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Substituent Effect on the Photolability of 4-Aryl-1,4-Dihydropyridines†

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ABSTRACT

The electronic nature of substituents attached to the 4-aryl moiety of 1,4-dihydropyridines strongly affects the photophysical and photochemical behavior of these family of compounds. The presence of an electron donor substituent on the 4-aryl moiety (or the absence of electron-withdrawing ones) modifies the luminescence lifetimes (τ < 100 ps) and diminishes the photodecomposition quantum yields. For electron-withdrawing substituents, the photodegradation quantum yield is affected by the media, changing more than two orders of magnitude as the polarity is increased. Studies in micellar media allow us to conclude that 4-aryl-1,4-dihydropyridines are located near to the interface; however, the surface charge of micelles has no effect on the photodegradation rate constant or the photoproducts profile. The main conclusion of this work is that the photolability of 4-aryl-1,4-dihydropyridines can be significantly reduced by the incorporation of antioxidant moieties.

INTRODUCTION

A large number of therapeutic drugs have been linked to the induction of photoallergic or phototoxic effects. Among them, we are interested in 4-aryl-1,4-dihydropyridines, compounds belonging to a family of substrates widely used as antihypertensive drugs (1,2). The use of these calcium channel blockers in long-term treatments has been associated with adverse photosensitive effects at the skin level, such as toxic epidermal necrolysis, Stevens–Johnson syndrome and erythema multiforme and exfoliative dermatitis (3,4). Different photophysical and photochemical behaviors have been reported for antihypertensive 4-aryl-1,4-dihydropyridines depending on the substituents present on the 4-phenyl ring (5). Also, it has been found that the capacity of these drugs to generate singlet oxygen, $O_2(^1\Delta_g)$, depends on the medium polarity and on the substituents on the 4-aryl moiety. They are also classified as good scavengers of $O_2(^1\Delta_g)$, and a mechanism has been proposed to explain their reactivity with reactive oxygen species (6).

Important efforts are being made to identify additional biological activity of dihydropyridines, besides their original pharmacological activity. For instance, 4-aryl-1,4-dihydropyridines have been recognized to display antioxidant protective effects (7,8), although it is not clear to date whether these contribute to their recognized pharmacological activity. The inclusion of phenolic moieties (9,10) or indole derivatives (11) on the 1,4-dihydropyridinic ring has been suggested as a good strategy for enhancing their antioxidant properties. Synthetic polyphenolic 1,4-dihydropyridines have a significant reactivity toward the superoxide radical anion, being their scavenging ability higher than that of Trolox or other commercial 1,4-dihydropyridines.

Taking into account the reports of such additional capacities provided by the introduction of new substituents on the 4-phenyl group, we studied and compared the photophysical and photochemical behavior of 1,4-dihydropyridines bearing either electron-withdrawing or electron-donating substituents on the 4-aryl moiety (Fig. 1), in solvents of different polarities. Due to the high lipophilicity reported for similar compounds (12), the behavior of the substrates in microheterogeneous micellar media was also included (Fig. 2).

MATERIALS AND METHODS

Drugs and reagents. Compounds **1** (4-phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-pyridinedicarboxylic acid diethyl ester), **2** (4-(4-hydroxyphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-pyridinedicarboxylic acid diethyl ester), **3** (4-(4-methyl-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-pyridinedicarboxylic acid diethyl ester) y **4** (4-(3-hydroxy-4-methoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-pyridine dicarboxylic acid diethyl ester) were gently donated by Laboratorio de Bioelectroquőmica, Universidad de Chile (9,13). Nimodipine (NIMO; 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-methoxyethyl 1-methylethyl ester) and felodipine (FELO; 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-pyridinedicarboxylic acid ethyl methyl ester) were purchased from Sigma and used as received. 5,10,15,20-Tetraphenyl-21H,23H-porphine (TPP), 9,10-dimethylanthracene (DMA) and phenalenone (PN) from Aldrich were used also without further purification. Rose bengal (RB) from Fluka was recrystallized from ethanol prior

