Photochemical outcome modification of diflunisal by a novel cationic amphiphilic cyclodextrin

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The effects of a novel cationic amphiphilic cyclodextrin (SC6CDNH2) on the photoprocesses of the phototoxic non-steroidal anti-inflammatory drug diflunisal (DF) have been investigated in aqueous medium. Association between DF and SC6CDNH2 was indicated by steady-state absorption, induced circular dichroism and fluorescence spectroscopy. Laser flash photolysis and steady-state photolysis experiments revealed a particular sensitivity of the DF photochemistry to the new microenvironment. Reduction of the triplet state generation efficiency, lengthening of its lifetime, changes in the photoionisation pathways, besides remarkable drug photostabilization and modification of the stable photoproducts distribution, were observed. A rationale for these modifications to the photochemistry of DF based on the multifaceted role of SC6CDNH2 in influencing the efficiency of the primary photochemical act and in interfering with secondary radical reactions is proposed. Relation of the overall results to the phototoxic effects displayed by the drug is also commented upon.

Introduction

Cyclodextrins (CDs) as drug complexing agents have been the object of intense interest for both fundamental aspects and practical purposes for a long time.[1] Recently, this attention has turned to the problem of biological photosensitisation by drugs.[2] Indeed, despite their excellent therapeutic activity, many pharmacologically important chemicals such as antibacterials, antimicotics and non-steroidal anti-inflammatory drugs (NSAIDs) can induce phototoxic, photoallergic and photomutagenic phenomena strictly related to the drug photochemical reactivity.[3] It has been reported that in some cases such effects can be substantially decreased in the presence of CDs with model cellular systems.[4–8] Application of CDs was, therefore, suggested as a useful strategy to minimise the biological damage induced by drugs and increase drug photostability. However, is should be stressed that drug–CD complexes usually dissociate once introduced into the body, where there is also exposure to a wide range of endogenous species.[7,9] Polymeric or supramolecular aggregates of CDs have the potential to overcome these drawbacks. Indeed, CD aggregates can combine macrocyclic and liposomal features to have release properties different from those of single CD molecules and bear a close structural relationship to naturally occurring membranes. It has been shown that amphiphilic CDs can display lyotropic and thermotropic mesophases, form monolayers at the air–water interface[10] and also form micelles.[11] Amphiphilic CDs have been admixed with phospholipid monolayers,[12] as well as liposomes,[13] and were dispersed in nanoparticles of pharmaceutical importance.[14] This has opened up new possibilities for their application as drug delivery systems. Recently, we have prepared novel vesicles[15,16] and micellar aggregates[16,17] entirely composed of neutral amphiphilic CDs. In these macrocycles the non-polar moiety is represented by alkylthio chains of varying length whereas the polar moiety is an oligo(ethylene oxide), which is expected to reduce immunogenicity as well as increase the overall colloidal stability of these CD aggregates, much like "stealth" liposomes.[18] Recently, we have synthesised (from precursor heptakis[2-ω-bromo-*O*-oligo(ethylene oxide)-6-hexylthio]-β-CD) a novel cationic amphiphilic cyclodextrin, heptakis[2-ω-amino-*O*-oligo(ethylene oxide)-6-hexylthio]-β-CD, SC6CDNH2 (Chart 1).[19a] Dynamic light scattering measurements showed that SC6CDNH2 forms nanoaggregates in aqueous solutions within the size range of 120 to 1000 nm, at concentrations between 1×10^{-6} and 6×10^{-4} M.[19b,c]

This paper centres on the effects of SC6CDNH2 nanoparticles on the photoprocesses of diflunisal (DF), 2′,4′-difluoro-4-hydroxy-[1,1′-biphenyl]-3-carboxylic acid. DF is one of the most common NSAIDs used in the market and is known to

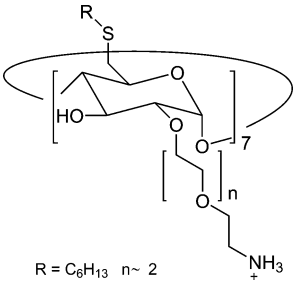

Chart 1

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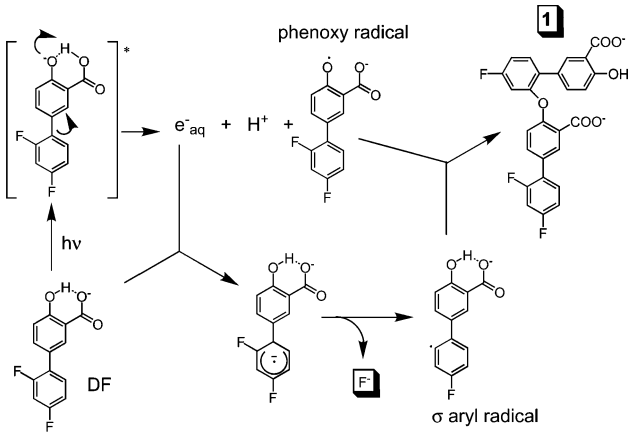


