



Examination of the kinetics of degradation of the antineoplastic drug 5-fluorouracil by chlorine and bromine



Wei Li^{a,b,*}, Jessica Tanumihardja^c, Takaaki Masuyama^d, Gregory Korshin^c

^a College of Forest Resources and Environment, Nanjing Forestry University, Longpan Road 159, Nanjing 210037, China

^b Key Laboratory of Pollution Processes and Environmental Criteria (Nankai University), Ministry of Education, Tianjin 300071, China

^c Department of Civil and Environmental Engineering, University of Washington, Box 352700, Seattle, WA 98195-2700, United States

^d Water Environment Laboratory, Department of Civil and Environmental Engineering, Tokyo Institute of Technology, Ookayama 2-12-1-M1-4, Tokyo 152-8552, Japan

HIGHLIGHTS

- The antineoplastic drug 5FU interacts readily with free chlorine and bromine.
- The highest rate of 5FU degradation takes place at ca. pH 7.
- 5FU bromination proceeds much faster than its chlorination.
- An intermediate 5FU species is generated during halogenation.
- Half-times of 5FU in conditions typical for water treatment were estimated.

ARTICLE INFO

Article history:

Received 13 December 2013

Received in revised form 5 May 2014

Accepted 29 May 2014

Available online 6 June 2014

Keywords:

5-Fluorouracil

Chlorination

Bromination

Kinetics

Degradation pathway

ABSTRACT

This study examined the degradation of the widely used antineoplastic drug 5-fluorouracil (5FU) by chlorine and bromine. 5FU was determined to interact readily with free chlorine and bromine but was stable in the presence of chloramine. The removal of 5FU followed a second-order kinetic pattern. Apparent rates (k_{app}) of 5FU removal by chlorine and bromine were strongly pH dependent and had maximum $14.8 \text{ M}^{-1} \text{ s}^{-1}$ and $1.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ k_{app} values, respectively at pH 7. Modeling of the dependence of the k_{app} values vs. pH indicated the presence of a relatively acidic (pK 6.4 vs. 8.5 of 5FU per se) 5FU intermediate generated in the presence of halogen species. Spectrophotometric measurements confirmed the increased acidity of 5FU chlorination products and allowed proposing a degradation pathway of 5FU by chlorine. This pathway suggests that 5FU chlorination proceeds via chlorine incorporation at the 6th carbon in the heterocyclic ring of 5FU.

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1. Introduction

Residuals of pharmaceuticals were first detected in the aquatic environment in the 1970-ties [1]. Considerable effort has been made since then to ascertain the occurrence, fate and ecotoxicity of diverse pharmaceuticals and personal care products in the environment [2,3]. These studies have been focused on antibiotics, steroid hormones, anticonvulsants and other commonly used prescription and over-the-counter pharmaceuticals as well on the broadly defined group of endocrine disrupting compounds (which include compounds other than pharmaceuticals, for instance bisphenol A

and synthetic musks). Among these contaminants, the occurrence and potential environment effects of anticancer (otherwise referred to as antineoplastic or chemotherapeutic) drugs have recently attracted considerable attention due to their intrinsically high toxicity and, in many cases, resistance to biodegradation [4]. Although in terms of mass fluxes their environmental loads are not as high as those of the commonly used pharmaceuticals, varying level of antineoplastic drugs, for instance 5-fluorouracil (5FU, its empirical formula and molecular mass are $\text{C}_4\text{H}_3\text{FN}_2\text{O}_2$ and 130.08 g/mol, respectively), cyclophosphamide, ifosfamide and others have been consistently observed in hospital effluents, municipal wastewater and affected surface waters [5–9].

5FU is one of the most widely administered anticancer drugs. It is classified as an antimetabolite that hinders cell growth through the inhibition of thymidilate synthetase, driving the biosynthesis

* Corresponding author. Tel.: +86 13512513085.

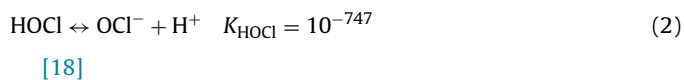
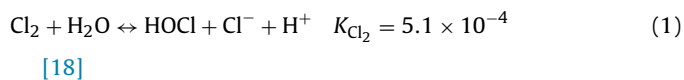
E-mail addresses: uwliwei@gmail.com, uwliwei@163.com (W. Li).

of deoxythymidine monophosphate, thereby obstructing thymidine synthesis and blocking normal DNA replication [10,11]. 5FU is administered by injection, infusion, orally or dermally, both in- and out-patiently. Research has shown that 60–90% of the taken 5FU is metabolized and then excreted, while the remaining 10–30% is excreted as the parent form that enters hospital or municipal wastewater [11].

Data on the actual concentration of 5FU in the aquatic environment are limited, mainly because of complexity of relevant analytical determinations and lack of consistent monitoring for cytostatic agents [12]. Rowney et al. [13] used data on the consumption of anticancer drugs, their excretion and fate and predicted that concentrations of commonly used anticancer drugs, including 5FU in treated sewage effluent could be as high as ca. 18 ng/L. While the observed or predicted concentrations of antineoplastic drugs in wastewater or surface waters tend to be relatively low, their use, especially in outpatient conditions is increasing rapidly. This in combination of the inherent resistance of such drug to degradation causes their environmental concentration to increase [14].

