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Photochemical transformation of flufenamic acid by artificial sunlight in aqueous solutions

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ABSTRACT

In the present article, we have studied the photochemical behavior of a common non-steroidal anti-inflammatory drug (NSAIDs) namely flufenamic acid (FLUA) in aqueous solution. The absorption spectrum of such compound shows a significant absorption beyond 290 nm and the photochemical irradiation within the range 300–450 nm leads to its complete transformation in roughly 6 h. The quantum yield of FLUA transformation measured at 290 and 310 nm was evaluated to about 1.1×10^{-4} without any significant effect of the excitation wavelength. The degradation process was inhibited in acidic solutions owing to the sharp increment in the absorption of FLUA in the wavelength region between 300 and 350 nm. The quantum yield was estimated to 1.2×10^{-4} at pH 7. The effect of oxygen on the photochemical behavior of FLUA has also been investigated. The obtained results clearly indicate that oxygen is not significantly involved in the photochemical degradation process. The phototransformation of the flufenamic acid appears to occur through one pathway that involves the photohydrolysis of trifluoromethyl group, and thus leads to the formation of one specific photoproduct, namely 2,3′-iminodibenzoic acid. This result was confirmed by the formation of the fluoride ions after irradiation during the irradiation of flufenamic acid. A mechanistic scheme for such transformation of flufenamic acid was proposed.

1. Introduction

Many pharmaceutical compounds used as human and veterinary drugs pass, at least in part, through sewage treatment plants (SWT) to end up in environmental natural waters. They are suspected to reach every environmental compartment. Indeed, it has been frequently reported that they have been detected in lakes, groundwater, and also in drinking water [1–5]. It has been largely reported that biodegradation and photodegradation are among major transformation processes influencing the fate of such pollutants in natural waters. However, Biological processes can induce a limited degree of transformation because of the biopersistence of many organic compounds as well as their generated byproducts that result from the incomplete biodegradation [6,7].

Since several pharmaceutical compounds are usually resistant to biodegradation, either direct or indirect photolysis may be considered as potential degradation routes of their transformation in surface waters [8]. Exposure to sunlight has already been confirmed as one of the most important way of their transformation in natural aquatic environments [9–11]. However, the photochemical transformation process efficiency in surface waters is dependent on various environmental factors such as the depth, turbidity, geographic latitude, season, weather and shadow [12].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs of diverse chemical composition and most often used in human and veterinary medicine, since they are available without prescription for treatment of fever and minor pains [13]. Many NSAIDs have been found or are expected to be present in the aquatic environment at significant concentrations [14–16]. In addition, this family compounds showed a remarkable reactivity toward the light. Indeed, they rapidly react under irradiation and can be largely eliminated from surface waters, owing to photolysis reactions. Direct photolysis by sunlight or artificial light constitutes the dominant degradation mechanism and the removal process for these products [17–20].

N-(α,α,α-trifluoro-*m*-tolyl) anthranilic acid known as flufenamic acid (FLUA) is a common non-steroidal anti-inflammatory

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drugs (NSAIDs) that belongs to the family of *N*-phenylanthranilic acid and resembles chemically to mefenamic and tolfenamic acids and other fenamates that are largely used in clinical issues [21]. flufenamic acid presents analgesic, anti-inflammatory and antipyretic properties and has been used in musculoskeletal as well as joint disorders [22].

FLUA is often found in the environment at significant concentrations [16]. The presence of mixtures of flufenamic and mefenamic acids in human urine samples in relatively important concentrations has also been demonstrated [23,24]. A very recent study also revealed the presence of flufenamic acid at considerable concentration, in rivers water [16]. Until now, however, there is very limited information concerning the photochemical behavior of flufenamic acid in aqueous solutions. In the present paper, we report results of its photochemical behavior from kinetic as well as analytical points of view. Our approach includes the selection of appropriate conditions in order to obtain the best results and to evaluate the effect of environmental parameters on the photolysis efficiency of flufenamic acid.

2. Materials and methods

2.1. Chemical and reagents

The "*N*-(α,α,α-trifluoro-*m*-tolyl) anthranilic acid" known as flufenamic acid (FLUA) was purchased from Fluka and used without any further purification. 2,3′-imino-dibenzoic acid was obtained from Alfa Chemistry as the purest grade available. Acetonitrile was purchased from Carlo Erba (HPLC grade). All solutions were prepared with deionized ultrapure water, which was purified with Milli-Q device (Millipore) and its purity was controlled by its resistivity (>18 MΩ cm). The measurements of pH were undertaken using a JENWAY 3310 pH-meter to ±0.01 pH unit and the ionic strength was not controlled during the irradiation experiments. The pH of the solutions was adjusted using dilute solutions of $HClO_4$ or NaOH.

Solutions were deoxygenated by nitrogen bubbling or oxygenated by oxygen bubbling for 30 min prior to irradiation at room temperature. For prolonged irradiations, the bubbling was maintained during the entire irradiation process.

