

## Photochemical fate of the vasodilator drug pentoxifylline in surface waters

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### ABSTRACT

This study is the first to comprehensively investigate the photochemical fate of pentoxifylline in natural water systems. Among all attenuation processes, indirect sunlight photolysis is very likely the primary process for pentoxifylline degradation. The combination of dissolved organic matter (represented by fulvic acid),  $\text{NO}_3^-$  and  $\text{HCO}_3^-$  closely simulated the photolysis rate in real surface water (Jingmei River, Taipei) ( $t_{1/2} = 34.7 \pm 2.2$  h), indicating that these three parameters are the most important determinants of the photolysis fate of pentoxifylline. The results also showed that  $\text{HCO}_3^-$  contributes to photodegradation of pentoxifylline in the  $\text{NO}_3^-$  system due to the participation of  $\cdot\text{CO}_3^-$ . Although pentoxifylline was degraded, total organic carbon remained constant during the photolytic process, indicating that byproducts were generated in the solution. Five byproducts that have not been previously reported are proposed for the first time in this study. Among all of the byproducts, two byproducts (P4 (M.W. = 250) and P5 (M.W. = 227)) were only detected in the presence of  $\text{NO}_3^-$  and  $\text{HCO}_3^-$ , implying that  $\cdot\text{CO}_3^-$  possibly caused different photolytic pathways of pentoxifylline.

**Key words** | bicarbonate, nitrate, pentoxifylline, sunlight photolysis, transformation byproducts

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### INTRODUCTION

Pentoxifylline, which belongs to a group of vasodilators called methylxanthines, is used for the treatment of peripheral arterial disease and helps with blood circulation in human bodies. Pentoxifylline increases the blood flow by decreasing the viscosity of blood and decreases the potential for platelet aggregation and thrombus formation.

According to National Health Insurance medicine usage data from 2015 in Taiwan, the usage of pentoxifylline was 21.5 tons. Due to its wide usage, pentoxifylline residues have been detected in various water matrices of different countries. For example, in Taiwan, pentoxifylline has been observed in drug production facilities and hospitals, with maximum concentrations of 1,370 and 302 ng/L, respectively (Lin *et al.* 2008). It has also been detected in the influents (98–191 ng/L) and effluents (56–147 ng/L) of wastewater treatment plants (WWTPs) and even in the groundwater (0.4–2.4 ng/L) in

Taiwan (Lin *et al.* 2009, 2015). In other countries, such as Romania and Canada, pentoxifylline has been detected at maximum concentrations of 299 and 45 ng/L in WWTP influents and effluents, respectively (Hua *et al.* 2006; Moldovan *et al.* 2009). Pentoxifylline has also been found in the Rhine River in Germany at a maximum concentration of 570 ng/L (Sacher *et al.* 2008). Several researchers have investigated the acute toxicity of pentoxifylline (Hansen 1994; Beshay *et al.* 2001; Ruddock & Hirst 2005); however, there is still a lack of information regarding its chronic toxicity, as well as potential risks to aquatic organisms due to the presence of pentoxifylline residues in aqueous environments.

Currently, little information is available regarding the environmental fate of pentoxifylline. Although pentoxifylline can be strongly hydrolyzed ( $t_{1/2} < 1$  day at pH = 13 at high temperatures (80 °C)), it is stable in typical environmental

waters (pH ~ 7, T ~ 20 °C) with very slow hydrolysis rates (no change in 4 days) (Mone & Chandrasekhar 2010); moreover, it cannot be eliminated through volatilization because its Henry's law constant is low ( $9.8 \times 10^{-14}$  atm m<sup>3</sup>/mole). Pentoxifylline has a low octanol-water partitioning coefficient ( $\log K_{ow} = 0.56$ ) (Udrescu *et al.* 2008), implying that it is unlikely to be attenuated through sorption or biotransformation in aqueous environments. Therefore, sunlight photolysis may be the predominant process determining the natural fate of pentoxifylline. Researchers have suggested that sunlight photolysis may significantly reduce many types of recalcitrant pharmaceuticals (e.g. cephalosporins, sulfonamides, fluoroquinolones,  $\beta$ -agonists, controlled drugs and chemotherapeutic drugs) in aqueous environments (Boreen *et al.* 2004; Wang & Lin 2012; Yang *et al.* 2013; Lin *et al.* 2014b; Sturini *et al.* 2015). However, to date, no information exists regarding the sunlight-mediated photochemical behavior of pentoxifylline.

