Source of catalysis of dephosphorylation of *p*-nitrophenyldiphenylphosphate by metallomicelles

Clifford A. Bunton,*[a] Paolo Scrimin*[b] and Paolo Tecilla[c]

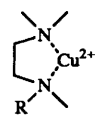
[a] *Department of Chemistry, University of California, Santa Barbara, CA 93106, USA*
[b] *University of Trieste, Department of Chemical Sciences, Via Giorgieri, 1 34127 Trieste, Italy*
[c] *University of Padova, Department of Organic Chemistry and Centro CNR Meccanismi di Reazioni Organiche, Via Marzolo, 1 35131 Padova, Italy*

A series of 2-(dimethylaminomethyl)-6-(alkylaminomethyl)pyridines of various lipophilicities have been synthesized: their complexes with Cu^{II} ions (2a–c: R = CH_3, $C_{12}H_{25}$, $C_{16}H_{33}$) catalyse cleavage of *p*-nitrophenyldiphenylphosphate (PNPDPP). The rate constants were compared with those obtained with Cu^{II} complexes made of ligands *N*-alkyl-*N*,*N*′,*N*′-trimethyl-1,2-diaminoethane (1a–c: R = CH_3, $C_{14}H_{29}$, $C_{16}H_{33}$). When the alkyl group is a C_{12} (or longer) chain complexes 1b,c and 2b,c form metallomicelles. The apparent pK_a of Cu^{II}-coordinated water is *ca.* 8 for 2a,b, and *ca.* 6 and *ca.* 7 for 1a and b, respectively. The aim of the work was to establish the source of rate acceleration in metallomicelles. Because the pyridine-based complexes 2a–c have only one free position for strong coordination to water, while complexes 1a–c have two such positions, complexes 1a–c can potentially activate both the nucleophile and the substrate. The results indicate that: (*a*) the nucleophilicity of the L–Cu^{II}–OH species is similar in metallomicelles and monomeric complexes; (*b*) free OH^- is a slightly better nucleophile than Cu^{II}-bound OH^- in all complexes but 1a; (*c*) electrophilic assistance is only present in the monomeric complex 1a and vanishes in metallomicelles.

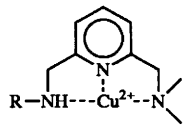
Metal ions are effective catalysts of hydrolyses of esters[1] and amides[2] in aqueous solution. At a pH near neutrality rates may be increased by several orders of magnitude. Complexation of water to transition metal ions markedly increases its deprotonation[3] so that hydroxy complexes exist at pH 6–9 and are effective nucleophiles. Typically, complexes with chelating ligands (L) are used to avoid precipitation of metal oxides or hydroxides. As a result there has been extensive work on optimization of the ligands[4] and metal ions. The metal ions can also act as electrophiles or Lewis acids and catalyse nucleophilic attack by coordinating with the substrates and, in principle, catalysis may involve both formation of the nucleophilic hydroxy complex and electrophilic assistance.

Association colloids, *e.g.* micelles, microemulsions or vesicles, increase the rates of many nucleophilic and electrophilic reactions,[5] so it was reasonable to examine metallosurfactants in this context. Bi- or tri-dentate ligands with hydrophobic, long-chain, alkyl groups have been prepared[6] and complexation with metal ions generates ionic or polar head groups which reside at the interface with water. In these systems rate enhancements are due to the metal ion catalysis and the ability of the association colloid to incorporate a hydrophobic substrate and bring it into contact with the metallo hydroxy residue.

Menger *et al.*[7] exploited these principles by showing that metallomicelles generated by the Cu^{II} complex **1b** are very effective dephosphorylating agents at pH > 6 where one of the associated water molecules is extensively deprotonated. Other groups[8] have exploited systems in which the coordinating subunits have a built-in alkoxy group as the nucleophile. The substrate for much of the work was *p*-nitrophenyldiphenylphosphate (PNPDPP). This hydrophobic substrate binds very strongly to aqueous micelles and reactions with nucleophiles are readily monitored by following the formation of *p*-nitrophenol or phenoxide ion. Spontaneous hydrolysis of this substrate is very slow at pH *ca.* 6, and the rate enhancement by micellized **1b** was estimated[7] to be > 10^5. Our aim was to isolate the factors that contribute to this catalysis.



1 a: R = CH_3
b: R = $C_{14}H_{29}$
c: R = $C_{16}H_{33}$



2 a: R = CH_3
b: R = $C_{12}H_{25}$
c: R = $C_{16}H_{33}$

With this evidence in mind we prepared surfactants with tridentate head groups (**2b,c**) so that only one water molecule or hydroxy group is strongly bound to Cu^{II}. Therefore if the OH^- group acts as a nucleophile there will be no position on Cu^{II} which can strongly interact with the phosphoryl oxygen, *i.e.* electrophilic catalysis should be unimportant. In octahedral Cu^{II} complexes there are four strong coordination positions and two weak apical ones.[9] Furthermore the strong binding[10] of the amines to Cu^{II} in **2a–c** (K_{Cu} > 10^{15}, for the LCu complex, see below) prevents precipitation of hydroxy complexes of aquo Cu^{II} and the formation of L_2Cu complexes, even at relatively high pH.

We also examined catalysis by monomeric complexes **1a**, **2a**, so that we could estimate the extent of non-micellar reactions. There are various treatments[5c] of micellar rate effects that take into account the importance of the concentration of reactants at the micelle–water interface and we planned to test these models with this system. To obtain an insight into the possible contribution of electrophilic catalysis, complexes **1a,c**, related to the system reported by Menger *et al.*,[7] were also examined.

