Coordination Chemistry Reviews 253 (2009) 2150–2165

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Amphiphilic metalloaggregates: Catalysis, transport, and sensing

Fabrizio Mancin[a], Paolo Scrimin[a], Paolo Tecilla[b,*], Umberto Tonellato[a]

[a] Dipartimento di Scienze Chimiche, and ITM-CNR, Padova Section, Università di Padova via Marzolo 1, I-35131 Padova, Italy
[b] Dipartimento di Scienze Chimiche, Università di Trieste, via L. Giorgeri 1, I-34127 Trieste, Italy

Contents

1. Introduction 2151
2. Metalloaggregates as hydrolytic catalysts 2151
   2.1. Background 2151
   2.2. Lipophilic transition metal ligands complexes as hydrolytic catalysts 2152
   2.3. Enantioselective cleavage of α-amino esters in metallomicellar aggregates 2153
   2.4. Chemical differentiation of vesicular bilayer 2155
   2.5. Anchoring amphiphilic metal complexes on the surface of a nanoparticle: a new paradigm for really cooperative hydrolytic metalloaggregates 2156
3. Lipophilic ligands as catalysts for transport processes 2158
   3.1. Ion transport across vesicular bilayers 2158
   3.2. Ion transport across bulk chloroform membrane 2159
4. Fluorescent chemical sensing in surfactant aggregates 2160
   4.1. Self-Assembled fluorescent chemosensors in aggregates 2161
   4.2. From micelles to silica nanoparticles 2162
5. Conclusions 2163
   References 2164

ARTICLE INFO

Article history:
Received 20 January 2009
Accepted 17 March 2009
Available online 27 March 2009

Keywords:
Surfactant aggregates
Catalysis
Transport
Chemosensing
Self-assembly

ABSTRACT

Surfactant aggregates and in particular micelles can be regarded as nanosized molecular containers which can capture and concentrate in their small volume lipophilic and ionic species. Exploiting the self-assembling nature of such aggregates is therefore possible to easily construct supramolecular assemblies in which several and potentially different functionalities may perform highly specific functions such as catalysis, transport, and sensing. In this review, we will report the achievements obtained with metallomicelles, which are surfactant aggregates able to concentrate at the aggregate–water interface a high number of metal ions. The most common strategy for the formation of metallomicelles is the use of lipophilic ligands able to bind the desired metal ion. The lipophilic complex thus formed can be micellized together with common surfactants forming a co-micellar aggregate or, depending on its structure, can form a homo-aggregate. The peculiar features of metallomicelles can be exploited in the metallo-catalyzed hydrolysis of several relevant substrates such as esters of carboxylic acids, amino acids and phosphoric acids with million-fold observed acceleration, at neutral pH. A detailed kinetic analysis has shown that the relevant parameters for the hydrolytic activity are (a) the proximity of the reactants in the aggregate; (b) the apparent lowering of the pK_a of the nucleophilic function (metal ion coordinated water molecule or other nucleophiles). Moreover, playing with the structure of the ligand other and more interesting features can be obtained. Important examples are the enantioselective cleavage of amino acid esters, the transport of ionic substrate across membranes and the controlled release of encapsulated molecules from liposomes. A completely different application of micellized ligands is sensing. In this case, the aggregate behaves as a template favoring the proximity between a fluorescent dye and the ligand so that complexation of the metal ion results in quenching of the fluorescence emission of the dye. Following this strategy self-assembled chemosensors for transition metal ions have been prepared.

* Corresponding author. Tel.: +39 040 5583925; fax: +39 040 5583903.
E-mail addresses: fabrizio.mancin@unipd.it (F. Mancin), paolo.scrimin@unipd.it (P. Scrimin), ptecilla@units.it (P. Tecilla), umberto.tonellato@unipd.it (U. Tonellato).

0010-8545/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ccr.2009.03.015

1. Introduction

In the last four decades, the world of surfactant-like aggregates has attracted quite a large interest from scientists with diverse backgrounds. A large variety of morphologies, besides those of the best known micelles and vesicles, have been uncovered for these systems comprising virtually any relatively large organic structure dispersible in water [1]. Such interest is partially justified by the relevance of surfactant aggregates in numerous industrial applications such as, for example, detergency, lubrication, medicinal chemistry, and cosmetology, although over the years new and intriguing properties, as well as new applications of the old ones, have been investigated in several different and apparently unrelated areas. As a matter of fact, surfactant aggregates are now used in research areas ranging form biomimetic to material chemistry [2].

At the most basic level of interpretation, the success of surfactant aggregates is related to their self-assembled nature and to their ability to form in water pseudo-phases with completely different properties with respect to the aqueous solution, where the surfactants are dispersed. Micelles, in particular, may be viewed as nanosized molecular containers able to capture in their small volume lipophilic and ionic species thanks to hydrophobic and/or electrostatic interactions [3]. This peculiar ability prompted, more than 20 years ago, a debate between chemists working in the emerging field of Supramolecular Chemistry [4], centered on the following conceptual point [5]: may surfactant aggregates, such as micelles and liposomes, be considered supramolecular receptors? Strictly speaking aggregates made by simple surfactants are not receptors. In fact, they do associate a variety of substrates, at least in aqueous solutions, but they bind them with little or no recognition, thus violating one of the main requisites of a proper receptor. Yet, the aggregates are formed by exploiting weak non-covalent interactions between the surfactants and as such they may be envisaged as supramolecular systems. They bring together binding sites but, normally, they do not arrange them in suitable patterns. Beside the classification problems, whose relevancy may appear not fundamental, the cross-fertilization between the two fields was strong and founding concepts of the supramolecular chemistry strongly influenced the field of surfactant aggregates chemistry. As a consequence, the aggregates were "engineered" in order to perform functions inspired by supramolecular systems and exploiting the self-assembling nature of such aggregates it was possible to design assemblies in which several and potentially different functionalities may perform highly specific functions such as recognition, catalysis, translocation and sensing [6].

A bridge between surfactant and supramolecular chemistry was the thread of our research work of those years, due to the fact that we had been working in the field of surfactant chemistry with the aim of realizing biomimetic-type catalysts. Over the years, we devoted much attention to the realization of functionalized micellar or vesicular systems as catalysts of the hydrolytic cleavage of esters or amides with remarkable results [7]. Later on, we switched our attention to metallo-micellar or metallo-vesicular systems which are aggregates made by or containing lipophilic metal complexes, prevalently based on Cu^{2+} or Zn^{2+} metal cations [8]. Results from our and other laboratories demonstrated that such metallo-aggregates are powerful catalysts for the hydrolytic cleavage of carboxylic and phosphoric acid esters. More importantly, these studies highlighted some special features emerging from the combination of metal complexes and surfactants, which led to the exploitation of new functions such as recognition (enantioselective hydrolysis), sensing and translocation of metal ions and organic molecules. These functions are typical of supramolecular systems so that metallo-aggregates may be viewed as supramolecular receptors of their own kind.

In this review, we will focus on these properties and functions trying to highlight aspects that make the reactivity and the other behaviors in metallo-aggregates peculiar respect to homogenous solution. Accordingly, rather than review the many systems reported in the literature, we will concentrate the attention on selected examples, taken mainly from our work, which better highlight the peculiarities of the system. For comprehensive reviews of several aspects of metallo-aggregates the reader may refer to the other excellent contributions to this special issue.

2. Metalloaggregates as hydrolytic catalysts

2.1. Background

Since the early work by Hartely (1935), micellar or vesicular aggregates are known to influence rates and equilibria [3]. Three decades later scientists developed a better definition of the structures and morphologies of the aggregates and started working on the reactivity in micelles, vesicles, microemulsions and the like as models of biological membranes [9]. The similarity with biological systems was extended to enzyme reactivity although this last aspect was often over-emphasized as the analogy is mostly restricted to formal kinetic aspects and is, in general, unjustified since very little, if any, substrate selectivity or stereospecificity was observed [10].

Today the origin of the changes in equilibria and reactivity is reasonably defined [11,12]. The key feature of any type of aggregate is that it incorporates lipophilic solutes and, if made of ionic components, attracts ions [13]. The kinetic effects (acceleration or retardation) much depend on the type of reaction, on the nature of the components and on the reactants. Taking aqueous micelles as exemplary and best known cases of aggregates of amphiphilic species, a given organic substrate is transferred from bulk solvent (water) to the aggregate pseudophase where it may experience: (i) a different, less polar, environment: this may be highlighted by the kinetic effects observed in simple unimolecular processes; (ii) the proximity of other reactant species that may be also transferred in the aggregate or surround it: this is the main source of the kinetic effects in the case of bimolecular (or higher order) reactions. However, taking the hydrolytic cleavage of activated esters (such as p-nitrophenyl acetate PNPA or hexanoate, PNPH) as a test reaction, it was found that aggregates made of "inert" surfactants (i.e. devoid of functional groups), such as cationic CTAB, anionic SDS, or neutral Triton X-100, (see Fig. 1), produce rather modest rate effects and not such to justify the hype for micellar catalysis [3]. The main message from these early studies was hence that rate enhancements for bimolecular reactions in aggregates is only the result of bringing together reagents in a small volume and not of some peculiar property of the "organized" medium, as the aggregate pseudo-phase was often termed.

In order to obtain more reactive systems mimicking on one hand the mode of action of enzymes and, on the other, act as catalysts in their own right, functionalized aggregates were investigated [7]. These are made of amphiphilic molecules featuring covalently bound nucleophiles or other reactive groups, so that any functionalized component is also a potential reactant for the hydrolytic cleavage of an activated substrate. In the case of micelles, most frequently such components were cationic and the reactive groups (NuH) used were often inspired by the reactive sites of popular enzymes (Fig. 1b). Very large rate enhancements relative to reactions in water were observed, particularly for solutions at pHs lower but not too far from the apparent pK_a of NuH, where the effective nucleophile is Nu^-. In fact, the main advantage in using cationic rather than neutral or anionic aggregates comes from the fact that the apparent pK_a of the reactive function is up to 1.5 units lower than that of water dispersed, non-aggregated, analogs. However,

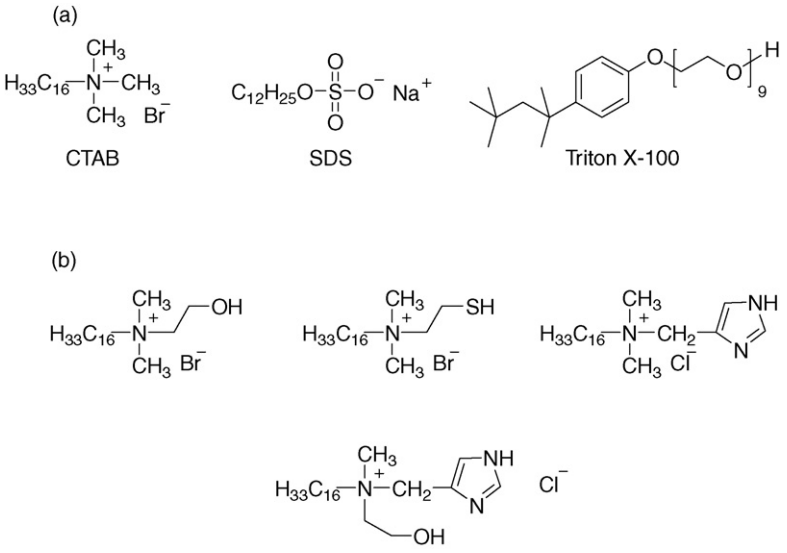


Fig. 1. (a) Chemical structures of common surfactants. (b) Examples of functionalized surfactants taken from Ref. [14].

by taking these factors into account, it turned out that in the great majority of the cases considered, the second-order rate constants of the reaction between Nu^- and the substrate were very similar in the aggregate and in the bulk phase [14]. Again, the rate accelerations observed also with functionalized aggregates were essentially due mostly to concentration effects [15].

There has been a heated debate on whether micellar aggregates work cooperatively or not. Obviously the answer much depends on the definition of cooperativity given. Certainly micelles and other aggregates like vesicles and liposomes are collection of monomeric species that can only operate as a collective entity and in this regard they are cooperative ensembles. However, most of the effects observed are due, as clearly stated above, to binding processes rather than to an actual involvement of more catalytic units operating in a concerted matter as one would expect for a really cooperative process. Thus the typical inflection in the rate vs. concentration profile observed in the plots reporting the reactivity of these aggregates is due to the formation of the aggregates (c.m.c.) and it indicates the formation of the pseudo-phase where the reactants will be hosted but it is not an indication of the cooperativity between single monomers embedded in the micellar aggregate. As a matter of fact whenever the reactivity has been studied with mixtures of functional and inert surfactants and their relative concentration was changed at fully bound substrate, only straight lines were observed, a behavior identical to that observed in homogeneous solutions and indicative of bimolecular, non-cooperative, processes. This, in our opinion, should settle the issue against cooperativity in these systems [16].

2.2. Lipophilic transition metal ligands complexes as hydrolytic catalysts

Functionalized aggregates can turn into much more effective catalysts for the hydrolysis of carboxylate or phosphate esters if they are made by or incorporate transition metal ions complexes to give assemblies termed metalloaggregates [17]. The idea of investigating metalloaggregates was inspired by the mode of action of metalloenzymes, such as the Zn^{2+} containing carboxypeptidase A, and supported by the well known catalytic effects played by metal cations in hydrolytic cleavage reactions [18]. These effects are known to involve: (a) Lewis acid catalysis; (b) charge neutralization; (c) activation of nucleophilic functions or coordinated water molecules by substantially decreasing their pK_a, and, hence, nucleophilic catalysis; (d) assistance in leaving group departure. Moreover, although it has been largely overlooked, the most relevant role of the metal ion is probably what is known as the template effect, i.e. the capability of the ion, bound to a properly designed ligand, to bind also the substrate so that reactant and substrate are brought into proximity and somehow organized or oriented.

