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Degradation of 17 Benzodiazepines by the UV/H_2O_2 Treatment

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Benzodiazepines are one group of psychoactive drugs widely detected in water environments, and their persistence during conventional wastewater treatment has raised great concerns. Here we investigated the degradation of 17 benzodiazepines in water by UV/H_2O_2 treatment. The results showed that the UV/H_2O_2 treatment significantly increased the degradation of 17 benzodiazepines in phosphate buffer solutions at pH 7.0. This can be attributed to the high reactivity of hydroxyl radicals (·OH) towards benzodiazepines with second-order rate constants of $3.48 \times 10^9\ M^{-1}\ s^{-1}$–$2.44 \times 10^{10}\ M^{-1}\ s^{-1}$. The degradation of alprazolam, a typical benzodiazepine, during the UV/H_2O_2 treatment was increased with the increasing H_2O_2 dosage. The solution pH influenced the alprazolam degradation significantly, with the highest degradation at pH 7.0. Water matrix, such as anions (Cl^-, HCO_3^-, NO_3^-) and humic acid, decreased the degradation of alprazolam by UV/H_2O_2 treatment. Based on the degradation products identified using quadrupole time-of-flight mass spectrometer, the degradation mechanisms of alprazolam by UV/H_2O_2 treatment were proposed, and hydroxylation induced by ·OH was the main reaction pathway. The degradation of 17 benzodiazepines by UV/H_2O_2 treatment in wastewater treatment plant effluent and river water was lower than that in phosphate buffer solutions. The results showed that the benzodiazepine psychoactive drugs in natural water can be effectively removed by the UV/H_2O_2 treatment.

Keywords: benzodiazepines, UV/H_2O_2, degradation products, water treatment, reaction kinetics, emerging chemical pollutants

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INTRODUCTION

Pharmaceuticals and personal care products (PPCPs) in water environments are a well-recognized concern due to their widespread occurrence and potential harm to environmental organisms (Yang et al., 2017; Danner et al., 2019; Patel et al., 2019; Lu et al., 2020, 2022). Benzodiazepines, a main class of psychoactive drugs, have pharmacological effects such as sedative-hypnotic, anxiolytic, anticonvulsant, antiepileptic, and muscle relaxant (Cunha et al., 2017). According to the annual report of International Narcotics Control Board (INCB), benzodiazepines have been used in more than 80 countries, and the global manufacture amount of benzodiazepines was over 195 tons in 2019. Most benzodiazepines, which cannot be completely metabolized in the body, are discharged, resulting in their wide occurrences in municipal wastewater, surface waters and seawaters at concentrations of 24.3–95.9 ng L^{-1} (Subedi and Kannan, 2015; Wu et al., 2015; Fernandez-Rubio et al., 2019). Existing previous studies have found that the conventional water and wastewater treatment processes, such as biological processes, coagulation, filtration and chlorination, are ineffective to remove benzodiazepines, which can lead to their discharge into the receiving waters (Cunha et al., 2017; Fick et al., 2017; Lei et al., 2021). The persistent nature of benzodiazepines may pose a negative impact on aquatic ecosystem. For example, diazepam at low environmental levels can decrease the growth rate of *Daphnia magna* and increase mortality rates of the young zebrafish (*Danio rerio*) (Kalichak et al., 2016; Rivetti et al., 2016). The additive effect of benzodiazepines at low concentrations has been confirmed. Benzodiazepines can alter the social behavior and feeding rates of freshwater fish-European perch (*Perca fluviatilis*) (Brodin et al., 2013; Cerveny et al., 2020). Consequently, it is essential to eliminate the residual benzodiazepines from water.

Advanced oxidation processes (AOPs) have been reported to be highly efficient processes for the degradation of refractory PPCPs (Miklos et al., 2018; Huang et al., 2020; Lee et al., 2020; Wang and Zhuan, 2020; Wu et al., 2020). Some AOPs, such as photo-Fenton, heterogeneous photocatalysis, UV/TiO_2 and UV/H_2O_2 have been explored to remove benzodiazepines in water (Bosio et al., 2019; Cunha et al., 2019; Mitsika et al., 2021). The photocatalytic degradation of the selected benzodiazepines (i.e., alprazolam and diazepam) was proved to be effective with a photo-Fenton reaction system (Mitsika et al., 2021). The heterogeneous photocatalysis using synthesized composites based on TiO_2 and activated carbon (TiO_2/AC) as catalysts under sunlight-simulated irradiation can remove over 97.5% of bromazepam, clonazepam, and diazepam from water (Cunha et al., 2019). The UV/TiO_2 and UV/H_2O_2 performed better under acidic conditions and removed 60–80% of alprazolam, clonazepam, diazepam, and lorazepam (Bosio et al., 2019). Limited previous studies examined the degradation of two benzodiazepines (i.e., diazepam and oxazepam) by UV/H_2O_2 treatments (Huber et al., 2003; Kosjek et al., 2012). Our previous studies also showed that the removal of diazepam was significantly enhanced by UV/chlorine and simulated sunlight/chlorine treatments due to the substantial contribution of ·OH (Yang et al., 2018; Yang et al., 2020). However, the kinetics and transformation products for ·OH reaction with other benzodiazepines are still missing.