Sunlight photochemical reactions in aqueous environments include direct and indirect photolysis (Schwarzenbach *et al.* 2005). The former occurs via light absorption by compounds, resulting in bond cleavage; the latter is triggered via light absorption by photosensitizers, such as dissolved organic matter (DOM), NO<sub>3</sub><sup>-</sup> and NO<sub>2</sub><sup>-</sup>, which produce reactive species that subsequently react with the target chemicals. HCO<sub>3</sub><sup>-</sup> has also been thought to affect the photolysis behavior; however, the overall effect of HCO<sub>3</sub><sup>-</sup> seems to be compound-dependent. Researchers have recently reported that the presence of HCO<sub>3</sub><sup>-</sup> enhances the photolysis rate of 5-fluorouracil, 4-halogenophenol, catechol and cephalosporins due to the generation of carbonate radicals ( $\cdot\text{CO}_3^-$ ) in the presence of NO<sub>3</sub><sup>-</sup> (Vione *et al.* 2009; Wang & Lin 2012; Lin *et al.* 2013). Many other studies have also reported that HCO<sub>3</sub><sup>-</sup> inhibits the photolysis rate when NO<sub>3</sub><sup>-</sup> is present in the solution (Lam *et al.* 2003; Chowdhury *et al.* 2011). HCO<sub>3</sub><sup>-</sup> is present at high concentrations in surface water (1–3 mM) (Hem & Geological Survey (US) 1985; Brezonik & Fulkerson-Brekken 1998), and the estimated concentration of  $\cdot\text{CO}_3^-$  ( $10^{-13}$ – $10^{-14}$  M) is higher than that of hydroxyl radicals ( $\cdot\text{OH}$ ) ( $10^{-16}$ – $10^{-18}$  M) (Mill *et al.* 1980; Russi *et al.* 1982; Huang & Mabury 2000b), with a difference of more than two orders of magnitude under sunlight irradiation. Therefore, it is interesting to investigate the influence of HCO<sub>3</sub><sup>-</sup> on the phototransformation behavior of pentoxifylline.

The purpose of this work was to investigate the sunlight photodegradation behavior of pentoxifylline in natural surface water environments. Water parameters, including DOM, NO<sub>3</sub><sup>-</sup> and HCO<sub>3</sub><sup>-</sup>, as well as their competing effects, were studied. Phototransformation byproducts and pathways during the solar photodegradation of pentoxifylline were also investigated. To the best of our knowledge, this is the first investigation of the sunlight photolysis of pentoxifylline in surface waters.

## MATERIALS AND METHODS

### Chemicals

Pentoxifylline (99%), formic acid, ammonium acetate, sodium nitrate (NaNO<sub>3</sub>) and sodium bicarbonate (NaHCO<sub>3</sub>) were purchased from Sigma-Aldrich (St Louis, MO, USA). HPLC-grade methanol was purchased from Avantor Performance Materials (Phillipsburg, NJ, USA). The Suwannee River Fulvic Acid (FA) standard (1S101F) was obtained from the International Humic Substance Society (St Paul, MN, USA). FA, NaNO<sub>3</sub> and NaHCO<sub>3</sub> were used as the source of DOM, NO<sub>3</sub><sup>-</sup> and HCO<sub>3</sub><sup>-</sup> in this study, respectively. Individual stock standard solutions (pentoxifylline, FA, NaNO<sub>3</sub> and NaHCO<sub>3</sub>) were prepared on a weight basis (1,000 mg/L) using Milli-Q water and were stored in amber glass bottles at 4 °C for a maximum of 30 days. The physicochemical properties of pentoxifylline are shown in Table S1 (available with the online version of this paper).