Our work started with the synthesis and investigation of hydroxy-functionalized lipophilic pyridine-based ligands such as **1** (Fig. 2), to cite the prototype of a large variety of compounds that may form micelles in aqueous solution [19]. They are rather strong ligands for a number of transition metal ions, in particular Cu^{2+}, and their complexes form aggregates or are easily included in aggregates of inert surfactants like cetyltrimethylammonium bromide (CTAB). Following a scrutiny of a number of activated esters of carboxylic or phosphoric acids as substrates, the most impressive results were obtained in the case of α-amino acid esters and the substrate of choice for the assessment of the efficacy of the systems was the *p*-nitrophenyl picolinate (PNPP, Fig. 2c). The pseudo-first-order rate constants measured are, in some cases, over a million-fold larger than those observed in pure buffer. Such accelerations are quite remarkable even if compared to those observed in the presence of Cu^{2+} ion alone, which, *per se*, is a good catalyst for this reaction. The efficacy of the metalloaggregates toward other types of substrates depends on the structure of the ligand and is generally very modest except in the case of aggregates containing the Cu^{2+} complex of **1** which accelerate efficiently the cleavage of simple carboxylic esters and phosphoric triester with, however, a different mechanism respect to PNPP [20]. The reaction pathway in the case of PNPP is that indicated in Fig. 2, involving: (i) formation of a ternary complex (ligand/metal ion/substrate); (ii) pseudo-intramolecular attack of the activated hydroxyl on the carboxyl of the ester resulting in its acylation; (iii) metal ion-mediated hydrolysis of the acylated intermediate. The deacylation of the intermediate is fast enough to ensure a fast turnover rate of the metalloaggregate, which thus behave as a true catalyst.

A careful kinetic investigation and the use of model compounds allowed the definition of the different contributions concurring to the observed catalysis. In particular, in the case of PNPP, Cu^{2+} ion alone accelerates the cleavage by about three orders of magnitude (Fig. 2b). The complex with monomeric ligand **2** brings a further increase in reactivity of about three times, showing that the formation of the ternary complex and the presence of the hydroxyl group as reactive group preserves the activity despite of the lower

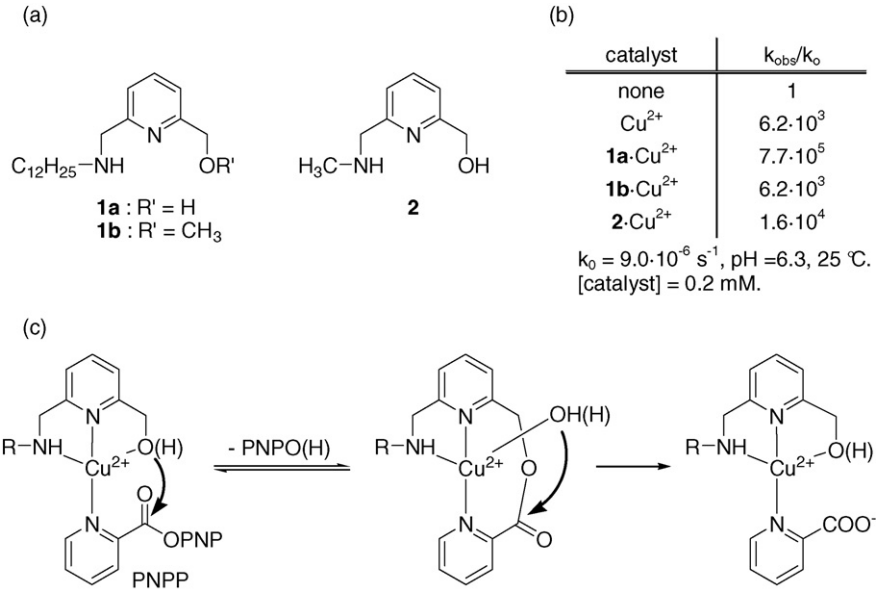


Fig. 2. (a) Example of a lipophilic ligand and its models. (b) Acceleration observed for the cleavage of PNPP in the presence of the copper complexes of ligands **1** and **2**. (c) Proposed mechanism for the cleavage of PNPP promoted by the copper complexes of ligands **1** and **2**. Structures and data are taken from Ref. [19].

Lewis acidity of the metal ion in the complex. The complex of the micellized ligand **1a** increases the reaction rate of about two orders of magnitude with respect to the monomeric complex. Moreover, the acceleration is strictly related to the presence of the 2-pyridine hydroxyl. In fact, the complex of the methylated analog **1b** looses efficacy and its activity is comparable to that of the free metal ion. The importance of the built-on nucleophile and of its correct positioning in the ternary complex has been also underlined in elegant work by the groups of Tagaki [21] and Engbersen [22].

On the whole, the picture emerging from these studies points to a central role of the template effect in the cleavage of amino-acid esters. In the ternary complex the metal ion brings together, with the correct geometry, the two reactants and activates the nucleophile for the trans-acylation process. The micellar aggregates ensure further kinetic benefits, which however, when properly analyzed, appear essentially related to concentration and local pH effects and not to some peculiar properties of the reaction media [23]. Therefore, the mechanism suggested in Fig. 2c applies equally to the reaction in micellar aggregate as well as in bulk solution and no differences are generally observed also in the case of ligands with different structures or bearing nucleophiles different than the hydroxyl group [24]. For remarkable exceptions see however the examples discussed in the next paragraph.

Several other examples of metallomicellar catalysts for the cleavage of activated carboxylic [25–28] and phosphoric [29–31] esters have been reported. The whole body of results, however, confirms the interpretation given above.

2.3. Enantioselective cleavage of α-amino esters in metallomicellar aggregates

The analysis of the hydrolytic reactivity in metallomicelles illustrated in the previous section relegates the aggregates to the role of mere containers in which the reagents are simply more concentrated with respect to the bulk solution. However, the situation is completely different when stereoselective processes are considered. It is, indeed, known since the work by Moss et al. more than 35 years ago that aggregation of chiral reactants may control the stereochemical course of a reaction leading to relevant effects in the stereoselection of the products [32]. In the case of α-amino ester hydrolysis, work from the Nolte group employing as catalyst histidine-containing peptides suggested that one of the most important aspects leading to high stereoselectivity is the compartmentalization within the same aggregate of the two chiral reactants [33]. This means that the reaction for the two diastereomeric couples occurs in different loci of the aggregate where small differences in polarity and/or solvation of the species lead to different reactivities.

Similar arguments are at the basis of the enantioselectivities observed by the Engbersen and You groups using chiral metallomicelles. Engbersen [34] prepared a family of enantiopure lipophilic ligands based on a 1,10-phenanthroline nucleus containing a 2-pyrrolidinemethanol substituent and investigated the cleavage of chiral N-protected amino acids esters in the presence of different surfactants and metal ions (Zn^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, and Cd^{2+}). The highest enantioselectivity was observed in the hydrolysis of *p*-nitrophenyl-*N*-dodecanoyl-R(S)-phenylalaninate (R(S)-C_{12}-PhePNP) catalyzed by the Co^{2+} complex of ligand **3** (Fig. 3) solubilized in Brij 35 micelles ($k_R/k_S = 15.3$). Interestingly, an inversion of enantioselectivity, although low, was observed by changing the surfactant in a comicellar system containing the **3**·Zn^{2+} complex: with Brij 35 as the cosurfactant the hydrolysis of (R)-C_{12}-Phe-PNP predominates over that of the (S)-enantiomer ($k_R/k_S = 2.41$), whereas with CTAB as the cosurfactant the enantioselectivity is reversed ($k_R/k_S = 0.54$). This fact together with the substantially lower enantioselectivity observed with less lipophilic amino acid esters stresses the importance of the aggregate in the chiral discrimination process: the reaction occurs in a less polar environment and the hydrophobic interaction of substrate and ligand in the ternary complex favors a higher degree of stereoselectivity, since this introduces an extra orientation requirement between catalyst and substrate.

Chiral lipophilic ligands with different structures were also investigated by You et al. [35]. The best results in terms of enantioselectivity were obtained with compound **4** of Fig. 3 which features a pyridine core functionalized with a 2-pyrrolidinemethanol substituent [35b]. Also in this case the activity depends from several factors comprising the structure of the ligand, the presence of the free hydroxyl group, the metal ion, the lipophilicity of the substrate and the surfactant used as comicellizing agent. The highest enantioselectivity was observed in the cleavage of (R)- and (S)-C_{12}-PhePNP ($k_R/k_S = 7.81$) catalyzed by the Cu^{2+} complex of ligand

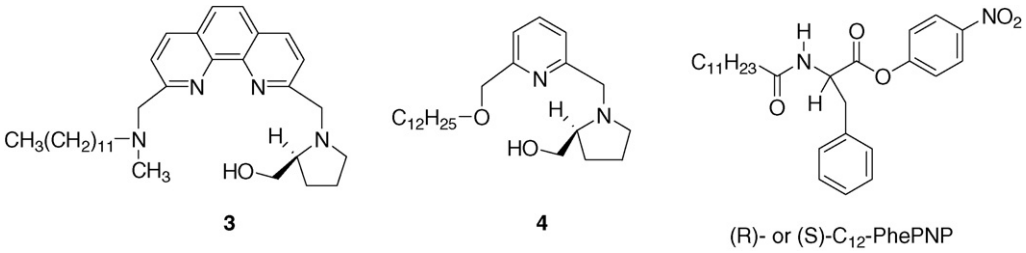


Fig. 3. Chiral ligands and substrate prepared by Engbersen (**3**, Ref. [34]) and by You (**4**, Ref. [35b]).

4 solubilized in Brij 35 micelles. Again the enantioselectivity was found to be strongly sensitive to the type of surfactant and to the lipophilicity of the substrate dropping about twofold when using CTAB as the cosurfactant or (R) and (S)-C_{12}-AlaPNP as the substrate.

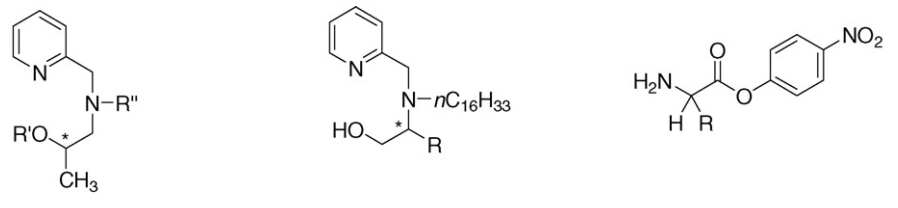
The above examples employ as substrates lipophilic N-acylated amino acids in order to maximize the hydrophobic interactions with the reacting lipophilic chiral metal complexes within the aggregate. Obviously, lacking a basic unit as the free amino group the substrate cannot form stable ternary complexes and may coordinate only weakly to the metal ion through the carbonyl oxygen. On the basis of the results obtained with PNPP, we reasoned that the interactions between the chiral reactants could be better exploited in a tight ternary complex leading to a more defined differentiation between the diasteromeric reacting couples and, consequently, to higher enantioselectivity [36]. Accordingly, we decided to investigate the cleavage of α-amino esters with the free primary amino group and, therefore, able to bind strongly to the metal ion. Fig. 4 reports the structure of some of the α-amino esters and lipophilic chiral ligands we have prepared and investigated together with the enantioselectivity observed in the cleavage of (R)- and (S)-PhePNP (k_R/k_S, in bracket) [37].

The most relevant observations are (a) in each case explored, the S-ligand reacts faster with the (R)-ester and *vice versa*; (b) the enantioselectivity is strictly related to the formation of a ternary complex (ligand/Cu^{2+}/ester) as indicated by the almost absence of selectivity (k_R/k_S = 1.5 with ligand **5a**) when Z-PhePNP is used as substrate and by a kinetic version of the Job plot showing that the maximum acceleration and enantioselectivity is obtained for a 1:1 ligand/Cu^{2+} complex; (c) within the ternary complex the ligand hydroxy function (with an apparent pK_a of 7.4 in the case of **5a**) is clearly involved in the reaction; (d) the proximity of the hydroxy function with the chiral center of the ligand as well as the bulkiness of the substituents at the chiral carbon of either the ligand or ester have little effect on the enantioselectivity; (e) the presence of the aggregate is essential to have acceleration and enantioselectivity. This last effect is particularly evident when comparing the reactivity of the micellized ligand **5a** with the non-micellized ligand **5b** (Fig. 6a): taking as reference the rate of the cleavage of PhePNP in the presence of only Cu^{2+} the reaction is accelerated by the **5a**·Cu^{2+} complex while it is inhibited by the **5b**·Cu^{2+} complex which also shows modest enantioselectivity. This behavior, which is observed also with PNPP [38], has been correlated with the shifting of the equilibrium of coordination of the alcoholic arm of the ligand. In fact, with the water-soluble, non-micellized, ligand **5b** the hydroxy function is not involved in the coordination to the metal ion. The coordination occurs only in the less polar micellar environment, and, consequently, only in micelles the system benefits of the more effective pseudo-intramolecular attack of the Cu^{2+}-bound hydroxy function. This modulation of the coordination sphere of the metal ion in surfactant aggregates appears to be a general phenomenon and has been observed also with other lipophilic metal complexes [39].