This work aimed to investigate the degradation mechanism of 17 benzodiazepines by UV/H_2O_2 treatment in water. The reaction kinetics for 17 benzodiazepines in UV and UV/H_2O_2 processes were determined, respectively. The experimental parameters such as dosage of H_2O_2, solution pH and coexisting constituents (i.e., Cl^-, HCO_3^-, NO_3^-, humic acid) were carefully evaluated. The degradation products and reaction pathways for a typical benzodiazepine (alprazolam) were tentatively revealed based on quadrupole time-of-flight mass spectrometer. Finally, the removal of 17 benzodiazepines by UV/H_2O_2 treatment was also conducted in wastewater treatment plant (WWTP) effluent and river water for practical application.

MATERIALS AND METHODS

Chemicals and Materials

Standards of 17 benzodiazepines (alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clozapine, diazepam, estazolam, flunitrazepam, flurazepam, lorazepam, midazolam, nordiazepam, nitrazepam, oxazepam, prazepam, temazepam) were obtained from Cerilliant Corporation (Texas, United States). The basic parameters of these 17 benzodiazepines were provided in Supplementary Information (**Supplementary Table S1**). Atrazine and *p*-chlorobenzoic acid (pCBA) were obtained from Sigma-Aldrich (Shanghai, China). Tert-butyl alcohol (TBA) was obtained from Aladdin Biochemical Technology Corporation (Shanghai, China). Hydrogen peroxide solution (H_2O_2, 30%, v:v) was obtained from Guangzhou chemical reagent factory (Guangzhou, China). Buffers and all other reagents used in the experiment were of analytical grade. HPLC grade methanol and acetonitrile were obtained from Merck Corporation (Shanghai, China).

The reaction solutions were prepared with Milli-Q water ($\geq 18.2\ M\Omega$ cm). River water (RW) and municipal WWTP effluent (WW) used in the irradiation experiments were sampled in Guangzhou, China. The detailed characteristics of RW and WW are presented in **Supplementary Table S2**.

Irradiation Experiments

The UV/H_2O_2 experiments were performed in a DS-GHX-V photochemical reactor (Doosi Instrument Corporation, Shanghai, China) with a magnetic stirrer, as shown in **Supplementary Figure S1**. A 20 W low-pressure mercury lamp with an output wavelength of mainly 254 nm was equipped as UV irradiation source. The UV lamp was located in the center of the photochemical reactor surrounded by a quartz cooling jacket, which maintained the solution temperature at 25 ± 1.0°C. Experimental solutions were added in a series of 50 ml quartz tubes with a Teflon-coated stir bar, which were placed on the top of the magnetic stirrer. The rotation speed was 100 rpm/min. Based on Canonica et al. (2008), atrazine was used as a chemical actinometer to determine the photon fluence rate under UV irradiation, and the value of photon fluence rate was determined to be 28.74 μE m^{-2} s^{-1} (**Supplementary Text S1**). The kinetic experiments of 17 benzodiazepines by UV/H_2O_2 treatment were conducted in the 10 mM phosphate buffer at pH 7.0. The initial concentration of each benzodiazepine, pCBA and H_2O_2 was set at 100 μg L^{-1} and 100 μM, respectively. The pCBA was simultaneously added in the reaction solutions to quantify hydroxyl radical (·OH) concentration during the UV/H_2O_2 treatment. At predetermined time intervals, 1 ml of the reaction solutions were withdrawn and quenched with TBA (10 mM) to measure the residual concentrations of 17 benzodiazepines and pCBA by ultrahigh-performance liquid chromatograph-triple quadrupole mass spectrometry (UPLC-MS/MS) method. All experiments were performed in triplicate with pH variation of below 0.1 unit.

Experiments were also performed to evaluate the effects of experimental parameters, including H_2O_2 dosage (0–200 μM), solution pH (3.0–11.0), inorganic ions (Cl^-, HCO_3^-, NO_3^-) and dissolved organic matter (humic acid, HA). A higher initial concentration of alprazolam (3,088 μg L^{-1}) and H_2O_2 dosage (1 mM) was conducted for UV/H_2O_2 treatment to facilitate the detection and identification of degradation products by ultrahigh-performance liquid chromatograph-quadrupole time-of-flight mass spectrometer (UPLC-QTOF-MS) method. Besides, the above kinetic experiments were also performed in river water and municipal WWTP effluent.

Analytical Methods

The water quality parameters were characterized as follows. The pH, conductivity, dissolved oxygen (DO) and oxidation reduction potential (ORP) were determined using a YSI Proplus multiparameter meter (YSI, United States). The dissolved organic carbon (DOC) was measured using a Shimadzu TOC-$V_{CSH/CSN}$ and TNM-1 analyzer (SHIMADZU, Japan). Total alkalinity was determined through acidic-titration using a pH 4.2 titration end-point (Yang et al., 2018). The H_2O_2 solution was determined by Jinghua UV1800 UV-Vis spectrophotometry (Shanghai, China) based on $\varepsilon = 40.0\ M^{-1}\ cm^{-1}$ at $\lambda = 240$ nm.