Results and discussion

Synthesis and complexation properties of the ligands

The ligand for formation of complex **1a** is commercially available while preparation of that for complex **1c** has been described previously.[11] The 2,6-bis(aminomethyl)pyridine ligands used for complexes **2** were synthesized from the

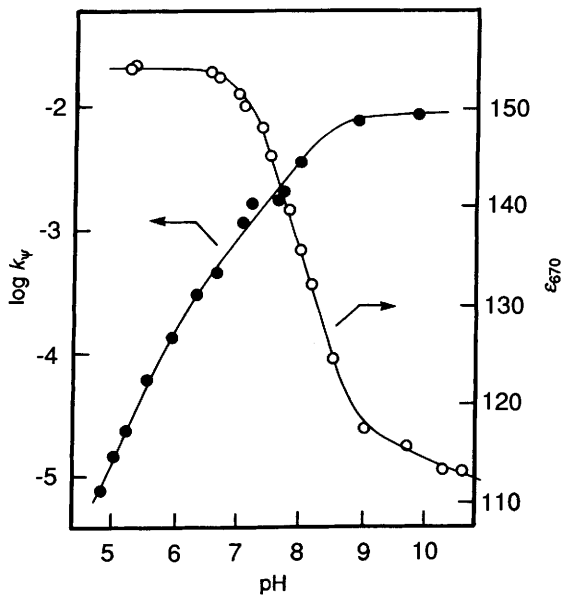


Fig. 1 ●, Log k_ψ *vs.* pH profile for the cleavage of PNPDPP by **2b** at 25 °C; [**2b**] = 2.1 × 10^{-3} mol dm^{-3}, [buffer] = 8 × 10^{-3} mol dm^{-3} above pH 6, [buffer] = 2 × 10^{-2} mol dm^{-3} below pH 6; ○, change of molar absorption, ε, at 670 nm for micellized **2b** as a function of pH in unbuffered solutions; [**2b**] = 2.1 × 10^{-3} mol dm^{-3}

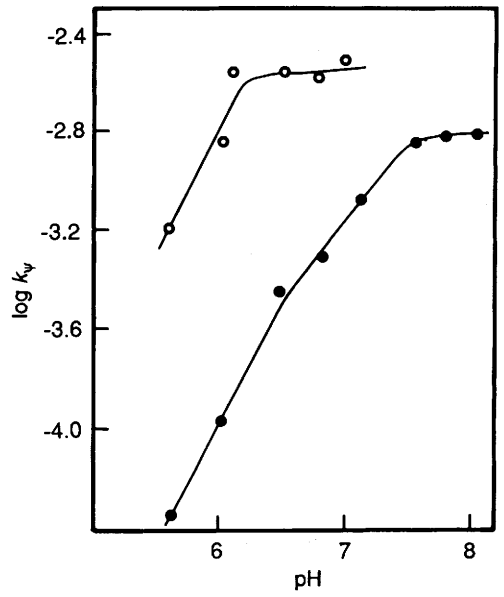


Fig. 2 ●, Log k_ψ *vs.* pH profile for the cleavage of PNPDPP by **1a** at 25 °C; [**1a**] = 2 × 10^{-3} mol dm^{-3}; [buffer] = 2 × 10^{-2} mol dm^{-3} (in 6 vol% of CH_3OH); ○, log k_ψ *vs.* pH profile for the cleavage of PNPDPP by co-micellar **1c**/$CTANO_3$ (due to the low solubility of **1c** alone); [$CTANO_3$] = 10 × [**1c**] = 1 × 10^{-2} mol dm^{-3}; [buffer] = 2 × 10^{-2} mol dm^{-3}

Table 1 Critical micelle concentrations of amphiphilic complexes **2b**, **c**[a]

Complex	[$NaNO_3$]/mol dm^{-3}	cmc/10^{-3} mol dm^{-3}
2b	0	1.0
2b	0.01	0.7
2b	0.03	0.3
2b	0.1	0.3
2c	0	0.3
2c	0.004	0.3
2c	0.012	0.3

[a] At 25.0 °C, pH 9, no buffer.

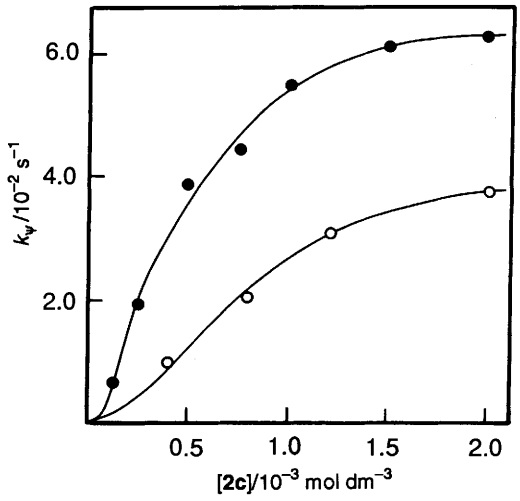


Fig. 3 Observed rate constants, k_ψ, for the cleavage of PNPDPP as a function of [**2c**] at pH 9 in 1 × 10^{-2} mol dm^{-3} CHES; ●, [$NaNO_3$] = 0; ○, [$NaNO_3$] = 2 × 10^{-2} mol dm^{-3}

corresponding 2-hydroxymethyl-6-aminomethylpyridines[12] by conversion of the alcoholic group into the chloride ($SOCl_2$) followed by reaction with dimethylamine. Details of the synthetic procedure are given in the Experimental. Formation of complexes with Cu^{II} is highlighted by the appearance of an absorbance with λ_{max} 660–670 nm and ε in the range 150–110 (dm^3 mol^{-1} cm^{-1}) depending on pH. This change in absorbance was attributed to deprotonation of H_2O bound to the Cu^{II} ion in the complexes. Fig. 1 shows the curve obtained with micellar **2b**; a similar curve was obtained with **2a**. The binding constants of the different ligands with Cu^{II} have not been determined. We assume, to a first approximation, that they are very similar to that reported for 2,6-bis(aminomethyl)pyridine[10] (log K_{Cu} for the 1:1 complex is 15.7) although micellization (and co-micellization with a cationic surfactant) may decrease the binding constants by up to two orders of magnitude.[13] However, this decrease should not significantly change the structures of the complexes. Complexes **2b** and **2c** are surfactants in water with formation of aggregates as shown by surface tension *vs.* concentration profiles. The critical micelle concentrations (cmc) determined from these profiles are in Table 1; at pH 9, the cmc of system **2b** depends markedly on added salt ($NaNO_3$), decreasing up to [$NaNO_3$] *ca.* 3 × 10^{-2} mol dm^{-3} and plateauing at higher concentrations. The cmc of system **2c** is not affected by the addition of $NaNO_3$. Surfactant **1b** has cmc = 1.8 × 10^{-4} mol dm^{-3} from surface tension data.[7]

Kinetics of hydrolysis of PNPDPP

Complexes **2a–c** catalyse the hydrolysis of PNPDPP to extents which depend on pH and the length of the hydrocarbon chain and are much higher for the micelle-forming derivatives **2b,c**. The rate *vs.* pH profile for reactions of complex **2b** is shown in Fig. 1 and gives a pK_a value of *ca.* 8 for the nucleophilic species, the Cu-bound water molecule, in full agreement with the value from the spectroscopic data, mentioned above. The same plot for **2a** also gives a value for pK_a of *ca.* 8. We note that pK_a for micellized **2b** is an apparent value and depends on concentrations of surfactant and added electrolyte. Micellar structure depends upon a balance of forces between the alkyl tails and the head-groups and the bulky head-group of **2b,c** tends to destabilize these micelles.