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†This article is part of the Special Issue dedicated to the memory of Elsa Abuin.
††Died October 25th, 2013. Dear Luis, rest in peace.
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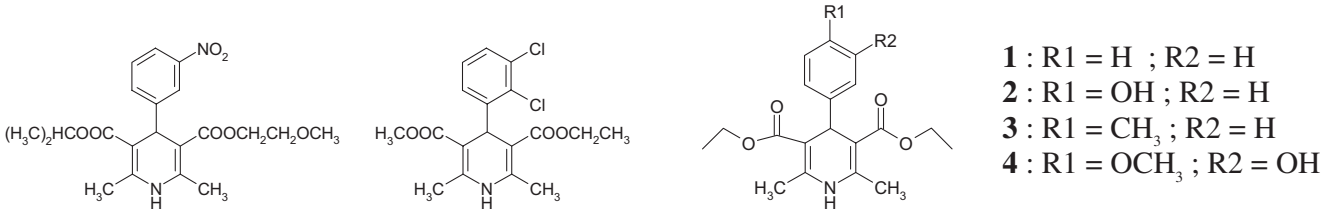

Figure 1. Chemical structures of the studied 4-aryl-1,4-dihydropyiridines.

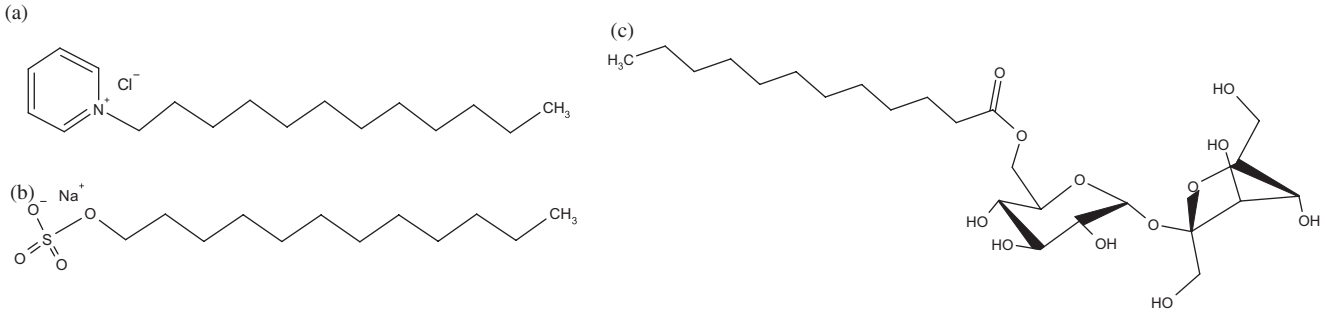

Figure 2. Chemical structures of the surfactants used for the micellar media studies: (a) dodecyl-pyridinium chloride (DPC) (b) sodium dodecyl sulfate (SDS); (c) mono-lauryl sucrose ester (MLS).

to use. cis-1,3-Pentadiene (cis-piperylene), also from Fluka, was distilled prior to use. All solvents (Merck) were of spectroscopic or HPLC grade. Water was purified and deionized using a Waters Milli-Q system. Sodium dodecyl sulfate (SDS), from Merck, and dodecylpiridinium chloride (DPC), from Aldrich, were recrystallized twice from acetone. The sucrose monoester β-D-fructofuranosyl-6-O-lauryl-α-D-glucopyranoside (MLS) was synthesized and isolated as described in the literature (14).

Apparatus and procedures. UV–Vis absorption spectra and steady-state kinetic experiments were performed in an Agilent 8453 diode-array spectrophotometer. Emission spectra were recorded in a FluoroMax4 Horiba Jobin Yvon spectrofluorometer. Micellar solutions were prepared adding the desired amount of surfactant to milliQ water and sonicating for 30 min. The final surfactant concentrations were SDS 40 mM, DPC 75 mM, and MLS 1.75 mM, five-fold above their respective critical micellar concentration. Incorporation of the drugs was made by adding solid compound to the micellar solutions until saturation of the microaggregates.