The 17 benzodiazepines and pCBA were analyzed on a Waters Xevo TQ-S triple quadrupole mass spectrometry equipped with a Waters Acquity ultrahigh-performance liquid chromatograph. A BEH C18 column (2.1 × 50 mm, 1.7 μm) was used for the separation. The (A) buffer solution (5 mM CH_3COONH_3 + 0.05% HCOOH) and (B) acetonitrile were used for the mobile phase with the gradient elution program. The gradient was programmed as follows: kept in 20% B at initial, increased to 95% at 5 min, decreased to 20% B to 5.5 min and post time was 1 min. The 17 benzodiazepines and pCBA were analyzed by multiple reaction monitoring (MRM) in positive and negative electrospray ionization mode, respectively. Details MRM transitions and collision were shown in **Supplementary Table S1**. The method quantitation limits (MQLs), method detection limits (MDLs), quality assurance (QA) and quality control (QC) have been reported in our previous study (Lei et al., 2021).

The degradation products of alprazolam during the UV/H_2O_2 treatment were analyzed by Agilent 6545 quadrupole time-of-flight mass spectrometer equipped with an Agilent 1290 II ultrahigh-performance liquid chromatograph. An Agilent Zorbax Eclipse Plus C18 column (3.0 × 150 mm, 1.7 μm) was used for the separation. For positive electrospray ionization (ESI+) analysis, the mobile phase consisted of (A) Milli-Q water with 0.1% formic acid and (B) acetonitrile with 0.1% formic acid at a flow rate of 0.3 ml min^{-1}. For negative electrospray ionization (ESI-) analysis, the mobile phase consisted of (A) buffer solution (1 mM CH_3COONH_3 + 0.1% CH_3COOH) and (B) acetonitrile with 0.1% acetic acid at a flow rate of 0.3 ml min^{-1}. The gradient was programmed as follows: kept in 10% B at first 2 min, increased to 98% at 21 min, kept in 98% B to 24 min, decreased to 10% B to 24.5 min and post time was 5.5 min. The column temperature was set at 30°C. The Agilent 6545 quadrupole time-of-flight mass spectrometer was performed in ESI + or ESI- mode with Dual AJS source. Details spectrometry conditions were shown in **Supplementary Table S3**. The acquired MS and MS/MS data were processed by Agilent MassHunter Workstation Software, containing Qualitative Analysis, Personal Compound database Libraries Manager and Molecular Structure Correlator.

RESULTS AND DISCUSSION

Removal of 17 Benzodiazepines by UV Photolysis and UV/H_2O_2 Treatment

Figure 1 depicts the removal of 17 benzodiazepines by UV irradiation and UV/H_2O_2 treatment in phosphate buffer solution at pH 7.0. Under direct UV photolysis, 97.8% of chlordiazepoxide was rapidly removed within 8 min. Clobazam and temazepam were degraded 42.6 and 47.5% within 20 min, respectively. For the other 14 benzodiazepines, the removal rates only ranged from 6.8 to 28.6% after 20 min of UV irradiation. Thus, the UV photolysis has a low potential to remove these benzodiazepines in water. Kosjek et al. (2012) also reported that oxazepam cannot be degraded in 90 min UV irradiation and only 8% of diazepam was degraded. The 17 benzodiazepines cannot be degraded by 100 μM H_2O_2 treatment within 20 min (data not shown). However, the removal of 17 benzodiazepines was dramatically enhanced by UV/H_2O_2 treatment. The removal rates of 17 benzodiazepines achieved 73.8–100% in 20 min UV/H_2O_2 treatment. This should be attributed to the high reactivity of hydroxyl radicals (·OH) towards benzodiazepines.

Kinetics of Benzodiazepines Removal

The degradation of 17 benzodiazepines followed pseudo-first-order kinetics. The observed rate constants were calculated and are presented in **Table 1** and **Supplementary Figure S2**.

Table 1 shows the $\varphi_{254nm}^{UV,BZDs}$ and $k_{BZDs}^{\cdot OH}$ for the reaction of 17 benzodiazepines degradations by UV photolysis and UV/H_2O_2 treatment. Compared to the other 16 benzodiazepines, chlordiazepoxide has a higher quantum yield of 4.67×10^{-2} mol E^{-1}, which is rapidly removed under direct UV photolysis. The reason might be attributed to the N_4 located in the nitrogen-containing heterocycles of the chlordiazepoxide, which would rapidly form N_4-oxide function under UV photolysis (Ouedraogo et al., 2009). The $\varphi_{254nm}^{UV,BZDs}$ for the remaining 16 benzodiazepines ranged from 0.51×10^{-3} to 4.28×10^{-3} mol E^{-1}. The ·OH reacted with benzodiazepines in phosphate buffer solutions non-selectively, with the $k_{BZDs}^{\cdot OH}$ from 3.48×10^9 to $2.44 \times 10^{10}\ M^{-1}\ s^{-1}$. The second-order rate constant for diazepam reacting with ·OH was determined to be $6.67 \times 10^9\ M^{-1}\ s^{-1}$, which was close to that reported in the previous study ($7.20 \times 10^9\ M^{-1}\ s^{-1}$) (Lopez et al., 2003), and comparable to the QASR predicted value ($1.14 \times 10^{10}\ M^{-1}\ s^{-1}$) (Minakata et al., 2009; Minakata et al., 2014). Slight differences in the second-order rate constants between benzodiazepines might be due to the different groups on the benzodiazepine ring. For example, alprazolam, estazolam, and midazolam had an imidazole or triazole ring group, which had higher reactivity towards ·OH than other benzodiazepine. Compared to chlorine and ozone, the ·OH showed a higher reactivity to benzodiazepines. The second-order rate constant of diazepam, oxazepam and nordiazepam reacting with HOCl was only 1.2, 8.73, and 0.19 $M^{-1}\ s^{-1}$, respectively, (Carpinteiro et al., 2017; Yang et al., 2018). The diazepam reacting with O_3 was only 0.75 M^{-1}