In this contest and taking into account the little effect played by steric interactions, the enantioselectivity observed in the cleavage of α-amino esters can likely be explained in terms of different solvation requirements of the two diastereomeric complexes formed by the ligand with the two enantiomers of the substrate (Fig. 5b). The occurrence of the reaction in regions of the aggregate of different hydration influences the nature of the actual nucleophile and, therefore, the rate of the reaction. In a more hydrated environment the slower nucleophilic attack of the Cu^{2+}-bound H_2O (or OH^-) prevails, while in a more hydrophobic region the faster nucleophilic attack of the Cu^{2+}-bound ligand hydroxy function (or alkoxide function) governs the reaction. The net result is the difference in reactivity of the two enantiomers of the substrate.

This behavior appears to be general and it has been observed also with the Cu^{2+} complexes of the ligands of general structure reported in Fig. 6 [40]. The highest enantioselectivity was observed with ligand **8** and was found dependent on the nature of the substrate and of the aggregate [40b]. Using PhgPNP as substrate an enantioselectivity ratio of 24 was obtained in the presence of CTAB, which increases to 28 on chancing the cosurfactant to the micelle forming ditetradecyldibutylammonium bromide (DMDBAB). In these conditions, and at a temperature of 5 °C an enantioselectivity ratio of 35 was recorded, one of the highest values ever reported for a relatively simple micellar catalyst.

Support to our interpretation of the source of selectivity comes from the studies of the reactivity of ligand **9**, structurally related



5a : R' = H, R'' n-$C_{16}H_{33}$ (7.4)
5b : R' = H, R'' CH_3 (1.6)
5c : R' = CH_3, R'' n-$C_{16}H_{33}$ (1.1)

6a : R = CH_3 (7.8)
6b : R = $CH(CH_3)_2$ (6.3)
6c : R = Ph (8.0)

PhePNP : R = CH_2Ph
PhgPNP : R = Ph
LeuPNP : R = $CH_2CH(CH_3)_2$

Fig. 4. Chiral ligands and substrates investigated by Scrimin and Tonellato. In brackets are reported the enantioselectivities (k_R/k_S) observed in the cleavage of both enantiomers of PhePNP under the following standard conditions: [Cu^{2+}] = 0.083 mM, [ligand] = 0.15 mM, MES buffer, pH 5.5, 25 °C. In the case of ligand **6**: [ligand] = 0.2 mM, [CTAB] = 2.0 mM. The enantioselectivity observed with **6a** under the standard conditions is 9.5. Ligands and data are taken from Ref. [37].

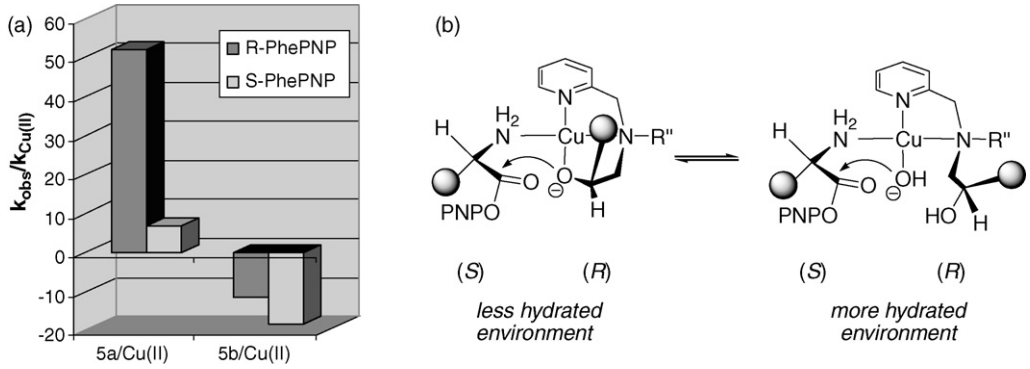
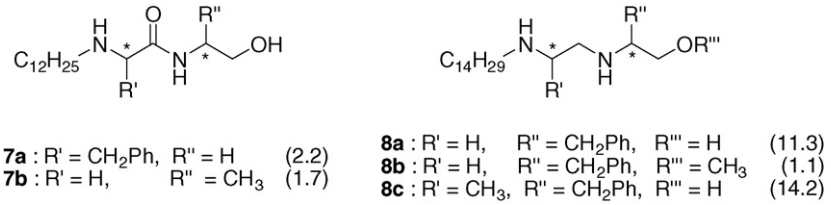


Fig. 5. (a) Relative rate effects respect to the Cu^{2+} ion in the cleavage of (R)- and (S)-PhePNP in the presence of the micellized ligand **5a** and the monomeric ligand **5b**. Conditions: $[Cu^{2+}] = 0.083$ mM, [ligand] = 0.1 mM, MES buffer, pH 5.5, 25 °C. (b) Representation of the shifting of the equilibrium of coordination of the alcoholic arm of the ligand driven by the hydration level of the microenvironment experienced by the ternary complex. Figures have been adapted from Ref. [37].



7a : R' = CH_2Ph, R'' = H (2.2)
7b : R' = H, R'' = CH_3 (1.7)

8a : R' = H, R'' = CH_2Ph, R''' = H (11.3)
8b : R' = H, R'' = CH_2Ph, R''' = CH_3 (1.1)
8c : R' = CH_3, R'' = CH_2Ph, R''' = H (14.2)

Fig. 6. Structure of the ligands investigated by Scrimin and Tonellato. In brackets are reported the enantioselectivities (k_R/k_S) observed in the cleavage of both enantiomers of PhePNP under the following conditions: $[Cu^{2+}] = [ligand] = 0.1$ mM, [CTAB] = 1.0 mM, HEPES buffer, pH 7.5, 25 °C. Ligands and data are taken from Ref. [40].

to **6b**, in vesicular aggregates made by dioctadecydimethylammonium bromide ($2C_{18}Br$) [41]. Vesicles (or liposomes when formed by natural phospholipids) are sphere-shaped aggregates, with diameter ranging from 20 to 500 nm, made of a bilayer of lipids trapping in its interior a water pool [42]. The membrane made of the bilayers is generally tightly packed providing an effective barrier for the permeation of polar species such as water and ionic species. The packing requirements of a surfactant in the vesicle bilayer are much more stringent than in a micelle and, as a consequence, the "order" of the aggregate is higher than the "order" of the micelle especially at a temperature below the phase transition temperature (Tc) when the membrane is in the gel state. Above this temperature, kinks occur in the hydrocarbon chains making the packing of the surfactants less efficient. Therefore, in the fluid state, the membrane becomes more disordered, less impermeable and the movement of the lipids in the bilayer is faster.

In view of the higher degree of organization of vesicles respect to micelles one could expect better results in term of enantioselectivity and indeed a three-fold increase is observed [41]. What is particularly informative is the Arrhenius profile measured for the reaction of the two enantiomers of the substrate (Fig. 7). The enantioselectivity is higher at low temperature and decreases sharply at temperatures near and above the phase transition of the membrane (indicated by the dashed vertical lines in the figure). Interestingly, this decrease is due to the slowing down of the reaction of the faster enantiomer while the effect on the rate of the slower enantiomer is almost negligible. This behavior is consistent with the above explanation of enantioselectivity driven by compartmentalization of the two reacting ternary complexes in different loci of the aggregate. The increase in temperature above the phase transition of the bilayer is associated with an increase of its fluidity and, consequently, the segregation of the different species becomes less efficient. The faster enantiomers moves into a more hydrated region, the mechanism of the reaction changes and the overall reaction rate becomes slower in spite of the increase of the temperature.

2.4. Chemical differentiation of vesicular bilayer

An interesting aspect of metal ion-promoted ester catalysis in aggregates and particularly in vesicles is the use of kinetic experiments to investigate important properties of the aggregates such as membrane permeably and mobility of the surfactants in the bilayer. Early work by the group of Moss showed that, under condition of impermeability of the vesicular bilayer to ions, the outer layer of vesicles made by functional lipids bearing hydrolytically labile groups can be chemically differentiated from the inner one [43]. These asymmetric vesicles can eventually be used to follow the trans-bilayer movement of lipids (flip–flop) or the permeation of ion across the membrane.

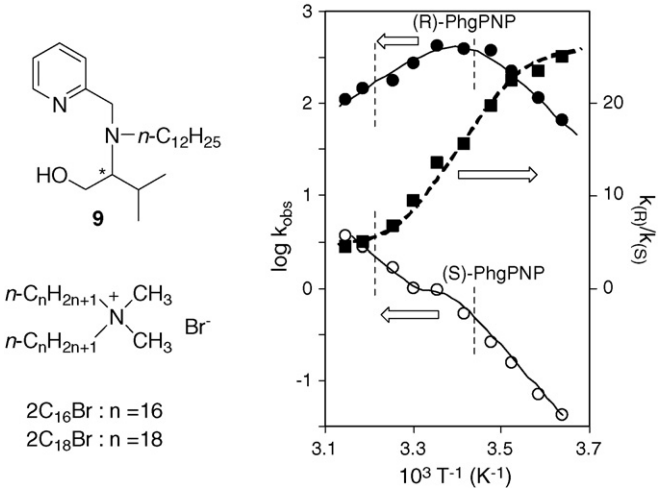


Fig. 7. Arrhenius-type plot for the cleavage of the two enantiomers of PhgPNP by the (S)-enantiomer of the Cu^{2+} complex of ligand **9** in a $2C_{18}Br$ vesicular matrix. The vertical dashed lines indicate the temperature interval of the aggregate phase transition. The figure has been adapted from Ref. [41].

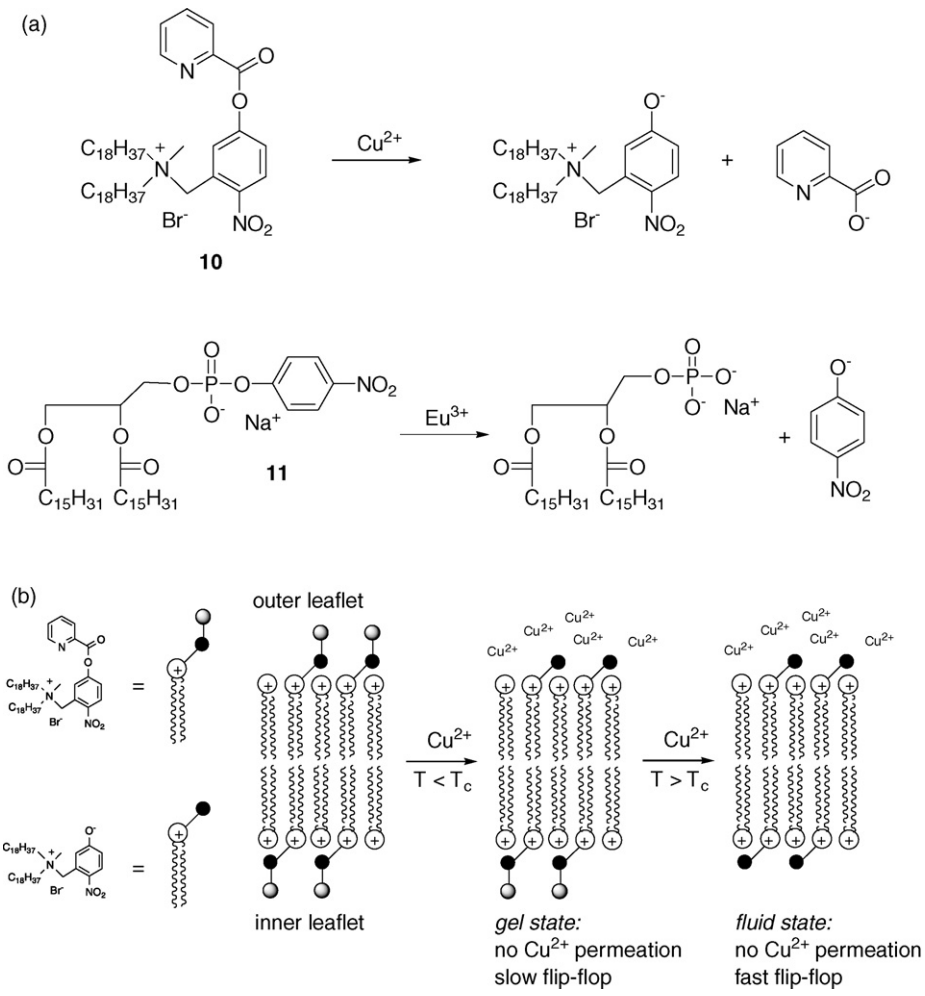


Fig. 8. (a) Cleavable probes used in metal ion promoted chemical differentiation of the surface of vesicular aggregates (**10**, Ref. [44]; **11**, Ref. [45]). b) Schematic representation of the experiment of chemical differentiation of a vesicle bilayer. In the gel state ($T < Tc$) the membrane is impermeable to the Cu^{2+} ions and the flip–flop movement is slow leading to the cleavage of only the esters residing in the outer leaflet. Rising the temperature above Tc the membrane is still impermeable to the metal ion but the flip–flop is accelerated exchanging rapidly the functionalized lipid between the two leaflets. This movement put all the esters in contact with the metal ion confined in the bulk water and the final result is the cleavage of all the esters.

