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Influence of structurally related micelle forming surfactants on the antioxidant activity of natural substances

Sara Battista, Patrizio Campitelli, Armando Carlone, Luisa Giansanti*

Dipartimento di Scienze Fisiche e Chimiche, Università degli Studi dell'Aquila, Via Vetoio 10, 67100 Coppito, AQ, Italy

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ABSTRACT

Physicochemical properties of micelles, like other lipid aggregates, mostly depend on the composition and on the structure of the surfactants used as monomers. The preparation and the characterization of three cationic *L*-prolinol derivative surfactants with different chain lengths and their corresponding *N*-oxide are described. UV measurements were carried out to investigate the effect of the inclusion in micelles on the degradation of *L*-ascorbic acid and (+)-usnic acid. An influence on antioxidant activity was exerted to an extent strictly dependent on *i*) surfactant chain length, *ii*) charge, *iii*) pH (in the case of (+)-usnic acid) and *iv*) on the hydrophilicity of the solute, determinant parameter for their location in the aggregates. In general the extent of the antioxidant activity of the system in the case of *N*-oxides micelles depends on surfactant chain length. On the other hand, cationic micelles formed by the surfactant with the shortest chain behave more like *N*-oxides ones rather than those formed by its relative structural homologues featuring longer alkyl chains, probably as a consequence of a concentration effect.

1. Introduction

It is well known that the structural characteristics of the components of lipidic self-assembled systems influence the morphology and physicochemical behavior of the aggregates (Israelachvili et al., 1976; Oliver et al., 2013) and are strictly related to their "classical" performance properties (*i.e.* wetting and foaming ability, solubilization and detergency) (Azira et al., 2008; Sehgal et al., 2003; Lichtenberg et al., 1983). For example, the length of the surfactant can significantly affect the properties of the aggregates it forms (Ceccacci et al., 2013; Costas-Costas et al., 2005; Wang and Gao, 2018; Ceccacci et al., 2008). Moreover, the charge of the polar headgroup of the surfactants plays a crucial role in determining the interaction of their aggregates with the solute and with the counterions in solution (Fuangswasdi et al., 2006; Demissie and Duraisamy, 2016; Joshi et al., 2002; Sinha and Bahadur, 2002; Vlachy et al., 2008). In general, a polar headgroup featuring a pyrrolidine ring is characterized by a lower conformational freedom with respect to the corresponding acyclic analogue, together with a different balance as a whole between the hydrophilic and the hydrophobic region of the molecules (Karukstis and McDonough, 2005). The possibility of modifying the pyrrolidine skeleton and the length of the alkyl chains, thus the physicochemical properties of the surfactant, makes pyrrolidinium based surfactants interesting in many research fields (Zhao and Zheng, 2011; Cai et al., 2012, Tian2016; Bombelli et al., 2008). Furthermore, *N*-oxide based surfactants (N-ox) show very interesting properties and are involved in a wide variety of industrial applications such as cleaning products (washing-up and laundry detergents), foaming and wetting agents, fabric softeners and thickeners in hair and body care products (Sauer, 1990; Vaikunth, 2019; Gunstone and Padley, 2018). In fact, they are zwitterionic (at physiological pH) amphiphilic molecules characterized by a strong polar N−O bond (and a high electron density on the oxygen) (Łukomska et al., 2015). Moreover, they are environmentally friendly (often they are classified as soft surfactants) (Lewińska et al., 2014) and very easy to prepare. Thanks to a number of peculiarities, such as pH-sensitivity, higher emulsifying ability and biodegradability, lower irritant action and toxicity, gelating and antioxidant properties, N-ox are regarded as very interesting molecules that could find application in a range of areas. Several reports describe the effect of changes in the molecular structure of mono- and di-twin (Lewińska et al., 2014; Piasecki et al., 2009) tailed and gemini (Bordi et al., 2010) N-ox on their self-aggregation behavior, their catalytic activity (Katritzky et al., 1988; Karlovská et al., 2006) and their influence on entrapped solutes (Niedziółka et al., 2012). In particular, it was described that the antioxidant activity of *L*-ascorbic acid (AA), well known for its reducing properties, increases in a dose-dependent manner in the presence of N-ox micelles in pure water

* Corresponding author.
E-mail address: luisa.giansanti@univaq.it (L. Giansanti).

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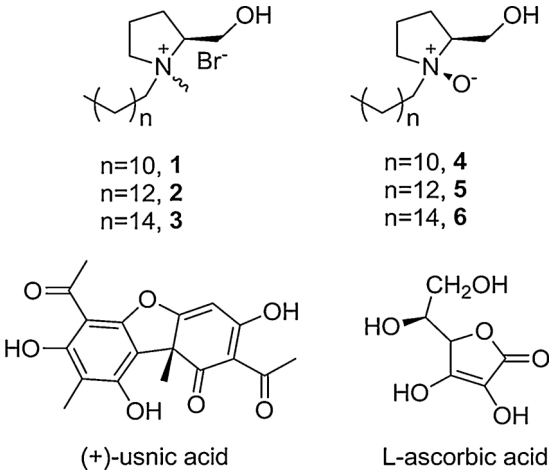


Chart 1. Cationic/*N*-oxide surfactants and natural substances used in this investigation.

(Piasecki et al., 2008).

Herein, we report an investigation on the aggregation properties of synthetic cationic surfactants (CSs) **1**-**3** derived from *L*-prolinol differing for the length of the alkyl chain, and their corresponding N-ox **4**-**6** (Chart 1). Moreover, the antioxidant activity of two natural compounds, (+)-usnic acid (UA) and AA, was evaluated with respect to *L*-prolinol derivatives micelles in aqueous solution, and H_2O_2 (in the case of UA) to catalyze the oxidation. AA is a hydrophilic molecule that easily undergoes a two-electron oxidation reaction under aerobic conditions. UA is a secondary metabolite of many lichens with antioxidant properties (Luzina and Salakhutdinov, 2018; Suwalsky et al., 2015) that is highly lipophilic even in its deprotonated forms thanks to the possibility to stabilize the negative charge on the β-triketone groups by resonance (Guo et al., 2008). The aim of this investigation is to study the effect of the presence of a *N*-oxide or a quaternary ammonium as polar headgroup and of the length of the alkyl chain on micelle properties and on the antioxidant activity of natural substances with different water solubility; the different chemical structure of the monomer could be crucial because it is known that the antioxidant activity is strictly dependent on the microenvironment surrounding the molecule (Dracha et al., 2011; Bae et al., 2012).