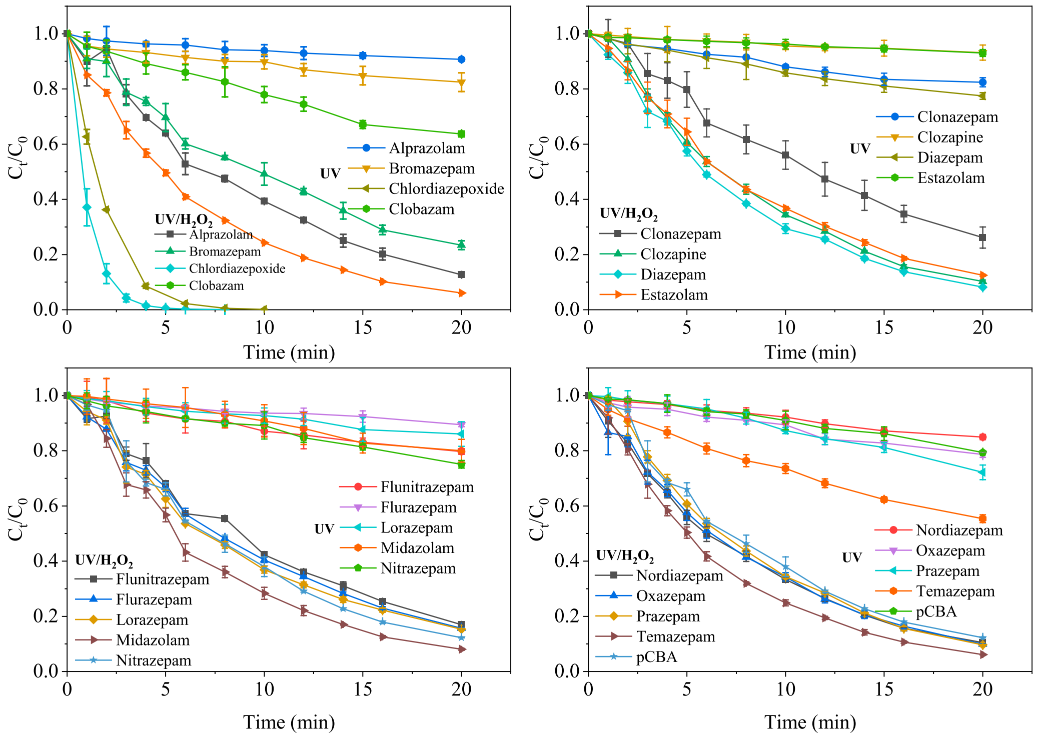

FIGURE 1 | The removal of 17 benzodiazepines and *p*-chlorobenzoic acid (pCBA) by UV irradiation and UV/H_2O_2 treatment. Experimental conditions $[\text{Benzodiazepines}]_0$ = 100 μg L^{-1}, $[\text{pCBA}]_0$ = 100 μg L^{-1}, $[H_2O_2]_0$ = 100 μM, pH = 7.0, E_p^0 = 28.74 μE m^{-2} s^{-1}.

TABLE 1 | The degradation kinetics of 17 benzodiazepines by UV irradiation and UV/H_2O_2 treatment.

Compound	k^{UV}_{BZDs} (s^{-1})	Quantum yield (mol einstein^{-1})	k^{obs}_{BZDs}(s^{-1})	$k^{\cdot OH}_{BZDs}$ (M^{-1} s^{-1})
Alprazolam	0.77×10^{-4}	0.86×10^{-3}	1.72×10^{-3}	5.83×10^{9}
Bromazepam	1.45×10^{-4}	1.33×10^{-3}	1.23×10^{-3}	3.83×10^{9}
Chlordiazepoxide	1.13×10^{-2}	4.67×10^{-2}	1.75×10^{-2}	2.44×10^{10}
Clobazam	3.83×10^{-4}	3.93×10^{-3}	2.33×10^{-3}	6.91×10^{9}
Clonazepam	1.70×10^{-4}	1.65×10^{-3}	1.15×10^{-3}	3.48×10^{9}
Clozapine	0.60×10^{-4}	0.51×10^{-3}	1.87×10^{-3}	6.40×10^{9}
Diazepam	2.18×10^{-4}	2.00×10^{-3}	2.10×10^{-3}	6.67×10^{9}
Estazolam	0.55×10^{-4}	0.65×10^{-3}	1.77×10^{-3}	6.06×10^{9}
Flunitrazepam	1.95×10^{-4}	1.67×10^{-3}	1.48×10^{-3}	4.55×10^{9}
Flurazepam	0.83×10^{-4}	0.89×10^{-3}	1.55×10^{-3}	5.20×10^{9}
Lorazepam	1.27×10^{-4}	1.54×10^{-3}	1.61×10^{-3}	5.23×10^{9}
Midazolam	1.70×10^{-4}	1.96×10^{-3}	2.17×10^{-3}	7.07×10^{9}
Nitrazepam	2.28×10^{-4}	2.04×10^{-3}	1.83×10^{-3}	5.65×10^{9}
Nordiazepam	1.37×10^{-4}	1.16×10^{-3}	1.90×10^{-3}	6.24×10^{9}
Oxazepam	1.97×10^{-4}	1.70×10^{-3}	1.92×10^{-3}	6.06×10^{9}
Prazepam	2.70×10^{-4}	2.62×10^{-3}	1.98×10^{-3}	6.08×10^{9}
Temazepam	4.87×10^{-4}	4.28×10^{-3}	2.35×10^{-3}	6.61×10^{9}

