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Naproxen sodium salt photochemistry in aqueous sodium dodecyl sulfate (SDS) ellipsoidal micelles

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Abstract

The photochemistry and other properties of the anti-inflammatory drug (NSAID) naproxen (NP) in sodium dodecyl sulfate, SD5, micellar aqueous solutions at pH = 7 (NP is in anionic form) were studied. The large value of the partition coefficient (P) was obtained, logP = 2.7, showing that the most part of NP is localized in the micellar phase. The solubilization in SDS micelles results in NP fluorescence and photodegradation quantum yields decrease. The 6-methox; 2-(1-hydroxyethyl)-naphthalene photoproducts and 6-methoxy-2-acetylnaphthalene were found by gas chromatography/mass spectrometry (GC/MS). Both photoproducts were formed in SDS solution in significantly smaller amounts than in water. Small angle neutron scattering (SANS) showed that the presence of NP has small effect on the micellar structure. Only a slight decrease of the ionization degree of the micelle was observed by SANS, suggesting that NP was localized in the vicinity of micellar surface. The NP triplet excited state, hydrated electron, NP radical cation and some other relatively long lived intermediate were observed by laser flash photolysis of NP in micellar solution. The decay kinetics of these intermediates was different with respect to that in the homogeneous media.

ABBREVIATIONS NP: Naproxen NB: Nabumetone NSAID: non-steroidal anti-inflammatory drug SDS: sodium dodecylsulfate SANS: small angle neutron scattering GC/MS: gas chromatography/mass spectrometry LFP: laser flash photolysis The reactivity of NP in SDS micellar environment was compared to that in the homogeneous media and the probable nature of the intermediate precursors of the final photoproducts are under the discussion.

Key words

Naproxen sodium salt, sodium dodecyl sulfate (SDS), micelles, small angle neutron scattering (SANS), photochemistry, fluorescence, laser flash photolysis.

1. Introduction

Naproxen (NP) ((1) in Scheme 1) is a nonsteroidal anti-inflammatry drug (NSAID) available over the counter used to alleviate moderate pain, fever and in flan matory diseases. It was-one of the most commonly prescribed medication in the Urited States, with more than eleven million prescriptions [1,2]. NP, as many other drugs $c_1h_2h_1$ consume by humans, has been detected in aqueous reservoirs [3] and, despite it is chern celow the limit of quantification, in living beings [4].



Scheme 1: Chemical structure c^{c} (1) anionic form of naproxen (NP) (sodium -2-(6-methoxynaphthalen-2-yl) proparoate and the photoproducts: (2) (6-methoxy-2-(1-hydroxyethyl) naphthalene, and (3) 6-methoxy-2-acetyl-naphthalene.

As other members of the family, NP is a well-known photosensitizing agent. Its photophysical and photochemical behavior has been studied in homogeneous media of different polarity [5–10]. Some scare data are available also for heterogeneous media, such as cyclodextrins (CDs), [11–13] and micellar aggregates, namely anionic sodium dodecyl sulfate (SDS) [7,11] and cationic cetyl trimethyl ammonium bromide (CTAB) [7].

The ionized form of NP (compound (1) in Scheme 1) has been studied in aqueous media [7,8,14] and other homogeneous media like ethanol [8] or acetonitrile [9]. These studies describe the intermediates involved in the photodegradation process as well as the final photoproducts. Whereas, in the heterogeneous hydrophobic environments the only aspects studied are the photomixture composition [11–13] or the singlet oxygen formation [7] after light irradiation of the drug. However, the ionized NP form can be accumulated in membranes [15], where photosensitizing effects produced by the drug are expected. Therefore, the investigation of NP photochemical behavior in restricted biological media would afford useful information about its bioaccumulation and phototoxicological effects in the patients treated,

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and also in living organisms, plants or animals, that can get in contact with them in the water reservoirs or by means of these aquatic species through the trophic chain.

SDS micelles have been demonstrated to be an appropriate biomimetic model [16,17]. It is well known that micelles and other restricted environments can act as supercages where the reactivity of the chemicals is changed in a specific way. The micellar aggregates either prevent the photodegradation of pharmaceuticals and natural compounds [18–20] or can promote the photodegradation of chemical contaminants presented in the water pools [18,20,21]. Interestingly, recent works showed that SDS aggregates protect the NSAID nabumetone (NB) against the photodegradation [17]. Therefore, we are curious about whether the SDS protection activity works with NSAIDs of different structure.

For all these reasons, the aim of the present work was to tudy the photophysical and photochemical behavior of the ionized NP in aqueous SDS race that solutions. We have used uv-vis absorption and fluorescence techniques to determine the drug distribution in the micelle/water system and photodegradation kinetics. Sm. II a gle neutron scattering (SANS) was used to examine the effect of drug presence on the micellar structure. Gas Chromatography/Mass Spectrometry (GC/MS) and later flash photolysis (LFP) gave the information about final and intermediate photoproducts.

The results obtained show that despite the neg tive charge of the aggregate surface, the most part of ionized NP is accumulated in the mic llar phase. So the SDS micelle allows the study of the photochemical behavior of the *ic aize* d NP in a restricted hydrophobic medium, carried out for the first time.

Anionic NP photoirradiation in aqueous SDS micellar solution gives rise to the same photoproducts as were detected previously in the most of the homogeneous media but in lower amount. The protection afforded by SDS micelle to NP from the light is due to the micellar stabilization of the radicals involved in the NP photoproducts formation. If to compare the photochemical behavior of 1^{P} with that of the structural related NSAID NB [17], it is possible to speculate that in both case. SDS is acting as the source of the hydrogen atoms needed to initially form reduce 1 photoproducts. Nonetheless, the oxidation rate of the alcoholic photoproduct (2) of NP to form the photoproduct (3) was found to increase in SDS.