The functional surfactants of Fig. 8a are examples of such chemical probes that can be utilized in metallocatalyzed processes. Because of the presence of the labile functional groups they may be catalytically hydrolyzed in the presence of Cu^{2+} (**10**) [44] or Eu^{3+} (**11**) [45] in a process that can be easily followed spectrophotometrically. When the proper metal ion was added to a solution of preformed vesicles, or covesicles with inert surfactants such as $2C_{18}Br$, below the phase transition temperature of the aggregate, only a fraction (around 60%) of the cleavable probes were hydrolyzed indicating that the metal ions interact only with the ester groups residing on the outer leaflet of the vesicles. On the other hand, above the phase transition temperature, when the membrane is in the fluid state, the esters are fully hydrolyzed and this was shown to occur not because of the permeation of the metal ion across the bilayer but rather because of an accelerated flip–flop movement of the functional surfactants which therefore exposes the ester moiety to the catalytic metal ion confined in the bulk water. With these experiments we were thus able to demonstrate that the membrane made by these unnatural lipids are impermeable to metal ions such as Cu^{2+} or Eu^{3+} and, using vesicles made by different blends of surfactant, that this property is independent from the charge, positive or negative, of the vesicle surface. Moreover, the kinetic results give information on the flip–flop rate of the lipids in these matrixes that, as expected, is strongly influenced by the fluidity of the membrane. The overall process is schematized in Fig. 8b.

2.5. Anchoring amphiphilic metal complexes on the surface of a nanoparticle: a new paradigm for really cooperative hydrolytic metalloaggregates

Contrary to self-assembled aggregates of amphiphilic molecules like those described above that are held together exclusively by hydrophobic interactions, recently thiol-terminating amphiphilic molecules have been used for the passivation of the surface of clusters of gold atoms (2–20 nm in size) taking advantage of the relatively strong thiol–Au bond (ca. 20 kcal/mol) [46]. These systems are quite similar to micellar aggregates with the important difference that, being each unit anchored on the surface of the gold core, they are kinetically very stable. Further, they survive also in non-aqueous environments. Thus, the incorporation of imidazole subunits in a self-assembled monolayer (SAM) covering an Au-nanoparticle gave results supporting cooperativity [47]. The system consisted of a mixed monolayer of dodecanethiol and an *N*-methylimidazole-terminated thiol. The catalytic activity of these Au-nanoparticles was tested on the substrate 2,4-dinitrophenylacetate (DNPA) in methanol–water (6:4) solutions in the pH-range 4.5–7.2. It showed the bell-shaped depen-

dence of observed second-order rate constant (k_2) with a maximum in the proximity of the pK_a of the *N*-methylimidazole consistent with cooperativity between two of them in the DNPA cleavage by the nanocluster (general acid/base or nucleophilic catalysis).

An even more interesting system was that provided by nanoparticles functionalized with dipeptides containing a histidine and a carboxylate from a terminal amino acid. In the catalytic site of many esterases these functional groups operate in a concerted fashion as general acid and general base (or nucleophile) in the catalytic process. In this case the complementary role of a carboxylate and an imidazolium ion was demonstrated by studying the hydrolysis at low pH [48]. The comparison of the activity against pH of these functional nanoparticles with that of a monomeric catalysts constituted by the same dipeptide in the hydrolysis of 2,4-dinitrophenylbutanoate (DNPB) showed that at all pH values the Au-nanoparticle catalyst outcompetes the monomeric catalyst, but, extremely interesting, the two curves show strikingly different profiles. The monomeric catalyst behaves as a system in which a catalytically relevant nucleophile is generated with pK_a 6.6, which is consistent with the basicity of the imidazole. On the contrary, the nanoparticle shows a more complex profile: a first nucleophilic species is generated with pK_a 4.2, then the curve flattens up to pH 7 where a second nucleophile is generated with pK_a 8.1. These pK_a values can be assigned to the carboxylic acid and the imidazolium, respectively. The reason of the higher value of the pK_a of the imidazolium in the nanoparticle is due to the anionic nature of the nanoparticle that disfavors the deprotonation of the imidazolium cation. What is particularly remarkable is the high activity, at acidic pH, of the nanoparticles-based catalyst showing over 300-fold rate acceleration with respect to the acetylated dipeptide. Mechanistically, this has been interpreted by involving a carboxylate anion in the cleavage that acts as a general base deprotonating a water molecule and a protonated imidazole acting as a general acid. The absence of this mechanism in the monomeric system clearly indicates that this behavior results from the confinement of the dipeptide on the monolayer covering the nanoparticle.

When a dodecapeptide, comprising a combination of a His, two Arg, and a Lys residue (among other amino acids), was grafted on Au-nanoparticles [49] we expected that their cooperativity could enable nucleophilic, general acid, and/or general base catalysis, but also stabilization of the negatively charged transition state that arises along the pathway of ester hydrolysis. Using the very same substrate of the previous example we observed that at low pH values the nanoparticle-based catalyst behaves very similarly to the previous dipeptide-based system, although the dodecapeptide-nanoparticle has an additional 10-fold gain in activity. This amounts to a 3000-fold rate acceleration over that exerted by the simple dipeptide. The larger catalytic efficiency was ascribed to a stronger acidity of the protonated imidazole group, which in the dodecapeptide has a pK_a value 0.9 units lower than in the dipeptide. This is due to the fact that now the nanoparticle has no longer a net negative charge as this is compensated by the presence of the cationic guanidinium groups. At higher pH values, the activity of the peptide-nanoparticle increases significantly with respect to the dipeptide-NP reaching an additional 40-fold rate acceleration. This can be ascribed to the presence of an additional nucleophile (the phenoxide of tyrosine) with an apparent pK_a of 9.9. Thus these amphiphilic peptide-functionalized nanoparticles provide an easily accessible entry to cooperative catalysts able to introduce new catalytic pathway in hydrolytic reactions not accessible with monomeric systems.

These clear evidences of cooperativity prompted us to study similar systems also in the cleavage of a challenging phosphate bond using metal ion catalysis. Thus we prepared gold nanoparticles passivated with a thiol terminating with the artificial amino acid ATANP [50], a derivative of serine in which the –OH has been replaced by triazacyclononane, a strong ligand for metal ions like Zn^{2+} and Cu^{2+} [51].

By studying the cleavage of the RNA-model substrate 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP) we obtained, by working at a fixed concentration of nanoparticle and progressively adding Zn^{2+} ions, a sigmoidal reaction profile that provides strong support in favor of a cooperative mechanism between several metal ions (see Fig. 9). Very interestingly an analogous micellar system behaved less efficiently lending further support to the presence of an additional, more efficient, cooperative mechanism in the nanoparticles.

A step further in the improvement of the catalytic unit was that to functionalize the monolayer with the more elaborate ligand bis-(2-amino-pyridinyl-6-methyl)amine (BAPA) [52a,b]. The BAPA-Zn^{2+} complex is known to be able to elicit the cooperation between metal Lewis acid activation and hydrogen-bonding to achieve increased hydrolytic activity toward phosphate diesters. The resulting Zn^{2+} nanoparticle proved to be one of the most effective catalysts reported so far for the cleavage of the DNA model phosphate, bis-*p*-nitrophenyl phosphate (BNPP) [52c]. The second-order rate constant observed was more than 60,000 higher than the reference rate for the basic catalyzed reaction and more than 100-fold better that of the monomeric complex. The dependence of the rate constants on the equivalents of Zn^{2+} added showed clearly

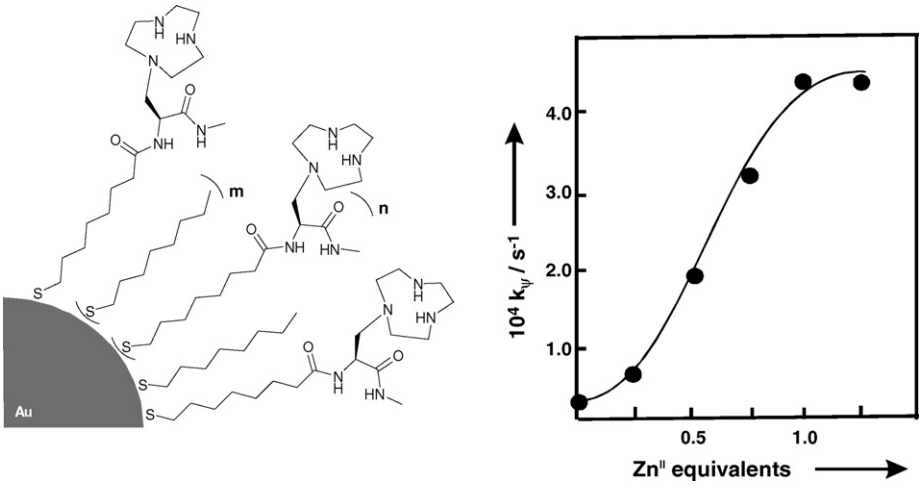


Fig. 9. Triazacyclononane-functionalized nanoparticles behaving cooperatively in the cleavage of HPPNP as evidenced by the sigmoidal reactivity profile shown on the right reporting the reactivity as a function of the equivalents of Zn^{2+} added. The figure has been adapted from ref. [51].

in this case the occurrence of two catalytically relevant situations: the first one, at low Zn^{2+} loading, involving a mononuclear complex and a second one at Zn^{2+} saturation, involving a dinuclear complex. Both conditions represent a significant increase in rate with respect to the monomeric complex.

However the most striking result was that provided by the cleavage of plasmid DNA. The hydrolytic cleavage of this substrate is easily detectable as the supercoiled conformation of the polymer (form I) converts into the nicked one (form II) following a single cut in one of the two strands. However, if a second cut occurs in the other strand in close proximity to the previous one a further change occurs with the linearization of the double strand (form III). Statistically this second cleavage occurs in the proper position only in 1% of the cases. Strikingly in this case linear DNA started forming after only 10% of the original supercoiled DNA was cleaved and already with 16% of it cleaved it was the most abundant form present. This clearly indicates that the multivalent nanoparticle was able to perform multiple cuts on the double strand, the obvious consequence of its multivalent nature. One may speculate that the nanoparticle by sticking to the polymer is able to hydrolyze at the same time several phosphate bonds belonging to both strands of the polymer thus linearizing it very efficiently, a behavior never observed with other catalysts. This is a very important result because for the first time a multivalent catalyst takes advantage of its multivalency on two counts. First it cleaves efficiently a specific functional group by converging several cooperating catalytic units on it. Second, using the same mechanism it cleaves simultaneously several functional groups on a multivalent target, the polymeric DNA backbone.

3. Lipophilic ligands as catalysts for transport processes

Ion transport across a membrane is a typical supramolecular function, which requires specific intermolecular interactions between the ligand and the transported ions in order to compensate for the loss of hydration energy during the translocation process across the apolar membrane interior [53]. Lipophilic ligands may behave as transport catalysts because they form lipophilic complexes able to solubilize metal ions in apolar environment such as, for example, micelles or vesicles. An interesting consequence of this property is metal ion sequestration from bulk water by functional surfactant aggregates with important applications in water detoxification [54]. A transport process is however more complex because it requires binding of the metal ion on one side of the membrane, translocation across the membrane and release on the other side [55]. Nonetheless we obtained some interesting results with lipophilic ligands in the transport of metal ions and amino acids as discussed in the following sections.

3.1. Ion transport across vesicular bilayers

Kinetic experiments using lipids functionalized with cleavable probes can be used to investigate the transport of catalytically active ions across the vesicular membrane. For example, with vesicles made by the above anionic lipid **11** we have observed that lipophilic diamines like *N*-hexadecyl-*N*,*N*,*N*-trimethylethylene diamine (TMED-C_{16}) may affect the permeability of the membrane to lanthanide ions in two different ways [45]: (a) by acting as carriers of the cations across the bilayer and (b) by making leaky patches in the membrane. This latter mechanism is less specific and is observed also when using as additives normal micellar surfactants such as, for example, CTAB. On the contrary, lipophilic diamines appear to operate in both ways and this was demonstrated by comparing the hydrolytic behavior induced by the addition of the additive with leakage experiments on vesicle encapsulating a fluorescent dye. The amines where much more effective than CTAB in inducing the permeation of the metal ions, while their efficacy in inducing the permeation of the anionic fluorescent dye was very similar to that of CTAB. The extra activity shown by the amines with the lanthanides was a clear evidence of their specific interaction with the metal ion that led to the formation of a lipophilic complex able to permeate across the vesicular bilayer.

Kinetic evidences for metal ion transport across the vesicular membrane can be obtained also by using lipophilic metal complex showing catalytic activity in the cleavage of activated esters. Examples of these ligands are compounds **12** and **13** shown in Fig. 10 [56]. When Cu^{2+} is added after the formation of vesicles made by $2C_{16}Br$ and containing these ligands, only those on the outer layer of the liposome interact with the metal ion and become catalytically active in the cleavage of PNPP. However, the activity observed for **12** was twofold better than that observed for **13**. Control experiments done by monitoring by UV–vis spectroscopy the formation of the Cu^{2+} complex, demonstrated that this difference is related to the ability of **12** to act as a carrier for Cu^{2+} and to transfer the metal inside the vesicle where *ca*. half of the ligand is present being equally distributed on the interior and exterior leaflets of the bilayer. Since the neutral substrate can easily permeate the vesicular membrane and assuming reasonably that the metal-ion-carrier-mediated permeation is faster than the PNPP cleavage, all ligands become exposed to the metal ions and the full reactivity of the system can be observed even when the metal ion is added after the formation of the vesicles. Clearly the trans-bilayer mobility of ligand **13** is far lower than that of **12** and the carrier mediated process becomes slower than the rate of substrate cleavage. So, only the fraction of ligand residing on the outer layer, about half of the total concentration, is transformed into a catalyst by complexation of the metal ion and the observed reactivity is about half of that of ligand **12**.