Fig. 2 shows similar profiles for complexes **1a,c**. The pK_a values for these systems are significantly lower than those for the two pyridine complexes **2a,b** being *ca.* 6 for micellar **1c** and *ca.* 7.3 for **1a**. The pK_a of the water bound to **1c** should be very similar to that of the C_{14} derivative, **1b**,[7] though in this work only an estimated value was given (< 6). Figs. 3 and 4 show catalysis of the hydrolysis of PNPDPP with increasing concentrations of complexes **2c** and **2b**, respectively. The two

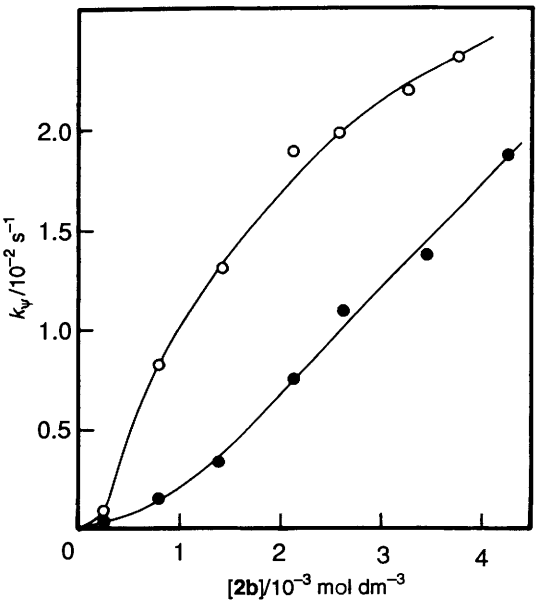


Fig. 4 Observed rate constants, k_ψ, for the cleavage of PNPDPP as a function of [**2b**] at pH 9 and 25 °C in 8 × 10^{-3} mol dm^{-3} CHES; ●, [$NaNO_3$] = 0; ○, [$NaNO_3$] = 4 × 10^{-2} mol dm^{-3}

complexes show remarkably different behaviour in that k_ψ for **2c** reaches a plateau value at 2 mmol dm^{-3} while with **2b** there is no tendency towards saturation. Furthermore $NaNO_3$ increases rates for micellar **2b**, but decreases those for **2c**. Without $NaNO_3$ the apparent binding constant of PNPDPP to micellar **2c** is 5.5 × 10^3 dm^3 mol^{-1}. A similar analysis for **2b** is not possible because of the almost linear dependence of k_ψ on concentration above the cmc. The behaviour of **2c** is that expected for the interaction of a hydrophobic substrate with micelles; that of **2b** needs further consideration.

This difference in behaviour between the two micellar systems is also highlighted by the effects of added salts (Figs. 5 and 6). The rate constants in solutions of the C_{16} derivative **2c** are decreased by addition of different salts and the effects appear to be controlled mainly by the affinity of the anions for the cationic centre[14] and less by their lipophilicities.[15] However, rate constants in solutions of the shorter chain derivative **2b** increase for up to 2–3 mmol dm^{-3} salt concentration and then decrease; this increase appears to be controlled mainly by the lipophilicity of the anion and less by its affinity to Cu^{II}. These responses to the addition of anions are paralleled by effects of buffer concentration on the rate constants (Fig. 7). In particular, buffers of different pK_a and, consequently, of different ionization states, have different rate effects with micellar **2b**. So, at pH 9.8 rates are higher in 2-(cyclohexylamino)ethanesulfonic acid (CHES) (pK_a = 9.3) than in 3-(cyclohexylamino)propanesulfonic acid (CAPS) (pK_a = 10.4) buffer because the first is largely anionic at this pH while the second is zwitterionic with less affinity for the cationic aggregate. The different behaviour of the two aggregates is probably due to different local environments, which, for **2b**, change on the addition of anions with a consequent increase in k_ψ. Such a change does not occur with **2c** and, consequently, the effect on k_ψ is governed by competition between OH^- and the added anions, for the cationic centre. The very high lipophilicity of PNPDPP excludes the alternative explanation of low substrate binding to the micelles. This change of local environment and, perhaps, of morphology of the aggregate with effects on k_ψ seems also to occur with increasing **2b** concentration. As shown in Fig. 4, k_ψ does not reach a plateau value with **2b** and there is a continuous increase in k_ψ as the concentration of the metalloamphiphile increases. Addition of $NaNO_3$ also increases k_ψ. CHES buffer has little

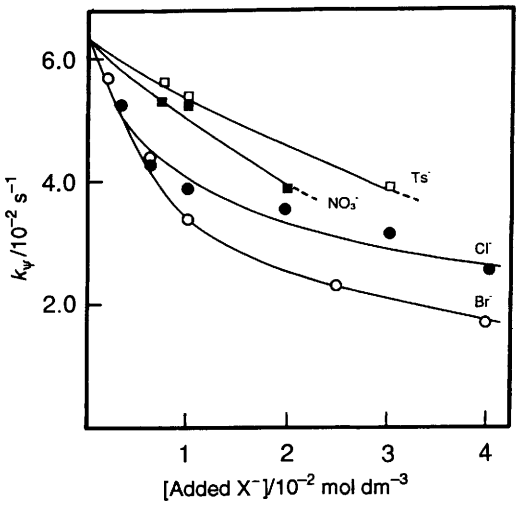


Fig. 5 Anion effects on the rate constant of cleavage of PNPDPP catalysed by micellar **2c**; conditions: pH 9, unbuffered, [**2c**] = 2.1 × 10^{-3} mol dm^{-3}, 25 °C

