaction est ralentie par l'addition de 2 mM de «ctab». Lors de l'hydrolyse de l'ester en présence soit d'un groupe acide carboxylique soit d'un atom d'azote hétérocyclique à proximité du centre réactionnel, la catalyse par la métallomicelle est beaucoup plus importante que dans les cas de composés modèles ne portant pas ces groupes. On fait l'hypothèse que ces groupes se coordonnent à l'ion métallique et rapprochent donc le centre réactionnel du groupe hydroxyle lié au métal; il en résulte une augmentation de la vitesse de formation de la liaison qui est l'étape déterminante dans l'hydrolyse de l'ester. Par rapport à l'hydrolyse de composés modèles ne comportant pas ces groupes, l'hydrolyse d'amides comportant un groupe carboxyle en position *ortho* du centre réactionnel ne conduit pas à des niveaux de catalyse par la micelle de cuivre plus élevés.

Mots clés : métallomicelles; hydrolyse, ester et amide.

[Traduit par la rédaction]

Introduction

The study of the catalysis of organic reactions by metallomicelles is currently of interest (1–4). We have previously reported (5) strong catalysis of amide hydrolysis in neutral solution by micelles formed after complexation of a hydrophobic ligand, *N,N,N′*-trimethyl-*N′*-hexadecylethylenediamine, with cupric chloride. The amide studied was 5-nitro-2-(trifluoroacetylamino)benzoic acid **1**. It is now of interest to determine whether the carboxylic acid group *ortho* to the amide reaction centre is essential for maximal catalysis by the copper-containing micelle and furthermore to compare ester and amide hydrolysis in pure metallomicelles and in the presence of co-micelles with either cetyltrimethylammonium bromide (ctab), a cationic surfactant, or with Triton X-100, a neutral surfactant. Engbersen and co-workers (6) reported stronger catalysis of the hydrolysis of phenyl picolinate in co-micelles of a copper-containing metallo-

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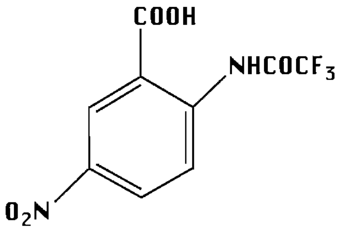
micelle with both ctab and with Brij 35 than in the pure metallo micelles.

We now report the catalyzed hydrolysis of amides 5-nitro-2-(trifluoroacetylamino)benzoic acid **1** and *N*-4-nitrophenyltrifluoroacetamide **2** and esters 2-acetoxy-5-nitrobenzoic acid **3**, 4-acetoxy-3-nitrobenzoic acid **4**, 8-acetoxy-5-nitroquinoline **5**, *p*-nitrophenylacetate **6**, and *o*-nitrophenyl acetate **7** in the presence of copper-containing metallomicelles. We have chosen to use the tetradecyl ligand *N,N,N*′-trimethyl-*N*′-tetradecylethylenediamine to prepare the metallomicelle, to avoid some solubility problems encountered with the hexadecyl compound.



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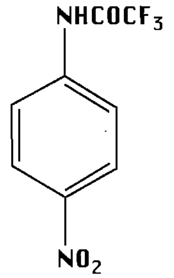

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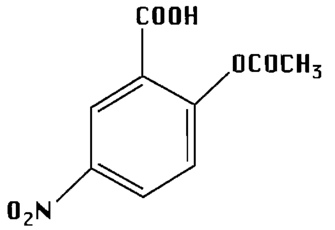

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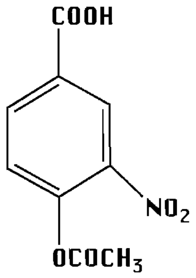

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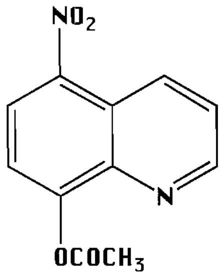

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Table 1. Pseudo-first-order rate constants ($10^4 \times k_1/\mathrm{s}^{-1}$) for the hydrolysis of amides (*a*)**1** and (*b*)(**2**) in the presence of copper-containing metallomicelles.