A topic related to the control of membrane permeability is the triggered release of the liposome content, which is obtained by a stimulus inducing dramatic alteration of the membrane structure [57]. As a consequence molecules confined in the inner water pool of the liposome are rapidly released in the bulk water. Cleavable surfactants, which under the action of different agents such as light, pH, etc. change their structure and alter the membrane permeability are good candidates for the development of such systems and, in some case, they have proven to be efficient vehicles for drug delivery to biologically relevant targets and their subsequent release [58]. By exploiting the lability of phosphate diesters to hydrolysis in the presence of lanthanide ions, we have developed a synthetic phos-

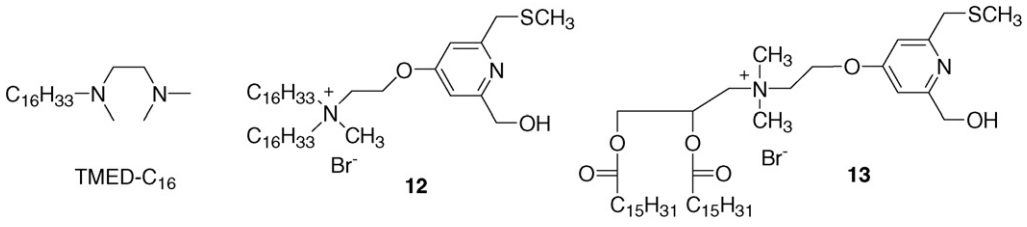


Fig. 10. Lipophilic ligands used in the investigation of the carrier mediated transport of metal ions across a vesicular membrane. The examples are taken from Refs. [45,56].

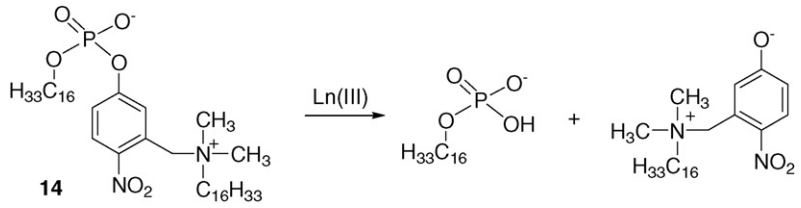


Fig. 11. Cleavable surfactant for the triggered release from liposome. The example is taken from Ref. [59].

pholipid for the contemporaneous monitoring of the hydrolysis and decapsulation of vesicles containing this lipid (Fig. 11) [59]. Cleavage of the phosphate diester leads to aggregates unable to sustain a chemical gradient and, consequently, this results in a faster release of a trapped dye. Cleavage of as much as 25–30% of the lipid residing in the outer layer of unilamellar bilayer vesicles causes the onset of the accelerated release. Because of their toxicity, lanthanides cannot be used to trigger the cleavage in a biological environment. However, phosphatase may lead to the same results so that these liposomes could be, in principle, used for the controlled release of drugs in phosphatase-rich regions.

3.2. Ion transport across bulk chloroform membrane

The above-mentioned transport mechanism of metal ion across a vesicular membrane requiring its complexation to a lipophilic ligand can be applied to rough but simpler model of it: the so-called "bulk membrane", i.e. an organic solvent separating two aqueous phases [60]. For this reason and for the relevant applications in the field of species separation, this membrane model has been widely used in transport studies [61]. Thus, following our studies on vesicular membranes (see above) we investigated the ability of simple lipophilic dipeptide-based metal ion ligands to act as selective carriers for the transport of transition metals across a liquid chloroform bulk membrane [62]. The experimental set-up and one example of such ligands are illustrated in Fig. 12.

The system is quite effective in the transport of Cu^{2+} from a buffered aqueous source (pH 5.6) to a 0.1 M HCl receiving phase across a bulk chloroform membrane. The efficiency depends (i) on the easy of formation, at the source phase–chloroform interface, of complex **15** that is neutral (and hence more soluble in the organic solvent) due to the deprotonation of the amide (with an apparent pK_a close to 5) and of the carboxylic group [63]; (ii) on the facile decomplexation at the acidic receiving phase. Under the pH conditions used the carriers are much less effective in the transport of Zn^{2+} and Ni^{2+} (by factors larger than 10^3 and 10^4, respectively) due to the fact that only Cu^{2+} among other transition metal ions can form neutral complexes at the pH value of the source phase. The driving force of the overall process is the decomplexation of the metal ion in the receiving phase and as long as the pH of the aqueous phase is maintained strongly acidic the transport proceeds until all the metal ion is translocated. The conditions for this type of "uphill" transport, *i.e.* against the concentration gradient, are clearly more difficult to realize in vesicular systems and are particularly relevant in separation processes.

Exploiting the formation of a ternary complex, ligand/Cu^{2+}/amino acid, we further investigated the transport of amino acids using lipophilic 1,2-diaminoethane-based ligands of the type illustrated in Fig. 13 [64].

These systems are quite effective and allow an effective "uphill" co-transport of ions and amino acids. The results obtained indicate that the transport occurs via the formation of the ternary complex and that the lipophilicity of the amino acid is an important factor in determining the rate of the process with the best conditions obtained when the carrier ligand and the transported amino acid have comparable affinity for the Cu^{2+} ion. Under these conditions the formation of complexes with 2:1 ligand (or amino acid)/metal ion stoichiometries, which compete for the formation of the active species, is minimized. However, the enantioselectivities observed in the transport of the two enantiomers of natural amino acids using chiral ligands are generally modest. In the best case, using ligand **17** and leucine as the amino acid, the enantioselectivity ratio (the initial rates of transport of the faster enantiomers relative to the slower) is slightly higher than 2. The process appears to be governed more by thermodynamic rather than kinetic factors with little relevance of steric interactions perhaps due to the flexibility of the complexes. The enantioselectivity effects observed in the cleavage of chiral amino acid esters by metallomicelles made of similar lipophilic ligands were much higher (see above) and this observation stresses the importance of the

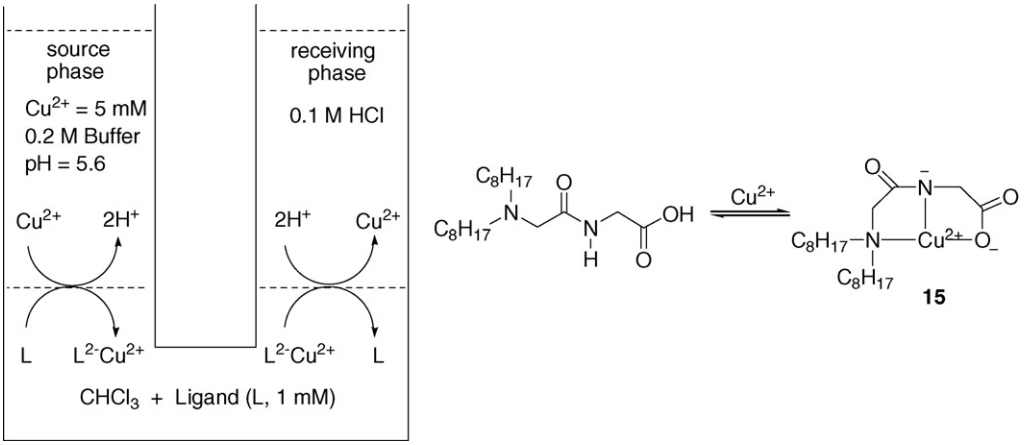


Fig. 12. Schematic illustration of the experimental set-up for the bulk membrane transport studies. In a U-tube a chloroform phase on the bottom separates two aqueous phases in the arms of the tube. All the phases are kept under stirring to avoid the formation of concentration gradients at the interfaces. The figure has been adapted from ref. [62].

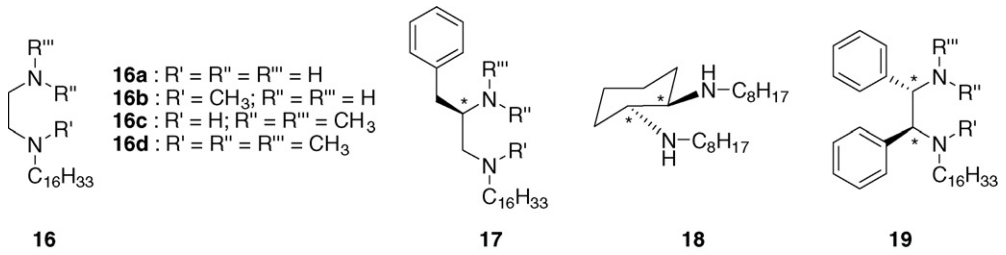


Fig. 13. Lipophilic ligands used for the co-transport of Cu^{2+} and amino acids. The ligands are taken from Ref [64].

micellar aggregate in the fine tuning of the reactivity of such systems.

4. Fluorescent chemical sensing in surfactant aggregates

More recently the attention has been concentrated on the uses of amphiphilic molecules in chemical sensing, a classical supramolecular function that can find interesting cross-fertilization with the field of surfactant aggregates. A chemosensor is a molecule that can selectively recognize and signal the presence of a specific analyte [65]. Among the different possible signalling methods, fluorescence is one of the most popular thanks to several advantages such as, for example, high sensitivity, high spatial and temporal resolution, relatively simple and low cost instrumentation which can be easily adapted for "in field" application [66]. In addition, the molecular dimensions of the chemosensor are well suited for detection in small compartments without strong physical interference. This feature makes such systems particularly attractive for medical and biomedical studies when, for example, intracellular monitoring of a given analyte is desired [67]. It is therefore not surprising that the number of reports dealing with fluorescent chemosensors for the detection of a variety of substrates is now very large and is increasing steadily [68]. Despite the structural diversity characterizing the design of fluorescent chemosensors three common elements are necessarily presents: (a) a recognition site for the interaction with the analyte; (b) a fluorescent dye which generate the signal; (c) a transduction mechanism which puts in communications the two subunits and converts the recognition of the analyte in the generation of the signal [69]. In the classical systems the binding module and the fluorescent dye are covalently linked but, more recently, self-assembling and self-organizing methodologies have attracted increasing attention in the design of chemosensors [70]. In this case, there is no need for covalent links between the two subunits which must, however, be designed in such a way to achieve their assembly in solution. Remarkably, the synthetic problems connected with the classical covalent systems can be, at least partially, overcome, and an efficient strategy for the easy realization and optimization of fluorescent chemosensors is provided.

The combination of surfactant aggregates and chemosensors may lead to interesting new properties which are essentially related to the two classical effects observed with aggregates: (a) the concentration of lipophilic or ionic species in the small aggregate volume; (b) the different microenvironment of the aggregate respect to bulk water which may modify the emission properties of the dye or protect the dye from the contact with micellar insoluble species. This last effect is known since long time and it is at the basis of well-established methods for determining relevant properties of the aggregates such as for example critical micellar concentration [9]. A very recent and more sophisticated example of this concept has been provided by the group of de Silva which has developed a family of multiplexing fluorescent sensors for the mapping of proton gradients near the surface of micellar aggregates [71].

The ability of aggregates to concentrate species is at the basis of several other examples in which better sensing performances or improved photophysical properties have been described [72]. Some selected examples are described in the following paragraphs focusing on the role played by the aggregate.

The group of Anslyn has reported enhanced detection of nitroaromatic and nitramine explosives such as TNT and RDX (Fig. 14a) using pyrene solubilized in a micellar Tween 80 solution [73]. These aromatic compounds are known to quench the fluorescence of pyrene as well as other polyaromatic hydrocarbons,

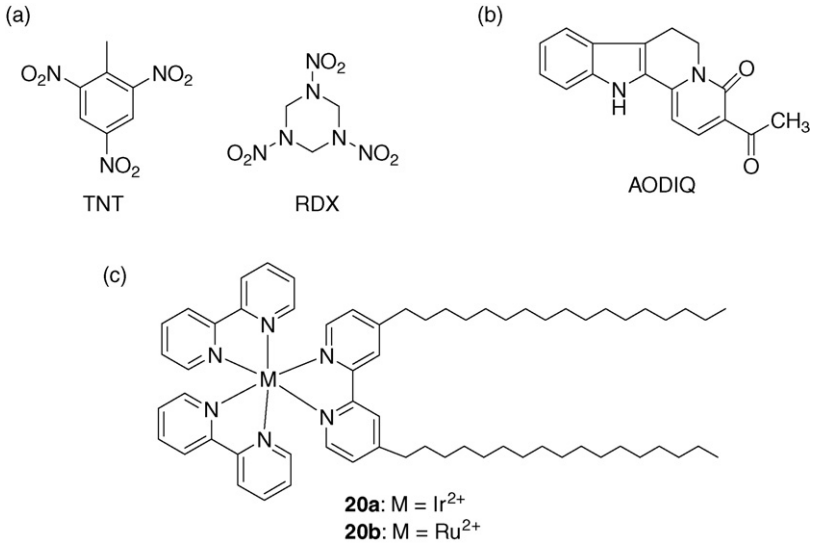


Fig. 14. (a) Nitroaromatic and nitramine explosives detected using pyrene solubilised in a micellar Tween 80 solution (Ref. [73]). (b) AODIQ dye used as Cu^{2+} sensor in SDS micelles (Ref. [74]). (c) Fluorescent metal surfactants acting as donor/acceptor components in a ET process promoted by their inclusion in surfactant aggregates (Ref. [75]).