Scheme 1 Photodegradation mechanism of DF in neutral aqueous solution.

induce phototoxic effects both *in vitro*[20,21] and *in vivo*[22] upon sunlight absorption. The present investigation, carried out by coupling steady-state and time-resolved photochemical techniques, aimed to shed light on the potential of the SC6CDNH2 nanoparticles to be used as a photoprotective drug-carrier systems.

For a better understanding of the results, we consider it useful to mention briefly the main photochemical features of DF in aqueous medium.

Our preceding study concerning the steady-state photochemistry of DF at neutral pH[20] has shown that under UVA excitation DF undergoes photodefluorination, an uncommon reaction in fluoroaromatics due to the strength of the C–F bond (dissociation energy *ca.* 523 kJ mol^{-1}). The main photoproduct isolated in anaerobic conditions was the 2′-(2‴,4‴-difluoro-3″-carboxy-[1″,1‴-biphenyl]-4″-oxy)-4′-fluoro-4-hydroxy-[1,1′-biphenyl]-3 carboxylic acid, **1** (see Scheme 1).

The high toxicity displayed by **1** itself towards cell membranes has led to this compound being identified as one of the main species responsible for photoinduced damage.[20] Our recent detailed report concerning the transient photochemistry of DF in neutral aqueous solution has shed light on the molecular mechanism of the drug's photodegradation.[23] As summarised in Scheme 1, the primary photochemical process is photoionisation. Electron photoejection takes place *via* mixed one- and two-photon pathways mediated by the excited singlet state and generating a phenoxy radical. Defluorination occurs *via* the radical anion, formed by a diffusion-controlled trapping of the hydrated electrons by the DF ground state. A σ-aryl radical is produced after loss of the fluoride anion. Formation of **1** is fully consistent with the occurrence of a cross-combination reaction, almost exclusively controlled by the Fisher–Ingold persistent radical effect,[24] between the phenoxy and the σ radical centres.

Experimental

Materials and methods

DF was purchased from Sigma Chemical Company (Milan, Italy) and was used as received. Water was purified through a Millipore Milli-Q system. All the experiments were performed in 10^{-2} M phosphate buffer at pH 7.4. The pH of solutions was measured with a glass electrode.

SC6CDNH2 solutions were prepared as follows: weighed amounts of SC6CDNH2 (average molecular weight 2702) were dissolved in chloroform and dried under nitrogen flux. To the resulting film was added phosphate buffer before sonication at 40 °C for 30 min.

Absorption and induced circular dichroism spectra (ICD) were recorded with a Beckman 650 DU spectrophotometer and a Jasco J-715 dichrograph, respectively. Fluorescence emission spectra were recorded with a Spex Fluorolog-2 (mod. F-111) spectrofluorimeter.

The reaction mixtures were analysed with a Hewlett-Packard LC-ESI-MS system equipped with an on-line photodiode array detector (DAD) and a LiChroCart RP-18 column (5 μm packing, 4 × 250 mm, Hewlett Packard). The gradient used for elution was CH_3CN in 0.01 M phosphate buffer (pH 7) from 0 to 75% in 25 min, at a flow rate of 1 mL min^{-1}.

Irradiation experiments were performed using a Rayonet photochemical reactor equipped with "black light" phosphor lamps emitting in the 310–390 nm range with a maximum at 350 nm. The incident photon flux on 3 mL quartz cuvettes was *ca.* 1×10^{16} quanta s^{-1}. The experimental procedures of irradiation and the light intensity measurements have been described previously.[25]

The photodegradation of DF was determined by LC-ESI-MS analysis, from the disappearance of the starting compound, up to *ca.* 25% conversion. The retention times for DF and photoproduct **1** were 13.7 and 12.8 min, respectively. A quantitative evaluation of injected material in the presence of SC6CDNH2 ensured that the column retained no inclusion products.