2.1. Experimental section

2.1.1. Instrumentation

UV measurements: Cary 50 UV − vis double beam spectrophotometer (Varian). ^{1}H and ^{13}C spectra: Bruker 400; δ in ppm relative to the residual solvent peak of $CDCl_3$ at 7.26 and 77.0 ppm for ^{1}H and ^{13}C, respectively. Conductivity and pH measurements: Amel Model 334-B.

2.1.2. Materials

All reagents employed for the synthesis of **1**-**6** were purchased from Sigma-Aldrich. CS **3** was prepared as previously described (Borocci et al., 2003). Yields were not optimized. TLC (Sigma-Aldrich): silica gel 60, F254.

2.2. Methods

2.2.1. General procedure for the synthesis of compounds 10–12

The appropriate alkyl bromide **7**-**9** (10 mmol) and *L*-prolinol (5 mmol) was dissolved in 10 mL of acetone. The solution was kept under stirring at 60 °C with reflux condenser overnight. Upon cooling, a white solid precipitated, and was subsequently washed with acetone (10 mL) and diethyl ether (20 mL). The recovered material was dissolved in EtOH and Na_2CO_3 was added until the disappearance of bubbling due to CO_2 formation. The excess of Na_2CO_3 was filtered off, the solvent was removed under reduced pressure and the product was crystallized from acetone. Compound **10**. White solid. Yield: 57%. ^{1}H-NMR ($CDCl_3$): δ = 3.84 (dd, 1H, $\underline{CH_2}$OH); 3.49 (dd, 1H, $\underline{CH_2}$OH); 2.88-2.53 (m, 6H, $\underline{CH_2}$N); 1.73-1.42 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.31 (m, 18 H); 0.99 (t, 3H, CH_3) 0.67 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 64.57; 61.83; 54.95; 53.23; 31.65; 29.06; 28.96; 28.90; 27.90; 27.55; 24.15; 22.94; 14.02. Compound **11**. White solid. Yield: 58%. ^{1}H-NMR ($CDCl_3$): δ = 3.84 (dd, 1H, $\underline{CH_2}$OH); 3.49 (dd, 1H, $\underline{CH_2}$OH); 2.88-2.53 (m, 6H, $\underline{CH_2}$N); 1.73-1.42 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.31 (m, 20 H); 0.99 (t, 3H, CH_3); 0.67 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 64.57; 61.83; 54.95; 53.23; 31.65; 29.06; 28.96; 28.90; 27.90; 27.55; 24.15; 22.94; 14.02. Compound **12**. White solid. Yield: 56%. ^{1}H-NMR ($CDCl_3$): δ = 3.84 (dd, 1H, $\underline{CH_2}$OH); 3.49 (dd, 1H, $\underline{CH_2}$OH); 2.88-2.53 (m, 6H, $\underline{CH_2}$N); 1.73-1.42 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.31 (m, 22 H); 0.99 (t, 3H, CH_3); 0.67 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 64.57; 61.83; 54.95; 53.23; 31.65; 29.06; 28.96; 28.90; 27.90; 27.55; 24.15; 22.94; 14.02.

2.2.2. General procedure for the synthesis of cationic surfactants 1–2

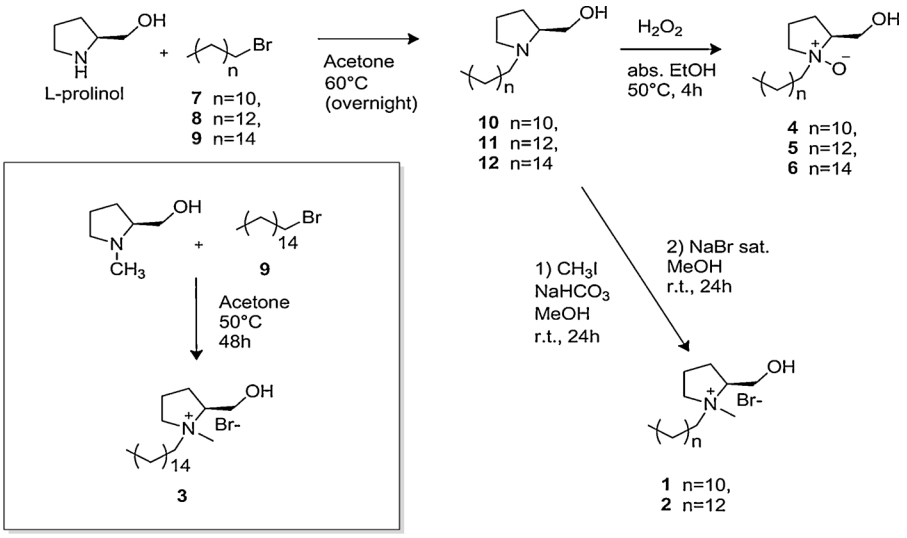
Products **1**-**2** were obtained by quaternisation of 1 mmol of the appropriate *L*-prolinol derivative **10**-**11** with 1 mL of CH_3I in methanol (20 mL) in the presence of 1 g $NaHCO_3$ at room temperature till complete conversion of the amine, generally 24 h. After filtration, the reaction mixture was evaporated to dryness and washed several times with cold diethyl ether until compounds were obtained as white solids. To exchange the counterion from I^- to Br^-, a saturated NaBr solution in MeOH was added and left under stirring at room temperature for 24 h; the solution was then evaporated to give the compounds **1**-**2**. The chlorine water assay was used to confirm the completeness of counterion exchange: 10 mg of **1** or **2** were added to 3 mL aqueous solution of $AgNO_3$ 0.25 M and HNO_3 0.25 M. The solution was centrifuged and the precipitate was treated with chlorine water (obtained from HCl and $KClO_3$). If iodide is present, even in traces, I_2 is formed by oxidation and it confers a violet color to the organic layer after extraction of the aqueous phase with chloroform. Compound **1**. White solid. Yield: 60%. ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}$OH); 3.89 (dd, 1H, $\underline{CH_2}$OH); 3.48 (m, 2H, N$\underline{CH_2}CH_2$OH); 3.27-3.22 (m, 4H, $\underline{CH_2}$N); 3.30 (t, 3H, $\underline{CH_3}$N); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.29 (m, 18 H); 0.99 (t, 3H, CH_3); 0.83 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 63.67; 63.34; 60.61; 47.97; 31.65; 29.04; 28.96; 27.81; 27.05; 23.34; 23.21; 22.94; 14.02. Compound **2**. White solid. Yield: 62% ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}$OH); 3.89 (dd, 1H, $\underline{CH_2}$OH); 3.48 (m, 2H, N$\underline{CH_2}CH_2$OH); 3.27-3.22 (m, 4H, $\underline{CH_2}$N); 3.30 (t, 3H, $\underline{CH_3}$N); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.29 (m, 20 H); 0.99 (t, 3H, CH_3); 0.83 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 63.67; 63.34; 60.61; 47.97; 31.65; 29.04; 28.96; 27.81; 27.05; 23.34; 23.21; 22.94; 14.02.

