Abstract: The aim of our study was to assess the possibility of using the photocatalytic process conducted in the presence of TiO$_2$ to obtain new stable derivatives of antibacterial drugs. The possibility of introducing hydroxyl, chlorine, or bromide groups into antibiotics molecules was investigated. The experiments were conducted in aqueous solutions in the presence of TiO$_2$-P25 as a photocatalyst, Cl$^-$ and Br$^-$ ions, and antibiotics belonging to eight different chemical classes. All experiments were initiated by UVa radiation. The kinetics of photocatalytic reactions and their quantum yield were determined, and the stable products were identified. All of the antibiotics used in the experiments underwent a photocatalytic transformation, and the quantum yields were in the range from 0.63 to 22.3%. The presence of Br$^-$ or FeCl$_3$ significantly increased the efficiency of the photocatalytic process performed in the presence of TiO$_2$, although Br$^-$ ion also acted as an inhibitor. Potentially biologically active chlorine derivatives from Trimethoprim, Metronidazole, Chloramphenicol, and bromine derivatives from Trimethoprim, Amoxicillin were obtained under experimental conditions. The potentially inactive halogen derivatives of Sulfamethoxazole and hydroxyl derivatives described in the literature were also identified.

Keywords: antibiotics; photocatalysis; synthesis; bromination; chlorination; identification of reaction products

1. Introduction

Rapid development of medicine and the resultant growth of demand for new antibiotics are the natural consequences of the civilization progress. Demand for such substances promotes their widespread use in animal husbandry but also the simultaneous rapid creation of resistance in the microorganisms, against which they are used [1,2]. The above stimulates an intensive search for new substances with the desired profile of biological activity. For this purpose, substances of natural origin are isolated and researched, new, and previously undescribed chemical compounds, as well as new derivatives based on already existing drugs, are synthesized [2,3].

Chemical industry vastly applies technologies that have not changed significantly over the years. However, the growing awareness of the environmental impact of the used reagents, catalysts, by-products, and solvents has made the environmental policy more stringent. Far more consideration is given to energy costs and important safety issues related to waste management [4–7]. For the above reasons, attempts have been made to develop new alternative methods of obtaining organic compounds, including drugs. In the preliminary assumptions, the following were considered significant:

- reduction of energy consumption,
- use of environmentally safe reagents, and
- minimization of the amount and toxicity of generated waste.

In the context of the above requirements, photocatalysis conducted in the presence of TiO$_2$ is seen as a promising innovative method of organic compound synthesis [4,5,7,8].
Chemical processes carried out in the presence of irradiated semiconductors (e.g., TiO$_2$) are initiated by the high-energy pair generated onto the surface of catalyst particles: an electron hole (h$^+$) and an excited electron (e$^{-*}$). In oxygen-saturated aqueous solutions, the pair h$^+$/e$^{-*}$ initiates the formation of free radicals, e.g., highly active hydroxyl radicals (HO$^*$) having a very strong oxidizing potential of +2.31 V and more persistent but less active superoxide radicals (O$_2$$^{-*}$) (Equations (1) and (2)) [9–11]:

\[
\begin{align*}
H_2O + h^+ &\rightarrow HO^* + H^+, \\
O_2 + e^{-*} &\rightarrow O_2^{-*}.
\end{align*}
\]

Organic radicals or organic cation radicals (R$^*$ or R$^{+*}$) may also be formed on the catalyst surface in the presence of organic substances (Equations (3) and (4)):

\[
\begin{align*}
RH + h^+ &\rightarrow R^* + H^+, \\
R + h^+ &\rightarrow R^{+*}.
\end{align*}
\]

Because of their high activity, HO$^*$ radicals can react non-selectively with all substances present in the solution. For instance, in reaction with organic compounds (RH), they can generate the organic radical R$^*$ (Equation (5)):

\[
HO^* + RH \rightarrow R^* + H_2O.
\]

Moreover, an addition of HO$^*$ radicals to unsaturated bonds of organic compounds can also take place in aqueous solutions (Equation (6)):

\[
HO^* + RH \rightarrow RHOH^*.
\]

Another known free radical mechanism involves the transfer of an electron from the organic compound to HO$^*$ radical, which results in the formation of organic cation radical (Equation (7)):

\[
HO^* + R \rightarrow R^{+*} + OH^{-}.
\]