Nanosecond laser flash photolysis

The samples were excited with the fourth harmonic of a Nd-YAG Continuum Surelite II-10 laser system (pulse width 6 ns FWHM, at $\lambda = 266$ nm) and the excited solutions were analysed at a right angle geometry using a mini mLFP-111 apparatus developed by Luzchem Research. Briefly, the monitoring beam was supplied by a ceramic xenon lamp and delivered through quartz fibre optical cables. The laser pulse was probed by a fibre that synchronised the mLFP system with a Tektronix TDS 3032 digitiser operating in the pre-trigger mode. The signals from a compact Hamamatsu photomultiplier were initially captured by the digitiser and then transferred to a personal computer that controlled the experiment with Luzchem software developed in the LabView 5.1 environment from National Instruments. The energy of the laser pulse was measured at each laser shot by a SPHD25 Scientech pyroelectric energy monitor. Oxygen was removed by vigorously bubbling the solutions with a constant flux of argon previously passed through a water trap. The solution (in a flow cell of 1 cm pathlength) was renewed after each laser shot. The sample temperature was 295 ± 2 K.

Results and discussion

Association of DF with SC6CDNH2

The interaction between DF and SC6CDNH2 was characterised by UV-VIS absorption, induced circular dichroism (ICD) and fluorescence spectroscopy. Fig. 1 shows the absorption spectrum of DF recorded in the presence of increasing amounts of SC6CDNH2. A remarkable decrease in the molar absorption coefficient of the 260 nm band, corresponding to transitions localised on the phenyl rings,[26] accompanied by an 8 nm red shift of the maximum upon addition of SC6CDNH2, was observed. Lesser spectral modifications were also noticed in the lower energy absorption band. Such behaviour compares with that exhibited by DF in the presence of either β-cyclodextrin[27] or micelles[28] and provides a first indication of the association between drug and SC6CDNH2.

A more direct proof of the host-guest complexation is afforded by induced ICD measurements. DF is not optically active. Addition of SC6CDNH2 induces optical activity. A positive and a negative band around 260 and 310 nm,

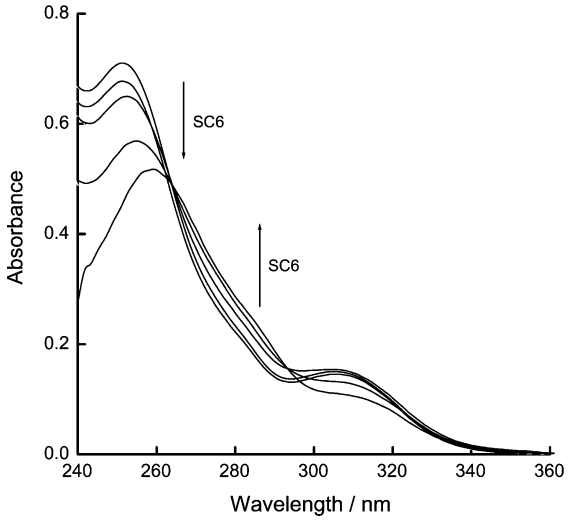


Fig. 1 Absorption spectra of 5×10^{-5} M DF in 10^{-2} M phosphate buffer solution, pH 7.4 in the presence of 0.0, 0.03, 0.06, 0.12 and 0.25 mg ml^{-1} SC6CDNH2. Cell path 1 cm. The spectra in the presence of SC6CDNH2 were recorded using a reference solution containing the same concentration of SC6CDNH2.

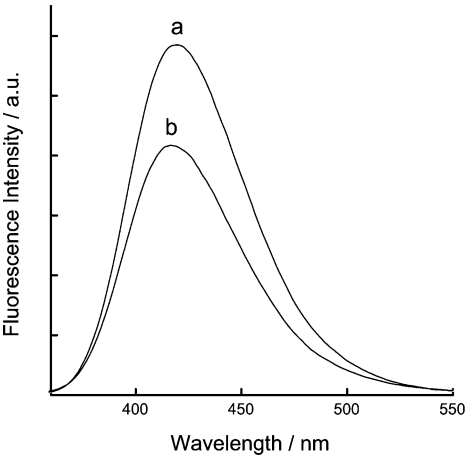


Fig. 3 Fluorescence spectra of 5×10^{-5} M DF observed in 10^{-2} M phosphate buffer solution, pH 7.4 (a) in the absence and (b) in the presence of 0.25 mg ml^{-1} SC6CDNH2. $\lambda_{exc} = 295$ nm.

respectively, arise indeed as a consequence of complexation with the chiral macrocycle (Fig. 2). The ICD bands are characterised by maxima corresponding to those of the absorption bands, ruling out the occurrence of exciton splitting phenomena.[29] The presence of the ICD signals affords some hints on the probable binding mode of DF with the host. Since these bands are in general strictly dependent on the distance between the host and the guest, their appearance indicates that the DF molecule is localised close to the chiral cavity of SC6CDNH2.

