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Hydroxyl radical induced degradation of ibuprofen

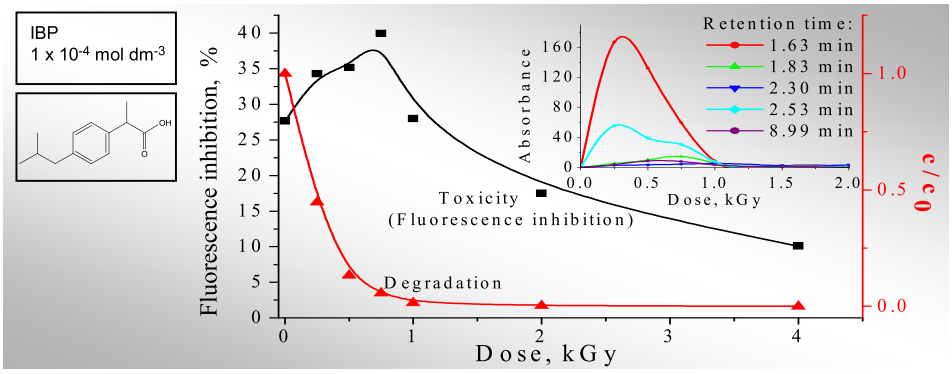
Erzsébet Illés [a,b,*], Erzsébet Takács [b], András Dombi [a], Krisztina Gajda-Schrantz [a,c,d], Gergely Rácz [b], Katalin Gonter [b], László Wojnárovits [b]

[a] Institute of Chemistry, Research Group of Environmental Chemistry, University of Szeged, Szeged, Hungary
[b] Institute of Isotopes, Centre for Energy Research, Hungarian Academy of Sciences, Budapest, Hungary
[c] Department of Inorganic and Analytical Chemistry, University of Szeged, Szeged, Hungary
[d] EMPA, Laboratory for High Performance Ceramics, Duebendorf, Switzerland

HIGHLIGHTS

- In hydroxyl radical attack on the ring mainly hydroxylated products form
- The hydrated electron attacks the carboxyl group.
- Oxidative conditions are more effective in ibuprofen decomposition than reductive.
- Ecotoxicity of ibuprofen solution first increases then decreases with irradiation.

GRAPHICAL ABSTRACT



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ABSTRACT

Pulse radiolysis experiments were used to characterize the intermediates formed from ibuprofen during electron beam irradiation in a solution of 0.1 mmol dm^{-3}. For end product characterization ^{60}Co γ-irradiation was used and the samples were evaluated either by taking their UV–vis spectra or by HPLC with UV or MS detection. The reactions of $^{\bullet}OH$ resulted in hydroxycyclohexadienyl type radical intermediates. The intermediates produced in further reactions hydroxylated the derivatives of ibuprofen as final products. The hydrated electron attacked the carboxyl group. Ibuprofen degradation is more efficient under oxidative conditions than under reductive conditions. The ecotoxicity of the solution was monitored by *Daphnia magna* standard microbiotest and *Vibrio fischeri* luminescent bacteria test. The toxic effect of the aerated ibuprofen solution first increased upon irradiation indicating a higher toxicity of the first degradation products, then decreased with increasing absorbed dose.

1. Introduction

Ibuprofen (IBP) ((*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid, $C_{13}H_{18}O_2$) is used for the relief of symptoms of arthritis, primary dysmenorrhoea, fever, and as an analgesic, especially to heal inflammatory disease(s). Ibuprofen is known to have an antiplatelet effect,

Abbreviations: UV–vis, ultraviolet–visible; HPLC, high-performance liquid chromatography; MS, mass spectrometry; IBP, ibuprofen; *EC50*, effective concentration for 50% luminescence reduction; AOP, advanced oxidation processes.

* Corresponding author at: Institute of Isotopes, Centre for Energy Research, Hungarian Academy of Sciences, Budapest, Hungary. Tel./fax: +36 62 544 338.
E-mail addresses: erzsebet.illes@chem.u-szeged.hu, illesbabo@yahoo.co.uk (E. Illés).

