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Research paper

Ultrafast photoinduced charge transfer character in ofloxacin singlet decay

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HIGHLIGHTS

- This study provides insights on the internal charge transfer, intersystem crossing, and triplet-triplet state absorption.
- Our study delves into the underlying mechanism of phototoxicity particularly through intramolecular charge transfer.
- The quantum yields of charge transfer and triplet-triplet state absorption are measured.

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ABSTRACT

The mechanism of intramolecular charge transfer (CT) and the following radiationless dynamics of ofloxacin pharmaceutical product were investigated using femtosecond absorption spectroscopy combined with quantum chemical calculations. The CT and the intersystem crossing (ISC) processes have been established to be the major relaxation pathways responsible for the ultrafast nonradiation of the excited S_1 state. The CT occurs within a time constant of ~1.4 ps. The following ISC is determined to be ~158 ps and triplet yield can be measured to keep ~0.33. Simultaneous, the quantum yields of CT and triplet-triplet state absorption are contributed to be 0.29 and 0.38, respectively.

1. Introduction

The fluoroquinolone antibiotics (FQs) are an important kind of antimicrobials whose potential clinical usefulness continues to expand [1–7], but they occasionally produce side effects such as acute dermatitis, which are usually confined to areas of the skin exposed to sunlight. S.H. Yun and S.J.J. Kwok pointed out that the exposure to the Sun's UV radiation is a major environmental risk factor for skin cancer, which afflicts more than 2 million people worldwide every year [8]. Primary acute and chronic lesions involving the photosensitized skin are erythema, edema, and pruritus, and, in more-severe cases, blistering and vesicles of the exposed parts [9]. These kind of skin alterations may deteriorate into cancer [10]. However, it remains unclarified for the phototoxic mechanism as the cause of abnormal photosensitivity and its relationship to chemical structure and essential photodeactivation. Many studies on the phototoxic properties of these fluoroquinolones have been reported in last decades. Moreover, relationship between the structure and side-effects of newly developed drugs has been evaluated. It is pointed out that absorbing maximally in the UV-A band around 320 nm, quinolones are phototoxic to mammalian cells in vitro and can elicit phototoxic reactions in human skin [11]. A typical example is that a kind of the quinolones like fleroxacin may be a potent mouse skin phototumorigen [11]. Based on experimental observations, researchers in different laboratories have further reported that lomefloxacin, ciprofloxacin and ofloxacin are also phototumorigenic in mouse skin [10]. The limited results suggest that the potential of ofloxacin and other quinolones to enhance phototumorigenesis deserves further investigation.

Fluoroquinolones can induce phototoxicity after irradiation, which limits their utilization in therapeutic applications [10,12,13]. A prime example is that ofloxacin inhibits the enzyme bacterial DNA gyrase and prevents replication of bacterial DNA during bacterial growth and reproduction. Moderate to severe photosensitivity/phototoxicity reactions, can be associated with the use of quinolones including ofloxacin after exposure to sun or UV light. For decades, there has been a considerable number of researches aiming at deep understanding both the unimolecular deactivation pathway of photoexcited pharmaceutical products and their photosensitizing capability in the presence of

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biological substrates [14,15]. Study suggests that sunlight exposure should be avoided by drug users especially during peak hours for their safety from photosensitivity. The understanding of the mechanism can enable clinicians to effectively guide patients regarding the safer use of photosensitive drugs during treatment.

In some FQs, the ππ* excited state is capable of some internal charge transfer caused by the existence of both an N electron-donating group and electron-withdrawing F substituent [16,17]. An electron-donating substituent inserted at the C-5 position of quinoline ring made the excited FQs return to their ground state via nonradiative pathways. There exist two important mechanisms for photosensitized biomolecule damage, including the oxidation of biomolecules through the generation of reactive oxygen species and the photoinduced electron transfer from biomolecules such as protein and DNA [14,18]. The electron transfer induced damage mechanism has proved to be crucial and ubiquitous [19,20]. It is revealed that the intramolecular photoinduced electron-transfer process can promote the biomimetic phospholipid membrane formation induced by the photochemical activation of a catalyst-sensitizer dyad [19]. The contribution of an electron transfer mechanism was clarified in human serum albumin damage [20]. Besides, the properties for electron transfer of antofloxacin and levofloxacin have been studied verifying the participation of the triplet states [16].

In this paper, we reported on a joint experimental and theoretical study of the excited-state dynamics of ofloxacin in solution after photoexcitation to the charge transfer electronic state. We employed femtosecond transient absorption spectroscopy to monitor the temporal evolution of the photoexcited ofloxacin in solution and elucidate unimolecular deactivation pathway, especially intramolecular charge transfer and the following ISC processes. The characteristic spectra bands were measured and analyzed in detail combined with quantum chemical calculations. The quantum yield and rate of intersystem crossing (ISC) are determined.