The addition of SC6CDNH2 also affects the fluorescence emission of the drug. As can be seen in Fig. 3, the fluorescence intensity of DF is decreased and the emission maximum blue-shifted *ca.* 5 nm. This behaviour is also similar to that observed in the presence of either β-cyclodextrin[27] or micelles.[28] While the decrease of the fluorescence intensity could be simply due to a polarity effect (both solutions are optically matched at the excitation wavelength), the shift towards high energy deserves some further comment. A recent study on the excited-state properties of DF in aqueous medium[23] showed a large Stokes shift between the absorption and the emission maxima, pointing to a large geometry difference between the ground and the relaxed excited state. It was demonstrated that such a large Stokes shift can be ascribed to two different phenomena coming into play upon light excitation (see Scheme 1): (1) a change in the dihedral angle between the two planes of the phenyl rings (twisted in the ground state and coplanar in the excited state), typical for biphenyl derivatives;[30] (2) an intramolecular proton transfer between the hydroxyl group and the carboxyl moiety, typical for salicylic acid derivatives.[31,32] In view of this, it could be suggested that the influence of the SC6CDNH2 microenvironment on the rotational barrier of the phenyl rings, on the excited state prototropic shift or on both could play a role in the blue shift observed. In our recent work on DF-β-CD complex we established that only the former is affected by complexation since both the hydroxyl and the carboxyl moietyes of DF are located virtually outside the cavity.[27] Nevertheless, we believe that in the present case the above photoinduced hydrogen shift could be influenced by SC6CDNH2 complexation owing to a reasonable electrostatic interaction between the carboxylate head of DF and the protonated amino groups of SC6CDNH2. With this in mind, a binding mode consistent with the hydrophilic groups of DF anchored to the positively charged external surface of the host and the neutral aromatic chromophore protruding towards the host interior and very close to the cyclodextrin cavity can be tentatively proposed. The spectral changes observed also in the lower energy absorption band (see Fig. 1), as well as the modification in the photoionisation pathways (see below), further support this proposal.

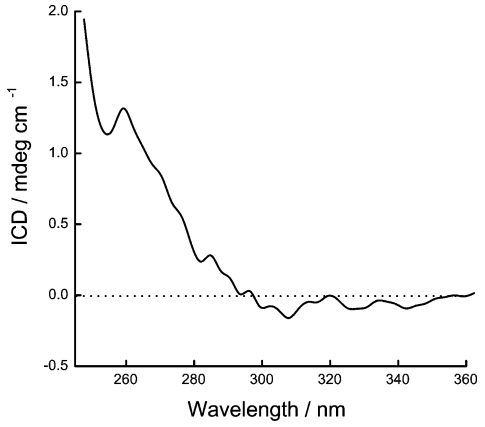


Fig. 2 ICD spectrum of 5×10^{-5} M DF observed in 10^{-2} M phosphate buffer solution, pH 7.4 in the presence of 0.25 mg ml^{-1} SC6CDNH2. Cell path 1 cm. The spectrum was recorded using a reference solution containing the same concentration of SC6CDNH2.

Laser flash photolysis studies

The transient spectra recorded upon 266 nm laser excitation in nitrogen-saturated solution containing DF (5×10^{-5} M) in the presence of SC6CDNH2 (0.25 mg ml^{-1}) were very similar to those observed in its absence, suggesting that no new DF transient species are generated besides those observed in aqueous solution. In fact, we monitored the typical band of the DF triplet centred at 380 nm, the broad absorption extending beyond 700 nm due to the hydrated electrons and the two bands at 340 and 540 nm of the phenoxy radical originating upon photoionisation.[23] Despite these spectral similarities, both kinetic behaviour and photogeneration efficiency of the transients were affected by the presence of the macrocycle. Fig. 4 shows the triplet decay observed in the presence and in the absence of SC6CDNH2. The kinetic trace obtained in the former case was well-fitted by a mono-exponential function with a rate constant of $k_{T(SC6CDNH2)} = 5.5 \times 10^4$ s^{-1}. Such a value is substantially smaller than that observed in aqueous medium [$k_{T(w)} = 1.6 \times 10^5$ s^{-1}],[23] ruling out a fast