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though it is relatively mild and short-lived when compared to that of acetylsalicylic acid or other better known antiplatelet drugs. It is most often sold with trade names Nurofen, Advil and Motrin.

IBP is a moderately toxic compound, its −log *EC50* value (*EC50*, effective concentration for 50% luminescence reduction) according to the Microtox luminescent bacteria test is reported to be 3.85 (Escher et al., 2005). The solubility of IBP in water is limited to about 1×10^{-4} mol dm^{-3} (Zwiener and Frimmel, 2000).

IBP shows little absorbance in the wavelength region of the solar spectrum, its photodegradation in surface waters is limited and its biodegradation is also slow (Packer et al., 2003). IBP is regularly detected in the effluents of wastewater treatment plants and in surface waters at ng–μg dm^{-3} level. Although this concentration level is very low, IBP and its probably more harmful metabolites – together with other drugs – may present a potential hazard for human health and also for the aquatic ecosystem.

The potential application of several advanced oxidation processes (AOP) for the degradation of IBP in dilute aqueous solutions has already been studied, using electro-Fenton, UVA photoelectro-Fenton and solar photoelectro-Fenton (Méndez-Arriaga et al., 2008; Skoumal et al., 2009), as well as photocatalysis and sonophotocatalysis (Madhavan et al., 2010; Méndez-Arriaga et al., 2010), ozonation (Huber et al., 2003), radiolytic (Zheng et al., 2011) and Ferrate(VI) processes (Sharma and Mishra, 2006). In AOP's the degradation is due mainly to reactions with hydroxyl radical. Hydroxylated IBP molecules were detected among the first degradation products by using mass spectrometry. This hydroxylation was assumed to take place on the side chains in the tertiary positions, suggesting $^{\bullet}$OH attack on the side chains (Skoumal et al., 2009; Madhavan et al., 2010; Méndez-Arriaga et al., 2010; Zheng et al., 2011). This suggestion is in contradiction with the findings on many other substituted aromatic molecules, where the main target of radical attack was the aromatic ring (Illés et al., 2012).

For compounds with low biodegradability the photogenerated $^{\bullet}$OH in surface waters around the 10^{-14} mol dm^{-3} concentration level is suggested to play an important role in their degradation (Packer et al., 2003; Jones et al., 2009). Studies on the $^{\bullet}$OH + IBP reaction may help to understand the fate of the compound in the environment.

High energy ionizing radiation treatment is also regarded as AOP. Radiolytic studies on IBP were previously carried out by measuring end products (Zheng et al., 2011). Jones (2007) used pulse radiolysis to determine the rate coefficients of hydroxyl radical and hydrated electron reactions with IBP. In the present study the kinetics and mechanism of $^{\bullet}$OH reaction with IBP will be investigated by transient and final-product techniques. We use irradiation of aqueous systems as the cleanest source of hydroxyl radicals. These investigations in general may help to establish AOP technologies for IBP removal, and – more specifically – they can contribute to develop an irradiation technology for this purpose.