The organic radical (R$^*$) reacts quickly with a molecule of dissolved oxygen, and a peroxide radical (ROO$^*$) forms as a result of this reaction (Equation (8)):

\[
R^* + O_2 \rightarrow ROO^*.
\]

However, it may also interact with another HO$^*$ radical to form a hydroxyl derivative (Equation (9)). This route leads to termination of the chain process:

\[
R^* + HO^* \rightarrow ROH.
\]

Reactions described above can even lead to a complete mineralization of organic compounds. Therefore, use of these processes has been considered, so far, mainly for the removal of hazardous organic substances from water and wastewater [12]. In solutions containing inorganic ions (X$^-$), the generation of other inorganic radicals (e.g., Cl$^*$, ClOH$^{+*}$, I$^*$) is also possible due to high oxidation potentials of h$^+$ and HO$^*$ (Equations (10)–(12)) [13–16]:

\[
\begin{align*}
X^- + h^+ &\rightarrow X^*, \\
HO^* + X^- &\rightarrow HOX^{+*}, \\
XOH^{+*} &\rightarrow X_2^{+*} + OH^-.
\end{align*}
\]

The values of reaction rate constants of HO$^*$ radicals with Cl$^-$, Br$^-$, and I$^-$ ions, as well as with superoxide radicals (O$_2$$^{-*}$) and organic compounds, are similar to the values
of recombination rate constants of these radicals \cite{15,16}. The aforementioned reactions are competitive to the interaction between $h^*$ and $\text{HO}^*$ with organic substrates.

Many researchers have indicated that these processes reduce the efficiency or inhibit the photocatalytic degradation of organic compounds due to the formation of radicals and anion radicals having a lower oxidizing potential than $\text{HO}^*$ radicals \cite{17,18}. On the other hand, Parker and Mitch \cite{16} have demonstrated that the halide ions present in the reaction medium can increase the phototransformation rate of organic substances by up to five times. Simultaneously, they have found the halogenated organic compounds among the products.

In recent years, the possibility of using photocatalysis as an alternative to conventional thermo-catalytic organic synthesis has been considered \cite{4,19,20}. The advantage of this solution is the possibility to work in mild temperature and pressure conditions, low cost of the catalyst and reduction of negative environmental costs of the process \cite{5}. The photocatalytic process conducted in the presence of TiO$_2$ has been described, inter alia, as a selective method for the synthesis of pharmaceutical precursors \cite{21}. It has also been proven that it can be conducted with a high efficiency in a non-aqueous medium \cite{8}. It is probable that application of the discussed method will enable introduction of halogen atoms, hydroxyl, carboxyl, alkyl, or alkoxy groups or into molecules of organic compounds.

The goal of our project is to evaluate the possibility of using the photocatalytic process to obtain new stable derivatives of antibacterial drugs, i.e., Trimethoprim (TMP), Sulfamethoxazole (SMX), Norfloxacin (NOR), Metronidazole (MTZ), Amoxicillin (AMX), Chloramphenicol (CAM), Doxycycline (DOX), and Erythromycin (ERY). These derivatives could have biological properties, including the activity against antibiotic-resistant microorganisms \cite{22}. The chemical structures of the studied antibiotics are shown in the Table 1.

| Name (Abbreviation), CAS Number | Summary Formula (Molar Mass) | Chemical Structure of Active Form \cite{23–29} | Manufacturer (Purity) |
|--------------------------------|-------------------------------|-----------------------------------------------|----------------------|
| Trimethoprim (TMP) 738-70-5    | $C_{14}H_{18}N_{3}O_{3}$ (290.32 g/mol) | ![Chemical Structure of Trimethoprim](image) | Sigma-Aldrich ($\geq 98\%$) |
| Sulfamethoxazole (SMX) 723-46-6| $C_{10}H_{11}N_{3}O_{2}S$ (253.28 g/mol) | ![Chemical Structure of Sulfamethoxazole](image) | Sigma-Aldrich ($\geq 98\%$) |
| Norfloxacin (NOR) 70458-96-7   | $C_{16}H_{18}F_{2}N_{3}O_{3}$ (319.34 g/mol) | ![Chemical Structure of Norfloxacin](image) | Supelco ($\geq 98\%$) |
| Metronidazole (MTZ) 443-48-1   | $C_{6}H_{4}N_{2}O_{3}$ (171.16 g/mol) | ![Chemical Structure of Metronidazole](image) | Fluka (analytical standard) |
2. Results and Discussion

2.1. Kinetics

Figure 1 shows exemplary changes in TMP concentration during UVa irradiation in the presence of the three catalytic systems and changes in DOX concentration during irradiation with TiO$_2$/FeCl$_3$. Dashed lines illustrate the theoretical changes in TMP concentration following the pseudo-first-order kinetics (with TiO$_2$/HCl and TiO$_2$/FeCl$_3$) and the zero-order kinetics (with TiO$_2$/NaBr/HCl).