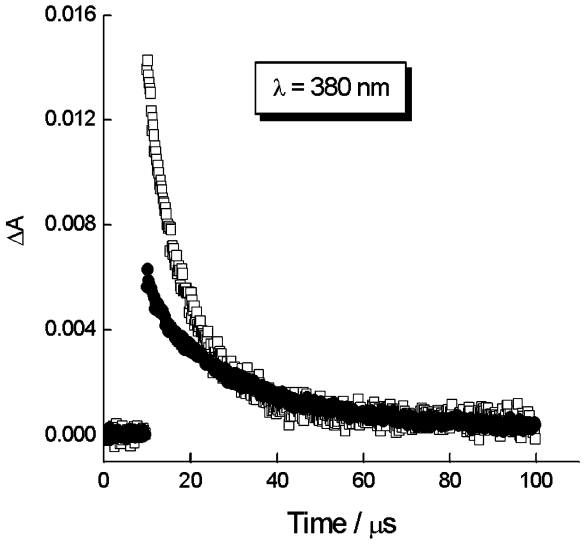


Fig. 4 Kinetic traces for the decay of the DF triplet state at 380 nm observed in an argon-saturated 5×10^{-5} M DF solution in 10^{-2} M phosphate buffer, pH 7.4 (□) in the absence and (●) in the presence of 0.25 mg ml^{-1} SC6CDNH2.

exit of the excited triplet state from the SC6CDNH2 structure. The lengthening of their decay is not uncommon for triplets upon incorporation in organised and constrained media such as micelles and cyclodextrins and is generally related to the protection exerted by the host cage against external quenching impurities and to a perturbation of the intersystem crossing (ISC) process to the ground state.[2,33] However, inhibition of triplet state-ground state interactions due to incorporation of only one molecule per SC6CDNH2 molecule can also be responsible for the behaviour observed. The above hypotheses agree with the lack of any effect on the triplet lifetime observed in organic solvents,[28] suggesting that the lengthening observed in our case is not correlated to changes of the local micropolarity.

Fig. 5 shows the triplet absorbance as a function of the laser intensity in the presence and in the absence of SC6CDNH2. The linearity observed agrees with monophotonic generation of the lowest triplet state of DF. Each slope is proportional to the product $\Phi_{ISC} \times \varepsilon_{T\text{-}T}$, where Φ_{ISC} and $\varepsilon_{T\text{-}T}$ are the ISC quantum yield and the absorption coefficient of the lowest excited triplet state of DF, either in the absence or in the presence of SC6CDNH2. Taking into account that the solutions are almost optically matched at the excitation wavelength (the difference in absorbtion by the two samples is less than 3%) and that a large change in $\varepsilon_{T\text{-}T}$ upon SC6CDNH2 complexation is fairly unlikely (no significant differences in the $\varepsilon_{T\text{-}T}$ of DF were in fact observed upon DF incorporation in either a CD cavity or micellar cage), the ratio of the slopes reported in Fig. 5 points to a *ca.* 50% reduction of the ISC quantum yield in the DF–SC6CDNH2 complex.

The modifications induced by SC6CDNH2 in the properties of the DF triplet state compare well with those noticed for other anti-inflammatory drugs included in β-cyclodextrin cavities[2] and are of important photobiological significance. Long-lived triplet states of several non-steroidal anti-inflammatory drugs are directly involved in bimolecular energy and electron transfer processes with oxygen and biomolecule components. These photoprocesses often generate noxious species such as singlet oxygen, superoxide anion, charged and neutral radicals, *etc.*, which are directly responsible for photoinduced disorders.[3] On the basis of the confinement of the DF triplet within the SC6CDNH2 network and the lower ISC yield, a decrease in the efficiency of some of these bimolecular reactions[20,21] is expected.

As mentioned in the introduction, DF photoionisation is not only the main photoprocess occurring upon light excitation but is also responsible for the stimulated DF defluorination through electron trapping. Fig. 6 shows the kinetic traces for hydrated electron decay in the presence and in the absence of SC6CDNH2. It shows that electron decay is faster in the former case [time constant $\tau_{eaq(SC6CDNH2)}$ *ca.* 380 ns compared with $\tau_{eaq(w)} = 890$ ns]. Although this finding could be attributed to additional quenching processes involving the participation of SC6CDNH2 itself, we believe that this might not be the case. It is well-known that hydrated electrons (i) are not expected to react at all with the cyclodextrin unit of the host[27] and (ii) are characterised by a reactivity with the cationic amino groups of the SC6CDNH2 periphery about three orders of magnitude smaller than that observed with the DF ground state in aqueous solution.[34] Rather, the faster electron capture observed in the presence of SC6CDNH2 seems to be