By contrast to the previous studies, the photodegradation of the ionic NP is suggested to be from the ³NP and not from the ¹NP, as most commonly invoked [5]. Fundamental insights into the probable mechanisms of the photoproducts formation are also obtained.

From a practical point of view, the outcomes suggest the possibility of bioaccumulation of the drug in hydrophobic domains of aquatic organisms by topical contact. The lower photoreactivity in the micelles than in water is a hopeful result from toxicological point of view, but it alerts about the undesirable increase of the persistence of pharmaceuticals in aqueous pools due to the presence of surfactants, which are also frequent contaminants of the aqueous media, coming from the health care products [22].

2. Experimental section

2.1. Materials

Naproxen sodium salt, (NP, M1275), was obtained from Sigma. Naproxen in molecular form (NP, C15483500), 99.6% of purity, was purchased from Dr Ehrenstorfer, GmbH. Sodium dodecyl sulfate, (SDS, 230425000) for biochemistry, 99% purity, was purchased from Agros Organic. HCl was from Sigma. The chemicals were used as received.

For the preparation of the samples for SANS measurements, D_2O (Sigma-Aldrich, 99.8% purity) was used instead of water. For all other experiments, samples were prepared with ultrapure water (18.2 M Ω ·cm, Millipore-filtered).

2.2. Solutions

Aqueous stock solutions of (1) SDS 0.2 M, (2) NP, 1mV and (3) NP 1 mM and SDS 0.2M, were initially prepared under mechanical stirring. The solutions with different concentrations of NP and SDS were obtained by mixing appropriate anounts of the stock solutions.

For NP solubility determination, fixed volume of the equeous solutions with different SDS concentration, in the range of 0-0.2 M, prepared by diluting solution (1) was added to an excess of molecular NP weighted in a tot az wild. The pH was modified by adding the appropriate amount of HCl concentrated solution.

For SANS, a stock solution of SDS $0.2M r D_2O$ was prepared. 1 mM NP in D_2O or in 0.2 M SDS solutions in D_2O were prepared by solution salt of the drug weighing and solubilizing.

Irradiated solutions of 1 mM NP in valuer and in 0.2 M SDS aqueous solutions were analyzed by GC/MS.

Except for solubility measurements, sodium salt of naproxen was used, then the samples have pH=7.

2.3. Methods

2.3.1. Uv-Vis Absorption and Emission Spectroscopies

In the solubility determination, solutions were subjected to a 72h of mechanical stirring in a dark room at 20°C. Saturated solutions were centrifuged in a Centrolit P-Selecta, with a max 12000 rpm, during 10 min. The supernatant was then diluted with water or SDS solution of the appropriate concentration, then NP concentration was determined by uv-vis absorption spectroscopy.

Measurements were performed on UV-Vis Hitachi, model 150-20, spectrophotometer. Absorption spectrum was obtained in the range $\lambda = 250-450$ nm, in a quartz cuvette with 1cm pathlength, using Milli Q water as a reference. NP absorption spectrum shows characteristics bands systems centered at 317, 330 nm [23–25]. The SDS addition does not produce any

spectral shift but does some variation of the NP absorbance (S1). NP concentration was determined from the value of A_{330} .

The extinction coefficient of the samples, at each pH in H_2O and SDS, was experimentally determined using Eq.1.

$$\varepsilon_{p^{H}}^{medium} = \alpha * \varepsilon_{NP^{-}}^{medium} + (1 - \alpha) * \varepsilon_{NPH}^{medium}$$
 Eq. (1)

Where α is the ionization degree of the drug at each pH, determined considering the aqueous pKa= 4.15 [26]; and ε is the corresponding molar absorptivity of each species, NP⁻ and NPH, in H₂O or aqueous SDS, experimentally determined (S2).

SDS volume fraction (ϕ_{SDS}) was calculated using SDS molar volume, \bar{V}_{SDS} =0.288 L/mol [27].

Steady-state fluorescence emission and excitation spect a vere recorded with a Perkin Elmer LS 50B spectrofluorimeter with the thermostated sample holder. The spectra were corrected using software provided with the apparatus.

The emission spectra were obtained with excitation wavelength λ_{exc} = 317 nm in emission wavelength range λ_{em} = 325-450 nm.

The fluorescence quantum yields, ϕ_f , were measured as described elsewhere [28] using the reference quantum yield (0.543) for quining sulfate in 0.1N sulfuric acid [29].

2.3.2. Small-Angle Neutron Scatterin & SANS)

SANS experiments were car ied out on the KWS-2 diffractometer at the Jülich Centre for Neutron Science (JCNS), Mühlch, Germany [30]. An incident radiation wavelength of 5 Å was used with detector distances of 1.7 and 7.6 m and a collimation length of 8 m, to cover a momentum transfer, q. rance from 0.008 to 0.5 Å⁻¹. In the standard mode, a wavelength spread $\Delta\lambda/\lambda=20\%$ was used. An samples were measured in quartz cells (Hellma) with a path length of 2 mm using D₂O as the solvent. The samples were placed in an aluminum rack where water was recirculated from an external Julabo cryostat, at 25 °C. This set-up enables a thermal control with up to 0.1 °C precision. Scattered intensities were corrected for detector pixel efficiency, empty cell scattering and background due to electronic noise. The data were set to absolute scale using Plexiglas as a secondary standard. The obtained macroscopic differential cross-section d $\Sigma/d\Omega$ was further corrected for the contribution from the solvent. The complete data processing was performed with the QtiKWS software provided by JCNS in Garching [30].