(*a*) 5-Nitro-2-trifluoroacetylamino benzoic acid (**1**)

[Cu(L)] (mM)	Chloride	Acetate	Nitrate
0	0.217	0.217	0.217
0.20	1.88		
0.20 + 2 mM Triton	0.305		
0.25	2.84	2.77	2.80
0.25 + 1 mM Triton	—	2.01	
0.40	3.12		
0.40 + 2 mM Triton	0.809		
0.50	6.54	6.83	6.57
0.50 + 1 mM Triton	—	6.37	
0.50 + 1 mM ctab	—	5.14	
0.60	5.43		
0.60 + 2 mM Triton	1.59		
0.75	8.96	9.11	8.95
0.75 + 1 mM Triton	—	8.59	
1.00	9.35	9.62	9.96
1.00 + 1 mM Triton	8.13	9.11	9.20
1.00 + 1 mM ctab	3.97	4.56	4.99
2.00	9.99	10.3	10.2
2.00 + 1 mM Triton	9.80		10.2
2.00 + 1 mM ctab	6.29	6.81	6.74

(*b*) Model compound *N*-4-nitrophenyltrifluoroacetamide (**2**)

[Cu(L)] (mM)	Chloride	Acetate	Nitrate
0	0.162	0.162	0.162
0.20	0.439	—	
0.20 + 2 mM Triton	0.307		
0.20 + 2 mM ctab	0.761		
0.25 + 1 mM Triton	0.52		
0.40	1.12	—	
0.40 + 2 mM Triton	0.673		
0.40 + 2 mM ctab	1.41		
0.50	1.43	1.49	1.39
0.50 + 1 mM Triton	—	1.29	
0.60	1.83	—	
0.60 + 2 mM Triton	1.11		
0.60 + 2 mM ctab	2.32		
0.75	3.00	2.85	3.02
0.75 + 1 mM Triton	—	2.46	
1.00	3.97	—	4.35
1.00 + 1 mM ctab	3.57	4.71	
1.00 + 1 mM Triton	3.57	7.54	3.62
2.00	7.78		6.67
2.00 + 1 mM ctab	6.49	7.41	
2.00 + 1 mM Triton	7.03	—	6.67

Results and discussion

1. Amide hydrolysis

Pseudo-first-order rate constants for the hydrolysis of amides **1** and **2** are given in Table 1. With both the chloride and acetate salts, identical rate constants were obtained for reactions using solutions obtained by dissolving solid samples of the copper–ligand complex (method *a*), and for solutions obtained by preparing the complex in situ (method *b*), see experimental section. For the nitrate salt, the rate constants were only obtained by method *b*, i.e., in solutions obtained by mixing the copper nitrate and ligand in situ, see experimental section.

For both compounds, similar rates were obtained with the chloride, acetate, and nitrate metallomicelles and the maximum observed catalysis for each compound was also similar for each micelle. This indicates that the reaction of the amide substrate is with a copper-bound hydroxyl rather than with hydroxide ion from the bulk solution. In the latter case we would have expected significant differences between the rates obtained in chloride, acetate, and nitrate micelles based on the pseudophase ion exchange kinetic model of micellar catalysis (7, 8), because the hydroxide ion would be competing with different counterions for available sites on the micelle surface. This is consistent with conclusions drawn by Menger et al. (1) for the copper-catalyzed hydrolysis of phosphate esters.

In most cases it can be seen that the rate of hydrolysis of compound **1** is slightly faster (1.3- to 4.9-fold) than that for compound **2**. The maximum observed catalysis of the hydrolysis of both compounds is similar, ranging from 46 to 47.5 for compound **1** and from 41 to 48 for compound **2**.

The rate–detergent profile in the miceles with chloride counterions showed an increase in rate as the detergent concentration was increased from 0.2 to 2 mM. Even at 0.2 mM the rate of hydrolysis was more than 10 times faster than in pure water alone. This is consistent with a critical micelle concentration (cmc) of 0.18 mM as reported by Menger et al. (1) for this micelle.

Effect of co-micelles

For compound **1**, which should be well solubilized by the metallomicelle due to the electrostatic attraction between the ionized carboxylic acid group and the cationic micelle, the rate of hydrolysis in the presence of a co-micelle was slower than in the pure metallomicelle. This inhibiting effect was larger for ctab co-micelles than for Triton X-100 co-micelles.