Photolysis experiments were carried out on 1×10^{-3} M solutions (3 mL) of the compounds in several selected solvents or micellar air-equilibrated or deaerated solutions in a 10 mm fluorescence quartz cell. The solutions were irradiated with a black ray UV lamp with a 366 nm filter. The radiant flux was determined using the self-sensitized photooxygenation of 9,10-dimethylanthracene in air-saturated Freon 113 ($\Phi = 0.566$) (15,16). The photon flux, q [einstein/s] was calculated according to Eq. (1):

$$q = \frac{\Delta A_{324} \times V}{\Phi(\lambda) \times \varepsilon_{324} \times t \times l}[\text{ einstein/s }] \qquad (1)$$

where: ΔA_{324} is the solution absorbance at 324 nm, V = volume of the solution [L], $\Phi(\lambda)$ = photooxygenation quantum yield at the excitation wavelength λ, ε_{324} = molar absorption coefficient at 324 nm [M^{-1} cm^{-1}]; t = irradiation time [s] and l = optical path length [cm].

A Shimadzu Gas Chromatograph model GC-2014AF/SPL equipped with a FID detector and a 30 m capillary column RTx-5 were used to monitor substrate consumption and to follow the cis-piperylene consumption and conversion into the trans-isomer. A Thermos Gas Chromatograph model DSQ II coupled with a mass detector and an RTx-5 MS column was employed to identify main photoproducts.

Luminescence lifetime measurements were carried out with the time-correlated single photon counting (TCSPC) technique using a PicoQuant FluoTime 200 Fluorescence Lifetime Spectrometer.

$O_2(^1\Delta_g)$ generation was studied with time-resolved phosphorescence experiments using PN as reference ($\Phi_\Delta = 0.93$ in benzene) (17), by comparing the response of the detector extrapolated to zero time at low laser power. Optically matched solutions of drug and actinometer in benzene were excited by the third harmonic (355 nm, *ca.* with 28 μJ per pulse as maximum power at 10 kHz, 10^4 accumulated laser pulses) of a FTSS355-Q Crylas Q series diode-pumped Nd:YAG laser system.

Chemical reaction rate constants were determined with 1×10^{-3} M solutions (3 mL) of studied compounds in several selected solvents using a 10 mm fluorescence quartz cell. The solutions were irradiated with visible light (50 W halogen lamp) properly filtered using appropriate cutoff filters to ensure selective excitation of the photosensitizer only (either RB or TPP). Circulating water maintained the cell temperature at 22 $\pm$ 0.5°C.

RESULTS

Absorption and emission properties

The absorption spectra of compounds **1**–**4** show a characteristic band centered at around 350 nm ($\varepsilon \sim 7 \times 10^{-3}$ M^{-1} cm^{-1}), corresponding to the 4-aryl-1,4-dihydropyridine chromophore (see Fig. 3). Table 1 collects the maximum absorption wavelength for these bands in different homogenous and heterogeneous media. For comparison, values of NIMO and FELO are also included. All these compounds exhibit also a similar emission band centered at around 420 nm in all media tested. The fluorescence lifetimes, measured at 420 nm, were very short ($\tau < 100$ ps) and neither triplet excited states nor any other long-lived transients could be detected with our setup. However, compounds **1**–**4** in benzene solutions were able to generate $O_2(^1\Delta_g)$, albeit with relatively low quantum yields ($\Phi_\Delta \sim 1 \times 10^{-3}$).

The emission of compounds 1–4 at 420 nm was quenched by cis-piperylene with low Stern–Volmer constants in the order of 0.8–4.3 M^{-1}. Cis-piperylene undergoes photosensitized cis-trans-isomerization in the presence of triplet excited states of higher energy (18), and it has also been involved in the deactivation of singlet excited states without cis-trans-isomerization (19,20), so