Solutions of SDS with two concentrations (0.05 and 0.2 M) without and with 1 mM of NP were studied. All samples were measured in D_2O in order to optimize the contrast and minimize the incoherent background in SANS experiments.

SANS curves were fitted using SAS View 4.2.1. software to an ellipsoid model [31,32] with a Hayter-Penfold MSA interparticle structure factor S(Q) for charged particles. The parameter $sld_{SDS\mbox{ micelle}}=0.337 \times 10^{-6} \text{ Å}^{-2}$, a dielectric constant of D₂O =77.936 [33] and the scale factor equal to 1, were fixed.

The aggregation number (N_{agg}) was determined as described in [34].

2.3.3. Photodegradation

Heraeus Noblelight photoreactor, with UV immersion lamp TQ 150 (high pressure mercury lamp), with emission maxima at $\lambda = 365$ nm and 313 nm (with lower intensity), was used to irradiate the solutions.

The wavelength of the radiation implicated in the most of the phytotoxic processes was in the range from 300 to 400 nm [35]. Because of that, the use of a mercury lamp radiating in the absorption region of both the initial NP and the photolys's products seemed to be reasonable.

The incident light intensity (I₀) was detected by a prices ium ferrioxilate actinometer solution (0.006 M). The photodegradation quantum yield at the emission wavelengths of the lamp are $\phi_{365} = 1.21$ and $\phi_{313} = 1.24$ [36]. Assuming total right absorption by the actinometer [37] and using the method described elsewhere [35]. The ortal intensity of the irradiating lamp was 4.15 $\times 10^{-6}$ Einstein L⁻¹ s⁻¹. NP absorption spectre in water and SDS (S1) show that the drug absorbs at $\lambda = 313$ nm whereas the absorption in at 365 nm is negligible. Since the intensity at 365 nm is 1.73 times higher than at 312 nm, as stated by the manufacturer, the estimated light intensity of the lamp at 313 nm was $1.5_2 \times 10^{-6}$ Einstein L⁻¹ s⁻¹.

The phototodegradation quantum vield of NP, ϕ_{PD} , was calculated from the experimental photodegradation rate constant, t_{PD} , as described in [38], using the characteristics of the photoreactor provided by the manufacturer.

2.3.4. Gas Chromato rupiny /Mass Spectrometry (GC/MS)

GC/MS analysis was made with an Agilen 7890A gases chromatograph. Agilent MS220 masses detector was equipped with a VF-5MS column (30 m length x 0.25 mm inner diameter with 0.25 μ m stationary phase thickness).

GC temperature was: injector temperature, 270°; interface temperature 290°; furnace temperature was held at 50° for 5 min, to 270°C at 10°C/min and held for 5 min. Mass detection realized by monitoring the masses between 50-500 amu.

2.3.5. Flash Photolysis

The absorption spectra and the decay kinetics of intermediates were measured using the nanosecond laser photolysis apparatus with the registration of UV-Vis absorption kinetics at a given wavelength in the range 400 - 800 nm [39,40].

Nitrogen laser (PRA LN 1000, with 1 ns pulse duration and 337 nm radiation wavelength, operating in the 10 Hz frequency mode) was used as an excitation source. Acquisition and averaging of kinetic curves were performed by UF258 transient recorder for PCI bus connected with a personal computer. Each experimental kinetic curve contained 12–14 bits of points with the distance between points being 2–400 ns. Dissolved air oxygen was removed by Ar bubbling during 20 min. All measurements were carried out in a quartz cell with an optical path length of 2 mm at 20 °C.

3. Results and Discussion

3.1. Naproxen in Aqueous SDS Solution.

The aqueous solutions of NP and SDS were characterized by fluorescence and absorption uvvis spectroscopies, as well as by small angle neutron scattering (SANS). Uv-vis spectroscopies give information about the drug and SANS does it about the aggregate.

3.1.1. Steady-State Fluorescence of NP in Aque Ju SDS Solutions

The effect of SDS concentration, varied in \therefore range 0-0.2 M, on NP fluorescence (FL) was studied at two drug concentrations, 0.0^{4} and 1 mM.

NP presents an emission maximum centered at 355 nm in water [28]. At both drug concentrations, SDS addition results in a quenching of fluorescence (Figure 1), showing that NP is passing from the aqueous to the micellar phase in spite of the negative charges of the drug and the micellar surface. The most probable location of the drug in the aggregate is close to the micelle surface, with the aromatic ring in contact to the hydrophobic tails and the carboxylic group nearby the micelle surface.



Figure 1: Plot of the ratio of NP fluorescence intensity in water, F_0 , and that in the presence of different SD. Concentrations (all of them above cmc) at emission wavelength. λ_{em} =355 nm, at 20°C. *Inset*: the plot of NP (0.04 mM) fluorescence quantum yield, ϕ_{fl} , vs SDS concentration.

The NP fluorescence quantum yierd, d_{fl} , (Figure 1, *Inset*), decreases with SDS concentration increase above cmc, from $\phi_{fl} = 0.49$ in H₂O (in agreement with the reported value 0.41 [28]) to $\phi_{fl} = 0.33$ in 0.2M SDS aqueo, s solution. Therefore, the contribution of the radiationless decay of NP first singlet excited suite, ¹NP, increases in the SDS micelle. This result is somewhat unexpected one since the number environment seems to afford a more rigid medium than water, restricting the vibrational freedom in ¹NP. Thus, one can suppose that some other deactivation pathways is active which overcome the vibrational relaxation effect. The more compact medium aftorded by the micelle in comparison with water could promote the intersystem crossing of the drug, in fact phosphorescence of NP was observed in SDS [41]. On the other hand, hydrogen bonds formation in protic solvents and some aprotic media are reported to produce quenching of NP fluorescence [28]. The hydrogen bond formation could be promoted by charge repulsion near the micellar surface.