s^{-1} (Huber et al., 2003). Thus, the UV/H_2O_2 treatment could effectively remove benzodiazepines from water.

In order to compare the relative contributions of UV photolysis and ·OH reaction during UV/H_2O_2 treatment, the 17 benzodiazepines were grouped according to the specific value for k^{UV}_{BZDs} and $k^{\cdot OH}_{BZDs}$. **Supplementary Figure S2** shows the pseudo-first-order rate constants (k_{obs}) for the reaction of 17 benzodiazepines by UV/H_2O_2 treatment. The observed fractions of k^{UV}_{BZDs} and $k^{\cdot OH}_{BZDs}$ were significantly different for 17 benzodiazepines. For chlordiazepoxide in the group I ($k^{\cdot OH}_{BZDs}/k^{UV}_{BZDs}$ <1), the direct UV photolysis played a dominant role in UV/H_2O_2 treatment. For temazepam, clobazam, clonazepam, prazepam, flunitrazepam, nitrazepam, bromazepam, diazepam, and oxazepam in the group II (1 < $k^{\cdot OH}_{BZDs}/k^{UV}_{BZDs}$ <10), both UV photolysis and ·OH reaction contributed to the degradation.

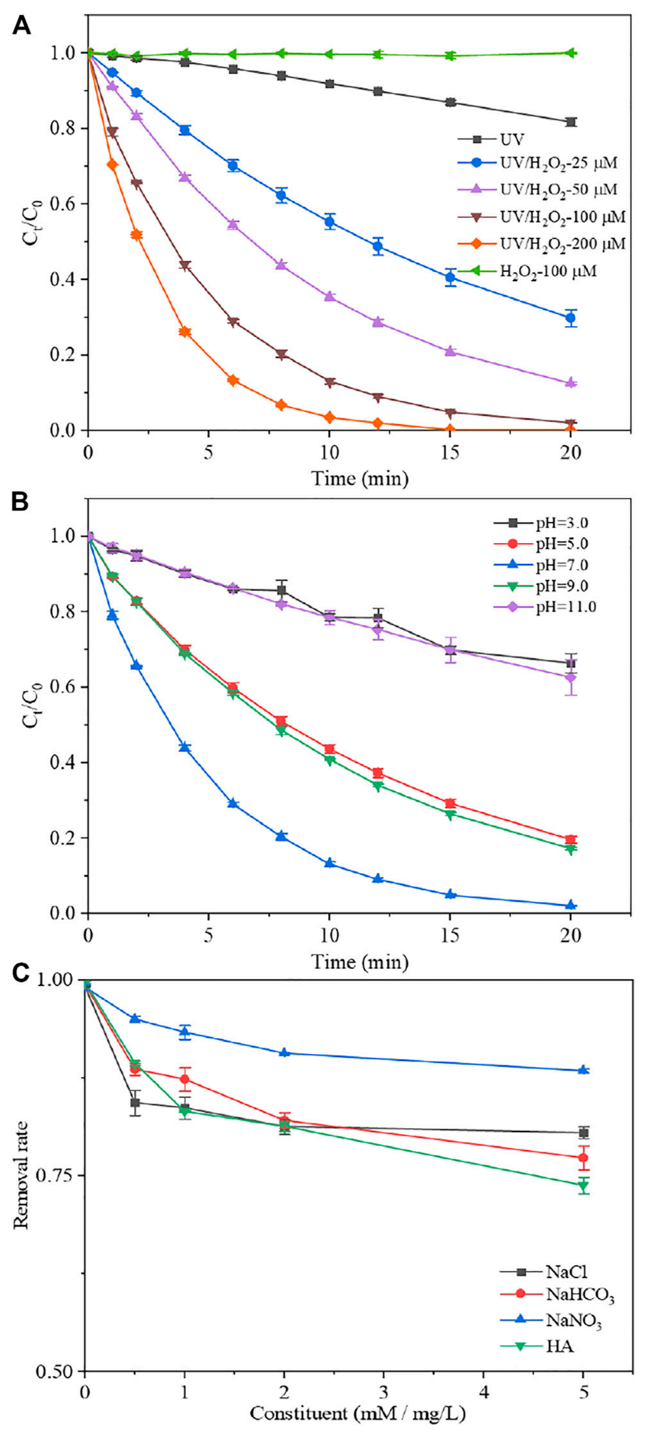

FIGURE 2 | Effect of H_2O_2 dosage **(A)**, solution pH **(B)** and inorganic ions (Cl^-, HCO_3^-, NO_3^-) and humic acid (HA) **(C)** on the removal of alprazolam by UV/H_2O_2 treatment. Experimental conditions: $[\text{alprazolam}]_0 = 308.8$ μg L^{-1}, $[H_2O_2]_0 = 0–200$ μM, pH = 3.0–7.0, $[Cl^-, HCO_3^-, NO_3^-]_0 = 0–5$ mM and $[HA]_0 = 0–5$ mg/L, $E_p^0 = 28.74$ μE m^{-2} s^{-1}.

