Abstract—The bromination of five selected pharmaceuticals (metoprolol, naproxen, amoxicillin, hydrochlorothiazide and phenacetin) in ultrapure water and in three water matrices (a groundwater, a surface water from a public reservoir and a secondary effluent from a WWTP) was investigated. The apparent rate constants for the bromination reaction were determined as a function of the pH, and the sequence obtained for the reaction rate was amoxicillin > naproxen > hydrochlorothiazide ≈ phenacetin ≈ metoprolol. The proposal of a kinetic mechanism, which specifies the dissociation of bromine and each pharmaceutical according to their pKa values and the pH allowed the determination of the intrinsic rate constants for every elementary reaction. The influence of the main operating variables was established. Finally, experiments on the degradation of pharmaceuticals was established. In addition, the presence of bromide in chlorination experiments was investigated. The presence of bromide in wastewaters and drinking waters in the range of 10 to several hundred μg L^{-1} accelerated slightly the oxidation of the selected pharmaceuticals during chlorine disinfection.

Keywords—Pharmaceuticals, bromine, chlorine, apparent and intrinsic rate constants, water matrices, degradation rates

I. INTRODUCTION

PHARMACEUTICALS and personal care products (PPCPs), and endocrine disrupting compounds (EDCs) are frequently detected in aquatic environments worldwide. The presence of these pollutants into different water systems is attributed to their incomplete removal at wastewater treatment plants (WWTPs), which are not designed for this task. Consequently, these contaminants have been spread through surface waters [1], which at the same time constitute an important source of drinking water. Additionally, some pharmaceuticals are again not completely removed at drinking water treatment plants (DWTPs) and thus, although at low concentrations in the range μg L^{-1} to ng L^{-1}, they have been identified in drinkable waters [2]. Due to this problem, different technologies have been proposed and developed with the aim to promote a more efficient degradation of these pollutants. These include the application of chemical processes, based in the use of single oxidants such as UV radiation, ozone, and hydrogen peroxide; or combinations of oxidants in the Advanced Oxidation Processes. In addition, as 98% of the drinking water treatment plants in Europe use chlorination as one of the main disinfection steps, chlorine (HOCl + OCI') has also been commonly applied in water treatments for the elimination of pharmaceuticals [3]-[4]. A new insight in the oxidation of water pollutants can also be developed by means of bromination reactions, specially in those waters with high bromide (Br^-) content [3], [5]. In this process, bromine (HOBr + OBr^-) is produced from the oxidation of bromide with chlorine. Due to the interest of this research field, a study was designed focused in the removal of several frequent pharmaceuticals by the application of chlorine and bromine. For this purpose, the pharmaceuticals selected were: the beta-blocker metoprolol (Met), the nonsteroidal anti-inflammatory compound (NSAID) naproxen (Nap), the antibiotic amoxicillin (Amox), the thiazidic diuretic hydrochlorothiazide (Hctz) and the analgesic phenacetin (Phen). In a first step, the apparent rate constants for the reactions of bromine with these pharmaceuticals dissolved in ultrapure (UP) water were determined as a function of the pH, and the reaction mechanism was proposed and used for the determination of intrinsic rate constants for the elementary reactions of each pharmaceutical with bromine species. Later, the oxidation of the selected pharmaceuticals dissolved in several water matrices was performed and the influence on the main operating variables was established. Finally, experiments were conducted for the pharmaceuticals oxidation by the simultaneous use of chlorine and bromine, with the aim of assessing the influence of bromide on the chlorination of contaminants in real waters.

II. EXPERIMENTAL SECTION

The selected pharmaceuticals were obtained from Sigma-Aldrich of the highest purity available (99%). Stock solutions of bromine were prepared by addition of 0.8 mM ozone solution to a 0.7 mM solution of potassium bromide at pH 4. Stock solutions of chlorine were prepared by diluting a commercial solution of sodium hypochlorite. The three water matrices selected were two natural waters (a groundwater (PZ), and a surface water from the public reservoir “Peña del Agulla” (PA)); and a secondary effluent collected from a WWTP located in Extremadura Community (BA).