For compound **2**, which is less well solubilized by the metallomicelle since it is a neutral compound, the addition of co-micelles of ctab at low concentrations of copper micelle (0.2–0.4 mM) resulted in a rate increase. At higher copper micelle concentrations the addition of co-micelles of ctab caused a reduction in the rate of hydrolysis. At all copper concentrations the addition of co-micelles of Triton X-100 resulted in a reduction in the rate of hydrolysis. The effect of these co-micelles on the rate of hydrolysis depends on how well the substrate is solubilized by the copper micelle alone and hence on the copper micelle concentration. If the substrate is completely solubilized by the copper micelle, then the addition of a co-micelle reduces the rate of hydrolysis, presumably as a result of the dilution of the substrate in the micellar pseudophase. On the other hand, if the substrate is not completely solubilized by the copper micelle, then the addition of a co-micelle improves solubilization of the substrate by the micelles and hence increases the rate of hydrolysis. Engbersen and co-workers (6) observed that the rate of hydrolysis of *p*-nitrophenylpicolinate in the presence of zinc- or copper-containing metallomicelles was increased by the addition of co-micelles of either ctab or Brij-35. This work was carried out at a low metallomicelle concentration (0.4 mM), so presumably the ester substrate was not fully solubilized and hence the addition of co-micelles increased solubilization of the substrate in the micellar pseudophase, thus increasing the observed rate of hydrolysis.

2. Ester hydrolysis

Pseudo-first-order rate constants for the hydrolysis of esters **3**, **4**, and **5** are given in Table 2. For 2-acetoxy-5-nitrobenzoic acid, **3**, the rate of hydrolysis increased to a maximum at 2 mM copper micelle. At this concentration the catalysis was 7100-fold compared to reaction in water. For *p*-nitrophenylacetate, a model compound without the acid group, the observed catalysis, was only 5-fold. For the isomer 4-acetoxy-3-nitro benzoic acid, **4**, the optimum rate of hydrolysis was also obtained at 2 mM copper micelle but in this case the catalysis was only 58-fold. The model compound without the acid group, *o*-nitrophenylacetate, had only a 4.5-fold catalysis. For 8-acetoxy-5-nitroquinoline, **5**, the rate increased to a maximum at 0.6 mM copper micelle, reflecting the hydrophobicity of this compound. The catalysis at this concentration was 66-fold. The model compound without the heterocyclic nitrogen atom, *p*-nitrophenyl acetate, had only 5-fold catalysis as above.

Thus the presence of an ionized carboxylate group *ortho* to the reaction centre (as in compound **3**) or a quinoline nitrogen atom close to the reaction centre (as in compound **5**) is very beneficial to the magnitude of catalysis of ester hydrolysis by copper-containing metallomicelles, in contrast to the situation observed above for amide hydrolysis. The beneficial effect of a pyridine nitrogen atom on the magnitude of catalysis of the hydrolysis of aryl esters of picolinic acid in metallomicelles has previously been reported (9). This was attributed to coordination of the nitrogen with the metal ion.

The presence of the carboxylic acid group *para* to the reaction centre, while beneficial to the magnitude of catalysis by copper metallomicelles, is less effective than one *ortho* to the reaction centre. This suggests that the effect of the ionized carboxylate group is not merely to assist in the solubilization of the substrate by the copper-containing cationic micelle, but rather to orient the substrate within the micelle so that the reaction centre is close to the metal ion and hence the metal-bound hydroxide. The quinoline nitrogen atom close to the reaction centre in compound **5** presumably has a similar effect.

The different behaviour of ester and amide hydrolysis to the copper-containing metallomicelles is of interest. It may possibly result from different rate-determining steps for the two reactions. For ester hydrolysis the rate-determining step is bond formation (10). However, for trifluoroacetanilides the rate-determining step has been shown to be solvent-assisted C—N bond breaking (11). Thus it follows that for ester hydrolysis with bond formation between the ester and the metal-bound hydroxide being rate determining, the proximity of these species within the micelle is catalytically important (see Scheme 1). For amide hydrolysis, however, with C—N bond breakage being rate determining, the substrate is already bound to the copper micelle and hence the orientational differences between compounds **1** and **2** in the micelle are not kinetically important.

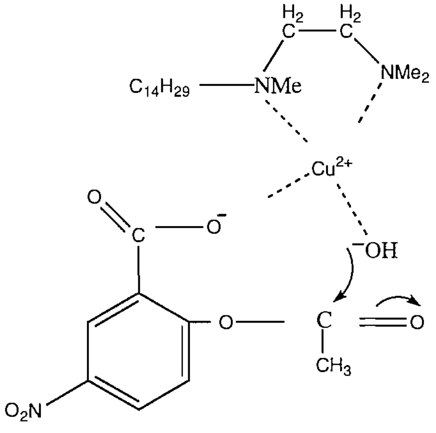
As for amide hydrolysis, the rate of hydrolysis of the esters is faster in a pure metallomicelle solution than in the presence of co-micelles except at very low metallomicelle concentrations. At 0.2 mM $CuCl_2$ the hydrolysis of compound **5** is more than 8 times faster than the uncatalyzed hydrolysis in water, once again indicating a cmc less than 0.2 mM. Addition of ctab (2 mM) to this reaction mixture resulted in a fivefold rate increase. At higher $CuCl_2$ concentrations (0.6–2.0 mM), how-

Table 2. Pseudo-first-order rate constants for the hydrolysis[a] of ester **3**–**5** in the presence of copper-containing metallomicelles.