2.2.3. Synthesis of cationic surfactant 3

CS **3** was obtained by quaternisation of 4.2 mmol of *N*-methyl-*L*-prolinol (0.5 mL) with 4.5 mmol of 1-bromohexadecane **9** (1.4 mL) in 5 mL of acetone. The reaction was kept under stirring at 50 °C for 48 h, according to a procedure described in literature (Borocci et al., 2003). After cooling at room temperature the product precipitated as a white solid and was washed several times with hexane. Yield: 73%. ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}$OH); 3.89 (dd, 1H, $\underline{CH_2}$OH); 3.48 (m, 2H, N$\underline{CH_2}CH_2$OH); 3.27-3.22 (m, 4H, $\underline{CH_2}$N); 3.30 (t, 3H, $\underline{CH_3}$N); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2$N); 1.37-1.29 (m, 22 H); 0.99 (t, 3H, CH_3); 0.83 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 63.67; 63.34; 60.61; 47.97; 31.65; 29.04; 28.96; 27.81; 27.05; 23.34; 23.21; 22.94; 14.02.

2.2.4. General procedure for the synthesis of N-Ox surfactants 4–6

The appropriate *L*-prolinol derivative **10**-**12** (1.5 mmol) was dissolved in absolute EtOH (0.5 mL), then 330 μL H_2O_2 (40% m/v, 3.9 mmol) were added dropwise. The solution was kept at 50 °C under stirring for 4 h. The reaction was cooled and a small amount of MnO_2



Scheme 1. General procedure for the synthesis of *L*- prolinol derivatives **1**-**6**.

was added to quench the excess of H_2O_2. Excess MnO_2 was removed by filtration, washed with 20 mL of ethanol and the solvent removed under reduced pressure. The residue was dissolved in 15 mL diethyl ether and the solvent was removed under reduced pressure three times giving **4**-**6.** Compound **4**. White solid. Yield: 70%. ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}OH$); 3.86 (dd, 1H, $\underline{CH_2}OH$); 3.48 (m, 2H, $N\underline{CH_2}CH_2OH$); 3.27-3.22 (m, 4H, $\underline{CH_2}N$); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2N$); 1.37-1.30 (m, 18 H); 0.99 (t, 3H, CH_3); 0.81 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 69.43; 66.90; 60.03; 31.65; 29.06; 28.96; 27.81; 27.50; 23.58; 23.09; 22.94; 14.02. Compound **5**. White solid. Yield: 73%. ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}OH$); 3.86 (dd, 1H, $\underline{CH_2}OH$); 3.48 (m, 2H, $N\underline{CH_2}CH_2OH$); 3.27-3.22 (m, 4H, $\underline{CH_2}N$); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2N$); 1.37-1.30 (m, 20 H); 0.99 (t, 3H, CH_3); 0.81 (s, 1H, OH). δ = 69.43; 66.90; 60.03; 31.65; 29.06; 28.96; 27.81; 27.50; 23.58; 23.09; 22.94; 14.02. Compound **6**. White solid. Yield: 68%. ^{1}H-NMR ($CDCl_3$): δ = 4.13 (dd, 1H, $\underline{CH_2}OH$); 3.86 (dd, 1H, $\underline{CH_2}OH$); 3.48 (m, 2H, $N\underline{CH_2}CH_2OH$); 3.27-3.22 (m, 4H, $\underline{CH_2}N$); 1.86-1.54 (m, 6H, $\underline{CH_2}CH_2N$); 1.37-1.30 (m, 22 H); 0.99 (t, 3H, CH_3); 0.81 (s, 1H, OH). δ = 69.43; 66.90; 60.03; 31.65; 29.06; 28.96; 27.81; 27.50; 23.58; 23.09; 22.94; 14.02.

2.2.5. Determination of surfactants 1–6 critical micellar concentration (cmc) through conductimetric measurements and evaluation of Krafft temperature

6 mL of distilled water were put in a test tube and initial conductivity was evaluated; small amounts of surfactant dissolved in water were added to the solution under stirring in order to obtain concentrations between 10^{-7} M and 10^{-3} M measuring the conductivity after each addition. Krafft temperature was evaluated keeping at 4 °C overnight an aqueous solution of surfactant at a concentration higher than *cmc* value. The experiments were done in triple determination.

2.2.6. Determination of surfactants 4–6 pK_a

The pK_a of each N-Ox was evaluated titrating it with HCl and exploiting the Gran plot. In a test tube 9 mL of distilled water and surfactant (final concentration equal to 3 *cmc* values) were put and a NaOH water solution ($1.35{\cdot}10^{-3}$ M) was added slowly until pH = 10. Small aliquots of a HCl 10^{-3} M water solution were added and the pH after stirring was measured every time well above the equivalent point. The collected data were used to construct the Gran plot according to the equation:

$$10^{pH}{\cdot}Va = K_a{}^{-1}(Ve\text{-}Va)$$

where Va is the total HCl volume added, Ve is the HCl volume added at the equivalent point and K_a is the acidic constant of the analyzed substance. The experiments were done in double determination.

2.2.7. AA degradation in water

In a cuvette 20 µL of AA $7.8{\cdot}10^{-3}$ M in water were added to 2500 µL of water; in case of a test with N-ox, this was present at a final concentration 20-fold above *cmc*. The decrease in time of the intensity of the AA absorbance peak at 265 nm in water was evaluated for 1 h. The experiments were done in triple determination.

