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# Aqueous chlorination of carbamazepine: Kinetic study and transformation product identification

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ARTICLE INFO

*Article history:*
Received 5 October 2012
Received in revised form
22 May 2013
Accepted 25 May 2013
Available online 15 June 2013

*Keywords:*
Pharmaceuticals
Carbamazepine
Chlorination
Kinetic
Transformation products
LC-MS

ABSTRACT

Carbamazepine reactivity and fate during chlorination was investigated in this study. From a kinetic standpoint, a third-order reaction (first-order relative to the CBZ concentration and second-order relative to the free chlorine concentration) was observed at neutral and slightly acidic pH, whereas a second-order reaction (first order relative to the CBZ concentration and first order relative to the free chlorine concentration) was noted under alkaline conditions. In order to gain insight into the observed pH-dependence of the reaction order, elementary reactions (i.e. reactions of $Cl_2$, $Cl_2O$, HOCl with CBZ and of $ClO^-$ with CBZ or of HOCl with the ionized form of CBZ) were highlighted and second order rate constants of each of them were calculated. Close correlations between the experimental and modeled values were obtained under these conditions. $Cl_2$ and $Cl_2O$ were the main chlorination agents at neutral and acidic pH. These results indicate that, for a 1 mg/L free chlorine concentration and 1–10 mg/L chloride concentration at pH 7, halflives about 52–69 days can be expected. A low reactivity of chlorine with CBZ could thus occur under the chlorination steps used during water treatment. From a mechanistic viewpoint, several transformation products were observed during carbamazepine chlorination. As previously described for the chlorination of polynuclear aromatic or unsaturated compounds, we proposed monohydroxylated, epoxide, diols or chlorinated alcohol derivatives of CBZ for the chemical structures of these degradation products. Most of these compounds seem to accumulate in solution in the presence of excess chlorine.



## 1. Introduction

Micropollutants are of great concern because of their potential impact on aquatic environmental systems. Pharmaceuticals are emerging micropollutants that have attracted considerable attention in recent years. A substantial variety of these compounds (e.g. antibiotics, analgesics, anti-inflammatories, antiepileptics, hypnotics) has been reported in aquatic systems in many countries worldwide (Halling-Sorensen et al., 1998; Ternes, 1998; Stumpf et al., 1999; Zuccato et al., 2000; Zwiener and Frimmel, 2000; Heberer, 2002; Wiegel et al., 2004; Boyd et al., 2005; Mompelat et al., 2008). This pollution

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0043-1354/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.watres.2013.05.047

mainly results from drug metabolite excretion by humans and animals, while emissions from pharmaceutical production sites, surplus household drugs or effluents from fish farms have also been reported (Halling-Sorensen et al., 1998; Zuccato et al., 2000). These compounds collected in wastewaters are subjected to different treatment processes. However, as many of them are only partially removed in classical municipal sewage systems, they are commonly released into effluents and surface waters (Mompelat et al., 2008). Traces of pharmaceuticals are consequently often detected in aquatic environments. In surface water, concentrations typically in the nanogram to microgram per liter range have been detected (Heberer, 2002; Paffoni et al., 2006; Togola and Budzinski, 2008). Although the concentrations are usually low, these biologically active molecules may still affect aquatic organisms (especially upon long-term exposure). Moreover, there may also be additive effects with other micropollutants. Surface water is a drinking water source in many areas and could be a common route by which humans are exposed to pharmaceuticals. Water treatment processes should thus be assessed relative to their drug removal potential. It is essential to focus on the pharmaceutical fate during chlorination or ozonation since many transformation products can be formed during disinfection steps.