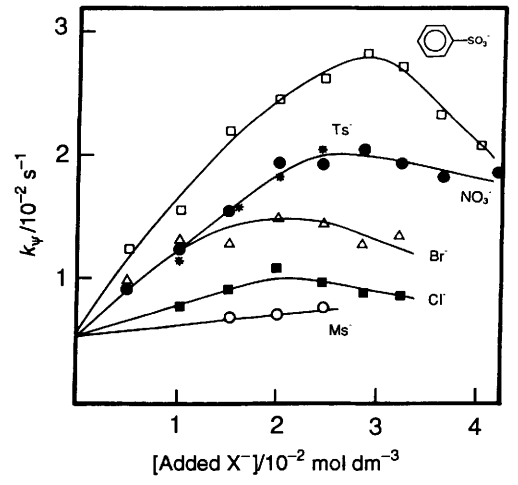


Fig. 6 Anion effects on the rate constant of cleavage of PNPDPP catalysed by micellar **2b**; conditions: pH 9, unbuffered, [**2b**] = 2.1 × 10^{-3} mol dm^{-3}, 25 °C

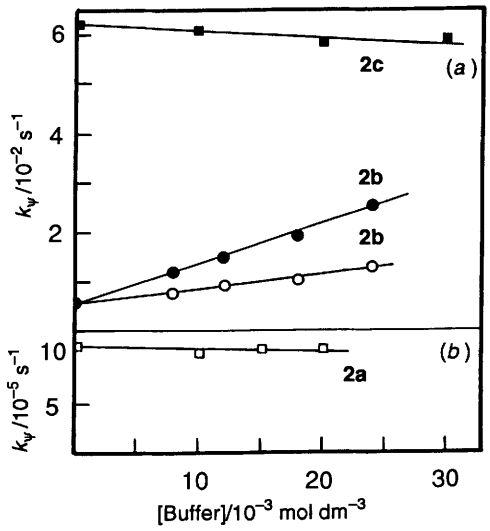


Fig. 7 Buffer effect on the rate constants of hydrolysis of PNPDPP catalysed by the different complexes at pH 9.8 and 25.0 °C; buffers were CHES for **2a**, **2b** and **2c** (filled points) and CAPS for **2b** (empty circles); [**2a**] = 2.5 × 10^{-3} mol dm^{-3}, [**2b**] = [**2c**] = 2.1 × 10^{-3} mol dm^{-3}

effect on the catalysis by monomeric **2a** or micellar **2c** (Fig. 7). Structures of micelles of **2b**,**c** are probably different in that the bulk of the head-group and the shortness of the alkyl tail causes

micelles of **2b** to have a very open structure which is sensitive to added solutes. In addition such open micelles will have lower surface charge densities than micelles of longer-tail surfactants which will decrease their affinity for OH^- and make it, and the dissociation of complexed H_2O, very sensitive to added electrolytes, *e.g.* added electrolytes may decrease head-group spacing and stabilize the micelles, which will increase the catalysis of hydrolysis. However, at the same time they will compete with OH^- and decrease the formation of reactive hydroxy complex. The larger alkyl tails of **2c** stabilize its micelles so that their morphology is not significantly affected by added electrolytes or buffers. We therefore conclude that the effects on catalysis by **2b** are due to changes in micellar structure.

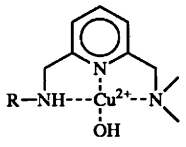
Provided that the metallosurfactants are fully incorporated in co-micelles the catalysis is unaffected by the length of the alkyl tails of **2b,c** (Fig. 8). Increases in the amount of **2b,c** relative to cetyltrimethylammonium nitrate ($CTANO_3$) cause an increase in k_ψ. As shown in the inset, 'dilution' of micellized **2c** by $CTANO_3$ sharply decreases k_ψ, but the effect is more complicated with **2b** where the opposing effects noted above lead to an initial rate increase followed by a modest decline.

The source of catalysis of dephosphorylation

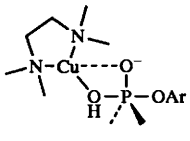
Reactions of PNPDPP with OH^- and the fully deprotonated monomeric hydroxy complexes **1a**, **2a** are overall second-order and rate-constants, k_2^w, are compared in Table 2. The behaviour of the C_{16} metallosurfactant **2c** is relatively simple in that k_ψ increases smoothly towards a plateau value of *ca.* 7×10^{-2} s^{-1} with fully-bound PNPDPP and the hydroxy Cu^{II} surfactant. This first-order rate constant at the micelle–water interface is very similar to that of 5.5×10^{-2} s^{-1} for the reaction of PNPDPP bound to micellized **1b**, provided that the pH is such that complexes are in the hydroxy forms (Fig. 3 and ref. 7). Therefore the reactivity of the $LCu^{II}OH$ group is, to a first approximation, independent of the amino ligand. However, the ligand significantly affects the acid dissociation of $LCuOH_2$. There is a statistical factor of two and electron donation by the pyridine moiety in **2a–c** decreases acid dissociation. The immediate problem is to identify the source of rate enhancements by metallomicelles of **2b,c** and **1b,c** under conditions which ensure complete deprotonation of bound H_2O.

As noted earlier, electrophilic assistance by Cu^{II} could be significant in hydrolyses catalysed by **1**, where, for example, the loss of a water molecule allows coordination of the phosphoryl oxygen in the square plane of Cu^{II}. Such assistance is less likely for hydrolysis catalysed by **2** where only an axial position is available for (weak) coordination. The similarity of values of k_ψ for reactions at micellar surfaces of **2c** and **1b** indicates that electrophilic assistance is not of major significance in the micellar-mediated reactions. However, the reactivity of the two monomeric ligands **1a** and **2a** is quite different. By comparing reactivities at pHs at which both complexes are largely present as hydroxy species, we see that **1a** is at least two orders of magnitude more reactive than **2a**, indicating that with monomeric **1a**, electrophilic assistance plays a role. In accordance with this observation, single Lewis acid catalysis has been estimated by others[16] to increase rate constants of dephosphorylation by two orders of magnitude.