To compare the efficiency of photocatalytic processes, for practical reasons, the average transformation reaction rate for the first 10 min of UV irradiation was calculated. The obtained results of all of the studied compounds are presented in Figure 2. These values are proportional to the efficiency of quantum transformation of the individual antibiotics.

| Name (Abbreviation), CAS Number | Summary Formula (Molar Mass) | Chemical Structure of Active Form [23–29] | Manufacturer (Purity) |
|--------------------------------|-----------------------------|---------------------------------|----------------------|
| Amoxicillin (AMX) 26787-78-0 | C$_{16}$H$_{19}$N$_3$O$_5$S (365.40 g/mol) | ![Chemical Structure](image) | Sigma-Aldrich (potency: $\geq 900$ µg/mg) |
| Chloramphenicol (CAM) 56-75-7 | C$_{11}$H$_{12}$Cl$_2$N$_2$O$_5$ (323.13 g/mol) | ![Chemical Structure](image) | Sigma-Aldrich ($\geq 98\%$) |
| Doxycycline hyclate (DOX) 24390-14-5 | C$_{22}$H$_{24}$N$_2$O$_8$ (444.44 g/mol) | ![Chemical Structure](image) | Sigma-Aldrich ($\geq 98\%$) |
| Erythromycin (ERY) 114-07-8 | C$_{37}$H$_{57}$NO$_{13}$ (733.94 g/mol) | ![Chemical Structure](image) | Sigma-Aldrich (potency: $\geq 850$ µg/mg) |

1 the core structure of antibiotics is highlighted pink.
To compare the efficiency of photocatalytic processes, for practical reasons, the averaged rate of photocatalytic transformation for all of the studied antibiotics was calculated. The results are presented in Table 1. The quantum efficiencies of antibiotics transformation ranged from 0.69% (ERY, TiO2/NaBr/HCl) to 0.79% (DOX, TiO2/FeCl3). A decrease in the antibiotics concentration was observed in each experiment. Most likely, these results were due to the photocatalytic transformation of drugs, with the exception of DOX reaction performed in TiO2/FeCl3 system. DOX formed a water-insoluble complex compound with the Fe3+ cations which was removed during the catalyst separation. Therefore, only an equilibrium amount of the antibiotic remained in solution. However, a further decrease in DOX concentration after irradiation longer than 10 min (Figure 1) was recognized as a transformation of this antibiotic, which occurred in parallel with sorption in TiO2/FeCl3 system.

Figure 1. Changes in TMP and DOX concentration during UVa irradiation of their solutions with the studied catalytic systems. The dashed lines illustrate the theoretical shape of the C/C0 = f(t) function according to pseudo-zero-order kinetics (TMP with TiO2/HCl and TiO2/FeCl3) or pseudo-first order (TMP with TiO2/NaBr/HCl and TiO2/FeCl3).

Figure 2. Comparison of the average rate of photocatalytic transformation for all of the studied antibiotics in the presence of catalytic systems: TiO2/HCl, TiO2/NaBr/HCl, and TiO2/FeCl3.

A decrease in the antibiotics concentration was observed in each experiment. Most likely, these results were due to the photocatalytic transformation of drugs, with the exception of DOX reaction performed in TiO2/FeCl3 system. DOX formed a water-insoluble complex compound with the Fe3+ cations which was removed during the catalyst separation. Therefore, only an equilibrium amount of the antibiotic remained in solution. However, a further decrease in DOX concentration after irradiation longer than 10 min (Figure 1) was recognized as a transformation of this antibiotic, which occurred in parallel with sorption in TiO2/FeCl3 system.
The quantum efficiencies of antibiotics transformation ranged from 0.69% (ERY, TiO\textsubscript{2}/NaBr/HCl) to 22.3% (TMP, TiO\textsubscript{2}/NaBr/HCl). In the case of MTZ, AMX, CAM, and ERY transformation, the reaction rates and the quantum yields in TiO\textsubscript{2}/NaBr/HCl system were very low; therefore, its practical application is excluded/meaningless.