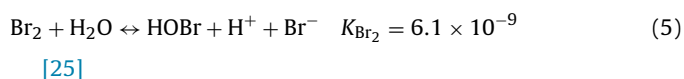
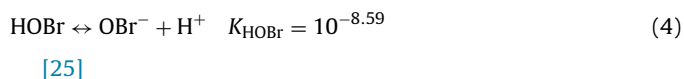
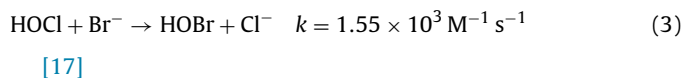
Anticancer drugs and/or their metabolites have complex carcinogenic, teratogenic and mutagenic effects. Several studies have examined the ecotoxicity of selected chemotherapeutic drugs [15,16]. Among several examined antineoplastic agents, 5FU was determined to have the highest acute toxicity to an indicator organism (*Pseudomonas putida*), with a 27–44 µg/L value of the EC₅₀. These results appear to show that while the currently reported environmental levels of 5FU are unlikely to cause acute toxicity to affected organisms, chronic exposures to low 5FU concentrations may still result in severe harm to exposed organisms. It is therefore necessary to develop efficient treatment methods to degrade 5FU and other anticancer drugs and to get more information about the nature of transformations of these drugs in water treatment processes.

Chlorination has been widely used in water treatment [17] due to the low cost and high disinfection efficiency of chlorine. Chlorine gas dissolved readily in water to form hypochlorous acid which dissociates to form OCl⁻ ion:



As chlorination is carried out at varying pHs, several species of chlorine (HOCl, OCl⁻, Cl₂, etc.) that have significant differences in their reactivity with microorganisms and micro pollutants will be present in the solution [19,20].

In addition to the species of active chlorine, effects of bromine-containing species need to be accounted because they tend to react faster with many organic species than their chlorine-containing analogues [21–23]. Bromide ion (Br⁻) occurs at widely varying concentrations in surface waters and wastewaters [17,23,24]. It is oxidized readily by HOCl to form hypobromous acid HOBr and associated compounds such as OBr⁻ and Br₂:



In this paper, we examine the kinetics and selected aspects of mechanisms of interactions of these halogen species with the typical anticancer drug 5FU whose presence, as was discussed above,

has been documented for a wide range of environmental conditions. The purposes of this paper are: (1) to study the reaction kinetics of 5FU by chlorination and bromination; (2) to model experimental kinetics data and determine major features of the reaction mechanism; (3) to evaluate the degradability of 5FU in water treatment operations employing disinfection by chlorine.

2. Materials and methods

2.1. Reagents

5FU (>99% purity) was purchased in powder form from Sigma Aldrich. Its structure and selected physico-chemical properties are shown in Table 1. All other reagents were of analytical grade. Hydrochloric acid (HCl) and sodium hypochloride (NaOCl) solution with 5% available chlorine were obtained from J.T. Baker. Potassium bromide (KBr), sodium thiosulfate (Na₂S₂O₃), and sodium hydroxide (NaOH) were purchased from Fisher Scientific. Sodium phosphate monobasic dihydrate and sodium phosphate dibasic anhydrous were used as buffers and purchased from J.T. Baker and Mallinckrodt, respectively. DPD free chlorine reagent for total chlorine measurement was purchased from HACH. All the working solutions were made fresh before experiments using Milli-Q (Millipore) water.

2.2. Halogenation experiments

Halogenation experiments were carried out in 250 mL flasks containing 200 mL 5FU solution. Chlorine stock solution was prepared by diluting 5% sodium hypochlorite solution. Chlorine concentration in the stock solution was measured using a HACH DR4000 spectrophotometer in accord with the method 8167 (HR) [26].

Chlorine in concentrations equivalent to Cl₂/5FU molar ratios ranging from 1 to 46 was injected into a continuously mixed 5FU solution. After a predetermined contact time, solution aliquots were withdrawn and quenched with Na₂SO₃ to stop the reaction. The concentration of 5FU in the quenched solution was measured as described below. 0.03 mol/L phosphate buffer was added to 5FU solutions to ensure their pH stability. The pH was adjusted as desired using 1 mol/L NaOH or HCl solution. Measurements of pH during the course of reaction showed that pH changes were within 0.1 unit from the initial value.

Experiments to examine 5FU bromination were carried out using a 1.54 µmol/L 5FU concentration and a 5.5 Cl₂/5FU molar ratio. The solutions also contained 8.5 µmol/L potassium bromide (KBr). Upon the injection of chlorine, the bromide was virtually instantaneously converted to free bromine including HOBr, OBr⁻ and Br₂. Reactions of bromine species with 5FU were examined at the ambient temperature (25 °C) for pHs below 5.8 and above 8.0. In the range of pH from 4.5 to 8, the degradation of 5FU was measured at 2 °C. Because in the pH range 5.8 to 8 the bromination of 5FU was too fast to be measured at ambient temperature, measurements at varying temperatures were carried at pH <5.8 to establish the corresponding temperature correction factor which was used to project results of 5FU bromination at the low temperature to ambient conditions. Other details of 5FU bromination experiments were identical to those used in the case of chlorination.

2.3. Spectrophotometric determination of 5FU

5FU concentrations were determined using a spectrophotometric approach. Absorbance spectra of standard and working solutions of 5FU at varying pHs were acquired using a Perkin Elmer Lambda 18 spectrophotometer using 1 cm quartz cells. The spectra of 5FU standard solutions with concentrations

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