2.2.8. AA and UA degradation in the presence of H_2O_2

In a cuvette, 20 µL of AA $7.8{\cdot}10^{-3}$ M in water or 2.5 µL of UA $3.75{\cdot}10^{-2}$ M in DMSO and a proper amount of H_2O_2 (mol H_2O_2/mol AA or UA 10/1) were added to 2500 µL of water containing or not each L-prolinol derivative at a final concentration $1.4{\cdot}10^{-4}$ M for N-ox (well above their *cmc*), 2 *cmc* values for CS and $5{\cdot}10^{-2}$M for **2** and **3**. The variation of the peaks at 265 nm for AA and at 290 nm and 330 nm for UA was followed over 30 min; the experiment was performed at pH 7.4 for AA and at pH 10.9 for UA. The experiments were done in triple determination.

3. Results and discussion

3.1. Chemistry

Surfactants **1**-**6** were obtained following the procedure reported in Scheme 1 by alkylation of secondary amine of *L*-prolinol with the corresponding n-bromoalcane to give the intermediate products **10**-**12**. These compounds were reacted with CH_3I to alkylate the nitrogen; the iodide ammonium products underwent a ion exchange by dissolving the iodide ammonium salt in a saturated NaBr methanol solution to yield CSs **1**-**3**. The precipitation of the surfactant counterions as silver salt by addition of a $AgNO_3$ solution established the completeness of the counterion exchange: the absence of iodide was confirmed by the addition of chlorine water to the obtained salt after an extraction with chloroform. Precipitation of counterions was carried out to avoid the perturbation of the oxidation assay by the surfactant alkyl chain. N-ox **4**-**6** were obtained by oxidation of the corresponding tertiary amine using aqueous hydrogen peroxide. While in case of CSs **1**-**3** a racemic mixture was obtained, only a single diastereoisomer with the amine oxide *syn* to the hydroxyl side chain was formed in case of **4**-**6**. This peculiar behavior is due to the stabilization of the product by intramolecular hydrogen bonding between the hydrogen of the hydroxyl group and oxygen of N-oxide moiety that brings to the formation of a

Table 1
cmc values of surfactants **1**-**6**.

Surfactant	*cmc* (M)
1	$(2.3 \pm 0.3) \cdot 10^{-2}$
2	$(2.6 \pm 0.4) \cdot 10^{-3}$
3	$(2.5 \pm 0.2) \cdot 10^{-4}$
4	$(1.4 \pm 0.3) \cdot 10^{-5}$
5	$(5.8 \pm 0.4) \cdot 10^{-6}$
6	$(1.5 \pm 0.5) \cdot 10^{-6}$

favored six-member ring (O'Neil and Potter, 1998).

3.2. Determination of cmc and Krafft T of surfactants 1–6

The *cmc* of surfactants **1**-**6** was evaluated by plotting the conductivity *versus* the concentration of each surfactant; the intersection point between the two linear trends described by the experimental values represents the *cmc*. The results are reported in Table 1.

As expected *cmc* value decreases as a function of the chain length of the surfactant in each series and it is lower for N-ox (**4–6**) with respect to CS (**1–3**) because the lower repulsions between the polar zwitterionic headgroups promote the aggregation at lower monomer concentration. Krafft temperatures for all surfactants were lower than 4 °C due to the absence of a precipitate after storage in these conditions.

3.3. Determination of surfactants 4–6 pK_a

In water N-ox are present in either the protonated or the deprotonated form because of the acid-base equilibrium; this phenomenon can strongly influence the properties of aggregates of pH-sensitive surfactants. The apparent pK_a of surfactants **4**-**6**, estimated using the Gran plot after the equivalent point, were all similar, as expected, and equal to about 5.4. Despite these values were obtained in aggregative conditions (titrations were carried out at concentrations above *cmc*), they are in good agreement with pK_a values reported in literature for *N*-oxide group (Búcsi et al., 2014; Huláková et al., 2015), suggesting that aggregation does not influence the protonation of the oxygen in the investigated N-ox, in contrast with the general observation for the nitrogen of tertiary amines (Mezei et al., 2012; Colomer et al., 2011; Giansanti et al., 2016).

3.4. AA degradation

The degradation of AA in water was investigated both in presence and in absence of micelles of N-oxs and CSs. The decrease of the absorbance intensity at λ_{max} of the reduced form of AA (265 nm) was followed to evaluate the influence of the different aggregates on the rate of oxidation. It has to be considered that, oxygen (the oxidant) may enter the micelles, in particular it tends to concentrate in the internal micelles core than near the headgroup region (Subczyński and Wiśniewska, 2000; Geiger and Turro, 1975). Moreover, in the case of ionic surfactants, the nature of the head group scarcely affects intramicellar oxygen solubilization that higher than in water and increases linearly with surfactant concentration (Prapaitrakul and King, 1985). On the other hand AA, more hydrophilic, is excluded from micelles hydrophobic core but can interact with the polar headgroup of the surfactant.

The degradation process was faster in the presence of N-ox micelles, in particular in the case of **5**, whereas the variation observed carrying out the same experiment in the presence of micelles of CSs was negligible as in the case of AA alone (black trace reported in Fig. 1 as an example). Our results show that *N*-oxide moiety seems to enhance AA oxidation, thus exalting its antioxidant activity, in good agreement with literature report (Piasecki et al., 2008). The fact that in the case of CSs this effect is not observed can be explained considering that the rate of

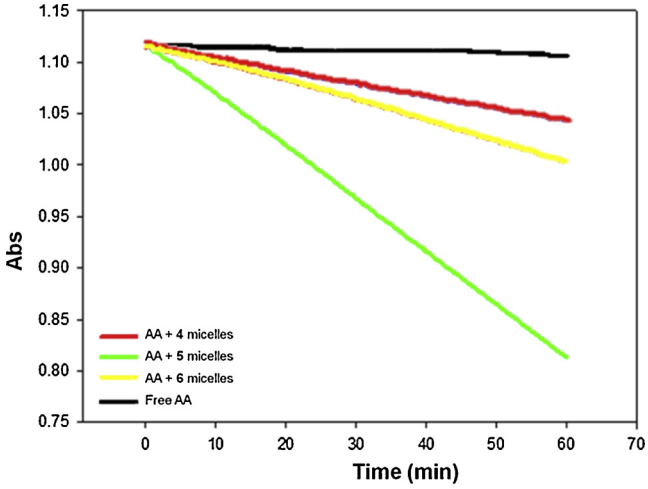


Fig. 1. Kinetic measurements of AA degradation at 265 nm in pure water in the presence of N-ox micelles.