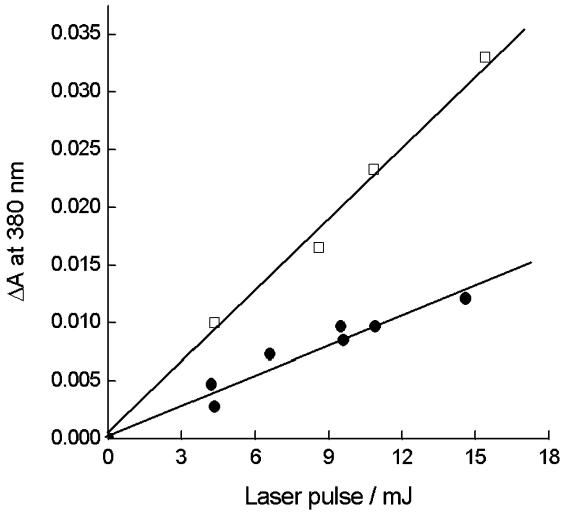


Fig. 5 Laser intensity dependence for the formation of the DF triplet state observed in an argon-saturated 5×10^{-5} M DF solution in 10^{-2} M phosphate buffer, pH 7.4 (□) in the absence and (●) in the presence of 0.25 mg ml^{-1} SC6CDNH2. ΔA taken 0.1 μs after the laser pulse. (No effect of laser power on the triplet lifetimes of the two samples was observed in the energy range explored).

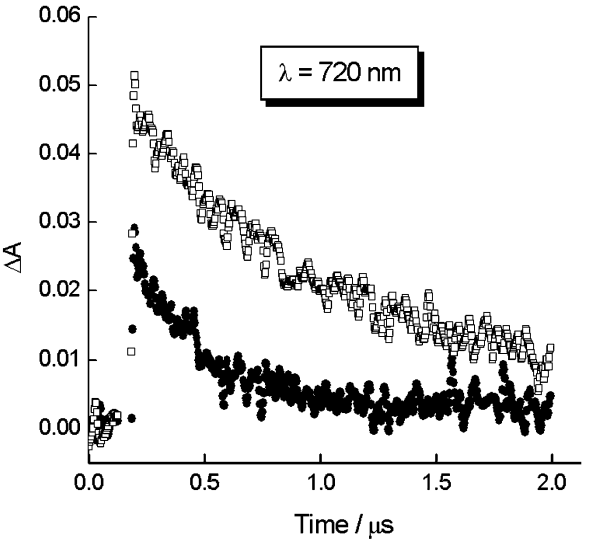


Fig. 6 Kinetic traces for the decay of the solvated electrons at 720 nm observed in an argon-saturated 5×10^{-5} M DF solution in 10^{-2} M phosphate buffer, pH 7.4 (□) in the absence and (●) in the presence of 0.25 mg ml^{-1} SC6CDNH2.

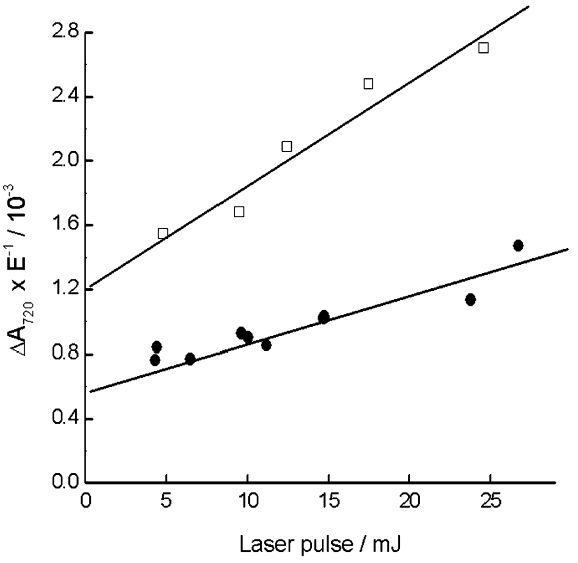


Fig. 7 Laser intensity dependence for the formation of solvated electrons observed in an argon-saturated 5×10^{-5} M DF solution in 10^{-2} M phosphate buffer, pH 7.4 (□) in the absence and (●) in the presence of 0.25 mg ml^{-1} SC6CDNH2. ΔA taken 0.05 μs after the laser pulse. (No effect of laser power on the hydrated electron lifetimes of the two samples was observed in the energy range explored).

gouverned by the typical scavenging mechanism that comes into play when solutes are incorporated into cationic micelles.[34,35] As proposed in such cases, hydrated electrons may undergo rapid trapping in the external cationic field such as that of SC6CDNH2 and subsequent reaction with the complexed DF.