### Surface water sampling

Grab samples (2 L) were collected in amber glass bottles from the Jingmei River, which is located in southern Taipei, in July 2012. The Jingmei River, one of the main rivers located in the southwest of the Taipei Basin, has a length of 28 km and a drainage area of 114 km<sup>2</sup>. The average flow rate of the Jingmei River is 1,952,460 m<sup>3</sup>/day. The stream drainage range of the upstream Jingmei River includes wastewater from approximately 150 hospitals and clinics and 10 animal husbandries, and our past works have shown that various pharmaceuticals were found constantly and at significant concentrations in this drainage

area (Lin *et al.* 2008, 2010a, 2010b, 2014a). All water samples (except for the ones used for the incubation experiments from the Jingmei River) were vacuum-filtered through 0.22- $\mu\text{m}$  cellulose acetate membrane filters (Advantec, Toyo Roshi Kaisha, Japan) and stored in a 4 °C refrigerator until analysis. The water parameters, including the pH, dissolved organic carbon (DOC),  $\text{NO}_3^-$  and alkalinity of the grab samples, were analyzed.

### Photolysis experiment setup

Photochemical experiments were conducted in a sunlight simulator (Suntest CPS; Atlas, Chicago, IL, USA) equipped with a 1.5-kW xenon arc lamp; detailed operating conditions have been previously reported (Lin *et al.* 2014a, 2014b). A Suprax filter was fitted to allow a total passing wavelength range of 290–800 nm, and the irradiation intensity and the illumination time was set to 765  $\text{W}/\text{m}^2$  and 40 h for all photolysis experiments, respectively. For the photolysis experiments, the target compound pentoxifylline and other reagents (FA,  $\text{NO}_3^-$  and  $\text{HCO}_3^-$ ) were spiked into Milli-Q water in the reactor to achieve the desired concentrations. Individual standards of pentoxifylline in Milli-Q water (20  $\mu\text{g}/\text{L}$ ) were placed in capped quartz glass reaction tubes (1.6-cm i.d.  $\times$  13.5-cm depth, volume of 27 mL) and exposed to radiation from a sunlight simulator maintained at  $20 \pm 1$  °C with a thermostat. Dark control experiments of the same concentrations were scrupulously maintained in darkness. The solution pH was adjusted to 7.0 (using 1.0 N sulfuric acid and 1.0 N sodium hydroxide) for all synthetic waters and was maintained at 7.0 throughout the reaction, except for those meant to simulate the Jingmei River waters (which were adjusted to a pH of 7.7 to match). The synthetic waters were prepared with the Suwannee River FA standard,  $\text{NaNO}_3$  and  $\text{NaHCO}_3$ . The overall experimental framework of this study is provided in Figure S1 (available with the online version of this paper).

### Incubation test

An incubation test was conducted in the dark at 20 °C for pentoxifylline (20  $\mu\text{g}/\text{L}$ ) in the Jingmei River water (unfiltered) for 46 h.

### Analysis methods

The chromatographic separation of pentoxifylline and byproducts was performed using an Agilent 1200 module (Agilent, Palo Alto, CA, USA) equipped with a ZORBAX Eclipse XDB-C<sub>18</sub> column (150  $\times$  4.6 mm, 5  $\mu\text{m}$ ). Mass spectrometric measurements were performed on a Sciex API 4000 (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization (ESI) interface. For the byproduct study, pentoxifylline was investigated at a high initial concentration (20 mg/L). The full scan mode was used to detect byproducts in the degradation mixture and to obtain the mass spectra of those byproducts (Figure S2, available with the online version of this paper). The signal areas of the byproducts were quantified with liquid chromatography-tandem mass spectrometry (LC-MS/MS). Detailed information regarding the LC-MS/MS operations and the byproduct investigation is presented in the Supplementary text.