AA oxidation is inversely proportional to the polarity of the surrounding media (Dracha et al., 2011); based on these premises, being the zwitterionic *N*-oxide group less polar than a charged quaternary ammonium and being AA located in the headgroup region, it is reasonable to speculate that in the case of N-ox micelles AA oxidation is favored. Moreover, it is reasonable to hypothesize that also water penetration in N-ox or CS micelles is different, with consequences on the polarity of the interfacial region of the aggregates and, in turn, on AA oxidation. The linearity of the obtained curve indicates that AA oxidation occurs at constant rate, *i.e.* the reaction is of zero order with respect to AA (thus the oxidation rate is independent from AA concentration). This behavior is typical of heterogeneous reactions at an interface such as micelles surface (Weitbrecht et al., 2003).

The same experiments were repeated in the presence of an excess H_2O_2 to accelerate the oxidation process: obviously AA oxidation was faster with respect to the uncatalyzed reaction and was complete within 30 min. In this case as well, in presence of N-ox micelles the process was accelerated especially in the case of **5** (Fig. 2A) whereas CS micelles did not affect AA oxidation with the exception of **1** (Fig. 2B). This anomalous result could be rationalized considering *cmc* values (Table 1). In fact, in the case of N-oxs the experiments were carried out well above their *cmc*. On the other hand, in the case of CSs, the experiments were carried out only at 2 *cmc* of each compound because of their higher *cmc* values. As a consequence, being **1** the surfactant that features the highest *cmc*, a very high amount of **1** was present in solution and this peculiar condition could influence the result obtained. To verify this hypothesis, we investigated the kinetic at 265 nm in presence of surfactants **2** and **3** at a concentration equal to the experiment performed with micelles **1**, *i.e.*$5 \cdot 10^{-2}$ M; the rate of the reaction slightly increased at increasing concentration both of **2** and **3**. Fig. 2C shows, as an example, the comparison of the results obtained for micelles **3** at two different concentrations. In the case of N-ox micelles, the increase of surfactant concentration does not affect at all the kinetic of the process (data not shown). These results indicate that this parameter can influence the investigated phenomenon and that at high concentrations the behaviour of CS micelles tends to that of N-ox ones.

3.5. UA degradation in the presence of H_2O_2

UV spectra of UA at various pH are reported in Fig. 3. It can be clearly observed that at basic (10.9), neutral (7.4) or slightly acidic (5) pH, at which the enolic OH in position 3 (the most acidic, pK_a 4.4) (Ingólfsdóttir, 2002) is deprotonated, a predominant peak at about 300 nm is present whereas at acidic pH, where all the hydroxyl functionalities are protonated, a second peak appears at about 400 nm. This

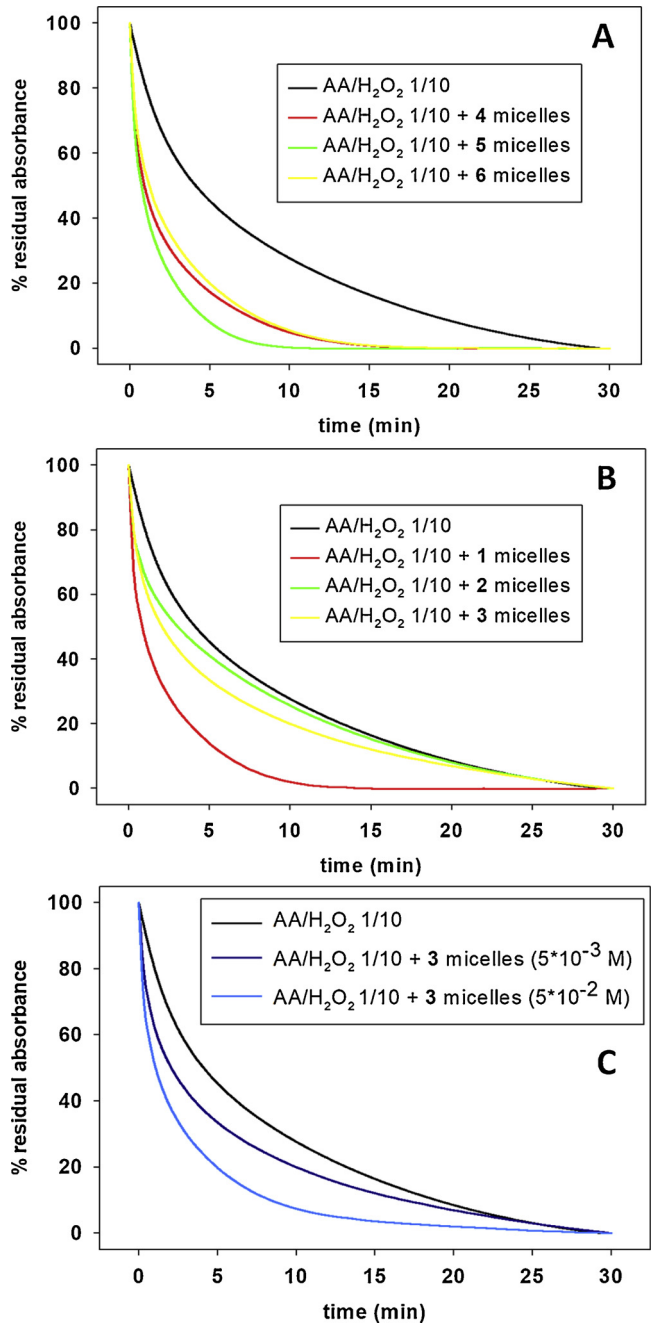


Fig. 2. Kinetic measurements (reported as percentage) of AA degradation by H_2O_2 at 265 nm in pure water A) in the presence of N-ox micelles, B) in the presence of CS micelles, C) in the presence of micelles formed by **3** at different concentrations.

behaviour is due to complex tautomeric equilibria of UA in solution that bring to the coexistence of species with different degree of protonation whose relative abundance is strictly dependent on the pH of the solution and on the polarity of the medium. The variations in signal intensities could be linked to the different interaction of the species present in solution with the solvent.