Some irregularity in the quenching behavior is observed around 0.08 M of SDS, more clearly reflected by ϕ_{fl} (Figure 1, *Inset*), indicating some change in the micellar structure. A similar behavior was previously observed at similar SDS concentrations in the spectroscopic properties of morin [42] and NB [17]. It was associated with the micelle growth and some variation of the shape of the micelle (see section 3.1.3).

3.1.2. Naproxen Solubility in Aqueous Micellar SDS Solutions

The distribution of molecular forms of the drugs in octanol/water is a property usually included in databases, whereas the value for the ionized forms is less available. In addition, these data could not reproduce the distribution in other micro-heterogeneous media e.g. in micellar solutions.

Several methods have been described to determine the distribution of the drugs in micellar solution [43]. Most of them involve the determination of the solubility of the drug in the aggregates. This parameter is easy to measure experimentally for the poorly soluble in water molecules, but it is difficult for highly soluble ones.

For these reasons, partition of NP in SDS micellar solution was estimated from the drug solubility in H₂O at increasing SDS concentrations over a $ran_{\varepsilon}^{\alpha}$ of pH at 20°C by uv-vis absorption spectroscopy [44]. This method allows partition tetermination of both, molecular and ionized NP, without the experimental determination of the ionized NP solubility. The solubility of the neutral drug is measured at different $\partial E^{\alpha} v$ here a mixture composition of both forms is known.

NP solubility linearly increases with SDS concentration at all pHs (S3) following the increase in the micelles concentration. Similar trend was observed in cationic, anionic or mixed cationic/non-ionic [45] or anionic/non-ionic [46] micelles.

As described in [44], the slope of the corresponding linear plots of the drug solubility in SDS solution related to that in water S_0^{SDS}/S_0^{177} vs. SDS volume fraction (Figure 2A) corresponds to NP partition coefficient P (S4) between the micellar and water phases.



Figure 2: **A**: The plot of the ratio of NP solubility in SDS and in water vs. SDS volume fraction, ϕ_{SDS} , at different pHs; **B**: plot of the slope of the curves in A (partition coefficient, P, (S4)) vs. NP ionization degree X_{NP}-. At 20°C.

As can be observed (Figure 2A), the slope of the plots, and therefore, the value of P increases with pH decrease. At low pH the ionization equilibrium shifts towards the molecular nonionized form of the drug, which clearly partitions better in the micelle. This result confirms that the disappearance of the negative charge from the drug increases its partition in SDS as previously suggested [45]. The repulsions between the charged drug and the micellar surface is the reason for the lower partition of anionic NP in anionic micelles compared to cationic or non ionic ones [45] and the anionic/non-ionic mixtures [46]. Therefore, electrostatic effects play the important role in the affinity of the drugs for the micelles.

In contrast to the previously described behavior [44], the plot of the value of P at each pH (slope of the curves included in Figure 2A) vs. NP ionization degree is not linear (Figure 2B). Exponential fitting of the data and further extrapolation to 100 % and 0% of ionization degree gives a partition coefficient of the ionized, P_{NP} =524 (logP=27), and the neutral, P_{NP} =2540 (logP=3.4), forms of NP. The partition coefficient value obtained for the neutral form of NP in SDS aqueous solution is in agreement with those reported for octanol/water, logP=3.3 [47] and log P = 3.18 [48]. By contrast, a significantly large. I value for ionized NP in SDS solution than that for octanol/water, log P= 0.32, was obtained [49]. The presence of water in the micelle could improve the solubilization of charged drugs. In fact, the larger number of ionized NP than that of the neutral one was found in lipid membranes [15]. Overall, partition coefficient values show that despite molecular form is partitioned better, the ionized NP also strongly tends to accumulate in the miceller of drug and therefore it would do this in hydrophobic biological environments.

Interestingly, this result suggests that partitioning could contribute to the accumulation of NP in the intestinal cells like in the storage, cells, and not only NP can be ion-trapped within the enteric cells as reported [50].

Once confirmed that NP in *ionized* form is mainly located in the micellar phase, next we studied the effect of the presence of the negatively charged NP on the micelle structure by SANS.

3.1.3. Small-Angle Neu. ron Scattering, SANS, Study of SDS Aggregates

SANS curves of SDS aggregates formed at 50 and 200 mM surfactant concentration in the presence of 1mM NP (Figure 3) were obtained in order to check whether the NP loaded micelle shape or size are changing with SDS concentration. These concentrations are well bellow and above that where the change in the fluorescence quantum yield of the drug was observed (Figure 1, *Inset*).



Figure 3: Small-angle neutron scattering data of SDS micelles free (circles and triangles) and loaded with 1 mM NP (diamonds and squares), at 0.05 M (\mathcal{O} , \Diamond) and 0.2 M (Δ , \Box) of SDS concentration, in D₂O at 25 °C. A: free and no ded micelles curves at both SDS concentrations. B: NP curves as in A, but with the tate (solid lines) to the ellipsoidal micelle model [31,32].

As can be seen, (Figure 3), the curvet for NP loaded SDS micelle nearly overlap those for micelles without NP, except at low a where the upturn in the scattering intensity is softened by the presence of the drug. This effect is more pronounced for micelles with larger amount of NP molecules (compare curves for 5') and 200 mM SDS concentration in the presence and in the absence of 1mM NP in Figure 3). The upturn at low q is related to the attractive depletion interactions in systems with poweristence of rods and spheres [51,52]. The upturn magnitude was taken as a measure of the extent of mixture of structures in SDS micelles [53]. Therefore, the presence of the charged NP seems to stabilize one type of micelle over the other, decreasing the depletion to res. This effect for NP is smaller than that for the neutral NB [17].