Carbamazepine (CBZ) is a dibenzazepine derivative (Fig. 1) with antiepileptic and psychotropic activities. This compound has been detected in municipal STP effluents and domestic wastewaters (Ternes, 1998; Seiler et al., 1999). Based on recently published $EC_{50}$ values, CBZ is considered to be non-toxic ($EC_{50} \geq 100$ mg/L) for most tested fish species, whereas it is likely very toxic ($EC_{50} < 1$ mg/L) for bacteria, algae and most tested invertebrate species (Halling Sorensen, 2000; Cleuvers, 2003; Ferrari et al., 2003; Hernando et al., 2006). The environmental impact of carbamazepine could consequently increase due to its low sorption properties and high resistance to biodegradation (Ternes et al., 2002). It is one of the most frequently detected pharmaceuticals in drinking water systems in Europe and USA, according to recent studies (Heberer et al., 2004; Stackelberg et al., 2004, 2007; Mompelat et al., 2008; Togola and Budzinski, 2008). In conventional drinking water treatment systems (clarification, filtration, chlorine disinfection), 85% carbamazepine removal was reported by Stackelberg et al. (2007). Rapid ozone removal of carbamazepine, with a second order rate constant of $7.10^5\ M^{-1}\ s^{-1}$ at pH 7 and 20 °C, has been noted during disinfection steps (Huber et al., 2003). Moreover, several oxidation products that are less reactive with ozone have been identified (McDowell et al., 2005). Concerning chlorination, a second order rate constant of $<0.1\ M^{-1}\ s^{-1}$ was estimated by Lee and von Gunten (2010) at pH 8, while carbamazepine was found to be highly persistent in chlorinated water by Gibs et al. (2007). From a mechanistic standpoint, in a recent study on oxcarbazepine, a keto analogue of carbamazepine, several transformation products were detected during chlorination and a transformation pathway was proposed (Li et al., 2011).

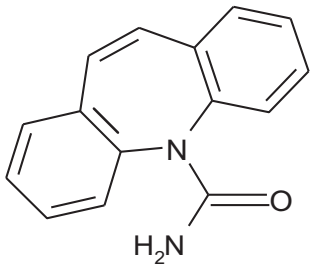


**Fig. 1 – Chemical structure of carbamazepine (CBZ).**

The present study was designed to assess carbamazepine reactivity and fate during chlorination steps. In the first part, kinetic studies were undertaken in pure aqueous solution at different pH levels. The reaction rate order and apparent rate constants of chlorination were determined. In the second part, carbamazepine chlorination pathways were studied. Oxidation products were tentatively identified by LC coupled with a UV diode array detector and mass spectrometer. The stability of these products was studied in the presence of excess chlorine.

## 2. Materials and methods

### 2.1. Standards and reagents

CBZ of higher than 99% purity was obtained from Sigma–Aldrich. Sodium hypochlorite solution, purchased from Acros Organics, was equimolar in free chlorine and chloride ($Cl^-$) ions (due to the dependence of $[Cl_2]$ on both $[Cl^-]$ and [HOCl] (reaction 8)), with 13.0% (w/v) of active chlorine. The other reagents ($Na_2S_2O_3$, $NH_4Cl$, NaOH, $H_2SO_4$, phosphate, etc.) were analytical grade or better and used without further purification. Solvents were LC or LC-MS grade. All stock solutions were prepared with water (18 MΩ cm, DOC < 0.1 mg/L) purified with a Milli-Q Millipore system.

### 2.2. CBZ chlorination experiments

All kinetic experiments were performed in a batch reactor (1 L) thermostated at 20 ± 2 °C, under pseudo-first-order kinetic conditions ($[HOCl]_T >> 10\ [CBZ]$). The initial CBZ concentration was 10 μM and at least 250 μM of free chlorine was added. The pH of the tested aqueous solutions (1 L) was adjusted using phosphate salts (10 mM). Under these conditions, no pH variation of more than 0.1 unit was observed and chlorine variations were shown to be less than 20% during the experiments. For each experiment, kinetic runs were initiated by injecting an aliquot of chlorine stock solution under rapid mixing. At constant time intervals, 3 mL of solution was withdrawn and added to 4 mL vials containing an excess of $Na_2S_2O_3$ or $NH_4Cl$ to quench the residual chlorine and the oxidation reaction. Samples were analyzed using liquid chromatography (LC) to determine the remaining CBZ concentration. To check the feasibility of using $Na_2S_2O_3$ or $NH_4Cl$ for quenching the chlorine reaction, samples of unquenched reaction solutions containing chlorine and CBZ were directly injected into the LC system at different kinetic run times in several experiments performed at pH 5, 7 and 11 and for chlorine concentrations of 600–5000 μM.

CBZ chlorination experiments were performed at an initial 100 μM CBZ concentration at pH 5, 7 and 9 to identify