Oxidation of UA in water at any pH investigated can be followed by UV measurements only if promoted by H_2O_2 (Fig. 4 and SI1). At pH 2 precipitation occurred with or without H_2O_2. At pH 10.9 the most evident variation of UV spectra of UA after 1 h was observed; it was, therefore, chosen to carry out the experiments in the presence of micelles under this condition. Soon after the addition of H_2O_2 the peak at 290 nm increased, but after 1 h it almost disappeared and the peak at

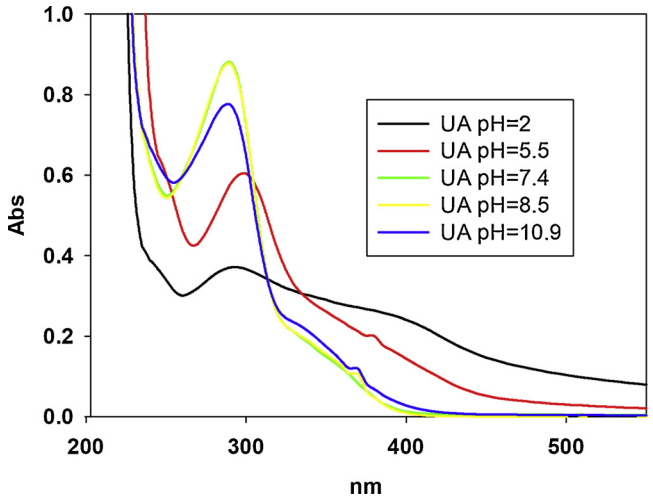


Fig. 3. UV spectra of UA in water at various pH.

330 nm slightly increased (Fig. 4A). On the other hand, at lower pH after 1 h the variations are negligible (pH 7.4 is reported as an example in Fig. 4B). This difference is reasonable due to the fact that the nature and the amount of oxidizable species present in solution vary as a consequence of pH: for example, the extent of water solvation of the deprotonated forms of UA *via* hydrogen bonding (that stabilizes them) increases as a function of pH. In the same way, also the oxidized species can be more or less stabilized at different pH. In general, the oxidation of the phenolic hydroxyl of UA is strongly affected by the environmental conditions (Iorgulescu et al., 2012). Obviously, the extent of the oxidation also affects the kinetic of the interconversion of the tautomeric forms that is proportionally hindered.

UA absorbance did not change at pH 10.9 in the presence of N-ox micelles (Fig. 5A and SI2). Adding H_2O_2 to the same solution (and in the same experimental conditions used with AA), similar variations to those observed with free UA at the same pH after 1 h appeared in the UV spectrum (suggesting that the same oxidation process occurred) without showing any dependence on the chain length of the surfactant. We reported as an example the results obtained in the case of **5** in Fig. 5A.

We followed the variation over time of the peak at 290 nm and 330 nm in the presence of N-ox micelles; a slight increase of the rate of disappearance of the peak at 290 nm with respect to UA was registered, especially with **4** (Fig. 6A). The height of the peak at 330 nm varied over time, to an extent depending on the length of the alkyl chain (Fig. 6B), indicating that a transient species was formed during the oxidation.

The dependence of the appearance of the peak at 330 nm on the structure of the surfactant could be due to the predominance of one of the tautomeric species that are in dynamic equilibrium (Iorgulescu et al., 2012); it is possible that the rapid interconversion of the tautomeric forms is, to some degree, hindered with the inclusion of UA in micelles, phenomenon that can affect the different equilibria involved in oxidation process. As a consequence, also the rate of formation and the nature of the species obtained by oxidation can be influenced to an extent strictly related to the surfactants molecular structure. It needs to be considered that the different partitioning of the compound inside the aggregates can play a pivotal role in the antioxidant activity rates (Richards et al., 2002; Frankel, 2001; McClemments and Decker, 2000; Costas-Costas et al., 2004); in the investigated systems the location and the amount of UA in micelles could vary because of the different chain length of the surfactant, characteristic that also affect the degree of hydration, the water penetration and the inner polarity (Long et al., 2015; Menger, 1979; Sato et al., 1988). It follows that the oxidation process, sensitive to the polarity of UA microenvironment, could also be perturbed. Moreover, the solubility in micelles of relatively polar

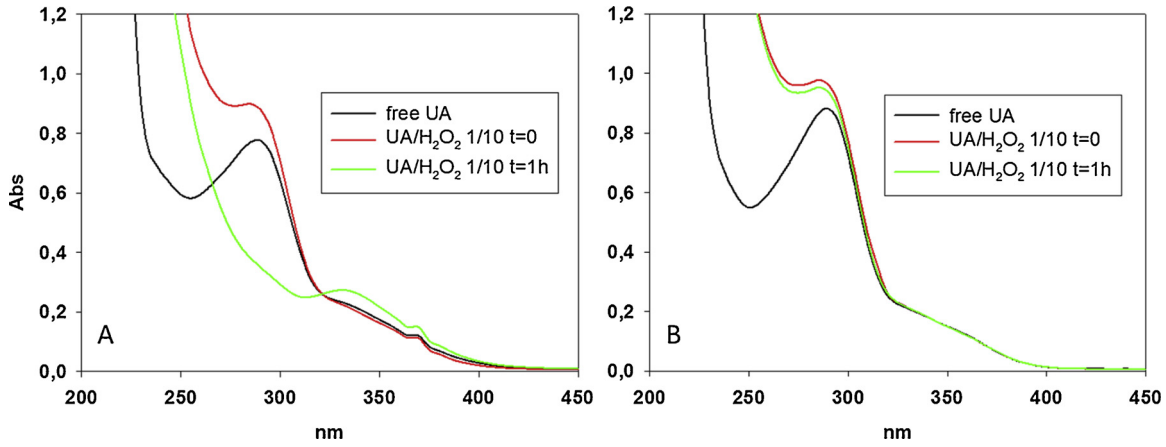


Fig. 4. Comparison of UV spectra in water at pH 10.9 (A) and 7.4 (B).

molecules such as UA in its deprotonated form increases in the case of surfactants with longer alkyl chains thanks to additional ion-dipole solute-surfactant interactions (Vinarov et al., 2018).