In the first group of experiments, pharmaceuticals (Ph) were individually dissolved into UP water at a constant temperature of 20±0.2 °C. The bromination reactions of phenacetin, metoprolol, naproxen, and hydrochlorothiazide were conducted under pseudo-first-order conditions, with excess of bromine. The selected pH was adjusted by using phosphoric acid/phosphate buffer. The experiments were started after addition of the adequate volume of the bromine stock solution for obtaining the desired initial concentration. At regular times, 2 mL samples were retired and rapidly
transferred into HPLC vials containing 10 µL of sodium thiosulfate to stop the reaction. In the specific bromination of amoxicillin, competition kinetics was followed for the determination of its rate constants, by introducing into the reactor 3-metoxyphenol as reference compound. Amoxicillin and 3-metoxyphenol, were previously dissolved in UP water in 20 mL flask reactors at the desired pH and different bromine doses were added. Once bromine was totally consumed (24 h), the residual concentrations of the pharmaceuticals and the reference compound were analyzed.

In the second group of experiments, the selected pharmaceuticals were dissolved all together into the three selected water matrices in 100 mL flask reactors and the runs started by injecting the required volume of the bromine stock solution to reach a concentration of 5-8 mg L\(^{-1}\). At regular reaction times, two samples were withdrawn from the reactor; the first was used to determine the remaining bromine concentration, and the second one to analyze the residual pharmaceuticals after quenching the reaction with thiosulfate. In addition, some chlorination experiments were performed with PZ and BA waters in the presence of different bromide doses. These experiments were conducted with an initial dose of chlorine of 5 mg L\(^{-1}\), and varying the bromide dose in the range 0-300 µg L\(^{-1}\) as typically found in real waters. Residual concentrations of pharmaceuticals were analyzed after total chlorine consumption.

Concentrations of pharmaceuticals were measured by HPLC in a Waters Chromatograph equipped with a 996 Photodiode Array Detector and a Waters Nova-Pak C18 Column (3.9 mm i.d. x 150 mm, 4µm particle size). A gradient elution of methanol (A) and aqueous solution of phosphoric acid 1x10\(^{-2}\) M (B) was used by varying the percentage of A from 10% to 90% (in volume) over 30 minutes. The flow-rate was of 1 cm\(^3\) min\(^{-1}\), and the detection was performed at 222, 226, 230, 226 and 240 nm for metoprolol, hydrochlorothiazide, naproxen, amoxicillin and phenacetin respectively. In the competition kinetics procedure, the concentrations of 3-metoxyphenyl were also assayed by HPLC at 226 nm. Bromine concentration in reaction samples was determined spectrophotometrically according to the ABTS method [6].

**III. RESULTS AND DISCUSSION**

**A. Determination of bromination rate constants for the selected pharmaceuticals**

As it has been reported previously in the study of the kinetics of bromination reactions of several organic compounds [7], these reactions follow second-order kinetics (first-order with respect to bromine and first-order with respect to the organic compound). The apparent second-order rate constant (k\(_{app}\)) usually shows a pH-dependence which could be explained by several species of both, bromine and pharmaceuticals that are present in the aqueous solution. Specifically for bromine, it must be noted that hypobromous acid dissociates into hypobromite ion (OBr\(^-\)) with a pK\(_a\)=8.9.

The evaluation of k\(_{app}\) rate constant for naproxen, metoprolol, phenacetin and hydrochlorothiazide was performed under pseudo-first-order conditions, with initial [Br\(_2\)] >> [Ph]. Figure 1 represents the values obtained for k\(_{app}\) for naproxen and Figure 2 for phenacetin, taken as examples. It can be deduced from the values of k\(_{app}\) that naproxen presents a much higher reactivity than the three remaining pharmaceuticals, which present rate constants in the same range, depending on the pH.

On the other hand, the bromination reaction of amoxicillin was too fast to measure the rate constant by using the pseudo-first order kinetic method; and then, competition kinetics was applied. 3-Methoxyphenol was selected as reference compound, since its rate constants with bromine were similar to those of amoxicillin and were previously known [5]. Following this procedure, the values of k\(_{app}\) for amoxicillin were obtained, being depicted in Figure 3. As observed, the reaction rate for amoxicillin was much higher than that of the
remaining pharmaceuticals, with values ranging between $2.35 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at pH=3 and $2.76 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at pH=9.