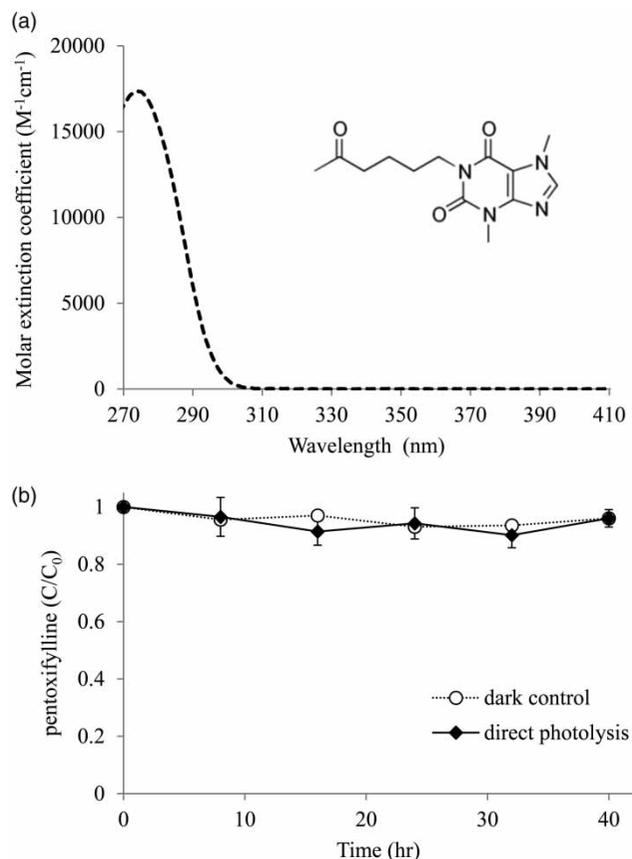
An ACD MS fragmenter (Advanced Chemical Development, Toronto, ON, Canada) was used to generate a tree fragmentation for the structure of pentoxifylline based on mass spectrometry fragmentation rules; additionally, the selected ESI ionization mode and the number of fragmentation steps were used to identify the byproducts of photolysis. The tree fragmentations of the parent compound pentoxifylline were used to identify the product ions from the mass spectra of their byproducts, and the product ions were then combined to predict the structures of the byproducts (Lin *et al.* 2014a; Lai *et al.* 2015).

A total organic carbon (TOC) analysis was conducted using an OI Analytical model 1030 (OI Analytical, College Station, TX, USA) with an autosampler (OI Analytical model 1088). Prior to the analysis, the samples were acidified and sparged with nitrogen to remove inorganic carbon. The standard solutions for calibration were prepared using potassium hydrogen phthalate.

## RESULTS AND DISCUSSION

### Direct photolysis

The UV-vis spectrum of pentoxifylline was measured at pH of 7.0. According to the absorption spectrum (Figure 1(a)),



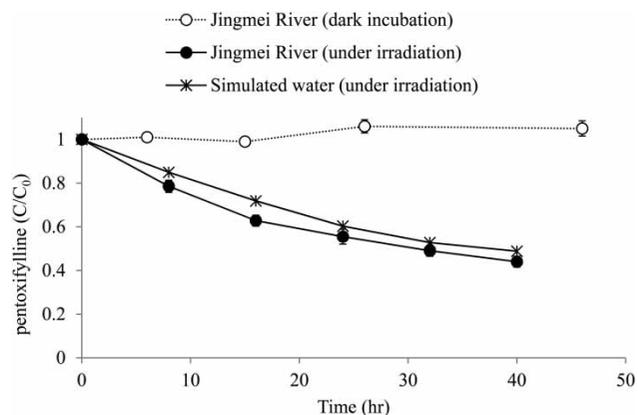
**Figure 1** | (a) The UV-vis absorption spectra of pentoxifylline in DI water; (b) the direct photolysis of pentoxifylline in DI water.