In TiO\textsubscript{2}/NaBr/HCl system, bromide radicals were generated at the expense of hydroxyl radicals (Equations (10)–(12)) [13–16]. An inhibition of the photocatalytic reaction indicates that MTZ, AMX, CAM, and ERY did not react with bromine-containing radicals. On the other hand, the transformation rate of TMP, SMX, and DOX was significantly increased in the presence of Br\textsuperscript{−} ions. According to Cheng et al. [30], the high susceptibility of the compound to photochemically initiated free-radical bromination is likely related to the presence of phenolic and amine moieties. However, the observed results for AMX and CAM did not confirm this assumption.

The transformation rate of AMX, SMX, CAM, and ERY in the presence of TiO\textsubscript{2}/FeCl\textsubscript{3} was significantly higher than that in TiO\textsubscript{2}/HCl system. The observed effect can be explained by an increase in the free radicals distribution, the electron transfer, the formation of coordination compounds and/or intensification of sorption processes of organic compounds in the presence of Fe\textsuperscript{3+} ions [12,31,32]. The reactions performed in the presence of TiO\textsubscript{2}/HCl and TiO\textsubscript{2}/FeCl\textsubscript{3} systems can be considered as a pseudo-first order, while those in the presence of TiO\textsubscript{2}/NaBr/HCl system as zero order (Figure 1). This fact has practical implications because the zero-order processes for TMP, SMX, NOR, and DOX do not slow down due to the decrease in the substrate concentration.

Low quantum efficiency of photocatalytic transformation may result from a short lifetime of HO\textsuperscript{•} radicals (<10\textsuperscript{−3} s), a low affinity of antibiotics to the catalyst surface (TiO\textsubscript{2}), the energy losses due to the collisions of substrates with solvent molecules, and the recombination of excited particles. However, the electrostatic affinity of halide anions (X\textsuperscript{−}) to the positively charged TiO\textsubscript{2} surface in acidic environment can remove some of the barriers. The resulting halide radicals have a longer life than that of HO\textsuperscript{•} one. They can penetrate deep into the solution and react with these substrate molecules which do not undergo sorption on the TiO\textsubscript{2} surface [14]. As a result, the barrier associated with a limited number of surface-active centers that can bind antibiotic reagents are reduced. Higher quantum yield of TMP and SMX transformation in the presence of TiO\textsubscript{2}/NaBr/HCl may indicate that Br\textsuperscript{•} radical involved in the transfer reaction from the heterogeneous catalyst surface to the homogeneous phase. In turn, among the AMX transformation products, bromine derivatives (Section 2.2) were identified, despite the fact that Br\textsuperscript{−} ion act as inhibitor of this reaction. It indicates that the mechanism of action of Br\textsuperscript{−} ion was not unidirectional.

2.2. Products of the Photocatalytic Transformation of Antibiotics

Figures 3–10 show the chromatograms of the aqueous solutions of the studied antibiotics after 30 min of UV irradiation in the presence of three catalytic systems and stored for 24 h before analysis. They also include the chemical formulas of the identified positive ions (M + H\textsuperscript{+}), differences (Δm) between measured and calculated m/z values, and the proposed structures of the products. The chromatograms of SMX and AMX irradiated in the presence of TiO\textsubscript{2}/FeCl\textsubscript{3} and MTZ irradiated in the presence of TiO\textsubscript{2}/NaBr/HCl are not shown in the text because there were no chromatographic peaks corresponding to stable compounds. The conversion rate of SMX and AMX was approximately 90 and 100%, respectively. Therefore, aliphatic, inorganic, or compounds bound and removed by components of the catalytic system could be the products of these antibiotic transformation.
Figure 3. BPI chromatograms of TMP solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 
Figure 4. BPI chromatograms of SMX solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 
Figure 5. BPI chromatograms of NOR solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 

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Figure 6. BPI chromatograms of MTZ solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 
Figure 7. BPI chromatograms of AMX solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 