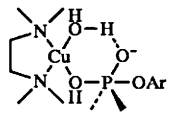
If we accept that formation of an effective nucleophile, $LCu^{II}OH$ (*e.g.* **3**), at low pH is of key importance in these metal



3



4a



4b

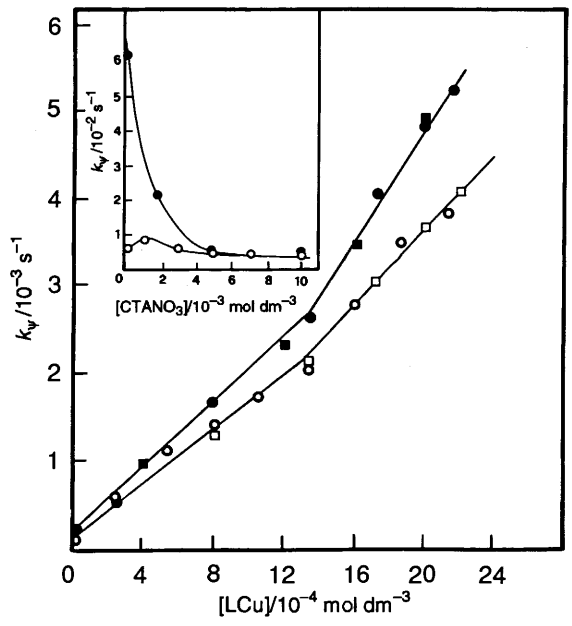


Fig. 8 Rate constants *vs.* complex concentration profiles for the cleavage of PNPDPP at pH 9 and 25.0 °C in co-micelles of **2b** and **2c** with $CTANO_3$; solutions were unbuffered except those without metal complex ([CHES] = 1×10^{-2} mol dm^{-3} in that case); filled symbols: $[CTANO_3] = 5 \times 10^{-3}$ mol dm^{-3}; open symbols: $[CTANO_3] = 1 \times 10^{-2}$ mol dm^{-3}; circles: LCu = **2b**; squares: LCu = **2c**. Inset: effect of $CTANO_3$ on the rate constants in 2×10^{-3} mol dm^{-3} micellized **2b**, ○, and **2c**, ●, in unbuffered solutions, pH 9.

Table 2 Second-order rate constants for nucleophilic attack on PNPDPP in micellar and non-micellar systems[a]

Nucleophile	k_2^w/dm^3 mol^{-1} s^{-1}	k_2^m/10^{-2} dm^3 mol^{-1} s^{-1}
OH^-	0.4	
1a–OH[b]	2	
1b–OH[c]		2.0
1c–OH[c]		2.2
2a–OH[b]	0.04	
2b–OH[c]		0.6
2c–OH[c]		2.6

[a] At 25.0 °C. [b] Values of k_2^w are from plots of k_ψ *vs.* [nucleophile]. [c] Values of k_2^m are from plots of k_ψ *vs.* [metallosurfactant] and eqn. (1).

ion catalysed hydrolyses we can compare nucleophilicities of OH^- in water and coordinated to Cu^{II} in the monomeric complexes **1a** and **2a**. The second-order rate constants are, respectively, 0.4, 2 and 0.04 dm^3 mol^{-1} s^{-1} (Table 2). Despite very large differences in basicities of OH^- in water and co-ordinated in complexes **2a** and **1a**, nucleophilicities are not very different. This result is understandable because hydrogen bonding to OH^-, which strongly decreases its nucleophilicity in water, is reduced by metal complexation, and there may be electrophilic assistance as well as nucleophilic participation by **1a**. Analogous results have been obtained by studying the nucleophilicity of Zn^{II}-bound OH^- in hydrolyses of esters by Kimura and Kotoke.[17] The fact that **1a** is more reactive than free OH^- supports an electrophilic assistance mechanism with this monomeric complex. However this assistance is less important than generation of coordinated OH^- as the nucleophile. The kinetic order shows that a second molecule of the complex is not involved in the reaction. On the assumption that monomeric **1a** catalyses the hydrolysis of PNPDPP in part by electrophilic assistance, the interaction could be directly with Cu^{II} with displacement of coordinated water **4a**. However, this water molecule is more acidic than bulk water, so the interaction could involve hydrogen-bonding through water to phosphoryl oxygen. The structure of the transition state should

be very similar to that of a (hypothetical) trigonal bipyramid and the postulated nucleophilic and electrophilic interactions are illustrated in **4b**. An apical water molecule should be a relatively ineffective electrophile and, hence, not relevant in the process.

Micellar and similar rate enhancements require transfer of reactants from water into the micelles which are treated as a distinct reaction region, *i.e.* as a pseudophase.[5c] In the simplest situation PNPDPP is fully micellar-bound and the pH is chosen so that the complex exists in the hydroxy form (**3**). The first-order rate constant with respect to PNPDPP is then the second-order rate constant in the micellar pseudophase multiplied by the concentration of the nucleophile in that pseudophase, *i.e.* at the micelle–water interface. This concentration can be expressed in various ways. We are interested in comparing second-order rate constants in the aqueous and micellar pseudophases, so it is convenient to express concentration in the latter region as a local molarity. For a functional micelle where every head-group is in the reactive form the local molarity is the reciprocal of the molar volume of the reaction region at the micelle–water interface, V_M (expressed in $dm^3\ mol^{-1}$),[5c] and this approach can be extended to co-micelles of functional surfactants.[18] A variety of values of V_M have been used in fitting micellar rate data to quantitative models.[15,19] For micelles with trimethylammonium head-groups these values range from 0.14 to 0.37 $dm^3\ mol^{-1}$ and they may depend not only upon the surfactant structure, but also upon the nature of the reaction.

In this work we take $V_M = 0.37\ dm^3\ mol^{-1}$ because of the large size of the head-groups of our metallomicelles and the second-order rate constant in the micellar pseudophase, k_2^m, is given by eqn. (1) where k_ψ^{max} is the rate constant for fully

$$k_2^m = k_\psi^{max} V_M \qquad (1)$$

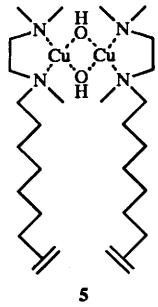
micellar-bound PNPDPP. If we assume that V_M is the same for micelles of **1c**, **2c** and of the C_{14} surfactant **1b** used by Menger *et al.*[7] we estimate k_2^m to be 0.020 $dm^3\ mol^{-1}\ s^{-1}$ for their system, which, as noted earlier, is very similar to $k_2^m = 0.026\ dm^3\ mol^{-1}\ s^{-1}$ for the reaction catalysed by our deprotonated C_{16} surfactant **2c** and the corresponding value with **1c** is 0.022 $dm^3\ mol^{-1}\ s^{-1}$. These results show that the nucleophilicity of a LCu^{II}–OH species in a metallomicelle is not affected by the change from a bidentate ligand as in **1b** to a tridentate ligand as in **2c** or of the alkyl tail from C_{14} to C_{16}. However, the large difference in the acid dissociation constants of **1b** and **2c** leads to very different overall rate constants at pH *ca.* 6 where only **1b** is extensively deprotonated. This result contrasts with those obtained with the monomeric ligands where complex **1a** is significantly more reactive than complex **2a**. So the experimental evidence indicates that electrophilic assistance vanishes upon micellization. One may speculate that the packing of **1b,c** in micellar aggregates does not allow the substrate to take advantage of the interaction with the metal ion and the hydrophobic environment at the same time. This question is discussed later.