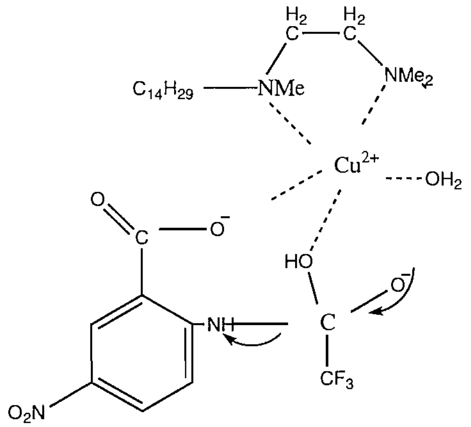
Conditions	$10^4\ k_1/s^{-1}$
2-Acetoxy-5-nitrobenzoic acid 3	
Water	0.02
0.50 mM $CuCl_2$	32.2
1.00 mM $CuCl_2$	101
2.00 mM $CuCl_2$	142
3.00 mM $CuCl_2$	140
1.00 mM $CuCl_2$ + 1 mM ctab	64.2
8-Acetoxy-5-nitroquinoline 5	
Water	0.66
2.00 mM ctab	0.465
4.00 mM ctab	0.350
6.00 mM ctab	0.377
0.20 mM $CuCl_2$	5.44
0.20 mM $CuCl_2$ + 2 mM ctab	27.9
0.40 mM $CuCl_2$	16.9
0.40 mM $CuCl_2$ + 2 mM ctab	17.1
0.50 mM $CuCl_2$	26.1
0.50 mM $CuCl_2$ + 1.5 mM ctab	20.1
0.50 mM $CuCl_2$ + 3 mM ctab	17.4
0.50 mM $CuCl_2$ + 1. mM Triton	40.4
0.50 mM $CuCl_2$ + 1.5 mM Triton	24.8
0.60 mM $CuCl_2$	43.7
0.60 mM $CuCl_2$ + 2 mM ctab	19.5
1.00 mM $CuCl_2$	29.2
1.00 mM $CuCl_2$ + 1 mM ctab	24.5
1.00 mM $CuCl_2$ + 2 mM ctab	23.5
1.00 mM $CuCl_2$ + 1 mM Triton	26.5
1.00 mM $CuCl_2$ + 2 mM Triton	23.7
2.00 mM $CuCl_2$	30.0
2.00 mM $CuCl_2$ + 1 mM Triton	26.8
3.00 mM $CuCl_2$	30.6
Model compound 4-nitrophenyl acetate	
Water	0.10
0.50 mM $CuCl_2$	0.27
1.00 mM $CuCl_2$	0.26
3.00 mM $CuCl_2$	0.542
4-Acetoxy-3-nitrobenzoic acid 4	
Water	0.17
0.20 mM $CuCl_2$	0.54
0.20 mM $CuCl_2$ + 2 mM Triton	0.25
0.40 mM $CuCl_2$	0.82
0.40 mM $CuCl_2$ + 2 mM Triton	0.54
0.60 mM $CuCl_2$	2.02
0.60 mM $CuCl_2$ + 2 mM Triton	1.21
1.00 mM $CuCl_2$	4.37
2.00 mM $CuCl_2$	9.93
3.00 mM $CuCl_2$	6.22
1.00 mM $CuCl_2$ + 1 mM ctab	2.74
Model compound 2-nitrophenyl acetate	
Water	0.134
0.50 mM $CuCl_2$	0.179
2.00 mM $CuCl_2$	0.547
3.00 mM $CuCl_2$	0.601

[a] Conditions: T = 31°C, pH 7.00 (Tris buffer 2.4 mM free base and 32.6 mM Tris HCl).

Scheme 1. Proposed mechanisms of copper-catalyzed amide and ester hydrolysis.



Rate-determining transition state for ester hydrolysis



Rate-determining transition state for amide hydrolysis

ever, the addition of ctab resulted in a reduction of the rate of hydrolysis.