For lorazepam, midazolam, nordiazepam, flurazepam, alprazolam, clozapine, and estazolam in the group III ($k^{\cdot OH}_{BZDs}/k^{UV}_{BZDs}$ >10), the ·OH reaction played a dominant role. The findings suggest that the treatment approach can be selected according to the occurrence of benzodiazepines in real water.

Effects of Operational Parameters

Experiments were performed to evaluate the effects of operational parameters and water quality on the degradation of a typical benzodiazepine, alprazolam, during UV/H_2O_2 treatment.

Effect of H_2O_2 Dosage

The degradation of alprazolam by UV irradiation, H_2O_2 oxidation and UV/H_2O_2 treatment in phosphate buffer at pH 7.0 is shown in **Figure 2A**. Alprazolam was not degraded by 100 μM H_2O_2 treatment. In the presence of direct UV irradiation, only 18.3% of alprazolam was removed within 20 min. The removal efficiency of alprazolam by UV/H_2O_2 treatment at a H_2O_2 concentration of 25 μM was up to 70.2% within 20 min. The apparent rate constant (k_{obs}) of alprazolam increased from 1.0×10^{-3} to 5.5×10^{-3} s^{-1} when the H_2O_2 concentration increased from 25 to 200 μM. A linear relationship between k_{obs} and H_2O_2 concentration ($R^2 = 0.99$) was observed, which was due to the enhanced formation of ·OH at higher H_2O_2 concentrations. Similar results have been reported in degradation of oxytetracycline and tetracycline by UV/H_2O_2 treatment (Lopez-Penalver et al., 2010; Liu et al., 2016).

Effect of Solution pH

Figure 2B depicts the effect of solution pH on the alprazolam degradation by UV/H_2O_2 treatment in phosphate buffer at pH 7.0. Results showed that the degradation of alprazolam was inhibited at both acidic and alkaline conditions, and the highest k_{obs} (3.27×10^{-3} s^{-1}) was observed at pH 7.0. The inhibition at pH 3.0 and 5.0 might be attributed to the strong scavenging effect of H^+, $H_2PO_4^{2-}$, and $H_2PO_4^-$ at acidic conditions (Kong et al., 2016). At alkaline conditions, the self-decomposition rate of H_2O_2 increased rapidly (Lee et al., 2020). In addition, hydroperoxide anion (HO_2^-) could consume ·OH and decreased the steady-state concentrations of ·OH (Tan et al., 2013; Liu et al., 2016).

Effects of Coexisting Constituents

Effects of anions (Cl^-, HCO_3^-, NO_3^-) and humic acid (HA) that are ubiquitous in water and wastewater on the alprazolam degradation by UV/H_2O_2 treatment were evaluated. As shown in **Figure 2C**, adding Cl^- (0–5 mM) has a negative impact on UV/H_2O_2 treatment. When 5 mM NaCl was added to aqueous solutions, the removal rate of alprazolam decreased by 16.7%. A possible reason was that ·OH could react with Cl^- to form reactive chlorine species (Cl_2^-, Cl^-, $ClHO^-$), whose redox potentials are much lower than that of ·OH (Truong et al., 2004; Deng et al., 2013). The addition of HCO_3^- also affected the removal rate of alprazolam. With the increasing concentration of HCO_3^- (0–5 mM), the removal rate dropped gradually. HCO_3^- is a well-known scavenger of ·OH in solutions. HCO_3^- reacted with ·OH to produce carbonate radicals, which are more selective and less reactive towards organic contaminants than ·OH (Xiang et al., 2016; Yang et al., 2019). As exhibited, NO_3^- showed a negligible impact on the removal rate of

TABLE 2 | The degradation products of alprazolam during the UV/H_2O_2 treatment.

Compounds	Retention time (min)	Experimental mass [(M + H)$^+$]	Proposed formula	MS/MS fragments	References
alprazolam	13.186	309.0919	$C_{17}H_{13}ClN_4$	205.0767 281.0718	Mitsika et al. (2021)
TP248	8.317	249.0534	$C_{11}H_9ClN_4O$	220.0271 179.0003	Finčur et al. (2017); Mitsika et al. (2021)
TP324-1	10.215	325.0864	$C_{17}H_{13}ClN_4O$	297.0661 221.0704	Finčur et al. (2017); Jimenez et al. (2017); Mitsika et al. (2021); Romeiro et al. (2017)
TP324-2	11.052	325.0864	$C_{17}H_{13}ClN_4O$	298.0688 221.0703	Finčur et al. (2017); Jimenez et al. (2017); Mitsika et al. (2021)
TP324-3	13.842	325.0864	$C_{17}H_{13}ClN_4O$	297.0698 271.0618	Finčur et al. (2017); Jimenez et al. (2017); Mitsika et al. (2021)
TP340-1	9.375	341.0800	$C_{17}H_{13}ClN_4O_2$	313.0604 237.0658	This study
TP340-2	12.006	341.0800	$C_{17}H_{13}ClN_4O_2$	313.0602 287.0577	This study