The next question is: does micellization affect the nucleophilicity of the LCu^{II}–OH species? For many micellar-mediated bimolecular reactions second-order rate constants at the micelle–water interface are similar to, or somewhat lower than, those of the corresponding reactions of the monomeric species in water.[5c] These generalizations also apply to reactions mediated by functional micelles, provided that effects of substrate incorporation and functional group deprotonation are taken into account. As noted earlier these comparisons depend upon assumptions regarding the dimensions of the reaction region at the micelle–water interface, so our model is only a first approximation.

The kinetic data for the reaction catalysed by the C_{16} surfactant **2c** are fitted by our very simple model. The situation is more complex for the C_{12} surfactant **2b** to some extent because we could not obtain, experimentally, limiting values of k_ψ because the lack of solubility prevented use of higher concentrations. However, we can generate co-micelles of **2b** and $CTANO_3$, which allows extensive micellar incorporation of PNPDPP, but 'dilutes' the LCu^{II}–OH species in the micellar pseudophase. To a first approximation, with fully-bound PNPDPP, the rate with added $CTANO_3$ is that in the (hypothetical) LCu^{II}–OH micelle multiplied by the mole fraction of the reactive nucleophile, *i.e.* by $[LCu^{II}\text{–}OH]/([LCu^{II}\text{–}OH] + [CTANO_3])$. This treatment neglects effects due to changes in the cmc due to added NO_3^- and probable changes in the value of V_M and is therefore especially suspect in dilute surfactant. However, the results are quantitatively reasonable, especially in the light of the similar reactivities measured for **2b** and **2c** in $CTANO_3$ co-micelles (Fig. 8). The second-order rate constants determined in this way (Table 2) are slightly lower than the second-order rate constant determined for homomicellar **1c**, **2c** mainly because we could not take into account the effect of added counter ion (NO_3^-), which probably decreases the rate constant in co-micelles. Considering this, and the above limitations, and comparing the reactivity of monomeric **2a** with metallomicelles we conclude that micellization does not affect the nucleophilicity of the LCu^{II}–OH species. This observation is in full accord with the results obtained with classical cationic micelles and hence metallomicelles do not constitute a class apart. Consequently, one need not invoke special features of Cu^{II} when bound in the micellar environment, *i.e.* micelles have no mysterious or unusual effects on the rates of these reactions. (However, we note that there are exceptions to this generalization, especially for some spontaneous hydrolyses in solution of chemically inert surfactants.[5c])

Quite unexpectedly, micellization does influence the interaction of the substrate with the metal ion resulting in the disappearance of any electrophilic contribution to the catalytic process by **1** where k_2^w for **1a** is much greater than k_2^m for **1b,c**. This result shows that with the diamino ligands micellization does not affect 'strong' interactions, *e.g.* with OH^-, but does affect weaker interactions, *e.g.* of phosphoryl oxygen in the transition state. These weaker interactions may involve second sphere coordination which will affect the hydrophilic–lipophilic balance at the micelle–water interface and therefore the orientation of PNPDPP in this region or effective competition with the counter ion present at the micelle–water interface.

We must also consider the possibility that in these systems micellization induces (at least in part) formation of dinuclear complexes[20] such as **5**. In such a complex, the nucleophilicity of



5

Cu-bound OH^- would be further reduced and coordination of the substrate to Cu^{II} would require the unlikely displacement of one OH^- (and not H_2O as in the mononuclear complex). Sluggish nucleophilic reactivity by similar dinuclear complexes has been reported by Linkletter and Chin.[21] However, since reactivity is very similar in homomicelles and co-micelles where dilution of the complex in non-functional surfactant would depress formation of **5**, we conclude that the formation of these

complexes is not the major cause of the decreased reactivity in aggregates.

Small morphological changes or secondary interactions in normal ionic micelles have only modest effects on nucleophilic reactivity and, in the first approximation, can be overlooked. In the case of aggregates made of **1b,c**, where micellization affects the electrophilic contribution to the catalytic process, the decrease in the reactivity (in comparison with monomeric **1a**) is remarkable. Similar small changes in the coordination sphere of Cu^{II} have been recently invoked[22] to explain enhanced enantioselectivities in hydrolyses of α-amino acid esters by chiral metallomicelles and may constitute an important feature in the modulation of reactivity in metalloaggregates.

Conclusions

Micellar effects on the catalysed hydrolysis of PNPDPP by Cu^{II} complexes are understandable in terms of concentration of reactants at micelle–water interfaces. The high rates of reaction, relative to those in the absence of catalyst, are due to the introduction of a new reaction path and the concentration effect. For complexes of tridentate ligands, **2a,b,c**, the micellar rate effects are consistent with pseudophase treatments and rate constants are similar for reactions with amphiphilic bi- and tridentate complexes. Unexpectedly reactions of the micellized bidentate complexes (**1b,c**) are slower than predicted from evaluation of the second-order rate constant for the reaction of the monomeric complex **1a**.

Finally we note that large rate accelerations have been recently reported when two metal ions are involved in the rate-limiting step of dephosphorylation.[23] Though, undoubtedly, at the micellar surface metal ions are brought in close proximity, the conditions for taking advantage of such bimetallic interaction is not attained in these metallomicelles.

Experimental

General

NMR spectra were recorded with a Bruker WP 200 SY spectrometer operating at 200 MHz and chemical shifts are reported relative to internal Me_4Si. *J* values are given in Hz. Surface tension measurements were performed with a Kruss type 8451 tensiometer. Kinetic traces were recorded on Perkin-Elmer Lambda 5 or Beckman instruments equipped with thermostatted cell holders. Temperature control was ±0.1 °C. Microanalyses were performed by the Laboratorio di Microanalisi of the Department of Organic Chemistry in Padova.