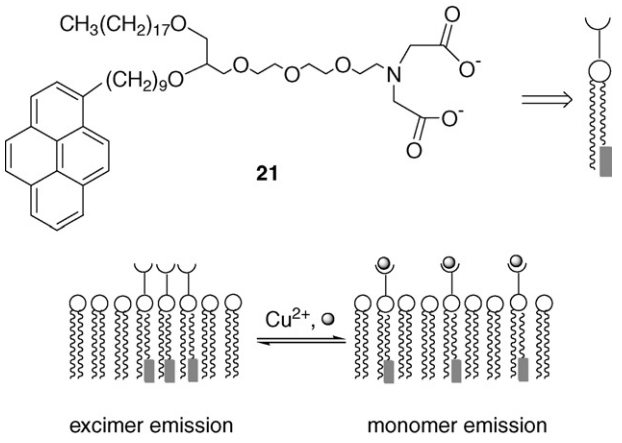


Fig. 15. Metal ion sensor based on the switching of the monomer–excimer equilibrium in liposome. The complexation of the metal ion to the pyrene-functionalized ligand favors the disassembly of the pyrene cluster leading to a variation in the emission of the dye. The example is taken from Ref. [76].

and the quenching ability differs among compounds. Therefore, by monitoring pyrene fluorescence it is possible to sense the presence of nitrated explosives. However, the quenching effect is weak and this limits the sensitivity of the detection assay. Solubilization of the pyrene dye in micelles enhances the quenching efficacy thanks to the concentration of the hydrophobic explosives in the apolar micellar core. Moreover, the micellar environment protects the fluorescent dye from O_2 quenching further increasing the sensitivity of the assay.

Surfactant-induced modulation of a fluorosensor activity has been reported also by Chattopadhyay and co-workers who investigated the effect of SDS on the Cu^{2+} quenching of the AODIQ dye (Fig. 14b) [74]. Interaction of Cu^{2+} with AODIQ leads to the quenching of the fluorescence emission of the fluorophore and allows the detection of the former in the micro or submicromolar range. The quenching efficiency of AODIQ increases strongly by inclusion of the dye in SDS micelles due to the concentration of the metal ion on the anionic micellar surface. Moreover, this effect depends on the concentration of surfactant thus allowing a fine-tuning of the sensing ability of the sensor.

An interesting example of communication between two fluorescent dyes promoted by their inclusion in surfactant aggregates has been provided by the group of De Cola [75]. They prepared metal surfactants by appending long hydrocarbon chains to iridium(II) and ruthenium(II) bypyridine complexes (**20**, Fig. 14c), two fluorescent dyes able to act as donor/acceptor components for electron transfer (ET) processes. The formation of co-micelles between the two metal surfactants results in a very efficient ET that takes place from the excited iridium-based complex to the ruthenium moiety which is not observed whit control metal complexes unable to form micelles. Clearly the close proximity of the fluorescent dyes in the comicellar aggregate switches on the ET process which is modulated by dilution of the metallosurfactants in micelles formed by CATBr. As a consequence the emission of the dyes can be tuned simply by varying the ratio of functional and inert surfactants.

A final example of metal ion detection in aggregates has been reported by Arnold and co-workers [76]. The system relies on the excimer–monomer equilibrium of a lipid functionalized in remote positions with pyrene and metal ion ligand subunits (**21**, Fig. 15). This lipid, dispersed in distearoylphosphatidylcholine vesicles, forms clusters with the pyrene moiety deeply inserted into the membrane, and the ligand subunit pointing toward the bulk water. The clusters show the typical pyrene excimers emission, which changes to the monomer one by addition of Cu^{2+}. In fact, as schematized in the bottom of Fig. 15, the complexation of the metal ion induces a dispersion of the functionalized lipids in the membrane with consequent destruction of the pyrene clusters. The sensor is really sensitive and detects nanomolar concentration of Cu^{2+} ions. A similar lipid functionalized with different binding subunits has been reported more recently by the group of Mallik [77]. One of the most interesting aspects of this approach is that the metal ion does not interact directly with the fluorescent dye but modifies its fluorescent emission influencing the monomer-excimer equilibrium. Therefore, at least in principle, the method is of general applicability and by tuning the selectivity of the binding subunit a series of sensors selective for different metal ions (or other substrates) may be prepared, as the sensing scheme does not depend on specific properties of the metal ion itself. This has been demonstrated by Sasaki and Padilla who have developed a sensor for Hg^{2+} ions using a similar pyrene-functionalized lipid but for the metal ion binding subunit which was changed to a mercury-selective dithioamide moiety [78].

4.1. Self-Assembled fluorescent chemosensors in aggregates

The selected examples described in the above section illustrate how the interaction of sensing systems with surfactant aggregates may lead to improved performances and new behaviors with respect to the bulk aqueous phase. Usually, in these systems a classical covalent chemosensor is included in the aggregate which offers a different environment respect to the bulk solvent. Few years ago we proposed a different approach based on the self-assembling of the chemosensor components, the fluorescent dye and the receptor, in a micellar aggregates made by conventional surfactants [79]. The assembling is simply driven by hydrophobic interactions: inside the aggregate the receptor and the fluorescent dye do not interact directly but their communication is favored by the close proximity between them in the small aggregate volume. The major advantage of this method lays in its simplicity because little or no synthetic modifications of the ligand and the dye are needed and this allows the easy formation of the sensor and the rapid screening of a large number of receptors, dyes, surfactants, and experimental conditions in order to optimize the sensing properties for a given application. Clearly, a transduction mechanism is needed to translate the substrate recognition event into the generation of the readable fluorescent signal and the individuation of such mechanism can be problematic due to the fact that ligand and fluorescent dyes are not covalently bound. For this reasons the concept was proved using Cu^{2+} as the analyte, a metal ion known to be an effective quencher of fluorescent dyes.

The first system we investigated used as ligand a lipophilic GlyGly dipeptide (*N*-decyl-glycylglycine, **22** in Fig. 16), structurally similar to those used in the Cu^{2+} transport experiments (see above), and as dye the fluorophore 8-anilino-naphtalensulfonic acid (ANS) [79]. The choice of this couple was based on the following two important factors: (a) at moderately acidic pH values the dipeptide ligand binds strongly and selectively Cu^{2+} ions due to the deprotonation of the amide nitrogen which does not occur with other divalent transition metal ions [63]; (b) the fluorescence emission of ANS is strongly sensitive to the environment polarity and the dye is practically non fluorescent in water while its emission intensity increases strongly in the less polar micellar environment [66]. This effect is important because it reduces the not-desired fluorescent emission from the dye not bound to the aggregate. In the presence of CTAB a comicellar aggregate containing the ligand and the dye is formed and upon binding of Cu^{2+} ions to **22** the fluorescence emission of ANS is strongly quenched allowing the detection of the metal ion in the micromolar concentration range (Fig. 16). Due to the selectivity of the ligand the quenching is observed only

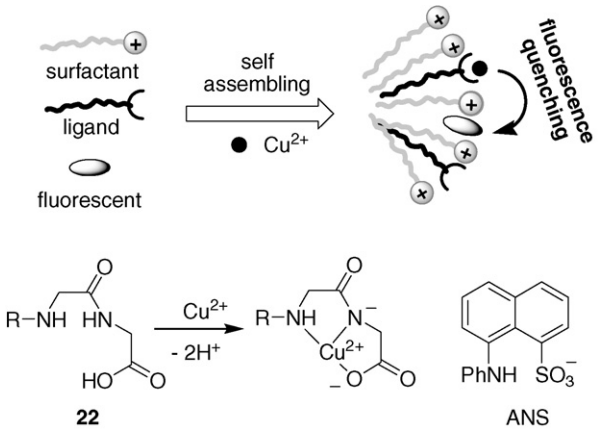


Fig. 16. Self-assembled fluorescent chemosensor in micelles. The example is taken from Ref. [79].

with Cu^{2+} ions and other transition metal ions like Zn^{2+}, Ni^{2+}, Mn^{2+}, Co^{2+}, Pb^{2+}, do not interfere with the sensing assay.

The main factor affecting the sensitivity of the system is the dilution of the sensor components in the aggregates which makes less favorable the interaction between the bound metal ion and the fluorescent dye. Accordingly, the detection range can be modulated by varying the ligand/total surfactant (ligand + CTAB) molar ratio, reaching the highest sensitivity at a limiting value of 1:2, and by decreasing the surfactant concentration down to values approaching the c.m.c. value of the resulting comicelles. As underlined above, an important aspect of this self-assembling approach is its simplicity and modularity: the sensor is made by simply mixing in water the ligand and commercially available surfactants and dyes. This allows a fast screening of several combinations and this point has been demonstrated by setting up a combinatorial experiment in which, keeping constant the ligand, 16 combinations of surfactant and dye were tested employing four different surfactants and four different dyes, all commercially available. The couple CTAB and 1-naphtylphosphate resulted to be the most sensitive among the combinations tested.

In a further elaboration of this system we used as ligands a lipophilic version of GlyLys and GlyGlu dipeptides, which, due to the ionization of the functional groups in the amino acid lateral chains, are amphiphilic both in the free and in the Cu^{2+}-complexed form [80]. These ligands form stable homo-micelles without the need of any added surfactant thus avoiding the dilution of the ligand in the non-functional micellar aggregates. The result is an improvement of sensitivity with detection limit for the metal ion in the sub-micromolar range.

Further examples of the application of this sensing scheme in the detection of quenching metal ions such as Ni^{2+}, Cu^{2+} and Hg^{2+} in self-assembled chemosensors in micelles and in Langmuir–Blodgett films have been provided by the groups of Pallavicini [81] and Le Blanc [82], respectively. Moreover, a breakthrough contribution was provided by Pallavicini and co-workers which were able to show that transduction mechanisms other than the heavy atom quenching can be operative in self-assembled micellar sensors. In particular they exploited the well-known photoelectron transfer (PET) process from amino groups to fluorescent dyes to modulate the fluorescence of pyrene entrapped in Triton X-100 micells. Fig. 17 illustrates an example of a sensor for pH windows [83].

The sensor is formed by the self-assembling of a lipophilic pyridine, a lipophilic amine and pyrene in Triton X-100 micelles. At low pH both pyridine and amine are protonated (Fig. 17a) and the fluorescence is "off", with the pyridinium fragment acting as a quencher by PET thanks to its electron-acceptor properties. As the pH rises above the pyridine pK_a, this fragment is no longer protonated (while the amine still is Fig. 17b) and thus the fluorescence goes "on". When the pH is increased further above the amine pK_a, this group also becomes deprotonated, and the fluorescence turns "off" again due to the quenching properties (by PET) of the electron-donating tertiary amino groups (Fig. 17c). In this way, the system behaves as an OFF-ON-OFF fluorescent sensor for pH windows. Playing with the pK_a of the amines and pyridines used it is possible to tune the wide of the window and its position along the pH axes. Following this approach the same group has reported other interesting results in the sensing of metal ions [84] and also in the determination of relevant chemical–physical properties of molecules such as their lipophilicity [85]. All these systems, along with others, are reviewed in a sister review in this special issue and represent and important step forward toward the general applicability of this self-assembling approach.

4.2. From micelles to silica nanoparticles

In the systems described in the previous section the micellar aggregates act as a matrix in which the components of the sensors self-organize in order to perform a specific function. However, the actual applicability of such systems is limited by several factors. In particular, surfactant aggregates are dynamic structures which form only above the critical micellar concentration and which are sensitive to experimental conditions, such as temperature and ionic strength. To overcome these limitations and to produce more stable systems one possibility is to use a different matrix to template the auto-organization of the chemosensor translating the above concepts in a more stable, covalently linked, system [69]. For fluorescence-based assays, glass can be a good candidate as an alternative matrix because it is inert, transparent to light and it can be easily functionalized by reaction with silane derivatives using well-established and simple experimental protocols. Follow-

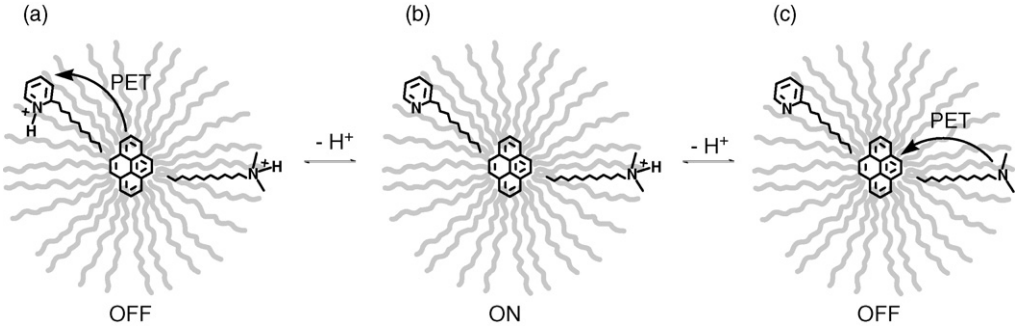


Fig. 17. Pictorial representation of the OFF-ON-OFF sensor for pH windows. The sensor is formed by the self-assembling in Triton X-100 micelles of a lipophilic tertiary amine, a lipophilic pyridine and a pyrene dye. The example is taken from Ref. [83].