2. Experimental

IBP and the chemicals for pH setting were purchased from Spectrum-3D or Carlo Erba. In end product experiments the irradiation was carried out by using a ^{60}Co γ-irradiation facility with 5 kGy h^{-1} dose rate. The pH values were set by HCl and NaOH. These solutes at low concentration do not influence considerably the radiolytic reactions of organic molecules. All experiments were carried out at room temperature. The samples were evaluated either by taking their UV–vis spectra using a JASCO 550 UV–vis spectrophotometer with a 1 cm cell, or by HPLC separation. For chromatographic separation two different systems were used. The Agilent 1100 HPLC system consists of a C18 Kinetex 2.6 μm 100A, 100×4.6 mm, Phenomenex column where the elution was performed using a 50:50 mixture of 1% aqueous acetic acid solution and acetonitrile (flow rate of 0.9 cm^3 min^{-1}). Linear gradient elution was used on an Agilent 1200 system equipped with an XB-C18 Phenomenex Kinetex (100×2.1 mm, particle size 2.6 μm) capillary column coupled with on-line mass spectrometer. In this latter case, the flow rate was 0.3 cm^3 min^{-1} and the mobile phases were acetonitrile and 0.1% aqueous acetic acid with the gradient: 0 min 15%, 15 min 50%, and 18 min 50% acetonitrile. For detection and identification of the parent compound and the degradation products a diode array detector at 220 and 260 nm and a tandem mass spectrometer were used. Mass spectrometric experiments were performed in the negative ion mode using an Agilent 6410 triple quadrupole mass spectrometer equipped with an ESI source. The following MS parameters were used for identification: drying gas N_2 (350 °C, 10 dm^3 min^{-1}); nebulizer pressure with 1.7 bar, capillary voltage with 3500 V and fragmentor voltage with 80 V.

The toxicity tests of the target compound and the degradation products formed were carried out using *Vibrio fischeri* bacteria (Luminescent bacteria test LCK 480) according to the DIN/EN/ISO standard no. 11348-2 by a HACH-LANGE GmbH LUMIStox 300 apparatus. The pH of samples was set to 7. The inhibition of the light emission in the presence of the sample was determined against a non-toxic control solution. The second toxicity test was performed on *Daphnia magna* zooplankton (DAPHTOXKIT F™). This organism originates from the second tropic level. Standard microbiotests were applied according to the ISO standard no. 6341, 1996. TOXKIT tests were suited for toxicity of all chemicals in aquatic and terrestrial environment. The mortality of the species was followed during 48 h incubation with 4 dilutions of the treated IBP solutions.

Pulse radiolysis investigations were carried out using 800 ns pulses of accelerated electrons, and an optical detection system with a 1 cm cell pass-length (Földiák et al., 1988).

The pH values were adjusted at 4.4 and 8.5, respectively. At pH 4.4 the concentrations of protonated and deprotonated forms of IBP are equal (pK_a), at pH 8.5 we investigated the reaction of deprotonated form. The results obtained at pH 8.5 were rather similar to those obtained at pH 4.4. The results at pH 4.4 will be detailed in the following sections.

3. Results and discussion

3.1. Hydroxyl radical reactions

Hydroxyl radical ($^{\bullet}$OH, 0.28), hydrated electron (e_{aq}^-, 0.28) and hydrogen atom (H$^{\bullet}$, 0.06) are the main products of water radiolysis. All of them can be classified as "reactive intermediates". The values in brackets are the yields, the so-called *G*-values in μmol J^{-1} units (Spinks and Woods, 1990). Fig. 1 depicts the UV absorption spectra of 1×10^{-4} mol dm^{-3} N_2O saturated IBP solutions before and after irradiation. When the solution is saturated with N_2O, the transformation

$$e_{aq}^- + N_2O + H_2O \rightarrow {}^{\bullet}OH + OH^- + N_2 \quad (1)$$

yields also OH radicals, the reacting radicals and their yields are: hydroxyl radical 0.56 μmol J^{-1}, hydrogen atom 0.06 μmol J^{-1}.

The intensity of the characteristic aromatic absorption band in the UV spectrum of IBP in the 250–300 nm region is very weak (Fig. 1). When the solution is irradiated with a dose of 0.25 kGy, the intensity of the band around 265 nm becomes higher, indicating the formation of changed aromatic molecules. In the radiolysis of many aromatic molecules hydroxylation was observed at the beginning of the transformations. This hydroxylation may take place in the side chains (Zheng et al., 2011) and also in the ring. Substitution in the side chain does not change the absorption spectrum at ~265 nm. A simple hydroxylation in the ring of IBP can result in two isomers. As the inset shows, a dose of 0.25 kGy results in transformation of more than 60% of the initial molecules to new molecules. The secondary degradation of the primary products may have already started. (The *G*-values of