- **a)** TiO$_2$/HCl
- **b)** TiO$_2$/NaBr/HCl
- **c)** TiO$_2$/FeCl$_3$
Figure 8. BPI chromatograms of CAM solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 
Figure 9. BPI chromatograms of DOX solution after 30 min of UV irradiation in the presence of (a) TiO$_2$/HCl, (b) TiO$_2$/NaBr/HCl, and (c) TiO$_2$/FeCl$_3$. 
According to the majority of researchers, the main pathway of degradation/transformation during the photocatalytic process involves free radical reactions. In the experiments performed, HO•, O2•−, as well as Cl•, Br• radicals and their derivatives (Equations (1), (2), and (10)–(12)), could be generated. Due to the type of radicals, the stable chlorine and bromine derivatives can form during the photocatalytic process. Table 2 provides information on the type of stable antibiotics derivatives obtained in the experiments.
Table 2. Stable complex products of antibiotics transformation in solutions after 30 min of irradiation.

| Antibiotics | Catalytic System | Degree of Antibiotics Conversion (%) ¹ | Derivatives with ² | Oxidation, Elimination or Condensation Products |
|-------------|-----------------|----------------------------------------|-------------------|-----------------------------------------------|
|             |                 |                                        | -OH -Cl -Br        |                                               |
| TMP         | TiO₂/HCl        | 87                                     | ++ + - - -         | +                                             |
|             | TiO₂/NaBr/HCl   | ~100                                    | ++ - ++ -          | +                                             |
|             | TiO₂/FeCl₃      | 97                                     | ++ ++ - -          |                                               |
| SMX         | TiO₂/HCl        | 53                                     | + - - -            | -                                             |
|             | TiO₂/NaBr/HCl   | ~100                                    | - - ++ -           | -                                             |
|             | TiO₂/FeCl₃      | 91                                     | - - - -            | -                                             |
| NOR         | TiO₂/HCl        | 75                                     | + - - -            | ++                                            |
|             | TiO₂/NaBr/HCl   | 81                                     | + - - -            | ++                                            |
|             | TiO₂/FeCl₃      | 78                                     | + - - -            | ++                                            |
| MTZ         | TiO₂/HCl        | 84                                     | + - - -            | -                                             |
|             | TiO₂/NaBr/HCl   | 15                                     | - - - -            | -                                             |
|             | TiO₂/FeCl₃      | 89                                     | - + - -            | -                                             |
| AMX         | TiO₂/HCl        | 64                                     | + - - -            | -                                             |
|             | TiO₂/NaBr/HCl   | 33                                     | - - ++ -           | -                                             |
|             | TiO₂/FeCl₃      | ~100                                    | - - - -            | -                                             |
| CAM         | TiO₂/HCl        | 50                                     | - + - -            | +                                             |
|             | TiO₂/NaBr/HCl   | 23                                     | - - - -            | +                                             |
|             | TiO₂/FeCl₃      | 80                                     | - - - -            | +                                             |
| DOX         | TiO₂/HCl        | 79                                     | + - - -            | +                                             |
|             | TiO₂/NaBr/HCl   | 94                                     | ++ - - -           | ++                                            |
|             | TiO₂/FeCl₃      | 75                                     | + - - -            | ++                                            |
| ERY         | TiO₂/HCl        | 65                                     | - - - -            | ++                                            |
|             | TiO₂/NaBr/HCl   | 18                                     | - - - -            | +                                             |
|             | TiO₂/FeCl₃      | 84                                     | - - - -            | ++                                            |

¹ after 30 min irradiation. ² + one stable derivative, ++ more than one stable derivative, - no stable derivatives.

The studied antibiotics differed in their susceptibility to introduction of halides or -OH group into the molecules. For example, there were no stable hydroxyl derivatives obtained from ERY. This antibiotic does not possess the multiple bonds susceptible to hydroxylation. ERY transformation was mainly based on the elimination of water and hydrogen molecules. In turn, only hydroxylation and degradation (oxidation) products were obtained from NOR and DOX in the experiments. Hydroxyl derivatives or oxidation, elimination, and condensation products resulted during the photocatalytic transformation of all studied antibiotics. These products have been reported in many papers containing the photocatalytic degradation pathways of antibiotics [33–36]. However, the application of these derivatives as precursors of new drugs has not been considered yet. It cannot be excluded that some of the products can also have the antibacterial properties.