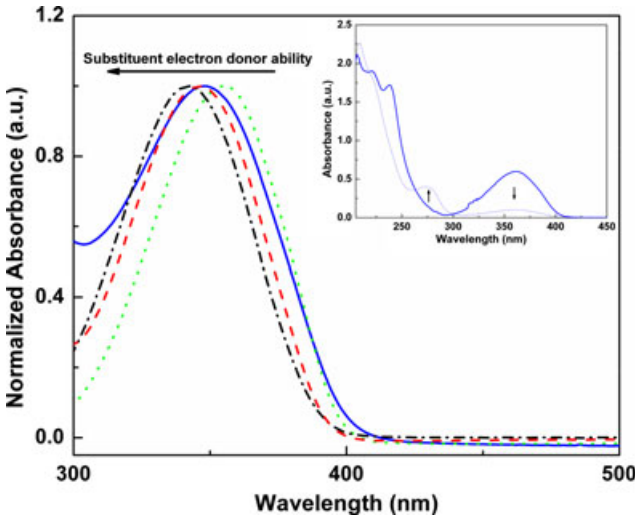

Figure 3. Absorption spectra of acetonitrile solutions of compounds: **2** (----), **3** (-·-·-), NIMO (——) and FELO (·····). Inset: Time course absorption spectra upon UV light irradiation of ethanolic solution of NIMO.

Table 1. Maxima absorption wavelengths for 4-aryl-1,4-dihydropyridines in several media.

	λ_{max} (nm)					
Media	1	2	3	4	NIMO	FELO
Acetonitrile	348	346	342	345	348	355
Benzene	344	343	339	342	345	353
Ethanol	356	355	350	353	356	362
Sodium dodecyl sulfate micelles (SDS)	361	360	352	360	360	364
Dodecyl-pyridinium chloride micelles (DPC)	362	360	356	359	362	366
Mono-lauryl sucrose ester micelles (MLS)	363	362	353	359	361	364

the conversion into the trans-isomer would be indicative of a triplet excited state participation in the luminescent decay.

Photodegradation kinetic parameters

The photodegradation quantum yields were obtained following the consumption of the drugs upon irradiation with UV light (365 nm). Table 2 collects the values obtained for the different compounds in homogeneous solvents with those in micellar solutions. The photodegradation quantum yields for compounds **1**–**4** were lower than the ones determined for NIMO and FELO in all the solvents and micellar solutions tested.

The main photodegradation products for compounds **1**–**4** were the corresponding pyridine derivatives, being pyridine the chromophore responsible for a new absorption band observed at 280 nm in the UV–Vis spectra (see Inset in Fig. 3).

Reactivity with singlet oxygen

The rate constants for reaction with $O_2(^1\Delta_g)$, k_R, were determined employing TPP or RB as sensitizer and monitoring the drug consumption by gas chromatography. DMA was used as actinometer to determine the $O_2(^1\Delta_g)$ steady-state concentration (21). The values of k_R obtained from the slope of the pseudo-first-order plots are shown in Table 3 (for more details see Supplementary Materials).

Table 2. Quantum yields of photodegradation of 4-aryl-1,4-dihydropyridines in different media.

	$\Phi_{photodeg}$ (10^{-5} molec./ abs. phot.)					
Medium	NIMO	FELO	1	2	3	4
Acetonitrile						
Aerated	20.0	8.30	1.3	2.9	2.2	6.1
Deaerated	23.4	1.40	<0.5	<0.5	1.6	2.4
Benzene						
Aerated	630	7.40	4.5	6.7	2.8	2.3
Deaerated	770	1.10	<0.5	<0.5	<0.5	1.5
Ethanol						
Aerated	1130	14.5	6.8	7.5	3.0	3.3
Deaerated	1810	0.70	<0.5	<0.5	2.6	2.5
Sodium dodecyl sulfate micelles (SDS)	240	23.6	8.8	9.4	3.7	1.7
Dodecyl-pyridinium chloride micelles (DPC)	85.0	11.3	26.3	9.8	11.1	0.5
Mono lauryl sucrose ester micelles (MLS)	140	12.5	46.1	11.8	2.9	1.9

$\Phi_{photodeg}$ errors are within 10% for all results.

Table 3. Chemical rate constants for reaction between singlet oxygen and 4-aryl-1,4-dihydropyridines.

	k_R (10^{-5} M^{-1} s^{-1})					
Medium	NIMO	FELO	1	2	3	4
Acetonitrile*	0.9	3.4	3.7	5.9	4.6	2.7
Benzene†	0.1	0.5	14.9	13.5	20.6	19.3
Ethanol‡	–	2.1	13.3	15.5	6.5	7.6

*k_R errors are within 10% for all results; Sensitizer †Bengal Rose, ‡TPP.