To gain insight into the influence of the SC6CDNH2 microenvironment on the photoionisation process, we measured the laser power effect on the absorbance, monitored at 720 nm (maximum of the hydrated electrons)[36] in the presence and in the absence of SC6CDNH2. Even in this new environment photoionisation takes place through a mixture of mono- and biphotonic mechanisms, similarly to that already observed in aqueous medium.[23] As shown in Fig. 7, the experimental data fit well the following equation:

$$\Delta A/E = a + bE$$

where E is the laser intensity, a is a coefficient depending on the quantum yield of the one-photon process and b is a factor depending on the extinction coefficients and yields of the intermediate steps in the two-photon process.[37]

From the slopes and the intercepts of the linear plots it is straightforward to note that accommodation of DF in the SC6CDNH2 network leads to a 50% drop in both the biphotonic and monophotonic photoionisation efficiencies. However, it has to be emphasised that the one-photon pathway dominates under environmental conditions due to the low intensity of irradiation. In general, quantum yields for the one-photon photoionisation pathways involving phenol moieties are expected to be particularly sensitive to the surrounding environment and the structure of the solvent around the OH groups is known to play a dominant role. In particular, the formation of H-bonded supramolecular structures in which the OH binds two water molecules by acting as both H-donor and H-acceptor is believed to be the key step in determining the efficiency of the monophotonic yield.[38,39] Elegant studies performed by Monti *et al.* highlighted a reduction in the efficiency of the one-photon photoionisation pathway of some phenol derivatives when the hydroxyl groups are deeply incorporated within cyclodextrin cavities.[40] Likewise, reduction of the yield in our case may be due to hindered formation of the H-bond between water and the hydroxyl of DF, probably due to its incomplete exposure. This view is consistent with our proposal of electrostatic interaction between DF and the charged SC6CDNH2 surface (see above). This result notably differs from that observed when DF is incorporated in either β-cyclodextrin or neutral micelles. In those cases, no reduction in the monophotonic photoionisation yield was observed, in accordance with localisation of the hydroxyl group of DF outside the host cavity.[27,28]

Steady-state photolysis studies

When DF was irradiated in the presence of SC6CDNH2 in an argon-saturated water solution, the photochemical scenario was drastically changed compared to that in aqueous solution. HPLC-ESI-MS analysis of the irradiated mixtures performed within 25% conversion revealed, in fact, remarkable changes in both the efficiency and nature of the photochemical outcome. Fig. 8 shows the transformation percentage observed in the presence and in the absence of SC6CDNH2.

Since the amount of incident radiation was virtually the same in both cases (the difference was less than 3%), from the ratio of the slopes obtained one can readily notice that a *ca.* 4-fold reduction of photodegradation is achieved in the presence of SC6CDNH2. Furthermore, formation of the cross-combination product **1**, the main product in aqueous solution, was totally suppressed. This result, beyond its photochemical interest, is remarkable in view of the toxicity of **1** mentioned above.[20,21]

Plausible reasons for the enhanced photostability of the DF-SC6CDNH2 complex, as well as for the suppression of the persistent radical effects leading to product **1**, may lie in the peculiar role of SC6CDNH2 in (i) reducing the efficiency of the one-photon photoionisation pathway and (ii) providing a suitable microenvironment to efficiently trap the two radical intermediates involved in the cross-combination reaction. A simplified description of the probable processes is proposed in Scheme 2 and discussed below.

On the basis of the two-fold reduction of the monophotonic photoionisation route, which dominates under the low light intensity of the steady-state irradiation, a similar reduction of the DF photodegradation would have been expected. Surprisingly, the reduction in DF photodegradation was greater than that of monophotonic photoionisation. This apparent