pentoxifylline can absorb light at wavelengths  $>290$  nm, implying that pentoxifylline may have direct photolysis potential. However, our experimental data (Figure 1(b)) showed that pentoxifylline was not degraded under direct photolysis at pH 7.0; this finding may occur because although pentoxifylline was promoted to an excited state, it quickly dropped to its ground state by heat transfer (vibrational loss of energy), luminescence (energy loss of light emission) or photosensitization (energy transfer promoting an electron in another chemical species) (Schwarzenbach *et al.* 2005).

### Indirect photolysis in natural surface waters

Although pentoxifylline cannot undergo direct photolysis, our results showed that it could be photodegraded via indirect photolysis. This phenomenon indicates that the components of the natural water matrix contribute to the

photodegradation of pentoxifylline. In natural surface water, DOM,  $NO_3^-$  and  $HCO_3^-$  are widely present, and these are major factors that affect the photolytic process. According to a survey of natural water bodies, the concentrations are generally in the range of 2.2–17.8 mg C/L for DOM, 0.2–20.1 mg N/L for  $NO_3^-$  and 1–3 mM for  $HCO_3^-$  (Cooper & Zika 1983; Hem & Geological Survey (US) 1985; Brezonik & Fulkerson-Brekken 1998; Huang & Mabury 2000b). In this study, DOM,  $NO_3^-$  and  $HCO_3^-$ , as well as the target compound pentoxifylline, were investigated at environmentally relevant concentrations. The Jingmei River (pH = 7.7, (DOC) = 1.5 mg/L, ( $NO_3^-$ ) = 1.2 mg/L, ( $HCO_3^-$ ) = 0.8 mM) was chosen for our investigation of the photolytic process of pentoxifylline in a surface water environment. The Jingmei River, located in southern Taipei, has a length of 28 km and a drainage area of 114 km<sup>2</sup>. Figure 2 shows that pentoxifylline can be photo-degraded in the Jingmei River ( $t_{1/2} = 34.7 \pm 2.2$  h). We also conducted a photolysis experiment in synthetic water containing the same  $NO_3^-$ ,  $HCO_3^-$  and DOM concentrations as the Jingmei River. We found that the photodegradation of pentoxifylline in synthetic water was very similar to that in the real Jingmei River water, indicating that  $NO_3^-$ ,  $HCO_3^-$  and DOM are the most important factors determining the photolytic fate of pentoxifylline in natural surface waters. This result is in accordance with our previous studies, which investigated the sunlight photolysis of cephalosporin antibiotics and also found that these three water parameters were the strongest determinants (Wang & Lin 2012). A dark



**Figure 2** | Indirect photolysis and dark incubation experiment of pentoxifylline in Jingmei River water (pH = 7.7, [DOC] = 1.5 mg/L, [ $NO_3^-$ ] = 1.2 mg/L, [ $HCO_3^-$ ] = 0.8 mM) and simulated water.

incubation experiment was conducted to examine the potential of sorption and biodegradation (Figure 2). The results showed that no degradation occurred during the 46 h of reaction time, indicating that pentoxifylline is unlikely to undergo sorption or biodegradation in aqueous environments. Consequently, sunlight photolysis should be the most important natural attenuation pathway for pentoxifylline. To better understand the effect of each water parameter and their combined effects on the photodegradation of pentoxifylline, we examined the photodegradation of pentoxifylline in deionized (DI) water spiked with DOM,  $\text{NO}_3^-$  and  $\text{HCO}_3^-$  in the following experiments.