The dye-sensitized photooxygenation of compounds **1**–**4** yields the corresponding pyridine derivatives as the main products, which were identified by GC-MS technique.

Figure 4 shows the chromatogram corresponding to a photooxidized compound **1**, where the main photoproduct can be observed.

DISCUSSION

Substituent effect on the absorption and emission properties

4-Aryl-1,4-dihydropyridines bear two independent π-systems separated by an sp^3 carbon, the total absorption of the molecule being the combination of both (22). This notwithstanding, the position of the characteristic absorption band of the 1,4-dihydropyridine chromophore depends on the substituent present on the 4-phenyl moiety. A different photochemical behavior is likewise observed when electronic excitation is promoted with short-wavelength light (below 300 nm, where only the aromatic ring is excited) or at longer wavelengths (above 350 nm, where 1,4-dihydropyridine is excited) (22). In this study we employed light of 365 nm for excitation, so we dealt with the chromophoric group corresponding to 1,4-dihydropyridine.

As can be seen in Table 1, compounds **2**, **3** and **4** bearing electron-donating 4-methyl-, 4-hydroxy- or 4-methoxy-3-hydroxy

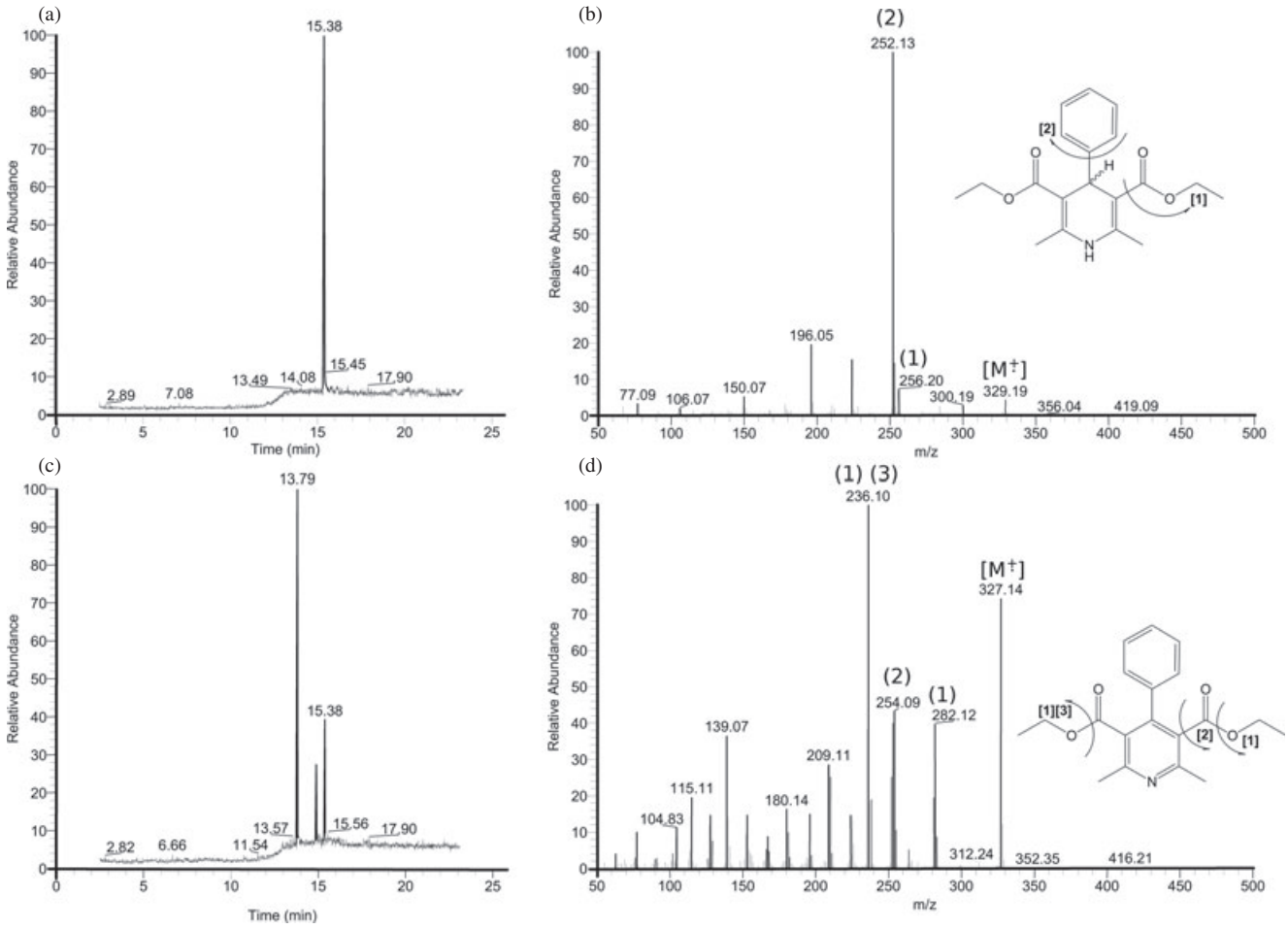

Figure 4. (a) GC-MS chromatogram of 5.0 mM compound 1 in acetonitrile; (b) EI + mass spectrum of compound 1 (retention time 15.38 min); (c) GC-MS chromatogram of 5.0 mM compound 1 in acetonitrile after 1 h of irradiation in the presence of TPP; (d) EI + mass spectrum of pyridine derivative main product at retention time 13.79 min.

substituents on the phenyl ring, show blueshifted bands, compared to NIMO or FELO, which have electron-withdrawing 3-nitrophenyl or 2,3-dichlorophenyl groups, respectively. Then, it is possible to conclude that the electronic transition involved depends on the substituent's electron ability, showing a hypsochromic shift due to the higher electron donor capacity of the 4-phenyl substituted group. The UV–Vis absorption spectra of 4-aryl-1,4-dihydropyridines in micellar media do not show