Chlorine-containing products formed only as a result of MTZ, CAM and TMP transformation (four products when the TiO₂/FeCl₃ is taken into account. These derivatives were absent during the photocatalytic degradation with TiO₂/NaBr/HCl. Most likely, in samples containing simultaneously Cl⁻ and Br⁻ ions, the generating of Br• radical is privileged (E⁰Br• < E⁰Cl•). A large amount of bromine-containing products formed only as a result of TMP, SMX, and AMX transformation. Some of identified derivatives possessed an intact core structure of antibiotics (Table 1) and preserved functional groups responsible for their antibacterial activity. TMP was the most susceptible antibiotic to potential modifications by the photocatalytic reaction. Its antibacterial activity is related to the diaminopyrimidine moiety, while most of modifications occurred in the benzene ring. This may indicate that the resulting TMP-derivatives have the antimicrobial activity. The assumption is confirmed by the studies on antibacterial activity of halogenated TMP derivatives which showed their high activity against drug-resistant pathogens [22]. In
the case of SNs, the introduction of additional substituents on the benzene ring or on the amino group decreases or abolishes the antimicrobial activity [37]. The removal or substantial modification of the side chain from the CAM molecule caused a similar effect [38]. These results indicate that the derivatives of SMX and CAM obtained by the photocatalytic process were most likely biologically inactive.

It should be mentioned that the presented studies are only preliminary findings. The biological activity of obtained derivatives against microorganisms should be verified. However, in the case of some antibiotics, the synthesis of new stable derivatives using the photocatalytic method with TiO$_2$ and popular inorganic salts is possible. At the moment, the main problem of the proposed synthesis method is a low mass efficiency of the process. Therefore, it requires optimization experiments, e.g., in the non-aqueous environment. It cannot be excluded that a limited solubility of the organic reagents in water may be a major barrier to increase the mass efficiency of products.

Unfortunately, a quantitative assessment of the yield of individual synthesized derivatives was impossible due to the lack of standards of the transformation product. The ratio of the formed products changed during the reaction. However, at the initial (basic) technological stage, the increase in the reaction selectivity could be possible by modifying the reaction conditions, the irradiation time, and/or the reactants composition. Moreover, carrying out the reactions in multiphase systems or with the continuous reception of reagents will potentially increase the selectivity.

3. Materials and Methods

3.1. Screenings of Photocatalytic Transformation of Antibiotics, Chemotherapeutic Agents or Their Precursors

The photocatalytic transformation process was carried out in a bath reactor in the presence of TiO$_2$-P25 (Aeroxide) suspension in an aqueous, acidic medium [39]. Antibiotics, chemotherapeutic agents, and their precursors (Table 1) were used to prepare the solutions (0.1 mmol/L) in deionized water (conductivity < 6 µS/cm).

The experiment was performed in three catalytic systems, i.e., TiO$_2$/HCl, TiO$_2$/NaBr/HCl, and TiO$_2$/FeCl$_3$. Solid TiO$_2$ (50 mg) was added to each antibiotic solutions (100 mL). Then, the HCl solution or, alternatively, 1 mL of NaBr solution (0.1 mol/L) and HCl solution or 1 mL of FeCl$_3$ solution (0.1 mol/L) were added to the antibiotics suspensions. The pH of these samples was 3.0 ± 0.1, and it was adjusted by adding appropriate amounts of the HCl solution. All mixtures in open glass crystallizers were magnetically stirred in the dark for 15 min and then irradiated using UVa lamps. The intensity of the radiation (I), determined by Parker’s actinometer, was 4.40 µE/min [40].

3.2. Analysis

At specified time intervals over the course of irradiation, samples were taken from the reactors. After catalyst separation by microfiltration, the samples were analyzed chromatographically using UPLC/DAD/Xevo G2-XS-QTOF equipment (Waters Corp., Milford, MA, USA) with Acquity UPLC BEH C18 (100 × 2.1 mm) column. A solution gradient A—H$_2$O (LC-MS grade, LiChrosolv®, Sigma-Aldrich, St. Louis, MO, USA) with 0.01% HCOOH (98–100% for LC-MS, LiChropure, Supelco, Bellefonte, PA, USA), B—CH$_3$CN (hypergrade for LC-MS, LiChrosolv®, Sigma-Aldrich, St. Louis, MO, USA), with 0.01% HCOOH, and optimized for each reagent was used as an eluent (Table 3).

The kinetics of reagents transformation was determined based on the results of analysis from the DAD detector. Simultaneously, the UPLC-MS base peak intensity (BPI) chromatograms was recorded. On their basis, the monoisotopic molecular masses of products were determined. For the selected products, the fragmentation spectra (MS/MS) at collision energies determined experimentally in the range of 10 ÷ 30 V were also established using tandem mass spectrometry.