Analogue experiments in the presence of CSs were carried out and a different behaviour with **2** or **3** compared to N-oxs ones was observed; upon addition of a CS to a solution of UA at pH 10.9 the peak at 330 nm increased (Fig. 5B and SI2) and the peak at 290 nm decreased, whereas in the case of the corresponding N-ox no variations were observed in the UV spectrum of UA (Fig. 5A and SI2). This evidence suggests that also in this case UA is located in a different region of the aggregates. Another aspect that could affect the location of the solute and, in turn, the polarity of its microenvironment is the presence of a strong hydrogen bond between the hydroxyl group and the *N*-oxide moiety (O'Neil and Potter, 1998): this interaction blocks the pendant arm linked to the OH in a folded conformation hampering its free rotation as in the case of CSs. Soon after the addition of the peroxide the peak at 330 nm diminished for **2** and **3**, whereas the peak at 290 nm increased. After 1 h the peak at 330 nm was again observable whereas the peak at 290 nm completely disappeared for **2** and **3** whereas for **1** was still present, in analogy with N-ox micelles. These results confirm the crucial role of the surfactant chain length that in this case is even determinant to invert the trend in the interaction with the solute: the behaviour of **1**, the CS with the shortest chain, is more similar to the one of zwitterionic N-oxs -in particular of **4**- rather than the other cationic analogues. This complex behaviour is determined by possible and probable tautomeric balance, by the polarity of UA environment, the polarizability of the antioxidant and the formation of hydrogen bonds in micelles. It seems that UA is more easily oxidized in the more polar environment formed by cationic micelles with respect to N-oxs ones, suggesting that the higher the polarity of the medium, the easier the oxidation process is, as reported in literature, because of an increased stabilization of polar oxidized products (that cannot delocalize the charge on the aromatic structure as reagents can) (Iorgulescu et al., 2012).

From the observation of the kinetic of UA oxidation at 290 nm (Fig. 6C) and 330 nm (Fig. 6D), the process is faster in presence of **2** and, more markedly, of **3** (that features the longest chain), more than with the corresponding N-ox or without micelles; in the case of N-oxs, after one hour it was observed mainly the appearance of the peak at 330 nm (thus the transient species related to its presence are still in solution), whereas with the corresponding cationic compounds its disappearance could be followed more extensively. A different behaviour was showed by the surfactant **1**: the observed kinetic was similar to the one of the N-oxs (even at 330 nm). In analogy to the case of AA, it was verified the effect of concentration of surfactants on the oxidation process of UA, by comparing the kinetic at 290 nm in presence of **3** at two different concentrations, *i.e.* around and well above its *cmc* (Fig. 7). Increasing the concentration of **3** at 10^{-2} M, the rate of the reaction decreased approaching the UA behaviour observed in the presence N-oxs micelles. The investigation of solutions containing **2** or **3** up to 10^{-3} M does not change with respect to what reported in Fig. 6 *(i.e.* with more diluted samples, data not shown): this result suggest that at low concentration chain length is the predominant factor, whereas at concentration around 10^{-2} M these parameter becomes crucial in affecting the antioxidant activity of a hydrophobic solute. Also in the presence of AA the similarity of behaviour between micelles of **1** and of N-ox increases as a function of surfactant concentration. This result indicates that the nature and the number of micelles in solution affected the kinetic of the oxidation process of anionic antioxidant compounds.

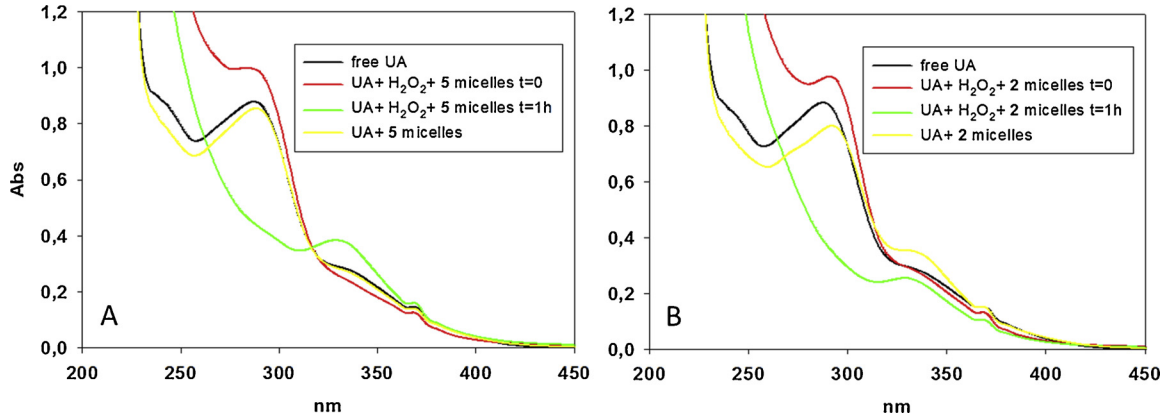


Fig. 5. Spectra of free UA (black trace) and of UA A) in the presence of N-ox micelles or B) in the presence of CS micelles at pH = 10.9 without H_2O_2 (yellow trace), soon after the addition of H_2O_2 (10 ten fold with respect to UA, red trace) and 1 h after the addition of H_2O_2 (green trace).