dependence on the nature of the head of surfactant. Table 1 shows the same position of the absorption bands for compounds **1**–**4** incorporated to micelles formed with different kinds of surfactants like sodium dodecyl sulfate (SDS, anionic), dodecyl-pyridinium chloride (DPC, cationic) and mono lauryl sucrose ester (MLS, nonionic). The maxima absorption wavelength in micellar media appears redshifted compared to homogeneous solvents, indicating that these compounds bind to the micelle and are located at the interface, in the region closer to where the water molecules can still penetrate.

The fact that compounds **1**–**4** exhibit more intense fluorescence than NIMO and FELO, can be explained taking into account the proposition of Fasani *et al.* (23). They stated that the lowest singlet excited state of these compounds is deactivated by a fast intramolecular electron transfer from the dihydropyridine ring (DHP) to the substituted phenyl ring (Ar), yielding a zwitterionic biradical as intermediary species ($DHP^{\bullet+}$–$Ar^{\bullet-}$). The intramolecular electron transfer should thus be favored for FELO and NIMO, which bear electron acceptor group in the phenyl moiety, but not for compounds **1**–**4** bearing electron donor moieties. Our observations are consistent with this expectation. Only a minor participation of triplet excited state could be expected on the basis of the low $O_2(^1\Delta_g)$ generation quantum yield and the lack of any transient absorption in the laser flash photolysis experiments. In fact, a weak triplet state formation has been observed and reported for compounds bearing 3-nitrophenyl substituents (24). Depending on the energy of the zwitterionic biradical, it could evolve (back electron transfer) to the ground state or to two different triplet species, located either in the aromatic moiety (DHP–^{3}Ar) or in the dihydropyridine ring (^{3}DHP–Ar) (22), our results indicate that for the studied compounds the energy of zwitterionic biradical is below both triplets, therefore back electron should regenerate the ground-state reactants.