This difference is most likely due to the differences in the extent of solubilization of the substrate by the copper micelles as described above for amide hydrolysis. This effect is similar to that observed in micellar reactions at concentrations higher than the optimum micelle concentration. Typically the rate vs. detergent concentration profile shows a decrease in the rate of reaction once the optimum concentration of surfactant is exceeded. The optimum rate of hydrolysis of compound **5** is observed at 0.6 mM copper micelle, the rate decreasing at higher concentrations. This indicates that the substrate is indeed completely solubilized at 0.6 mM.

Experimental section

Materials

The required ligand was prepared by the method of Menger (1) using 1-bromotetradecane and *N*,*N*,*N*′-trimethylethylenediamine in basic solution. The complex with cupric chloride was prepared in absolute ethanol and the resulting blue-green precipitate was recrystallized from acetonitrile to give blue crystals; mp 104–105°C (lit. (1) mp 104–105°C). The identity of this product was confirmed by electrospray mass spectrometry.

The complex with copper acetate, mp 88–90°C, was prepared in an analogous way. The positive ion electrospray mass spectra (ESMS) of all of the complexes were identical, with peaks corresponding to the protonated ligand $m/z = 299.1$ and $Cu(L)CH_3COO^+$ $m/z = 420$ and 422. The presence of acetate in the ion in all of the complexes was attributed to the ESMS mobile phase, which contained methanol, water, and acetic acid. The co-micellar ctab and Triton X-100 were available commercially (BDH).

Purified water was prepared from distilled water by treatment with a Millipore system to achieve a resistivity of at least $17\ M\Omega\ cm^{-1}$.

Tris buffer pH 7.0 was prepared from Tris free base (50 mL, 0.1 M) and hydrochloric acid (46.6 mL, 0.1 M). This mixture was then diluted to 100 mL with purified water.

Substrates

Compound **1** was available from previous work (5). *N*-4-Nitrophenyltrifluoroacetamide **2**, mp 150°C (lit. (12) mp 147°C), was prepared by trifluoroacetylation of *p*-nitroaniline with trifluoroacetic anhydride in dry ether at 0–5°C. Iced water then added to the reaction mixture and the precipitate was filtered and recrystallized from a mixture of methanol and ethanol. Esters **3**, **4**, and **5** were prepared by acetylation of the corresponding phenols with acetic anhydride using the method of Ciampa (13): 2-acetoxy-5-nitrobenzoic acid **3**, mp 152–154°C (lit. (14) mp 153–154°C); 4-acetoxy-3-nitrobenzoic acid **4**, mp 150°C (lit. (15) mp 152°C); 8-acetoxy-5-nitroquinoline **5**, mp 110°C (lit. (16) mp 112–113°C).

Kinetics

(a) Using previously prepared complex (Cu(L)Cl_2 or acetate

A stock solution of the complex (10 mM) was prepared in purified water. The required volume of this solution was added to a volumetric flask; then the required volume of Tris buffer (pH 7.0) was added and the solution was diluted to the mark with purified water. A sample of this solution (3 mL) was then thermally equilibrated in a cuvette in the cell compartment of the Varian DMS 70 UV–VIS spectrophotometer. The reaction was initiated by the addition (microsyringe) of a stock solution (20 μL) of the required substrate (0.01 M) in acetonitrile. Product formation was followed at 375 nm for compounds **1** and **2**, at 380 nm for compounds **3** and **6**, at 415 nm for compounds **4** and **7**, and at 430 nm for compound **5** using a linear recorder. The infinity value and rate constant were calculated by a computer program designed to give the best straight line fit to data (time–absorbance pairs) collected over at least two half-lives. Good agreement between experimental and calculated rate constants and infinity values was obtained for all reaction systems.

(b) Using mixed solutions of ligand and $CuCl_2$, acetate, or nitrate

The required volumes of solutions of the copper salt in water and ligand in water were mixed to provide equimolar amounts of each species and then the required volume of Tris buffer was added. The reactions were initiated and followed as above (*a*).

(c) Using co-micelles

Required volumes of ligand and copper salt were mixed to obtain equimolar amounts of both species followed by aliquots of either ctab or Triton X-100 and Tris buffer (pH 7.0). The mixture was diluted to the mark with purified water. The reactions were initiated and followed as described above (*a*).

Mass spectra

Electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer (VG Bio Tech, Altringham, Cheshire, U.K.) using a mobile phase of 50:50 aqueous methanol also containing 1% acetic acid. Electrospray mass spectra of each preformed complex and the corresponding ligand – copper salt mixture were identical.

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