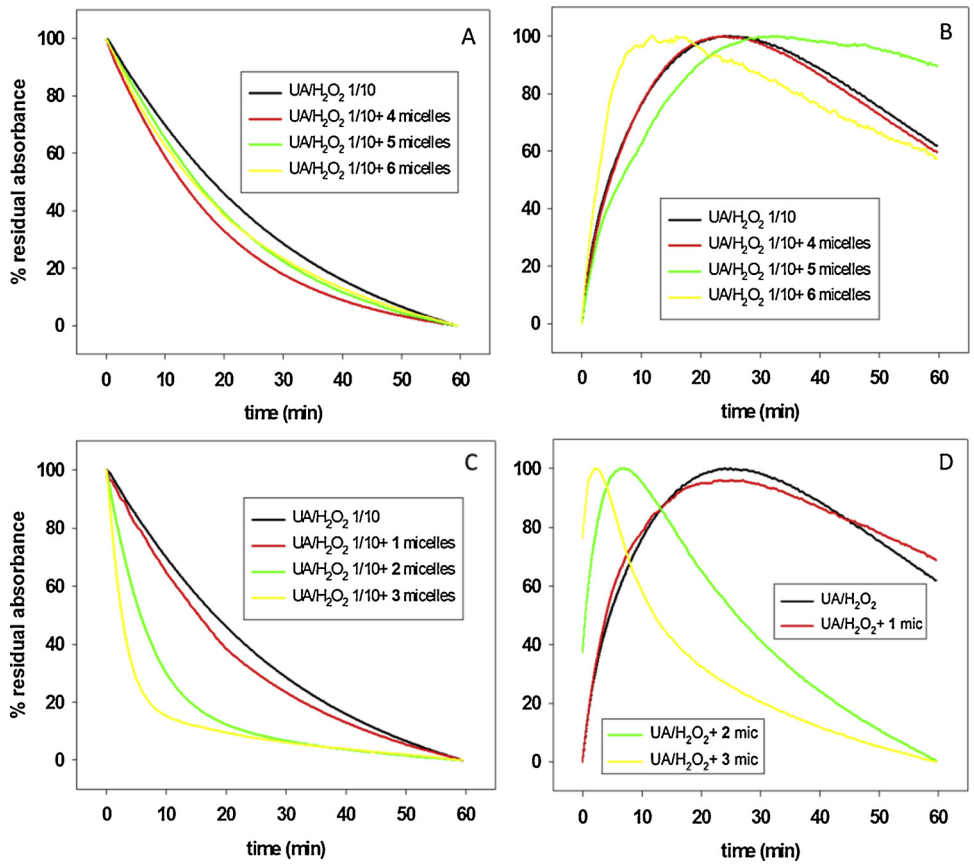


Fig. 6. Kinetic measurements (reported as percentage) of the peak in the presence of N-ox micelles at A) 290 nm or B) 330 nm or in the presence of CS micelles at C) 290 nm or D) 330 nm of UA degradation by H_2O_2.

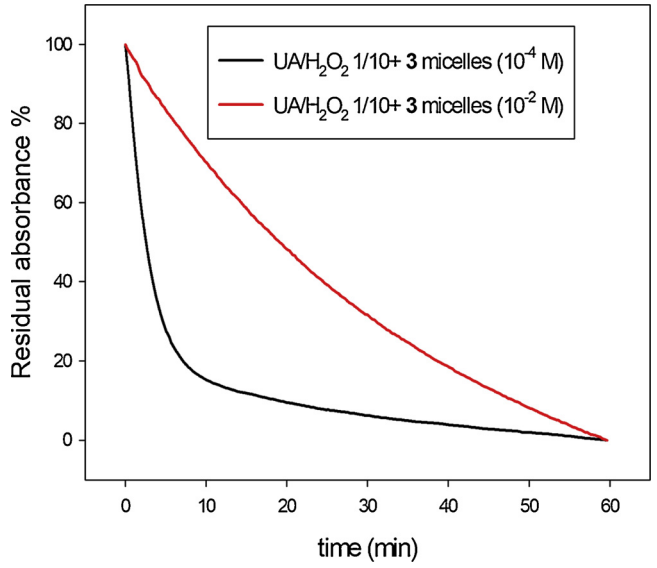


Fig. 7. Comparison of kinetic measurements of UA degradation by H_2O_2 in the presence of micelles of **3** at different concentrations (290 nm).

Comparing AA to UA the effect of the presence of cationic or N-oxs was opposite. A possible explanation could be the different dimensions and charge densities of the antioxidants. In fact, in the case of UA, bigger than AA, the negative charge is delocalized on the aromatic structure (Guo et al., 2008), whereas in the case of AA the charge is more localized. Both these features can influence either the location of the antioxidant in/nearby the micelles and its reactivity; if the interaction between the anionic antioxidant and the cationic headgroups is too strong the formation of a ion-pair can reduce its reactivity by decreasing its availability to react with the oxidant (oxygen or H_2O_2). Moreover, also the ease of access of the antioxidant in the different micelles can vary in the case of cationic or zwitterionic micelles and in the case of oxygen or H_2O_2 as oxidant species. If the antioxidant compound can penetrate too deeply in the aggregates, the oxidant species cannot be able to react with it. In both cases the longer the alkyl chain, the faster the process. In general, polar solutes that can form hydrogen bond are scarcely internalized in micellar cores and are preferentially located at micellar interface (that is often considered an "alcohol-like" medium) (Sepulveda et al., 1986); in particular, AA and UA (almost fully deprotonated at basic pH 10.9) should be with the O···H bonds aligned tangentially to water-micelles interface or with the hydrogen atoms pointing at the bulk (Quina et al., 1995). However, considering the high lipophilicity of UA even in its anionic form, it will be positioned more deeply in the internal core (more hydrophobic and less solvated) with respect to AA; such a difference in the microenvironment influence the oxidation process even because can bring to separation or concentration of the reactant species.

As a whole, our results are in good agreement with the so called "polar paradox" of antioxidant in lipid dispersion as oil-in-water emulsions and membranes and also in tissues. According to this theory, the antioxidant activity of lipophilic molecules is greater than hydrophilic ones in lipid aggregates. This effect is related to the different partitioning of the antioxidant molecules and to their interactions with surfactants and water as a function of their polarity (Laguerre et al., 2017). Obviously, also the concentration of the antioxidant plays a major role (Budilarto and Kamal-Eldin, 2015). In particular, it was demonstrated the existence of a cut-off effect: the antioxidant activity raises as a function of its chain length up to a maximum value and it

start to diminishes if chain length further increases (Laguerre et al., 2009). In our investigation a phenomenon similar to cut-off effect occurred in the case of CSs and UA in the presence of H_2O_2, even if the effect of surfactant concentration cannot be neglected.

4. Conclusions

The effect of charge and chain length of N-oxs and CSs structurally related on their aggregation and on the antioxidant properties of a hydrophobic or hydrophilic compound were fully investigated. While on the aggregation features the variations were not surprising, a neat dependence of antioxidant efficacy on the surfactant chain length, charge and of the lipophilicity of the solute was observed. In particular, micelles formed by zwitterionic N-oxs exalt the antioxidant properties of water-soluble antioxidant such as AA conversely to cationic micelles. On the other hand, in the presence of the latter ones a hydrophobic antioxidant molecule is more active than in the presence of N-ox micelles. These differences can be explained by taking into consideration the effects of micelles on the polarity of the microenvironment of the antioxidant, on its polarizability and its location in the aggregates, on the pH of the solution and, in the case of UA, also on the coexistence of different tautomeric species in dynamic balance. As a whole, the micellar effects on the reaction can be interpreted in terms of subtle and complex equilibria among repulsive and attractive interactions between molecules (surfactants and antioxidant). Further investigations are under way to evaluate the effect of the same surfactants when included in mixed liposomes on the physicochemical properties of the aggregates and of the antioxidant activety of the included solute. This aspect, commonly neglected in the investigations on the physicochemical properties of liposomes, is particularly important because the antioxidant activity is often strictly related to the biological activity of many active principles.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Declaration of Competing Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.chemphyslip.2019.104818.

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