2.2. Irradiation systems

For kinetic purposes, aqueous solutions were irradiated in a quartz cell (1 cm optical path length) using an arc Xenon lamp from OSRAM (XBO 1600 W/XL OFR). The emission of the lamp extends from 270 nm to 850 nm with a maximum at 650 nm. The entire system is equipped with a Schoeffel monochromator to select the appropriate wavelengths for monochromatic irradiations. Two different wavelengths were used: 290 nm and 310 nm. The bandwidth was set to 10 nm. The initial concentration of the solution was checked by HPLC analysis after oxygen or nitrogen bubbling. Potassium ferrioxalate was used as a chemical actinometer [25]. The light intensity was found equal to 1.5×10^{15} photons $cm^{-2}\,s^{-1}$ and 2.2×10^{15} photons $cm^{-2}\,s^{-1}$ at 290 nm and 310 nm respectively. By modifying the bandwidth modified the light intensity changes. For analyses purposes, excitations within the range 300–450 nm were performed. The irradiation device consists of a vertical Pyrex tube (20 mm internal diameter with a total volume of 100 mL) equipped with a water cooling jacket to limit thermal reactions. It is located along one of the focal axes of a cylindrical mirror with an elliptic base. A fluorescent lamp TLD15 W/05 emitting within the range 300–450 nm is located along the other focal axis. The distance between the lamp and the reactor was constant and equal to approximately 13 cm.

2.3. Analysis

The disappearance of FLUA and the formation of the byproducts were followed by HPLC technique that consists on a Waters 540HPLC chromatograph system equipped with a Waters 996 photodiode array detector. The chromatograms were extracted at 288 nm as detection wavelength. The separation of the solutions components was accomplished by using a reverse phase Nucleodur column (C18–5 μm; 250–4.6 mm). The flow rate was 1.0 mL/min and the injected volume was set to 50 μL. The elution was accomplished with water that was acidified with formic acid (0.1%) and acetonitrile using an isocratic program (60% water and 40% acetonitrile).

The quantum yield of FLUA disappearance was measured at 290 and 310 nm by using the following expression: Φ = number of decomposed molecules of pollutant/number of photons absorbed by pollutant.

LC/MS studies were carried out with Q-TOF-Micro/water 2699 from UBSTART center at the University Blaise Pascal. It is equipped with an electrospray ionization source (ESI) and a Waters photodiode array detector. Each single experiment permitted the simultaneous recording of both UV chromatogram at a preselected wavelength and an ESIMS full scan. Data acquisition and processing were performed by MassLynx NT 4.0 system.

The evolution of fluoride ions concentration as a function of irradiation time was obtained by ionic chromatography (IC) using a Dionex ICS-1500 equipped with an ionPac CG16 (analytical column 5 × 250 mm).

UV–vis spectra were recorded on a Cary 300 scan (Varian) spectrophotometer.

3. Results and discussion

3.1. Spectrophotometric study

The absorption spectrum of flufenamic acid at a concentration of 5.0×10^{-5} mol L^{-1} in aqueous solution and at pH of 5.6 exhibits a band with a maximum at 288 nm (ε_{288} = 19,400 $mol^{-1}\,L\,cm^{-1}$) and a shoulder at about 325 nm (ε_{325} = 8800 $mol^{-1}\,L\,cm^{-1}$). For acidic conditions, namely a pH 2.1, the absorption spectrum consisted of two well-defined bands at 283 nm (ε_{283} = 6500 $mol^{-1}\,L\,cm^{-1}$) and 345 nm (ε_{345} = 3650 $mol^{-1}\,L\,cm^{-1}$). It is worth noting that a significant absorption at λ > 300 nm is observed (Fig. 1), which indicates a significant overlaps with the emission spectrum of the solar radiation that reaches the biosphere.

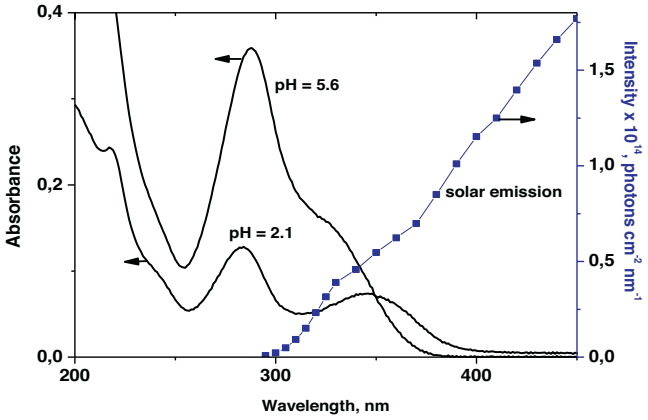

Fig. 1. Characteristic UV spectra of FLUA (2.0×10^{-5} mol L^{-1}) at pH 5.6 and pH 2.1 in aqueous solution compared to the solar emission spectrum.