Substituent effect on the photodegradation kinetics

Photodegradation quantum yield values (see Table 2) were lower for compounds **1**–**4** than those for NIMO and FELO. Thus, the

presence of a substituent with electron donor ability diminishes the photolability of 4-aryl-1,4-dihydropyridines. We also observed for NIMO that the photodegradation quantum yield increases in the absence of oxygen. This result conflicts with those of Fassani *et al.* (25) on nifedipine, a 4-(2-nitrophenyl)-1,4-dihydropyridine, but is consistent with the report for nicardipine, another 3-nitrophenyl substituted 1,4-dihydropyridine, for which the photodegradation quantum yield increases by *ca.* 15% in the presence of oxygen (23). It is reassuring that Görner (24), recently described the contribution of the triplet state to the photodegradation of NIMO. Evidence of the NIMO triplet excited state participation was also established in a previous work (26). This finding supports the idea of the triplet excited state of NIMO participating in the photodecomposition pathway, due to the high capacity of the nitrophenyl moiety for stabilizing the zwitterionic biradical intermediate. In addition, according to the literature (27), aromatization of dihydropyridine ring is the regular photodegradation pathway, but usually very inefficient. The magnitude of this process is clearly determined by the C4–H bond strength, so the presence of substituents able to weaken this bond (through steric or electronic effects) will facilitate this type of reaction. When structural modifications increase singlet lifetime, photodegradation quantum yield is also increased. It has to be mentioned that phenyl group and its substituents have a fair effect, with the remarkable exception of nitro group in position 2′, which enables a faster intramolecular reaction (behavior reported for Nifedipine) (27).

These facts are consistent with our previous proposals (28), where we observed that photodegradation process for 4-aryl-1,4-dihydropyridines seems to be very dependent on the capacity of the molecule to stabilize the zwitterionic biradical intermediate involved. Indeed, the evidence demonstrates that only the presence of the electron acceptor nitro group facilitates the charge separation, situation less favored when chlorine atoms or electron-donating groups are the substituents. When the formation of the zwitterionic intermediate is favored, the media have a noticeable effect on the photodegradation. For NIMO, solvent molecules modulate photodegradation pathway not only by stabilizing charged intermediates but also by providing a proton acceptor to trigger the path to products. On the other hand, FELO and compounds **1**–**4**, less prone to photodegradation, show no noticeable influence of the media in the process. We also proposed that in microorganized media, like micelles, the charge at the surface will promote different orientations for the zwitterionic intermediate involved. However, the measured consumption quantum yields are similar for the two ionic surfactants (SDS and DPC), indicating that proton removal has the same efficiency in both systems so, despite orientation, the proton to be abstracted is equally accessible.

Substituent effect on the reactivity toward singlet oxygen

From the data in Table 3, it can be concluded that compounds **1**–**4** bearing electron-donating substituents on the phenyl moiety show higher chemical reactivity toward $O_2(^1\Delta_g)$ than their homologues NIMO and FELO. The higher reactivity of these compounds could be explained in terms of the electron donor inductive capacity of 4-methylphenyl, 4-hydroxyphenyl and 3-hydroxy-4-methoxyphenyl groups, which favors the electrophilic attack by $O_2(^1\Delta_g)$ to one of the carbon–carbon double bonds of the dihydropyridinic ring (6). The inductive electron effect should be operative only between the dihydropyridinic ring and the substituted phenyl group, because as was already aforementioned, the sp^3 hybridization of carbon atom in position 4 and the lack of coplanarity between phenyl and the dihydropyridine ring preclude any electronic resonance effect.

CONCLUSION

We found that when an electron donor substituent is present on the 4-aryl moiety (or in the absence of electron-withdrawing ones), the fluorescence lifetime of dihydropyridines decreases and their photolability is diminished, without change in the reaction mechanism. The photodegradation quantum yield is affected by the media only when an electron-withdrawing group like 3-nitrophenyl moiety is present, changing more than two orders of magnitude as polarity is increased. The studies in micellar media allow us to conclude that the studied 4-aryl-1,4-dihydropyridines are located close to the interface, but the surface charge of micelles does not affect their photodegradation rate constant nor the products profile. The presence of electron-donating substituents also increases the reactivity of these compounds with $O_2(^1\Delta_g)$. In summary, the incorporation of moieties able to enhance antioxidant capability is also reducing in significant amount the photolability of 4-aryl-1,4-dihydropyridines, probably due to the less favored formation of the intermediate zwitterion biradical transient species. This point could be very interesting, if this kind of compounds besides their diminished photolability show lower phototoxicity, the zwitterion biradical could probably be the responsible for the photoadverse side effects of 1,4-dihydopyridines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Chemical rate constants determination with photochemical generation of singlet oxygen.

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