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Effect of radical peroxide promoters on the photodegradation of cytarabine antineoplastic in water

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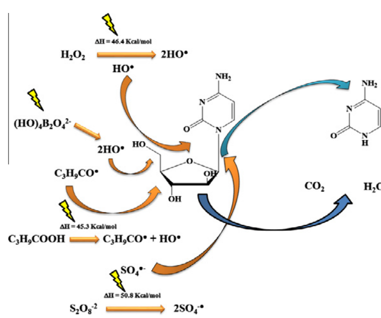
HIGHLIGHTS

- UV radiation is not effective to degrade cytarabine at both acidic and neutral pHs.
- Cytarabine degradation was more effective with the UV/$S_2O_8^{2-}$ process.
- ΔH values were +46.4 for $H_2O_2 \rightarrow 2HO^{\cdot}$ and +50.8 kcal mol^{-1} for $S_2O_8^{2-} \rightarrow 2SO_4^{\cdot}$.
- Cytosine was the main degradation byproduct detected with all processes studied.
- The influence of radical promoters, pH, type of water, and anions was studied.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to investigate the degradation of cytarabine antineoplastic in water using hydroxyl, sulfate, and *t*-butoxyl radicals produced by the photoactivation of hydrogen peroxide, persulfate, perborate, and *t*-butyl hydroperoxide, and to evaluate the effect of the groups adjacent to the peroxo-bond (–O–O–) of these compounds on the formation energy of radical species, using second-order Møller–Plesset perturbation theory (MP2) calculations. Analyses were also conducted on the effect of operational variables (initial cytarabine concentration, pH, radical promoter concentration, chemical composition of water, presence of radical scavengers, and natural waters) on cytarabine degradation and the total organic carbon concentration. Cytarabine photodegradation was more effective in the presence of $S_2O_8^{2-}$, followed by H_2O_2, $(HO)_4B_2O_4^{2-}$, and C_3H_9COOH, obtaining degradation percentages of 96%, 81%, 65%, and 48%, respectively, at 120 min of treatment. These results are explained, in part, because the UV/$S_2O_8^{2-}$ system was the least affected by the presence of radical scavengers and was therefore the most effective system for cytarabine removal from surface and wastewater. The main degradation byproduct was cytosine.

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1. Introduction

The amount of pharmaceuticals (human and veterinary medicinal compounds) in waters is still relatively low, but their continuous inflow may pose a long-term risk for aquatic and terrestrial organisms [1]. Antineoplastics, designed to destroy excessively

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proliferating cells such as carcinogenic cells, may have mutagenic and genotoxic effects and must be removed from wastewaters to avoid damage to humans and the environment [2]. According to Kümmerer et al. [2] antineoplastics are not biodegraded in water treatments and may persist in sewage sludge.

Various treatments have been applied to remove antineoplastics from aqueous media. Kiffmeyer et al. [3] studied the biological degradation of a mixture of five cytostatics (cisplatin, cyclophosphamide, cytarabine, 5-fluorouracil and methotrexate) in a laboratory-scale activated sludge plant and reported that cisplatin and cyclophosphamide were not biodegradable and only 60 ± 8% of the initial concentration of cytarabine (51.4 μM) was degraded after 14 days, whereas 5-fluorouracil and methotrexate were degraded almost completely in 6 days. In contrast, Pérez-Rey et al. [4] achieved the total degradation of the antineoplastics 5-fluorouracil, cytarabine, azathioprine, and methotrexate after 60 min of treatment with ozone at pH 3; moreover, Ames test results demonstrated that the degradation byproducts were not mutagenic.

Technologies based on advanced oxidation processes have proven highly effective to degrade pharmaceutical compounds in aqueous solution [5]. They are based on the generation of species with high oxidizing power (e.g., $HO^{\cdot}$ radicals) that interact with the pollutant and degrade it into byproducts with lower molecular weight, even achieving its complete mineralization. In a previous study [6], we investigated the degradation of cytarabine with UV radiation (UV, UV/H_2O_2, and $UV/K_2S_2O_8$) and found that the addition of H_2O_2 or $K_2S_2O_8$ considerably increased the degradation effectiveness through the generation of $HO^{\cdot}$ and $SO_4^{\cdot-}$ radicals. The rate constants of the reactions between cytarabine and the $HO^{\cdot}$ and $SO_4^{\cdot-}$ radicals were $k_{HO}^{\cdot}cyt = 3.15 \times 10^{10}\ M^{-1}\ s^{-1}$ and $k_{SO_4^{\cdot-}cyt} = 1.61 \times 10^{9}\ M^{-1}\ s^{-1}$. Furthermore, toxicity studies of the $UV/S_2O_8^{2-}$ system showed no formation of degradation byproducts with higher toxicity than cytarabine. Cytarabine degradation by oxidative and reductive radical species was also investigated by using gamma irradiation [7], showing an initial radiation-chemical yield ranging from 0.033 to 0.94 μmol J^{-1}.