Next, the intrinsic rate constants for the elementary reactions of every individual pharmaceutical species with each bromine species were determined following the procedure described elsewhere [8]. Thus, values of the intrinsic rate constants summarized in Table 4 were determined. Finally, the apparent rate constant can be calculated at any specific pH from the values of the intrinsic rate constants for each compound. Figures 1-3 also represent these calculated values of $k_{\text{app}}$ vs. pH. A quite good agreement can be observed between the experimental values (symbols) and the calculated (lines), which constitutes a confirmation of the goodness of the proposed reaction mechanism.

### Table I: Intrinsic Rate Constants (M^{-1} S^{-1}) for the Bromination of Each Pharmaceutical Species

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>$k_1$</th>
<th>$k_2$</th>
<th>$k_3$</th>
<th>$k_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>3.9</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>$2.1 \times 10^4$</td>
<td>270</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>$2.4 \times 10^4$</td>
<td>$2.4 \times 10^4$</td>
<td>$9.9 \times 10^6$</td>
<td>$3.8 \times 10^9$</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>540</td>
<td>1.7</td>
<td>$7.4 \times 10^7$</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>3.3</td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B. Bromination of pharmaceuticals in water matrices**

The simultaneous removal of the selected pharmaceuticals in the water matrices described in the Experimental Section (i.e., the groundwater PZ, the surface water from a public reservoir PA, and the secondary effluent from a WWTP plant BA) was studied in order to assess the influence of the water matrices nature on the efficiency of the pharmaceuticals bromination process. These experiments were carried out at 20 °C, and varying the initial bromine dose and pH. Figure 4 shows the removals obtained after 60 min of reaction for naproxen, phenacetin, hydrochlorothiazide and metoprolol, being amoxicillin not shown because of its total disappearance almost instantaneously. By considering a specific compound, the elimination decreased according to the trend: PZ > PA > BA waters, which agrees with the sequence of increasing COD and TOC values. In effect, the increasing contents of organic and inorganic matter (represented by COD, TOC and ammonia) consume higher amounts of the oxidant agent, and consequently, less bromine is available for the removal of the pharmaceuticals. Moreover, it is also observed that the pharmaceutical elimination trend was: amoxicillin > naproxen $\gg$ hydrochlorothiazide $\approx$ phenacetin $\approx$ metoprolol, which also agrees with the $k_{\text{app}}$ values at pH=7 shown in Figures 1-3.
As a consequence of these results, the presence of bromide in wastewaters and drinking waters in the range of 10 to several hundred µg L⁻¹ accelerates slightly the oxidation of the selected pharmaceuticals during chlorine disinfection. The positive effect of the presence of bromide leading to bromine oxidation is partially hindered since bromine reacts more rapidly with reactive moieties of the NOM such as amine- or phenolic moieties than chlorine [9].

IV. CONCLUSIONS

The results obtained in the bromination of five selected pharmaceuticals (metoprolol, naproxen, amoxicillin, phenacetin and hydrochlorotiazide) lead to the following conclusions:

- The bromination process of the individual compounds in UP water provides a wide range of apparent second-order rate constants depending on the pH. In general terms, amoxicillin presented high reaction rates, naproxen intermediate rates, and the three remaining pharmaceuticals presented similar rate constants in the slow range.
- By taking into account the dissociation constants of these compounds and the pH influence, a reaction mechanism is proposed, which allowed the evaluation of the intrinsic rate constants for the elementary bromination reactions of each pharmaceutical.
- In the simultaneous bromination of the five pharmaceuticals in three water matrices, the elimination decreased according to the trend: PZ > PA > BA, which agrees with the sequence of increasing COD and TOC values, that consume a higher amount of the oxidant agent.
- The presence of bromide in wastewaters and drinking waters accelerates slightly the oxidation of the selected pharmaceuticals during chlorine disinfection.

REFERENCES