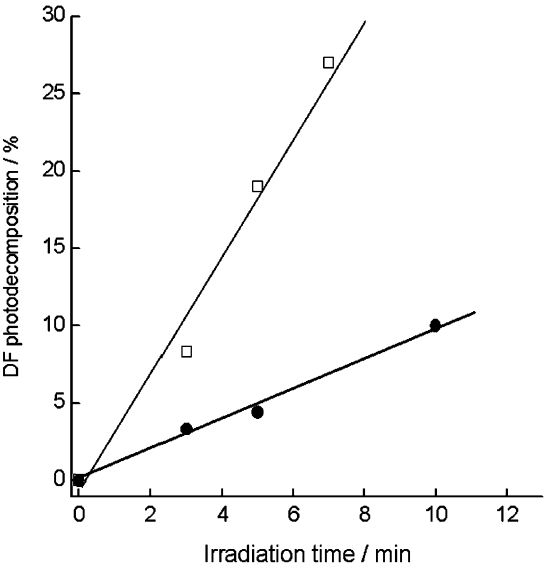
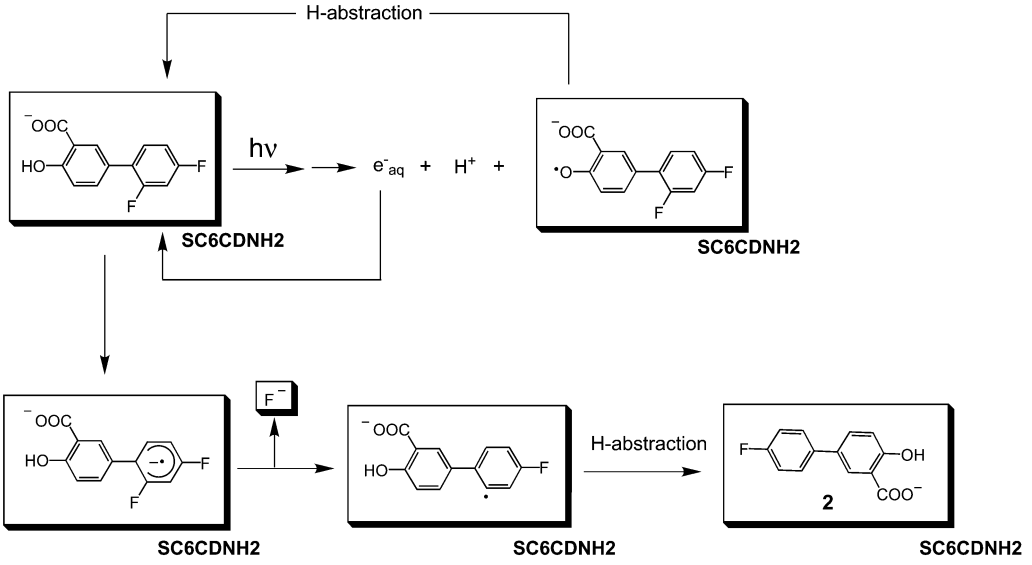


Fig. 8 Percent photodegradation of DF observed in an argon-saturated 5×10^{-5} M DF solution in 10^{-2} M phosphate buffer, pH 7.4 (□) in the absence and (●) in the presence of 0.25 mg ml^{-1} SC6CDNH2.



Scheme 2 Proposed photodegradation pathways of DF in neutral aqueous solution in the presence of SC6CDNH2.

discrepancy might be explained on the basis of a H-abstraction reaction of the phenoxy radical from the SC6CDNH2 structure. Indeed, such a process would lead back to the starting compound, accounting for the observed results. This hypothesis is supported by the fact that in view of the more hydrophobic character of the phenoxy radical compared to DF, it is reasonable to assume that it tends to remain within the host microenvironment. The low yield of the phenoxy radical observed in our case (data not shown), similarly to the DF-β-CD complex, is consistent with fast disappearance of this intermediate within the SC6CDNH2 network. Although phenoxy radicals are generally characterised by low reactivity for H-abstraction,[41] it is widely reported that they can become much more reactive in the presence of good hydrogen sources such as cyclodextrins, with 14 available hydrogen atoms bonded to secondary carbons and in close proximity to the radical center.[42–44]

The total inhibition of the cross-combination product **1** can also be related to an intermolecular reaction involving the σ-aryl radical generated upon defluorination. Given the high H-abstraction reactivity of this radical species,[45,46] it is expected to react promptly with SC6CDNH2 before exiting and to convert to the monofluorinated photoproduct **2**. Unfortunately, it was not possible to isolate such a stable product on a preparative scale nor to gain direct evidence for the σ-aryl radical, due its well-known optical transparency in the monitored wavelength range.[45,46] However, the appearance of one major peak at $m/z = 231$, in accordance with the structure of **2**, besides that of the starting compound ($m/z = 249$) in the LC-ESI-MS analysis of the irradiated mixture, is in agreement with the above proposal.

Conclusions

This study has provided the first example of how a new cationic amphiphilic cyclodextrin can influence significantly the photochemistry of a photosensitising drug. The triplet state of DF, playing an important role in the photosensitising side-reactions, is generated with lower efficiency and remains trapped within the SC6CDNH2 network. The photoreactivity of the associated guest is lowered and the product distribution is drastically modified. The photoproduct mainly responsible for the toxic effects is completely suppressed in the presence of SC6CDNH2. The two radical species generated upon photoexcitation, the phenoxy and σ-aryl radicals, remain confined within the SC6CDNH2 and are quenched through intermolecular H-abstraction The overall photobehaviour of DF in the SC6CDNH2 microenvironment seems gouverned by a synergism of effects due to the multifaceted role of SC6CDNH2 in influencing the primary photochemical events and secondary radical reactions of this drug. The overall results make this tailored cyclodextrin an interesting system for increasing drug photostability and minimising the biological damage. The results of *in vitro* photosensitisation experiments to elucidate this issue will be reported in due course.

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