At both SDS concentrations, SANS curves of NP loaded aggregates are well fitted to an ellipsoidal micelles nodel (Figure 3B), similar to the case of free micelles [17,54]. The fitting parameters (Table 1) were compared to those for the free micelle previously reported [17]. The average amount of NP molecules per one micelle, estimated from Nagg (Table 1), equals to 1 and 0.25 at 0.05 and 0.2M of SDS, respectively.

System	Polar Radius/Å	Equatorial Radius/Å	Charge/e	Volume fraction	Nagg
SDS dil [*]	14.29 ± 0.039	22.31 ± 0.027	16.79 ± 0.068	0.0125	46
NP: SDS dil	14.28 ± 0.040	22.34 ± 0.028	14.63 ± 0.057	0.0123	47
SDS conc*	15.04 ± 0.011	23.14 ± 0.011	53.61 ± 0.540	0.0484	55

NP: SDS conc 15.05 ± 0.01	23.04 ± 0.039	46.78 ± 0.315	0.0485	54
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Table 1: Parameters of fitting to ellipsoid micelles model of SANS curves for SDS solutions in D_2O , at 298 K, with 1mM NP (rows 2 and 4) and without NP (rows 1 and 3) (*data taken from ref. [17]). Concentration of SDS was 0.05M (files1 and 2) and 0.2M (files 3 and 4).

As can be observed (Table 1) the micelles grow with surfactant concentration. The presence of charged NP has no effect on the size, shape and aggregation number of the SDS micelle. Although, the micelle growth with SDS concentration could promote the non radiative transitions in ${}^{1}S$, as suggested in the previous section, giving rise to the quenching of NP fluorescence observed (see section *3.1.3.*).

The NP presence in SDS solution results in a slightly lower surface charge of the micelle at both surfactant concentrations (Table 1). This indicates a domease in the ionization degree of the aggregate with the presence of the charged drug and points to NP location in the vicinity of the micelle surface. The electrostatic repulsion between the drug and the negative micelle surface could also promote the intermolecular hydrogen bond formation of NP with water contributing to the observed quenching of flucted science of the drug in the SDS micelle, as it was also speculated in the previous section

3.2. Photodegradation of Naproxen u. Aqueous Micellar SDS Solutions

The photodegradation of NP (1mN) in water and in the presence of 0.2M SDS was studied.

Irradiation of NP in water and in SLS micellar solution with light of 313 nm initially leads to a decrease in intensity of the NP band at $\lambda_{em} = 355$ nm (F₃₅₅) showing the drug photodegradation and to the concurrent increase of the intensity of a new band of some product at $\lambda_{em} = 440$ nm (F₄₄₀) (Figure 4).



Figure 4: Fluorescence spectra of 1 mM NP at different irradiation times in: **A:** water, and **B:** 0.2M SDS. *Insets*: plots of the intensity of the bands corresponding to NP at λ_{em} =355 nm (F₃₅₅) and the photoproduct at λ_{em} =440 nm (F₄₄₀) vs. the irradiation time. The black lines correspond to the fittings of the data to a zero order kinetic. The spectra were obtained with λ_{exc} = 317 nm.

Initial NP photodegradation follows a zero order kinetic in both media, as previously reported [12,13]. The rate constant values were determined from the fitting of the slope of the plot of F_{355} vs. irradiation time, (Figure 4A and 4B, *Insets*), corrected by the fluorescenceconcentration proportionality constant of NP, obtained at each set from the ratio of fluorescence intensity and drug concentration before irradiation, F_0/C_0 . The zero order rate constant values of $k_{\text{PD}} = (1.29 \pm 0.38) \ 10^{-6}$, and $k_{\text{PD}} = (1.21 \pm 0.22) \ 10^{-6} \text{ M s}^{-1}$, were obtained for the NP photodegradation in water and SDS micelle, respectively. The photodegradation quantum yield, ϕ_{PD} , calculated from k_{PD} were $\phi_{PD} = (4.21 \pm 1.22) \times 10^{-2}$ and $(3.94 \pm 0.70) \times 10^{-2}$ 2 for NP in H₂O and SDS, respectively. These results s¹ yw that encapsulation in SDS micelle does not protect the drug against light at the initian tage of photolysis. No data in other micellar media have been found in the literature. But this behavior seems to be different to that described in other heterogeneous media. For instance, inclusion complex formation of NP with hydroxypropyl- β -CD (HP- β -CD) protect the drug against light [13]; whereas, that with β -CD does not [12], or even increases NP photodegradation [11], depending on the technique used. Therefore, the reactivity of the drug triggered by light is highly dependent on the environment. However, this relationship is not very clear (see below).

Further irradiation of NP in water results in the disappearance of the product fluorescence at λ_{em} =440 nm, while the intensity is the fluorescence region of NP, F₃₅₅, even increases, followed by a slow decline a long irradiation times (insert in Figure 4A). Such behavior suggests the photodegradation of the photoproduct with λ_{em} =440 nm. However, this photoproduct seems to be relatively photostable in SDS solutions (insert in Figure 4B).

NP photodegradation s k own to form several photoproducts [5]. The photoproducts most frequently found are 'Scheme 1): 6-methoxy-2-(1-hydroxyethyl)-naphthalene, (2), and 6-methoxy-2-acetyl-na⁺₁.halene, (3). The absorption spectrum of (2) overlaps to that of the undegraded drug (1), and it is expected to emit at the same wavelength [11,12], whereas (3) shows an absorption maximum at 312 nm [11] and it emits at 440 nm [12].

NP photodegradation quantum yield obtained from fluorescence could be underestimated depending on the amount of (2) formed in each medium, as pointed out in the case of β -CD [11,12]. In fact, $\phi_{PD} = 0.11$ was obtained for NP in water [12].