### Influence of DOM

In this study, we used the Suwannee River FA standard to simulate and study the influence of DOM on the photolysis of pentoxifylline. The results shown in Figure 3 demonstrate that pentoxifylline can be slightly photodegraded in the presence of FA (5 and 10 mg/L), indicating that DOM-derived reactive species can interact with pentoxifylline. DOM can be excited to an excited triplet state ( $^3\text{DOM}^*$ ) and thereby produce photoreactants such as singlet oxygen ( $^1\text{O}_2$ ), peroxy radicals ( $\cdot\text{ROO}$ ) and aqueous electrons ( $e_{\text{aq}}^-$ ) (Sandvik *et al.* 2000; Boreen *et al.* 2005), which react with pentoxifylline accordingly. However, the effect of DOM on the photolysis of pentoxifylline was not significant, perhaps because DOM itself may also serve as a sink for these reactive species (Wenk *et al.* 2011; Wang & Lin 2012).

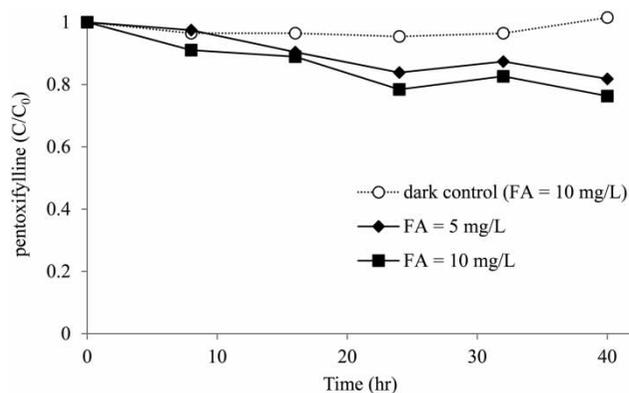


Figure 3 | The influence of DOM on the photolysis of pentoxifylline.

### Influence of $\text{NO}_3^-$

Under the photolytic irradiation of  $\text{NO}_3^-$ , a common water component,  $\cdot\text{OH}$ , was produced (Haag & Hoigne 1985; Zepp *et al.* 1987), which has a strong oxidizing ability on most organic compounds. In this study, the effect of  $\text{NO}_3^-$  on the photolytic degradation of pentoxifylline was investigated in the range of 1–30 mg/L (Figure 4(a)). The results showed that the photodegradation rate of pentoxifylline increased when the  $\text{NO}_3^-$  concentration increased. The photolysis half-life ( $t_{1/2}$ ) was significantly shortened from  $73.7 \pm 16.7$  to  $26.4 \pm 4.4$  h when the  $\text{NO}_3^-$  concentration increased from 1 to 5 mg/L. Further increases in the  $\text{NO}_3^-$  concentration (10 and 30 mg/L) led to further decreases in the photolysis half-life ( $13.9 \pm 1.1$  and  $5.4 \pm 1.1$  h). Other studies have also demonstrated that the presence of  $\text{NO}_3^-$  in an aqueous solution results in an accelerated photodegradation of organic compounds (Andreozzi *et al.* 2003; Calza *et al.* 2012; Koumaki *et al.* 2015).