alprazolam. With addition of 5 mM NO_3^- in aqueous solutions, the removal rate only decreased 8.7%. This result may be due to the low concentration level of NO_3^- was used in this study. Besides, NO_3^- may have a weak scavenging effect on ·OH. Previous studies reported that low concentration of NO_3^- had a slight impact on 1,4-dioxane degradation by UV/H_2O_2 treatment (Lee et al., 2020). The addition of humic acid (HA) had an obviously inhibitory effect on the removal rate of alprazolam. The removal rate reduced from 98.7 to 73.8% when HA was added from 0 to 5 mg/L in aqueous solutions. Generally, the HA is the main component of dissolved organic matter (DOM). It has a fast-quenching effect on ·OH and acts as a scavenger in UV/H_2O_2 treatment. HA can significantly impact the oxidative degradation of micropollutants through electrostatic interactions (Kim et al., 2017), photosensitization (Latifoglu and Gurol, 2003) and binding effects (Yang et al., 2021). Thus, the possible reasons for our findings were as follows: Firstly, HA can compete with alprazolam for ·OH reaction; Secondly, the high concentration of HA could impede the UV irradiation and reduce the ·OH generation (Xie et al., 2019; Yang et al., 2021).

Products of Alprazolam Degradation

Six degradation products of alprazolam during UV/H_2O_2 treatment were detected by quadrupole time-of-flight mass spectrometer. The experimental mass, proposed formula, MS/MS fragments are listed in **Table 2**, and their chromatographic and mass spectrogram are provided in **Supplementary Figures S3–S6**. The TP340-1 (*m/z* 341.0800) and TP340-2 (*m/z* 341.0800) were firstly reported as degradation products of alprazolam for UV/H_2O_2 treatment. Two degradation products with *m/z* 341.0800 were detected at different retention times 9.375 and 12.006 min, indicating the addition of ·OH group on the benzene ring. But the exact substitution position could not be confirmed by MS/MS fragments. The TP248, TP324-1, TP324-2, and TP324-3 have been reported in the removal of alprazolam by heterogeneous photocatalysis and photo-Fenton oxidation processes (Finčur et al., 2017; Jimenez et al., 2017; Mitsika et al., 2021). According to two characteristic fragment ions m/z 220.0271 and 179.0003 amu, TP248 (*m/z* 249.0534) might be generated from the removal of phenyl group in alprazolam and the simultaneous addition of a hydroxyl group. The TP324 (*m/z* 325.0864) was observed in three different retention times 10.215, 11.052, and 13.842 min, respectively. Thus, TP324 (*m/z* 325.0864) should be ·OH adding in different positions of alprazolam.

Based on the identification of the degradation products, the hydroxylation substitution reaction was the major pathway for alprazolam degradation during UV/H_2O_2 oxidation process. The ·OH is known as a reactive electrophilic reagent that reacts rapidly and non-selectively with most electron-rich sites of organic pollutants, mainly via H-atom abstraction, addition to olefins, and addition to aromatic compounds. As shown in **Figure 3**, the degradation of alprazolam could be divided into route A and route B. In route A, hydroxylation occurred at the initial of alprazolam degradation, producing hydroxylated alprazolam, TP324-1, TP324-2, and TP324-3. Further hydroxylation can form multi-hydroxylated byproducts TP340 (*m/z* 341.0800). In route B, the alprazolam (*m/z* 309.0919) might cleavage between seven number nitrogen-containing heterocycles and the benzene ring, corresponding to detach the phenyl group. Followed by hydroxylation, hydroxylated byproducts TP-248 (*m/z* 249.0534) was generated, according to the previous studies (Mitsika et al., 2021).

Degradation of 17 Benzodiazepines in Real Water Samples

The degradation of 17 benzodiazepines by UV/H_2O_2 treatment was evaluated in the phosphate buffer solutions, river water (RW) and municipal WWTP effluent (WW), as shown in **Figure 4**. The k_{obs} for the 17 benzodiazepines decreased from 26.9% (bromazepam) to 65.0% (prazepam) in RW and from 46.1% (chlordiazepoxide) to 84.0% (clobazam) in WW, compared to those in the phosphate buffer. The obvious inhibitory effect can

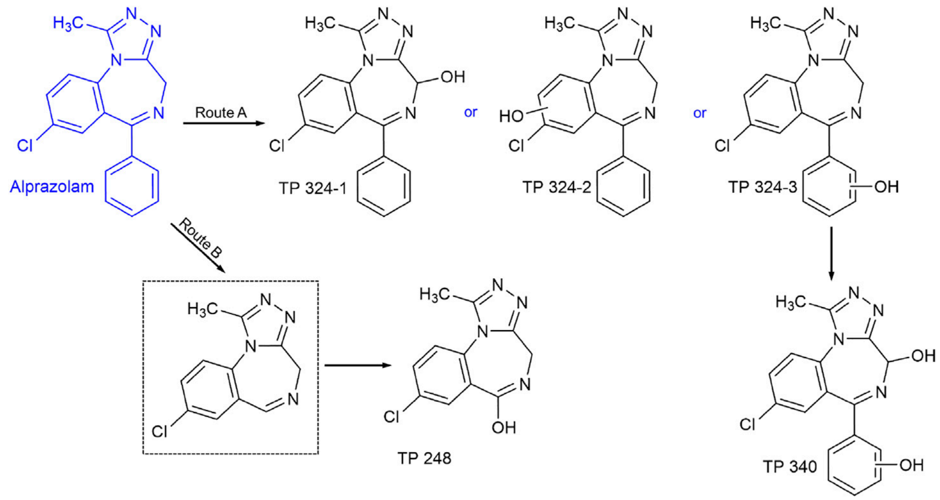

FIGURE 3 | Proposed degradation pathways of alprazolam in UV/H_2O_2 oxidation.