Fluorescence is a very useful tool to detect photodegradation and formation of small amounts of fluorescent compounds. However, it is not able to accurately quantify the photodegradation degree if the signals of the drug and photoproducts overlap, as it was previously pointed out for absorption spectroscopy [11]

Therefore, further experiments are required in order to confirm the effect of NP encapsulation in SDS micelle on NP photoreactivity and to check the nature of the photoproducts formed in both media.

3.2.1. Gases Chromatography/ Mass Spectrometry (GC/MS) Photoproducts Determination

Naproxen 1mM samples irradiated at 1, 2, 25 min in H₂O, and at 2, 3, 25 min in 0.2M SDS, were analyzed by GC/MS. At all irradiation times, two photoproducts namely, 6-methoxy-2 (1-hydroxyethyl) naphthalene, (2), and 6-methoxy-2-acetyl-naphthalene (3) (Scheme 1), were found. These compounds appeared in a great majority of the media studied [5–8,11,12].

The peaks of both photoproducts presented higher counts in water (S5) than in SDS (S6) at all the irradiation times checked. This finding demonstrated under budly, that NP encapsulation in the restricted SDS micellar environment protects the drug against photodegradation. The formation of the alcoholic derivative (2) in higher amoun in vater than in SDS, confirms the larger photodegradation quantum yield in water than the total by fluorescence, due to the overlapping of this photoproduct and the undegraded NP emission spectrum [11,12]. The toxicity of (2) over the hepatic cells is the highest of all the possible photoproducts formed by the drug irradiation, but it is dangerous only in large amounts [55]. Thus, toxicity mediated by the final photoproducts is expected to decreas and the restricted medium of the SDS micelle.

The analysis of the evolution of the plake of both photoproducts with the irradiation time shows that the signal from (3) (the aldeh, 'e photoproduct) increases with the irradiation time in both media (S5 and S6). By contract, different behavior of the alcoholic photoproduct (2) is observed when NP is irradiated in CDS micelle with respect to that in water. In water, the highest amount of (2) (S5) appears per very short irradiation time; and it disappears as the irradiation time increases. This 'rend clearly shows that the alcoholic photoproduct (2) suffers quick secondary photodegraction in aqueous medium. However, when NP is irradiated in SDS, MS peak of (2) (S6) increases continuously with irradiation time (from 2, 3 to 25 min), even at higher irradiation times (data not shown). Nonetheless its concentration remains always much lowe, then that in water at any time. This behavior demonstrates that SDS micelle strongly avoids the alcoholic photoproduct (2) formation.

The percentage of (3) in the photomixture increases: 1.3, 1.2, 5.4 % with irradiation time (1, 2, 25 min) in H₂O, and 3.3, 3.5, to 15.7 % (2, 3, 25 min) in SDS. So, (2) is the main component in both media; this result is in good agreement to the previous studies in SDS [11]. However, (3) was reported as the main component of the photomixture in water [14], but in this case the sample was analyzed after 4h of irradiation. This difference observed in photomixture composition in water is in good agreement to the disappearance of the alcoholic photoproduct with the irradiation time.

The photomixture composition at different irradiation times shows the oxidized compound (3) appears faster in SDS than in H₂O. This photoproduct (3) can be formed by two different pathways [5]: (i) via NP radical cation after it's decarboxylation in the presence of O_2 ; or (ii) via the benzylic radical transformed to (2) in the presence of O_2 followed by the oxidation or

photooxidation of the alcohol (2) (S7). SDS has been recently reported to prevent efficiently the oxidation of NB [17], NSAID structurally related to NP but without acidic nature. Since, NP radical cation is formed in biphotonic process then the mechanism (i) seems to be not very important under the natural conditions (see next section).

3.2.2. Intermediates of Photolysis of NP in Aqueous Micellar SDS Solutions

In laser flash photolysis experiments, SDS concentration was 0.2 M and that of NP in the range 0.5 - 3 mM. These concentrations were selected in order to get enough absorption of NP at 337 nm (N₂-laser wavelength), and to keep condition that amount of NP molecule per micelle is less than 1. At this conditions there is practically no ffects related to the interaction of two or more NP molecules within a given micelle.

The nanosecond laser flash photoexcitation of NP in neutral anueous SDS solution (where NP seems to be in ionized form NP) results in the formation of at least three intermediates observed immediately after the laser pulse (Figure 5, curve 1). They are characterized by transient absorption with maxima at 440 and 720 nm with shoulder near 620 nm and by significantly different lifetimes (16 μ s, 0.08 and 1 μ), respectively). The proposed kinetic scheme of the primary photoprocesses of NP in SDS aqueous solutions are included in S8.



Figure 5: UV-vis transient absorption spectra of intermediates obtained upon laser flash photolysis of aerated aqueous solutions of NP (1 mM) in the presence of SDS (0.2 M) in 0.02

(1), 0.25 (3) and 15 (4), μ s after the laser pulse and (2) is the difference of absorption spectra (1) and (3) representing the absorption spectra of e_{aq} .

The relatively narrow band with characteristic maximum at 440 nm can be assigned to the triplet excited state (³NP) [7,9]. The broad absorption with maximum around 720 nm and short lifetime is the well known characteristic of the hydrated electron e_{aq}^{SDS} as it was previously observed in homogeneous water solutions [7,9]. The shoulder near 620 nm seems to be due to the contribution of naproxen neutral radical (NP⁺) or as previously reported to radical cation (NP⁺⁺) [9].