Materials

$Cu(NO_3)_2$ was analytical grade commercial product. Metal ion stock solutions were titrated against EDTA following a standard procedure.[24] Buffer solutions were prepared using twice distilled water. The buffer components[25] were used as supplied by the manufacturers. PNPDPP[26] and $CTANO_3$[27] were synthesized according to reported procedures. Commercial *N,N,N',N'*-tetramethyl-1,2-diaminoethane was distilled prior to use and stored in the dark at 5 °C. The synthesis of compound **1c** has already been reported.[11]

General procedure for the synthesis of compounds 2a–c

2-Hydroxymethyl-6-(alkylaminomethyl)pyridine[8a,28] (6 mmol) was dissolved in 20 cm^3 of freshly distilled $SOCl_2$ and stirred, protected from moisture, at room temperature overnight. $SOCl_2$ was then removed under reduced pressure (**CAUTION**: reacts exothermically with water!), the solid was treated with toluene (20 cm^3) and the toluene evaporated to leave a white solid. This solid was slowly dissolved in a 33% ice-cool solution of dimethylamine in dry ethanol and stirred at room temperature for two days. Evaporation under reduced pressure of the solvent gave a slightly brown solid. To obtain the free amine the material obtained from the starting aminopyridine with the shortest alkyl chain (alkyl = methyl) was passed down a column of basic ion-exchange resin (IRA 400, Fluka) using methanol as solvent, while the more lipophilic derivatives (alkyl = dodecyl and hexadecyl) were treated with 0.01 mol dm^{-3} NaOH and extracted with $CHCl_3$. The crude free amine obtained after evaporation of the organic solvent was subsequently purified by chromatography on a silica column (CH_2Cl_2:CH_3OH:NH_4OH, 84:15:1). The following compounds were obtained.

2-(Methylaminomethyl)-6-(dimethylaminomethyl)pyridine (2a). A pale yellow oil, 40% yield. $\delta_H(CDCl_3)$ 2.05 (1 H, br s, NH), 2.28 [6 H, s, $N(CH_3)_2$], 2.47 [3 H, s, $N(CH_3)$], 3.58 (2 H, s, NCH_2), 3.84 (2 H, s, NCH_2), 7.17, 7.24 (2 H, 2 d, *J* 7.22, Py H3 and H5) and 7.61 (1 H, t, *J* 7.22 Py H4) (Found: C, 66.85; H, 9.63; N, 23.35. Calc. for $C_{10}H_{17}N_3$: C, 67.00; H, 9.56; N 23.44%)

2-(Dodecylaminomethyl)-6-(dimethylaminomethyl)pyridine (2b). A yellow thick oil, 65% yield. $\delta_H(CDCl_3)$ 0.84 (3 H, br t, CH_3), 1.23 [18 H, m, $(CH_2)_8$], 1.53 (2 H, m, CH_2CH_2N), 1.95 (1 H, br s, NH), 2.27 [6 H, s, $N(CH_3)_2$], 2.64 [2 H, t, *J* 6.5, $(CH_2)_nCH_2N$], 3.56 (2 H, s, NCH_2), 3.88 (2 H, s, NCH_2), 7.14, 7.23 (2 H, 2d, *J* 7.02, Py H3 and H5) and 7.59 (1 H, t, *J* 7.02, Py H4) (Found: C, 75.60; H, 11.81; N, 12.55. Calc. for $C_{21}H_{39}N_3$: C, 75.62; H, 11.78; N, 12.60%).

2-(Hexadecylaminomethyl)-6-(dimethylaminomethyl)pyridine (2c). A yellow oil, becomes solid in the refrigerator, 68% yield. $\delta_H(CDCl_3)$ 0.81 (3 H, br t, CH_3), 1.23 [26 H, m, $(CH_2)_{13}$], 1.51 (2 H, m, CH_2CH_2N), 1.85 (1 H, br s, NH), 2.26 [6 H, s, $N(CH_3)_2$], 2.61 [2 H, t, *J* 6.6, $(CH_2)_nCH_2N$], 3.53 (2 H, s, NCH_2), 3.86 (2 H, s, NCH_2), 7.16, 7.25 (2 H, 2 d, *J* 7.0, Py H3 and H5) and 7.60 (1 H, t, *J* 7.0, Py H4) (Found: C, 77.00; H, 12.21; N, 10.70. Calc. for $C_{25}H_{47}N_3$: C, 77.06; H, 12.16; N, 10.78%).

Kinetic studies

Solutions were prepared in twice distilled water. In the absence of buffer, the pH was adjusted in the cuvette by addition with a microsyringe of the appropriate amount of a 0.1 mol dm^{-3} NaOH solution. For buffered solutions the appropriate amount of buffer was added in the cuvette to obtain the buffer concentration reported in the results. pH control after each kinetic run showed no change in the buffered solution while those unbuffered showed only a small decrease of *ca.* 0.2 pH units. Clearly with the systems devoid of added buffer the copper complexes act as buffers since the kinetics were performed at a pH close to the pK_a of the Cu-bound H_2O. Solutions without surfactants contained 6% (v/v) of CH_3OH to ensure complete solubilization of the substrate. Kinetics were typically started by addition of 0.02 cm^3 of a 2×10^{-3} mol dm^{-3} solution of substrate in CH_3CN in 2 cm^3 of solution and followed by monitoring the absorbance increase at 400 nm (pH > 6.3) or 317 nm (pH < 6.3) for at least five half-lives. Rate constants were obtained by linear plots of $\log(A_\infty - A_t) - \log(A_\infty - A_0)$ *vs.* time whenever A_∞ could be determined and by non-linear regression analysis of the absorbance data *vs.* time in the other cases.

Acknowledgements

C. A. B. thanks the US Army Office of Research for financial support; P. S. thanks the Fulbright Foundation for a travel grant and the CNR (Rome) for financial support.

References

1 (*a*) J. Chin and V. Jubian, *J. Chem. Soc., Chem. Commun.*, 1989, 839; (*b*) J. Chin and M. Banaszczyk, *J. Am. Chem. Soc.*, 1989, **111**, 2724;

(*c*) P. Hendry and A. M. Sargeson, *J. Am. Chem. Soc.*, 1989, **111**, 2521; (*d*) J. R. Morrow and W. C. Trogler, *Inorg. Chem.*, 1988, **27**, 3387; (*e*) J. R. Morrow and W. C. Trogler, *Inorg. Chem.*, 1989, **28**, 2330; (*e*) H. Sigel, *Coord. Chem. Rev.*, 1990, **100**, 453; (*f*) J. A. Connolly, M. Banaszczyk, R. C. Hynes and J. Chin, *Inorg. Chem.*, 1994, **33**, 665; (*g*) M. Wall, R. C. Hynes and J. Chin, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1633.