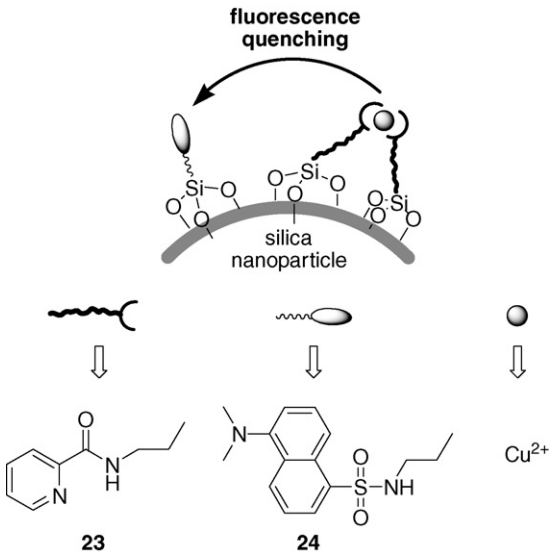


Fig. 18. Self-organized chemosensor on silica nanoparticles. The example is taken from Ref. [92].

ing this concept Crego-Calama and Reinhoudt have introduced a methodology to prepare glass surfaces functionalized with fluorescent probes which involves the sequential chemical modification of amino terminated self-assembled monolayers (SAMs) on glass with a fluorescent probe and a specific amino-capping functionality [86]. Such chemically modified surfaces can be used as a simple recognition material for metal ion such as Pb^{2+} while the fluorophore acts as a reporter. The resulting chemosensor is not strictly "self-assembled", because the coupling of the SAMs to the surface is covalent and not reversible. However, the new properties of the material derive from a spontaneous assembly of the subunits on the surface and, therefore, these systems might properly be referred to as "self-organized".

The grafting of the components of the sensor on a glass surface gives a stable material suitable for the development of optodes or sensor arrays [87]. However, for several biological applications such as, for example, intracellular monitoring of physical or chemical parameters, nanometric-sized particles are strongly preferred because of the lower physical and chemical perturbation of the sample and of the higher spatial resolution. This has brought to the development of a large number of nanosensors based on different types of nanoparticles comprising, for example, silica [88], gold [89], and organic polymer nanoparticles [90], quantum dots [91], etc. Our contribution to the field was to translate the self-assembling concept proved in micellar aggregates to surface functionalized silica nanoparticles. In the first system we investigated [92], commercially available silica nanoparticles (20 nm diameter) were functionalized with the triethoxysilane derivatives of the ligand picolinamide (**23**), selective for Cu^{2+}, and of the fluorophore dansylamide (**24**, Fig. 18). The grafting of the sensor components to the particle surface ensures the spatial proximity required to signal Cu^{2+} by quenching of the fluorescence emission. In 9:1 DMSO/water solution, the coated silica nanoparticles (CSNs) selectively detect copper ions down to micromolar concentrations. Similarly to the micelle-based systems, the operative range of the sensor can be tuned by the simple modification of the components ratio.

An intriguing aspect of CSNs is that their structure closely reminds that of a frozen co-micelle with a relatively high degree of organization of the sensor components in an extended and not dynamic network. This organization may lead to the onset of cooperative or collective processes which have indeed been observed in dendrimers [93], in nanoparticles [94] and in self-assembled monolayers on gold [95] but not in surfactant aggregates [96] probably due to the dynamic and poorly organized nature of these systems. This was the case also with our system and we were able to demonstrate cooperation of the ligand subunits grafted to the particles surface to form binding sites with an increased affinity for the substrate. Quite likely, this can be ascribed to the surface-organization of the picolinamide subunits that may lead to the formation of multivalent binding sites (e.g. with a 2:1 ligand/metal stoichiometry as indicated in Fig. 18) with a greater Cu^{2+} affinity. A further example of collective process observed by us using silica nanoparticle [97] and by Larpent and co-workers [98] using polystyrene nanoparticles is the amplification of the emitted signal due to the fact that a single Cu^{2+} ion is capable of quenching the emission of several surrounding dyes.

Finally silica nanoparticles present other loci, beside the surface, that can be used for the organization of a chemosensor. In particular the particle interior can be functionalized [99] and even organized in well separated compartments [100]. This peculiarity, which is clearly not present in micellar aggregates, has been exploited for the realization of a sensor for Cu^{2+} [101] and a ratiometric sensor for Pb^{2+} [102].

5. Conclusions

In this review, we have highlighted some of the supramolecolar functions that can derive from the interaction of lipophilic metal complexes and surfactant aggregates. Surfactant aggregates, and in particular micelles, act as supramolecular receptors concentrating in a small volume, mainly by hydrophobic and electrostatic interactions, lipophilic and ionic species. When lipophilic metal complexes are involved, this leads to the formation of metallomicelles in which a high local concentration of metal ions is realized at the water–aggregate interface. These metal ion-loaded superstructures may further interact with organic reactive molecules promoting their chemical transformation. Catalysis, and in particular catalysis of the cleavage of activated carboxylic and phosphoric acid esters, is one of the first functions that has been investigated with these systems. High, some time impressive, rate accelerations have been reported also in the case of the more inert phosphate esters. A careful kinetic analysis has shown that these effects are overwhelmingly due to the concentration of the reacting species in the small aggregate volume, while other factors such as, for example, peculiar properties of the reaction medium or specific organization of the reactants represent notable exceptions. Nonetheless, the accelerations are real and metallomicelles are powerful catalysts able to cleave at neutral pH carboxylic and phosphoric acid esters with high efficiency. Taking into considerations that several organic pesticides and chemical weapons are phosphate-based compounds the potential applications in environment protection and remediation are evident.

The interaction of lipophilic ligands and surfactant aggregates may lead, under specific circumstances, to more sophisticated functions. This is, for example, the case of the enantioselective cleavage of amino acid esters. In this process, the aggregate is fundamental in providing different reaction loci to the reacting systems and in controlling the activation of the nucleophilic function. The result is a high enantiodiscrimination, which may be exploited in the kinetic resolution of racemic mixtures of amino acid esters. Other supramolecular functions are the chemical differentiation of vesicle bilayers, the transport of ions and organic molecules across membranes, and the fluorescent chemical sensing. In this last case micelles again play the role of supramolecular containers promoting the self-assembling of the lipophilic ligand and of the fluorescent dye. The resulting co-aggregate acts as a chemosensor with important benefits essentially related to its self-assembled nature.

Finally, we would like to point out that some of the concepts related to surfactant aggregates can be transferred to nanoparticles which, in this context, can be regarded as "frozen" micelles. This is for example the case of hydrolytic catalysis and chemical sensing with self-assembled chemosensors. Moreover, due to the less dynamic nature of these systems, cooperative or collective effects can be more easily observed respect to the poorly organized micellar aggregates. The evolution toward these "covalent aggregates" represents an important new direction in our research interests.