The e_{aq}^{SDS} absorption spectrum (Figure 5, curve 2) calculated by subtraction of the initial transient absorption (Figure 5, curve 1) and the residual transient absorption observed after e_{aq}^{SDS} decay (Figure 5, curve 3) is very similar to that in pure weter [56]. It is reasonable to expect that e_{aq}^{SDS} is localized in a water phase since e_{aq}^{SDS} escapes from the micelle to the water bulk due to the electrostatic repulsion from the negative. V charged micelle.

The dependence of e_{aq}^{SDS} yield on the laser energy was quadratic in SDS solutions as well as it was found earlier in homogeneous media [9]. Therefore, the NP photoionization is a biphotonic process. The e_{aq}^{SDS} decay kinetics is morphylone potential with first order rate constant (k_e) near $1.3*10^7$ s⁻¹ in deaerated SDS solutions the value is more than two and one orders of magnitude larger than that observed in pure water ($\leq 1*10^5$ s⁻¹ [56]) and in the case of SDS aqueous solutions of the related compound NL [17]. It was speculated that the fast decay of e_{aq}^{SDS} in SDS solutions of NB was due to the quenching of e_{aq}^{SDS} by the residual amount of NB in the water phase. The amount of residual ionized NP in the water phase is significantly larger than that of NB, which results in significantly faster decay of e_{aq}^{SDS} in spite of the negative charge of ionized NP.

The decay of e_{aq}^{SDS} becomes nuticeably faster under the aerated conditions. The value of the rate constant of e_{aq}^{SDS} quenching by molecular oxygen equal to $1.5*10^{10}$ M⁻¹s⁻¹ was estimated using the oxygen concentration of 0.28 mM [57] in air saturated water. It is well known that the quenching of e_{aq}^{SDS} us molecular oxygen is controlled by diffusion. The formation of reactive radical O₂⁻¹'s unpected, but with the yield not more than 20% due to the very short lifetime of e_{aq}^{SDS} . In the case of NB in SDS solutions the life-time of e_{aq}^{SDS} was long enough for the complete quenching of e_{aq}^{SDS} by O₂ in aerated solutions and the expected yield of O₂⁻¹ was close to 100% [17]. Therefore, in this regard the photosensitization effect of NP is five times smaller than that of NB.

The ³NP and NP radical absorption with maxima at 440 and 620 nm, respectively, were observed after the complete decay of e_{aq}^{SDS} (Figure 5, curve 3).

The decay kinetics of NP radical observed in SDS solution was the first order with rate constant near 1×10^6 s⁻¹ and it was independent on the presence of air. This value is similar to that observed for the decay of NP radical cation in homogeneous aqueous solution [9] but clearly smaller than e_{aq}^{SDS} decay.

The decay kinetics of NP radical in SDS solution was independent on [NP]. Thus, a dimer formation between NP radical and NP is not important under the experimental conditions used

in the present work. This observation is in contrast to that for radical cations of naphthalene and some derivatives which reacts with their ground state to form radical cation of dimer at large enough concentration of naphthalene [58,59]. In spite of the fact that electron donating substituents in naphthalene moiety favors the dimer cation formation, in the case of NP in SDS solution, the micelle prevents the bimolecular reaction of NP radical in one micelle with NP in the other. Although-minor amounts of dimers could be formed in reaction of NP radical with residual NP in water phase or in small amount of micelles with a couple of NP molecules. However, based on previous calculations (Section 3.1.3.), the amount of micelles with more than two NP molecules is practically negligible for the solutions with concentrations of SDS and NP used.

The absorption of NP radical was compared to that of e_{aq}^{SDS} (see Fig. 5, spectra 2 and 3). It is reasonable to suppose that e_{aq}^{SDS} and NP radical are formed in equal amount. The value $\varepsilon = 3*10^3 \text{ M}^{-1} \text{ cm}^{-1}$ for NP radical at 620 nm was estimated using $C_{qq}^{SL,3}$ extinction coefficient equal to that in water $(1.85*10^4 \text{ M}^{-1} \text{ cm}^{-1} \text{ [56]})$. This value is significantly smaller than that for NB radical cation in SDS solution [17], which is not expected on the bases of their similar structure. This behavior suggests that the amount of radical with this slow decay is smaller than the total amount of radicals formed. Thus, one can suppose that the most part of NP radicals initially formed decays with the rate constant comparable with or even faster than that of e_{aq}^{SDS} decay. The fast decay part of NP radical was difficult to extract quantitatively because of the NP radical absorption over constant of e_{aq}^{SDS} .

The rate of the slow decay of NP radic.' in SDS solution is of the same order than that in homogeneous media, where decarbo. vlation was demonstrated to be the main pathway for the NP radical deactivation [5].

The biphotonic photoionization of N^P seems to play an insignificant role in normal conditions since it needs the large power right. So, in SDS the main photodegradation pathway seems to be through the benzylic radical (R[•] S7) and then the formation of (3) from (2) by oxidation, demonstrating that the oxidation of (2) is promoted in SDS (see discussion in section 3.2.1.), by contrast to the behavior recently observed for NB [60]. In addition, the reaction of ³NP seems to be more in product in the photoproduct formation.

The ³NP decay kinetics in deaerated SDS solution is monoexponential with first order rate $k=6.2 \cdot 10^4 \text{ s}^{-1}$. Although, this value is of the same order of magnitude as those reported for ³NP decay in homogeneous media [7,9]; however by contrast to the homogeneous media, the triplet-triplet annihilation of ³NP was not observed in SDS solution, due to the small diffusion coefficient and screening of ³NP localized in micellar phase.

The decay of ³NP accelerates significantly in the presence of molecular oxygen in SDS solution. The value of quenching rate constant of ³NP by O_2 equal to $1.8*10^9 \text{ M}^{-1}\text{s}^{-1}$ was calculated using the oxygen concentration in air saturated water 0.28 mM [57]. The quenching of ³NP by O_2 occurs by triplet-triplet energy transfer, which is the diffusion-controlled process with spin-statistical factor 1/9. The formation of reactive singlet oxygen ¹O₂ was detected in homogeneous media [61] as well as in SDS [7].