2. Experimental section

Ofloxacin (OFLX, 99% purity) was purchased from Sigma, and used without further purification. Water was used as a solvent. The concentration of ofloxacin in water was 1 mM at room temperature and a fresh sample was prepared for each measurement. The absorption spectra were recorded on the UV–VIS spectrometer (INESA, L6) in a 1 mm quartz cell. Ultrafast broadband absorption measurements were performed based on a Ti:sapphire femtosecond laser system. Details of the femtosecond laser system have been described elsewhere [21,22]. Briefly, the seed beam is generated by a commercial Ti:sapphire oscillator pumped by a CW second harmonic of an Nd:YVO_4 laser, and then amplified by an Nd:YLF pumped regenerative amplifier to generate a 1 kHz pulse train centered at 800 nm of approximately 35 fs pulse width and with maximum energy of 1 mJ/pulse. A fraction of the laser is frequency doubled in a 1 mm thick BBO crystal, yielding pulses at 400 nm with an energy of 100 μJ, which are used to pump the NOPA to produce the pump pulses at 330 nm. The pump pulse energy used here is attenuated to be about 2.5 μJ in experiments. The NOPA pulse needs to be temporally compressed in order to obtain the minimum pulse width compatible with their bandwidth. A white light continuum generated by focusing the fundamental light at 800 nm on a 1 mm sapphire plate is reflected from the front and back surfaces of a quartz plate to obtain the probe and reference beams. The pump and probe pulses intersect in the sample at an angle of ~4°, and the reference beam is transmitted through the sample at a different spot. The relative polarization of the pump and probe pulses is set to the magic angle for all the measurements. A linear translation stage is used to delay the probe beam to monitor the pump-probe dynamics. The resulting spectra are detected by a CCD camera (PI-MAX, 1024 × 256 pixel array) equipped with a spectrometer (Princeton, SpectraPro 2500i). The instrumental response function of the system, determined by cross correlation between the excitation and probe pulses using the optical Kerr-gate method, is typically better than 250 fs.

All quantum chemical calculations are performed using the Gaussian09W suit of program [23]. The geometries of the ground and excited states of ofloxacin are optimized using MP2 and B3LYP with 6-311G basis set in gas phase and aqueous solution, respectively. The initial geometrical parameters are used from the data performed by Bayari [24]. The stationary points are also confirmed by the vibrational frequencies analysis. The energies of excited states are performed using the B3LYP function based on optimized geometries of the ground and excited states, respectively. The B3LYP function provides accurate excited-state ordering, excited-state transition energies, oscillator strengths, transition dipole moments and singlet-triplet energy gaps, particularly when solvent effects are taken into account, which has been performed in other molecular systems. Solvent effects are expected to lead to large ground- and excited-state energy changes in heteroaromatic compounds [25,26]. Thus, the effect of the bulk solvent dielectric on the ground-state geometries and on the excited-state vertical energies was modeled by performing self-consistent reaction field (SCRF) calculations using the polarizable continuum model (PCM) with the integral equation formalism.

3. Results and discussion

3.1. Static absorption and transient absorption spectra

The static UV–VIS absorption spectrum of ofloxacin in aqueous solution was depicted in Fig. 1. The spectrum exhibits obviously several discrete absorption bands in UV region. The intense absorption maxima in UV-A and UV-B regions are located at 331 nm and 288 nm, respectively, which are similar with those reported before [27,28]. Navaratnam et al. also mentioned that the intensity or the absorption maximum of ofloxacin is independent on the change of solvents [27]. And the photodegradation of ofloxacin engenders under UV-A and UV-B irradiations [28]. It is noted that the first absorption band is located in the UV-A range and corresponds to the first excited S_1 state of molecules. Simultaneously, in our calculations, all results reveal that the lowest excited S_1 state originates a 96 ← 95 transition and has a large transition dipole moment. The 95 and 96 orbitals are the HOMO and LUMO, and belong to π and π* characters in the Franck-Condon region, respectively, as shown in Fig. 2. It has been also demonstrated that the bands in UV-A have molar absorption coefficients in the order of $1–3 \times 10^4\,M^{-1}\,cm^{-1}$ and could be assigned to fully allowed $\pi \rightarrow \pi^*$ transitions.

The pump wavelength was set to be 330 nm and coincides with the peak of the ππ* absorption band of the molecules. The transient

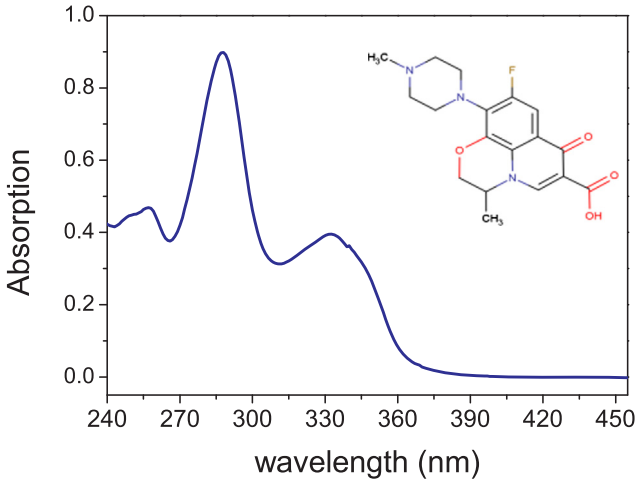

Fig. 1. Static absorption spectrum of ofloxacin in aqueous solution. The structure of ofloxacin was inserted in the figure.