References

[1] (a) D. Myers, Surfactant Science and Technology, 3rd ed., Wiley Interscience, New York, 2005;
(b) R.J. Farn, Chemistry and Technology of Surfactants, Blackwell Publishing, Oxford, 2006.
[2] D.F. Evans, H. Wennerström, The Colloidal Domain. Where Physics, Chemistry, Biology, and Technology Meet, VCH, New York, 1994.
[3] J.H. Fendler, E.J. Fendler, Catalysis in Micellar and Macromolecular Systems, Academic Press, New York, 1975.
[4] J.M. Lehn, Supramolecular Chemistry, VCH, New York, 1995.
[5] F.M. Menger, Angew. Chem. Int. Ed. Engl. 30 (1991) 1086.
[6] P. Scrimin, P. Tecilla, Curr. Opin. Chem. Biol. 3 (1999) 730.
[7] U. Tonellato, Colloid Surf. Sci. 35 (1989) 121.
[8] P. Scrimin, P. Tecilla, U. Tonellato, in: B.T. Golding, R.J. Griffin, H. Maskill (Eds.), Hydrolytic Catalysts as Metalloenzime Models in "Organic Reactivity: Physical and Biological Aspects, The Royal Society of Chemistry, Cambridge UK, 1995.
[9] J.H. Fendler, Membrane Mimetic Chemistry, Wiley, New York, 1982.
[10] H. Ringsdorf, B. Schlarb, J. Venzmer, Angew. Chem. Int. Ed. Engl. 27 (1988) 113.
[11] (a) H. Morawetz, Adv. Catal. 20 (1969) 341;
(b) J.M. Brown, S.K. Baker, A. Colens, J.R. Darwent, in: P. Dunnill, A. Wiseman, N. Blakebrough (Eds.), Enzymic and Non-enzymic Catalysis, Horwood, Chichester, 1980, p. 111.
[12] T. Dwars, E. Paetzold, G. Oehme, Angew. Chem. Int. Ed. 44 (2005) 7174.
[13] C.A. Bunton, F. Nome, F.H. Quina, L.S. Romsted, Acc. Chem. Res. 24 (1991) 357.
[14] R. Fornasier, U. Tonellato, J. Chem. Soc., Faraday Trans. 76 (1980) 1301.
[15] C.A. Bunton, G. Savelli, Adv. Phys. Org. Chem. 22 (1986) 213.
[16] P. Scrimin, in: A.D. Hamilton (Ed.), Supramolecular Control of Structure and Reactivity, vol. III, Wiley, Chichester, 1996, p. 101.
[17] (a) W. Tagaki, K. Ogino, Top. Curr. Chem. 128 (1985) 144;
(b) F.M. Menger, L.H. Gan, E. Johnson, D.H. Durst, J. Am. Chem. Soc. 109 (1987) 2800;
(c) S.H. Gellman, R. Petter, R. Breslow, J. Am. Chem. Soc. 108 (1986) 2388;
(d) J.G.J. Weiningen, A. Koudijs, J.F.J. Engbersen, J. Chem. Soc., Perkin Trans. 2 (1991) 1121;
(e) R. Fornasier, P. Scrimin, P. Tecilla, U. Tonellato, J. Am. Chem. Soc. 111 (1989) 224.
[18] E.L. Hegg, J.N. Burstyn, Coord. Chem. Rev. 173 (1998) 133.
[19] P. Scrimin, P. Tecilla, U. Tonellato, J. Org. Chem. 59 (1994) 18.
[20] P. Scrimin, P. Tecilla, U. Tonellato, J. Org. Chem. 56 (1991) 161.
[21] (a) K. Ogino, N. Kashihara, T. Ueda, T. Isaka, T. Yoshida, W. Tagaki, Bull. Chem. Soc. Jpn. 65 (1992) 373;
(b) K. Ogino, K. Inoue, W. Tagaki, Tetrahedron Lett. 33 (1992) 4194.
[22] J.G.J. Weijnen, A. Koudijs, G.A. Schellekens, J.F.J. Engbersen, J. Chem. Soc., Perkin Trans. 2 (1992) 829.
[23] P. Scrimin, P. Tecilla, U. Tonellato, C.A. Bunton, Colloids Surf. A 144 (1998) 71.
[24] (a) F. Hampl, F. Liska, F. Mancin, P. Tecilla, U. Tonellato, Langmuir 15 (1999) 405;
(b) F. Mancin, P. Tecilla, U. Tonellato, Langmuir 16 (2000) 227.
[25] E. Kimura, H. Hashimoto, T. Koike, J. Am. Chem. Soc. 118 (1996) 10963.
[26] A. Polyzos, A.B. Hughes, J.R. Christie, Langmuir 23 (2007) 1872.
[27] L.-G. Qiu, X. Jiang, L.-N. Gu, G. Hu, J. Mol. Catal. A: Chem. 277 (2007) 15.
[28] D. Juan, J. Bingying, K. Xingming, Z. Xiancheng, X. Qingxian, J. Colloid Interf. Sci. 256 (2002) 428.
[29] J.G.J. Weijnen, J.F.J. Engbersen, Recl. Trav. Chim. Pays-Bas 112 (1993) 351.
[30] Y.Y. Lim, E.H.L. Tan, L.H. Gan, J. Colloid Interf. Sci. 157 (1993) 442.
[31] (a) C.A. Bunton, P. Scrimin, P. Tecilla, J. Chem. Soc., Perkin Trans. 2 (1996) 419;
(b) P. Scrimin, G. Ghirlanda, P. Tecilla, R.A. Moss, Langmuir 12 (1996) 6235.
[32] R.A. Moss, C.J. Talkowski, D.W. Reger, C.E. Pewell, J. Am. Chem. Soc. 95 (1973) 5215.
[33] M.C. Cleij, W. Drenth, R.J.M. Nolte, J. Org. Chem. 56 (1991) 3883.
[34] J.G.J. Wijnen, A. Koudijs, J.F.J. Engbersen, J. Org. Chem. 57 (1992) 7258.
[35] (a) J.-S. You, X.-Q. Yu, X.-S. Li, Q.-S. Yan, R.-G. Xie, Tetrahedron Asym. 9 (1998) 1197;
(b) J.-S. You, X.-Q. Yu, K. Liu, L. Tao, Q.-X. Xiang, R.-G. Xie, Tetrahedron Asym. 10 (1999) 243;
(c) J.-S. You, X.-Q. Yu, X.-Y. Su, T. Wang, Q.-X. Xiang, M. Yang, R.-G. Xie, J. Mol. Catal. A: Chem. 202 (2003) 17.
[36] R. Fornasier, P. Scrimin, U. Tonellato, N. Zanta, J. Chem. Soc., Chem. Commun. (1988) 716.
[37] P. Scrimin, P. Tecilla, U. Tonellato, J. Org. Chem. 59 (1994) 4194.
[38] G. De Santi, P. Scrimin, U. Tonellato, Tetrahedron Lett. 31 (1990) 4791.
[39] G. Ghirlanda, P. Scrimin, P. Tecilla, A. Toffoletti, Langmuir 14 (1998) 1646.
[40] (a) M.C. Cleij, P. Tecilla, U. Tonellato, P. Scrimin, Gazz. Chim. Ital. 126 (1996) 827;
(b) M.C. Cleij, F. Mancin, P. Scrimin, P. Tecilla, U. Tonellato, Tetrahedron 53 (1997) 357.
[41] M.C. Cleij, P. Scrimin, P. Tecilla, U. Tonellato, Langmuir 12 (1996) 2956.
[42] D.D. Lasic, Liposomes: From Physics to Applications, Elsevier, Amsterdam, 1993.
[43] (a) R.A. Moss, S. Bhattacharya, S. Chatterjee, J. Am. Chem. Soc. 111 (1989) 3680;
(b) R.A. Moss, S. Ganguli, Y. Okumura, T. Fujita, J. Am. Chem. Soc. 112 (1990) 6391;
(c) R.A. Moss, J.M. Li, J. Am. Chem. Soc. 114 (1992) 9227;
(d) R.A. Moss, Pure Appl. Chem. 66 (1994) 851.
[44] G. Ghirlanda, P. Scrimin, P. Tecilla, U. Tonellato, J. Org. Chem. 58 (1993) 3025.
[45] P. Scrimin, P. Tecilla, R.A. Moss, K. Bracken, J. Am. Chem. Soc. 120 (1998) 1179.
[46] L. Pasquato, P. Pengo, P. Scrimin, J. Mater. Chem. 14 (2004) 3481.
[47] L. Pasquato, F. Rancan, P. Scrimin, F. Mancin, C. Frigeri, Chem. Commun. (2000) 2253.
[48] P. Pengo, S. Polizzi, L. Pasquato, P. Scrimin, J. Am. Chem. Soc. 127 (2005) 1616.
[49] P. Pengo, L. Baltzer, L. Pasquato, P. Scrimin, Angew. Chem. Int. Ed. 46 (2007) 400.
[50] P. Rossi, F. Felluga, P. Scrimin, Tetrahedron Lett. 39 (1998) 7159.
[51] F. Manea, F. Bodar-Houillon, L. Pasquato, P. Scrimin, Angew. Chem. Int. Ed. 43 (2004) 6165.
[52] (a) G.Q. Feng, D. Natale, R. Prabaharan, J.C. Mareque-Rivas, N.H. Williams, Angew. Chem. Int. Ed 45 (2006) 7056;
(b) M. Livieri, F. Mancin, G. Saielli, J. Chin, U. Tonellato, Chem. Eur. J 13 (2007) 2246;
(c) R. Bonomi, F. Selvestrel, V. Lombardo, C. Sissi, S. Polizzi, F. Mancin, U. Tonellato, P. Scrimin, J. Am. Chem. Soc. 130 (2008) 15744.
[53] T.M. Fyles, Chem. Soc. Rev. 36 (2007) 335.
[54] (a) M. Hebrant, S.G. Son, C. Tondre, P. Tecilla, P. Scrimin, J. Chem. Soc., Faraday Trans. 88 (1992) 209;
(b) S.G. Son, M. Hebrant, P. Tecilla, P. Scrimin, C. Tondre, J. Phys. Chem. 96 (1992) 11072;
(c) C. Tondre, S.G. Son, M. Hebrant, P. Tecilla, P. Scrimin, Langmuir 9 (1993) 950;
(d) M. Hebrant, P. Tecilla, P. Scrimin, C. Tondre, Langmuir 13 (1997) 5539.
[55] F.M. Menger, J.J. Lee, J. Org. Chem. 58 (1993) 1909.
[56] P. Scrimin, P. Tecilla, U. Tonellato, J. Am. Chem. Soc. 114 (1992) 5086.
[57] D.D. Lasic, Trends Biotechnol. 16 (1998) 307.
[58] (a) Y. Rui, S. Wang, P.S. Low, D.H. Thompson, J Am. Chem. Soc. 120 (1998) 120;
(b) B. Bondurant, D.F. O'Brien, J. Am. Chem. Soc. 120 (1998) 13541;
(c) F.M. Menger, J.S. Keiper, Angew. Chem. Int. Ed. 37 (1998) 3433.
[59] P. Scrimin, S. Caruso, N. Paggiarin, P. Tecilla, Langmuir 16 (2000) 203.
[60] J.D. Lamb, J.J. Christensen, R.M.J. Izatt, J. Chem. Educ. 57 (1980) 227.
[61] T.M. Fyles, W.F. Van Straaten-Nijenhuis, in: D.N. Reinhoudt (Ed.), Comprehensive Supramolecular Chemistry, vol. 10, Elsevier, Oxford, UK, 1996, pp. 53–77.
[62] M.C. Cleij, P. Tecilla, U. Tonellato, P. Scrimin, J. Org. Chem. 62 (1997) 5592.
[63] H. Siegel, R.B. Martin, Chem. Rev. 82 (1982) 385.
[64] (a) P. Scrimin, U. Tonellato, N. Zanta, Tetrahedron Lett. 29 (1988) 4967;
(b) P. Scrimin, P. Tecilla, U. Tonellato, Tetrahedron 51 (1995) 217.
[65] (a) A.W. Czarnik (Ed.), Fluorescent Chemosensors for Ion and Molecule Recognition, ACS Symposium Series, vol. 538, American Chemical Society, Washington, DC, 1993;
(b) T.S. Snowden, E.V. Anslyn, Curr. Opin. Chem. Biol. 3 (1999) 740;
(c) L. Fabbrizzi, M. Licchelli, P. Pallavicini, L. Parodi, A. Taglietti, in: J.-P. Sauvage (Ed.), Transition Metal in Supramolecular Chemistry, Wiley, Chichester, 1999, pp. 93–134.
[66] (a) A.P. de Silva, H.Q.N. Gunaratne, T. Gunnlaugsson, A.J.M. Huxley, C.P. McCoy, J.T. Rademacher, T.E. Rice, Chem. Rev. 97 (1997) 1515;
(b) A.P. de Silva, P. Tecilla, J. Mater. Chem. 15 (2005) 2637.
[67] D.W. Domaille, E.L. Que, C.J. Chang, Nat. Chem. Biol. 4 (2008) 168.
[68] Selected recent reviews:
(a) E.M. Nolan, S.J. Lippard, Chem. Rev. 108 (2008) 3443;
(b) A.P. de Silva, T.P. Vance, M.E.S. West, G.D. Wright, Org. Biomol. Chem. 6 (2008) 2468;
(c) P.A. Gale, Chem. Commun. (2008) 4525;
(d) E.V. Anslyn, J. Org. Chem. 72 (2007) 687;
(e) S. Royo, R. Martínez-Máñez, F. Sancenón, A.M. Costero, M. Parra, S. Gil, Chem. Commun. (2007) 4839.
[69] F. Mancin, E. Rampazzo, P. Tecilla, U. Tonellato, Chem. Eur. J. 12 (2006) 1844.
[70] (a) M. Arduini, E. Rampazzo, F. Mancin, P. Tecilla, U. Tonellato, Inorg. Chim. Acta 360 (2007) 721;
(b) B.T. Nguyen, E.V. Anslyn, Coord. Chem. Rev. 250 (2006) 3118;
(c) L. Fabbrizzi, M. Lichelli, A. Taglietti, Dalton Trans. (2003) 3479.
[71] S. Uchiyama, K. Iwai, A.P. de Silva, Angew. Chem. Int. Ed. 47 (2008) 4667.
[72] (a) K. Niikura, E.V. Anslyn, J. Org. Chem. 68 (2003) 10156;
(b) H. Sakamoto, T. Yamamura, K. Takumi, K. Kimura, J. Phys. Chem. 20 (2007) 900;
(c) J. Wang, X. Qian, J. Qian, Y. Xu, Chem. Eur. J. 13 (2007) 7543;
(d) Y. Zhao, Z. Zhong, Org. Lett. 8 (2006) 4715;
(e) S. Bhattacharya, A. Gulyani, Chem. Commun. (2003) 1158;

(f) S. Uchiyama, G.D. McClean, K. Iwai, A.P. de Silva, J. Am. Chem. Soc. 127 (2005) 8920.
[73] A.D. Hughes, I.C. Glenn, A.D. Patrick, A. Ellington, E.V. Anslyn, Chem. Eur. J. 14 (2008) 1822.
[74] A. Mallick, M.C. Mandal, B. Haldar, A. Chakrabarty, P. Das, N. Chattopadhyay, J. Am. Chem. Soc. 128 (2006) 3126.
[75] A. Guerrero-Martínez, Y. Vida, D. Domínguez-Gutiérrez, R.Q. Albuquerque, L. De Cola, Inorg. Chem. 47 (2008) 9131.
[76] D.Y. Sasaki, D.R. Shnek, D.W. Pack, F.H. Arnold, Angew. Chem. Int. Ed. Engl. 34 (1995) 905.
[77] B.C. Roy, B. Chandra, D. Hromas, S. Mallik, Org. Lett. 5 (2003) 11.
[78] D.Y. Sasaki, B.E. Padilla, Chem. Commun. (1998) 1681.
[79] P. Grandini, F. Mancin, P. Tecilla, P. Scrimin, U. Tonellato, Angew. Chem. Int. Ed. 38 (1999) 3061.
[80] M. Berton, F. Mancin, G. Stocchero, P. Tecilla, U. Tonellato, Langmuir 17 (2001) 7521.
[81] (a) Y. Diaz-Fernandez, A. Perez-Gramatges, V. Amendola, F. Foti, C. Mangano, P. Pallavicini, S. Patroni, Chem. Commun. (2004) 1650;
(b) Y. Diaz-Fernandez, A. Perez-Gramatges, S. Rodriguez-Calvo, C. Mangano, P. Pallavicini, Chem. Phys. Lett. 398 (2004) 245;
(c) P. Pallavicini, L. Pasotti, S. Patroni, Dalton Trans. (2007) 5670;
(d) Y. Díaz-Fernández, S. Rodríguez-Calvo, A. Pérez-Gramatges, P. Pallavicini, S. Patroni, C. Mangano, J. Colloid Interf. Sci. 313 (2007) 638.
[82] Y. Zheng, J. Orbulescu, X. Ji, F.M. Andreopoulos, S.M. Pham, R.M. Leblanc, J. Am. Chem. Soc. 125 (2003) 2680.
[83] Y. Diaz-Fernandez, F. Foti, C. Mangano, P. Pallavicini, S. Patroni, A. Perez-Gramatges, S. Rodriguez-Calvo, Chem. Eur. J. 12 (2006) 921.
[84] P. Pallavicini, Y.A. Diaz-Fernandez, F. Foti, C. Mangano, S. Patroni, Chem. Eur. J. 13 (2007) 178.
[85] G. Chirico, M. Collini, L. D'Alfonso, F. Denat, Y.A. Diaz-Fernandez, L. Pasotti, Y. Rousselin, N. Sok, P. Pallavicini, ChemPhysChem 9 (2008) 1729.
[86] M. Crego-Calama, D.N. Reinhoudt, Adv. Mater. 13 (2001) 1171.
[87] L. Basabe-Desmonts, J. Beld, R.S. Zimmerman, J. Hernando, P. Mela, M.F. GarcVa ParajW, N.F. van Hulst, A. van den Berg, D.N. Reinhoudt, M. Crego-Calama, J. Am. Chem. Soc. 126 (2004) 7293.
[88] S.M. Buck, Y.E.L. Koo, E. Park, H. Xu, M. Brasuel, M.A. Philbert, R. Kopelman, Curr. Opin. Chem. Biol. (8) (2004) 540.
[89] W. Zhao, M.A. Brook, Y. Li, ChemBioChem 9 (2008) 2363.
[90] O.S. Wolfbeis, J. Mater. Chem. 15 (2005) 2657.
[91] R.C. Somers, M.G. Bawendi, D.G. Nocera, Chem. Soc. Rev. 36 (2007) 579.
[92] E. Brasola, F. Mancin, E. Rampazzo, P. Tecilla, U. Tonellato, Chem. Commun. (2003) 3026.
[93] F. Vogtle, S. Gestermann, C. Kauffmann, P. Ceroni, V. Vicinelli, V. Balzani, J. Am. Chem. Soc. 122 (2000) 10398.
[94] (a) M. Montalti, L. Prodi, N. Zaccheroni, G. Falini, J. Am. Chem. Soc. 124 (2002) 13540;
(b) M. Montalti, L. Prodi, N. Zaccheroni, A. Zattoni, P. Reschiglian, G. Falini, Langmuir 20 (2004) 2989;
(c) L. Prodi, New J. Chem. 29 (2005) 20.
[95] R.C. Major, X.-Y. Zhu, J. Am. Chem. Soc. 125 (2003) 8454.
[96] E.L. Doyle, C.A. Hunter, H.C. Phillips, S.J. Webb, N.H. Williams, J. Am. Chem. Soc. 125 (2003) 4593.
[97] E. Rampazzo, E. Brasola, S. Marcuz, F. Mancin, P. Tecilla, U. Tonellato, J. Mater. Chem. 15 (2005) 2687.
[98] R. Méallet-Renault, R. Pansu, S. Amigoni-Gerbier, C. Larpent, Chem. Commun. (2004) 2344.
[99] P. Teolato, E. Rampazzo, M. Arduini, F. Mancin, P. Tecilla, U. Tonellato, Chem. Eur. J. 13 (2007) 2238.
[100] A. Burns, H. Ow, U. Wiesner, Chem. Soc. Rev. 35 (2006) 1028.
[101] M. Arduini, S. Marcuz, M. Montolli, E. Rampazzo, F. Mancin, S. Gross, L. Armelao, P. Tecilla, U. Tonellato, Langmuir 21 (2005) 9314.
[102] M. Arduini, F. Mancin, P. Tecilla, U. Tonellato, Langmuir 23 (2007) 8632.