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One other relatively long-lived transient absorption near 450 nm remained even after the decay of the ³NP was complete (Figure 5, curve 4). The decay kinetics of this transient is first order with rate constant $k=1.5 \cdot 10^4 \text{ s}^{-1}$. A transient with very similar absorption spectra was observed recently in water-acetonitrile mixture and assigned to the decarboxylated radical of ionized NP formed from the triplet state of ionized NP [10] that can be assigned to the benzylic one (R[•] S7). The lifetime of that radical in water-acetonitrile mixture was near 700 ns, which is two orders of magnitude shorter than the lifetime of similar transient observed in the present work in aqueous SDS solution. One can conclude that SDS micelles offer a stabilization effect on the precursors of the final products of NP photolysis. This result is in good agreement to the alcoholic photoproduct formation as limiting step of the drug photodegradation. The proposed mechanism is included in S7.

The stabilization could be related to the subtraction of the hydrogen needed to form the photoproduct from SDS as demonstrated in β -CD inclusion complex [11]. By contrast, to the β -CD, SDS seems to be less readily to donate a hydrogen iton, than the homogeneous media.

Overall, the behavior of transient photoproducts of NP in aqueous SDS solution has the specific features if to compare with that in home encous environment. On one hand, the formation of active form of oxygen is still efficient and thus NP could be a potential photosensitizer contributing to the overall phototexicity. However, it is interestingly that SDS micelles stabilize the precursors of the final products of NP photolysis.

Conclusions

The photochemistry of widespread onu-inflammatory drug naproxen in anionic form in aqueous solutions of anionic miccules SDS was investigated for the first time. Several techniques were used in order to reveal basic features of the NP photochemistry in micellar environment. The nature and kinetics of the relatively stable final and short lived intermediate photoproducts were obtained.

It was shown that despite 1 eutral molecular form of NP partitions better in micellar phase, the anionic one also hig. y partitions in anionic SDS micelles. Partition of the drug into the micellar phase prometes the quenching of NP fluorescence, but it has soft impact on the micelle features.

SDS micelles protect anionic NP from the photodegradation. The process of NP photodegradation includes the formation of the triplet excited state. One of the secondary but supposed the key reaction of the triplet state results in the reduction with formation of radicals which are stabilized by micelles. This radical screening seems to be responsible for NP⁻ protection from the light by SDS micelles.

The specific protective effect on the photodegradation of NP in the SDS micelle was found. SDS micelles significantly avoids the alcoholic photoproduct (2) formation which is formed at the initial stage of the NP photodegradation. Whereas the oxidation of the alcoholic photoproduct (2) is faster in SDS than in water. From a practical point of view, the results suggest the possibility of bioaccumulation of the drug in hydrophobic parts of biological structures. The lower photoreactivity in the micelles than in water is a hopeful result from toxicological point of view, but on the other hand it would increase the persistence of the pharmaceutical in the natural environment.

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Figure Captions

Figure 1: Plot of the ratio of NP fluorescence intensity in water, F_0 , and that in the presence of different SDS concentrations (all of them above cmc) at emission wavelength λ_{em} =355 nm, at 20°C. *Inset*: the plot of NP (0.04 mM) fluorescence quantum yield, ϕ_{fl} vs SDS concentration.

Figure 2: **A:** The plot of the ratio of NP solubility in SDS and in water vs. SDS volume fraction, ϕ_{SDS} , at different pHs; **B:** plot of the slope of the curves in A (partition coefficient, P, (S4)) vs. NP ionization degree X_{NP}-. At 20°C.

Figure 3: Small-angle neutron scattering data of SDS micell is the (circles and triangles) and loaded with 1 mM NP (diamonds and squares), at 0.05 N. ($\bigcirc \heartsuit$) and 0.2 M (Δ , \Box) of SDS concentration, in D₂O at 25 °C. A: free and lot ded micelles curves at both SDS concentrations. B: NP curves as in A, but with the fits (solid lines) to the ellipsoidal micelle model [31,32].

Figure 4: Fluorescence spectra of 1 mM NP at different irradiation times in: **A:** water, and **B:** 0.2M SDS. *Insets*: plots of the intensity of the bands corresponding to NP at λ_{em} =355 nm (F₃₅₅) and the photoproduct at λ_{em} =440 m (F₄₄₀) vs. the irradiation time. The black lines correspond to the fittings of the data to a zero order kinetic. The spectra were obtained with λ_{exc} = 317 nm.

Figure 5: UV-vis transient absorption spectra of intermediates obtained upon laser flash photolysis of aerated aqueous solutions of NP (1 mM) in the presence of SDS (0.2 M) in 0.02 (1), 0.25 (3) and 15 (4), up after the laser pulse and (2) is the difference of absorption spectra (1) and (3) representing the absorption spectra of e_{aq} .

Scheme 1: Chemical structure of: (1) anionic form of naproxen (NP) (sodium -2-(6-methoxynaphthalen-2-yl) propanoate and the photoproducts: (2) (6-methoxy-2-(1-hydroxyethyl) naphthalene, and (3) 6-methoxy-2-acetyl-naphthalene.

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Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NP in ionized form (NP⁻) highly partitions into sodium dodecyl sulfate (SDS) micelles. SDS micelle protects NP⁻ from light degradation.

The photoproducts formed are the same in SDS than in water but in lower amount.

SDS micelle stabilizes the radicals involved in the photoproducts formation.

Photodegradation pathway is by ³NP⁻ decarboxylation.