2 (*a*) A. Schepartz and R. Breslow, *J. Am. Chem. Soc.*, 1987, **109**, 1814; (*b*) J. T. Groves and R. R. Chambers, Jr., *J. Am. Chem. Soc.*, 1984, **106**, 630; (*c*) J. Chin, V. Jubian and K. Mrejen, *J. Chem. Soc., Chem. Commun.*, 1990, 1326; (*d*) L. M. Sayre, *J. Am. Chem. Soc.*, 1986, **108**, 1632.

3 F. Basolo and R. G. Pearson, *Mechanisms of Inorganic Reactions*, Wiley, New York, 1967, 2nd edn., p. 32.

4 J. Chin, *Acc. Chem. Res.*, 1991, **24**, 145 and references therein.

5 (*a*) J. H. Fendler and E. J. Fendler, *Catalysis in Micellar and Macromolecular Systems*, Academic Press, New York, 1975; (*b*) J. H. Fendler, *Membrane Mimetic Chemistry*, Wiley, New York, 1982; (*c*) C. A. Bunton and G. Savelli, *Adv. Phys. Org. Chem.*, 1986, **22**, 213.

6 (*a*) W. Tagaki and K. Ogino, *Top. Curr. Chem.*, 1985, **128**, 144; (*b*) P. Scrimin and U. Tonellato in *Surfactants in Solution*, eds. K. L. Mittal and D. O. Shah, Plenum Press, New York, 1991, vol. 11, p. 349; (*c*) S. H. Gellmann, R. Petter and R. Breslow, *J. Am. Chem. Soc.*, 1986, **108**, 2388.

7 F. M. Menger, L. H. Gan, E. Johnson and D. H. Durst, *J. Am. Chem. Soc.*, 1987, **109**, 2800.

8 (*a*) P. Scrimin, P. Tecilla and U. Tonellato, *J. Org. Chem.*, 1991, **56**, 161; (*b*) J. G. J. Weijnen, A. Komdijs and J. F. J. Engbersen, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1121; (*c*) J. G. J. Weijnen and J. F. J. Engbersen, *Recl. Trav. Chim. Pays-Bas*, 1993, **112**, 351.

9 B. J. Hathaway in *Comprehensive Co-ordination Chemistry*, eds. G. Wilkinson, R. D. Gillard and .A. McCleverty, Pergamon Press, Oxford, 1987, vol. 5, pp. 596–634.

10 Y. Couturier and C. Petitfaux, *Bull. Soc. Chim. Fr.*, 1978, I-435.

11 P. Scrimin, P. Tecilla and U. Tonellato, *Tetrahedron*, 1995, **51**, 217.

12 C. Tondre, S.-G. Son, M. Hebrant, P. Scrimin and P. Tecilla, *Langmuir*, 1993, **9**, 950.

13 P. Scrimin, P. Tecilla, U. Tonellato and T. Vendrame, *J. Org. Chem.*, 1989, **54**, 5988.

14 R. M. Smith and A. E. Martell, *Critical Stability Constants*, Plenum Press, New York, 1975, vol. 4.

15 L. S. Romsted in *Surfactants in Solution*, eds. K. L. Mittal and B. Lindman, Plenum Press, New York, 1984, vol. 2, p. 1015.

16 P. Hendry and A. M. Sargeson, *Inorg. Chem.*, 1990, **29**, 92.

17 (*a*) E. Kimura and T. Koike *Comments Inorg. Chem.*, 1991, **11**, 285; (*b*) T. Koioke and E. Kimura, *J. Am. Chem. Soc.*, 1991, **113**, 8935.

18 (*a*) C. A. Bunton, in *Solution Chemistry of Surfactants*, ed. K. L. Mittal, Plenum Press, New York, 1979 vol. 2, p. 519; (*b*) C. A. Bunton, F. H. Hamed and L. S. Romsted, *J. Phys. Chem.*, 1982, **86**, 2103; (*c*) R. Fornasier and U. Tonellato, *J. Chem. Soc., Faraday Trans.*, 1980, **76**, 1301.

19 K. Martinek, A. K. Yatsimirski, A. V. Levashov and I. V. Berezin in *Micellization, Solubilization and Microemulsions*, ed. K. L. Mittal, Plenum Press, New York, 1977, vol. 1, p. 489.

20 E. Arenare, P. Paoletti, A. Dei and A. Vacca, *J. Chem. Soc., Dalton Trans.*, 1972, 736.

21 B. Linkletter and J. Chin, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 472.

22 P. Scrimin, P. Tecilla and U. Tonellato, *J. Org. Chem.*, 1994, **59**, 4194.

23 (*a*) D. Wahann, R. C. Hynes and J. Chin *J. Chem. Soc., Chem. Commun.*, 1994, 1441; (*b*) B. K. Takasaki and J. Chin, *J. Am. Chem. Soc.*, 1994, **116**, 1121; (*c*) M. Wall, R. C. Hynes and J. Chin, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1633; (*d*) A. Tsubouchi and T. C. Bruice, *J. Am. Chem. Soc.*, 1994, **116**, 11614.

24 Z. Holzbecher, *Handbook of Organic Reagents in Inorganic Analysis*, Wiley, Chichester, 1976.

25 N. E. Good, G. D. Winget, W. Winter, T. N. Connolly, S. Izawa and R. M. M. Smith, *Biochemistry*, 1966, **5**, 467.

26 W. M. Gulick Jr., and D. H. Geske, *J. Am Chem. Soc.*, 1966, **88**, 2928.

27 (*a*) E. L. Colichman, *J. Am. Chem. Soc.*, 1950, **72**, 1834; (*b*) E. J. Bair and C. A. Kraus, *J. Am. Chem. Soc.*, 1951, **73**, 1129.

28 P. Scrimin, P. Tecilla and U. Tonellato, *J. Org. Chem.*, 1994, **59**, 18.

Paper 5/04221F
Received 30*th June* 1995
Accepted 8*th September* 1995