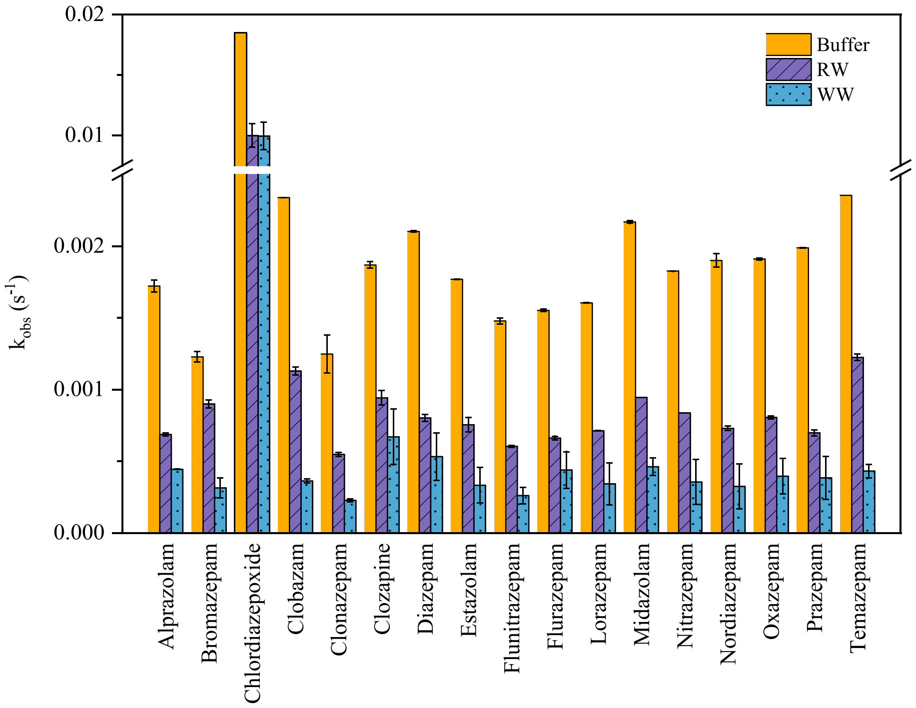

FIGURE 4 | The degradation kinetics of 17 benzodiazepines by UV/H_2O_2 treatment in the phosphate buffer solutions, river water (RW) and municipal WWTP effluent (WW). Experimental conditions $[\text{benzodiazepines}]_0$ = 100 μg L^{-1}, $[H_2O_2]_0$ = 100 μM, pH = 7.0, E_p^0 = 28.74 μE m^{-2} s^{-1}.

be explained by the anions and dissolved organic matter in the RW and WW, which had been demonstrated according to **Figure 2** and previous studies (Deng et al., 2013; Wang et al., 2017; Ribeiro et al., 2019). The WW had the higher DOC concentration (7.2 mg L^{-1}), Cl^- concentration (78.1 mg L^{-1}), NO_3^- concentration (32.1 mg L^{-1}), and alkalinity (2.03 mg L^{-1}) than that of RW (4.2 mg L^{-1} DOC, 40.3 mg L^{-1} Cl^-, 22.9 mg L^{-1} NO_3^-, and 1.28 mg L^{-1} alkalinity). Consequently, the benzodiazepine psychoactive drugs can be effectively removed by the UV/H_2O_2 treatment in real water.

CONCLUSIONS

The UV/H_2O_2 treatment dramatically enhanced the removal of benzodiazepines in aqueous solutions, compared to UV irradiation or H_2O_2 oxidation. This can be attributed to the high reactivity of ·OH reactivity towards benzodiazepines. The determined $k^{\cdot OH}_{BZDs}$ in phosphate buffer solutions at pH 7.0 ranged from 3.48×10^9 M^{-1} s^{-1} to 2.44×10^{10} M^{-1} s^{-1}. The water quality parameters, such as H_2O_2 dosage, solution pH and co-existing species, had a significant effect on the removal of alprazolam by UV/H_2O_2 treatment. Six degradation products of alprazolam were detected. The hydroxylation was proposed to be the main reaction mechanism in UV/H_2O_2 treatment. This study demonstrated that UV/H_2O_2 treatment is capable of degrading benzodiazepines in natural waters.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

W-DY: Formal analysis, Investigation, Writing–original draft. PY: Investigation. BY: Conceptualization, Writing–review and editing, Funding acquisition, Resources, Supervision. XL: Investigation. JF: Investigation. Z-TM: Investigation. J-LS: Writing–review and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fenvs.2021.764841/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.