Fragmentation spectra were used to determine the structures of antibiotics derivatives. The analytical procedure used did not allow the identification of aliphatic compounds. The
products were regarded as stable if they were present in the samples for more than 24 h after the end of UV-irradiation (the photocatalytic reactions).

Table 3. Composition of eluents used in the UPLC analysis.

| Antibiotic | Mobile Phase: A—H₂O with 0.01% HCOOH, B—CH₃CN with 0.01% HCOOH; Flow: 0.35 mL/min |
|------------|-----------------------------------------------------------------------------------|
| TMP and SMX | initial- A 95%, B 5%; 3.5 min- A 80%, B 20%; 6.5 min- A 50%, B 50%; 7.5 min- A 50%, B 50%; 8.3 min- A 95%, B 5% |
| NOR        | initial- A 95%, B 5%; 6.0 min- A 80%, B 20%; 6.5 min- A 60%, B 40%; 8.0 min- A 60%, B 40%; 9.0 min- A 95%, B 5% |
| MTZ        | initial- A 95%, B 5%; 6.0 min- A 85%, B 15%; 7.0 min- A 50%, B 50%; 8.0 min- A 50%, B 50%; 8.5 min- A 95%, B 5% |
| AMX        | initial- A 99%, B 1%; 3.5 min- A 98%, B 2%; 6.5 min- A 70%, B 30%; 7.5 min- A 70%, B 30%; 8.3 min- A 99%, B 1% |
| CAM        | initial- A 90%, B 10%; 6.0 min- A 60%, B 40%; 7.0 min- A 40%, B 60%; 8.0 min- A 40%, B 60%; 9.0 min- A 90%, B 10% |
| DOX        | initial- A 90%, B 10%; 3.0 min- A 80%, B 20%; 8.0 min- A 10%, B 90%; 8.3 min- A 10%, B 90%; 9.0 min- A 90%, B 10% |
| ERY        | initial- A 93%, B 7%; 2.0 min- A 90%, B 10%; 6.0 min- A 60%, B 40%; 8.0 min- A 60%, B 40%; 9.0 min- A 93%, B 7% |

3.3. Calculations

An average photodegradation rate of reaction lasting 10 min was calculated according to the following equation:

$$ r = \frac{(C_0 - C_t)}{t}, \quad (13) $$

where \( r \) is the average reaction rate (\( \mu \text{mol}/\text{L} \text{min} \)), \( C_0 \) is the initial concentration of antibiotic (\( \mu \text{mol}/\text{L} \)), \( C_t \) is the antibiotic concentration after 10 min of UVa irradiation (\( \mu \text{mol}/\text{L} \)), and \( t \) is the irradiation time (min).

An average quantum yield of the reaction lasting 10 min was determined based on the following equation:

$$ \Phi = \left( \frac{r \times V_s}{I} \right) \times 100\%, \quad (14) $$

where \( \Phi \) is the average quantum yield of the reaction (%), \( V_s \) is the volume of irradiated antibiotic solution (L), and \( I \) is the radiation intensity.

4. Conclusions

The heterogeneous photocatalytic process conducted in an acidic environment in the presence of TiO₂-P25, as well as chloride and bromide ions, allowed the formation of stable chlorine derivatives of TMP, MTZ, and CAM and bromine derivatives of TMP, SMX, and AMX. In the presence of excess bromide ions, the photocatalytic reaction can be described as zero-order. These ions significantly increased the efficiency of TMP, SMX, and DOX transformation and inhibited the MTZ, AMX, CAM, and ERY transformation. The results indicate that the action of Br⁻ ion could depend on the susceptibility of antibiotics to radical bromination. This conclusion, however, did not apply to AMX transformation. Taking into account the type of changes in antibiotics molecules, the resulting derivatives (with the exception of SMX derivatives) may have biological activity. The addition of Fe³⁺ salts accelerated the reactions performed in the presence of Cl⁻ ions. However, in the TiO₂/FeCl₃ system, six of eight studied antibiotics underwent oxidation, degradation, or hydroxylation only. No halogen derivative was identified among the transformation products of three antibiotics, i.e., NOR, DOX, and ERY. In the case of ERY and CAM, no stable hydroxyl derivatives were identified. Most likely, the presence of multiple bonds in the antibiotic molecule was a necessary but not sufficient condition for the formation of derivatives with introduced halide or hydroxyl group. Nevertheless, the preliminary
results confirm the formation of new biologically active compounds by the photocatalytic transformations of antibiotics.

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