Various authors [6,8–14] have compared the degradation of organic compounds by $HO^{\cdot}$ and $SO_4^{\cdot-}$ radicals, most frequently finding that the utilization of $SO_4^{\cdot-}$ radicals achieved: (i) faster degradation kinetics, (ii) greater degradation percentages, (iii) higher mineralization percentages, and (iv) lower toxicity of degradation byproducts. These findings have mainly been attributed to: (a) the generation of both $SO_4^{\cdot-}$ and $HO^{\cdot}$ radicals from the photochemical activation of $S_2O_8^{2-}$, (b) the higher radical quantum yield for UV-254 nm/$S_2O_8^{2-}$ (1.8) *versus* UV-254 nm/H_2O_2 (1.0), (c) the almost 10-fold slower recombination rate of $SO_4^{\cdot-}$ radicals ($k_{SO4}^{\cdot} = 4 \times 10^{8}\ M^{-1}\ s^{-1}$) in comparison to $HO^{\cdot}$ radicals ($k_{OH}^{\cdot} = 5.5 \times 10^{9}\ M^{-1}\ s^{-1}$), and (d) the greater selectivity of $SO_4^{\cdot-}$ radicals to degrade the organic compounds. However, the effect of the substituent groups adjacent to the peroxo-bond (–O–O–) of the radical generators, which can have a direct influence on the energy required to break this bond, has not yet been evaluated.

The main objective of this study was therefore to investigate the degradation of cytarabine by means of hydroxyl and sulfate radicals from the photoactivation of hydrogen peroxide, persulfate, perborate and *t*-butyl hydroperoxide, and to evaluate the effect of the substituent groups on the formation energy of each radical species, based on MP2 calculations. Analyses were also conducted on the effect of operational variables (initial cytarabine concentration, pH, radical promoter concentration, chemical composition of water, presence of radical scavengers, and natural waters), on cytarabine degradation and the time course of total organic carbon concentration.

2. Experimental

2.1. Reagents

All reagents used in the present study (cytarabine, hydrogen peroxide, potassium peroxodisulfate, sodium perborate, *t*-butyl hydroperoxide, sodium hydroxide, methanol, *t*-butanol, sodium bromide, sodium carbonate, sodium chloride, sodium nitrate, and sodium nitrite) were supplied by Sigma–Aldrich. Fig. S1, in Supporting information, displays the molecular structure of the four radical promoters used in this work and Fig. S2 illustrates the speciation diagram of cytarabine as a function of solution pH [15]. Ultrapure water was obtained by using Milli-Q® equipment (Millipore).

2.2. Experimental system

Cytarabine degradation experiments were conducted in a photoreactor formed of concentric tubes: a stainless steel outer tube (13 cm inner diameter and 30 cm height) and quartz inner tube (5.5 cm inner diameter and 45 cm height). The inner tube contained a medium-pressure mercury lamp (150 W) emitting radiation in a wavelength range of 238–334 nm, and the space between the lamp and inner wall of the tube contained a sample holder with capacity for 6 quartz reaction tubes (1.5 cm diameter and 20 cm height). Solutions in reaction tubes were maintained at constant temperature by using a Frigiterm Ultrathermostat and were maintained in agitation by means of a magnetic agitation system.

2.3. Cytarabine photodegradation

Experimental cytarabine photodegradation data were obtained as follows: a concentrated (411 μM) cytarabine solution was prepared by adding 0.1 g of cytarabine to a 1 L volumetric flask and filling with ultrapure water. An aliquot (27 mL) of ultrapure water was placed in the reaction tubes, and an aliquot (3 mL) of concentrated cytarabine solution was added to obtain a total volume of 30 mL at the desired initial concentration (41.1 μM). The desired pH is achieved by addition of 0.1 N HCl or NaOH solutions as necessary. Different amounts of radical promoters (hydrogen peroxide, persulfate, perborate, and *t*-butyl hydroperoxide) were added to reach the selected concentrations. Cytarabine degradation kinetics were monitored by drawing 1 mL samples at regular time intervals (5, 10, 20, 30, 45, 60, 90, 120 min) to measure the concentrations of cytarabine, the total organic carbon, and the degradation byproducts.

The exposure of hydrogen peroxide, peroxodisulfate, perborate, and *t*-butyl hydroperoxide to UV light gives rise to highly active species, including hydroxyl, sulfate, and *t*-butoxyl radicals. These species possess a high potency to oxidize organic compounds. The capacity of these species to degrade cytarabine was evaluated in experiments using different initial concentrations (100, 500, 1000 and 10,000 μM) of promoters of these radicals and an initial cytarabine concentration of 41.1 μM.

The participation of $HO^{\cdot}$ radicals in the degradation of cytarabine by the $UV/S_2O_8^{2-}$, $UV/(HO)_4B_2O_4^{2-}$, and UV/C_3H_9COOH systems was evaluated by conducting experiments in presence of 100 μM of *t*-butanol.

Cytarabine photodegradation was carried out in the presence of anions commonly found in natural waters (Cl^-, CO_3^{2-}, NO_3^-, NO_2^-, and Br^-), adding the appropriate amount of precursor salt to obtain an initial anion concentration of 10 mg L^{-1} which has an equivalence of 282, 167, 161, 217 and 125 μM, respectively.

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