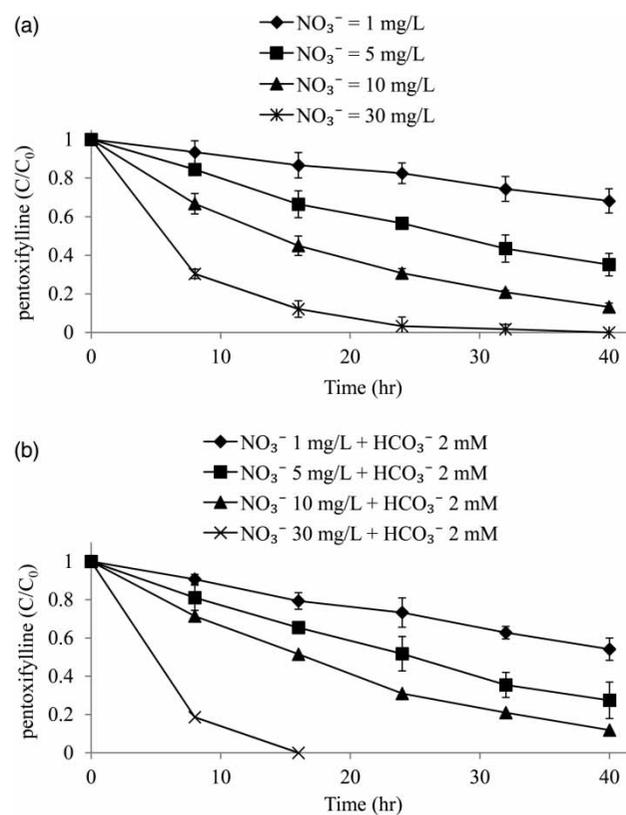


Figure 4 | The influence of (a)  $\text{NO}_3^-$  and (b)  $\text{NO}_3^- + \text{HCO}_3^-$  on the photolysis of pentoxifylline.

### Influence of $\text{HCO}_3^-$ in the $\text{NO}_3^-$ system

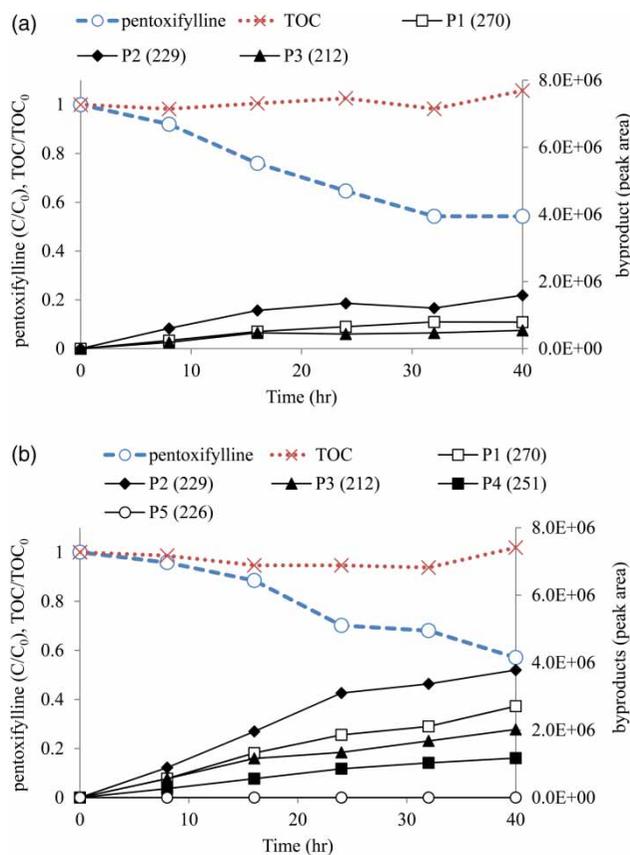
Figure 4(b) shows the photodegradation of pentoxifylline in the presence of both  $\text{NO}_3^-$  and  $\text{HCO}_3^-$ . The results illustrate the contribution of  $\text{HCO}_3^-$  in the photolysis of pentoxifylline (the half-lives are shown in Table S2, available with the online version of this paper). For example, in the  $\text{NO}_3^-$  system (1 mg/L) alone, the half-life of pentoxifylline was  $73.7 \pm 16.7$  h; however, in the presence of  $\text{HCO}_3^-$  (2 mM), the half-life was altered to  $47.8 \pm 6.3$  h.  $\text{HCO}_3^-$ , one of the most common constituents in natural surface waters, has been considered to scavenge  $\cdot\text{OH}$  and subsequently generate  $\cdot\text{CO}_3^-$  (Buxton *et al.* 1988):



Compared to  $\cdot\text{OH}$ ,  $\cdot\text{CO}_3^-$  is a highly selective oxidant and is less scavenged by DOM, which leads to a higher steady-state concentration in natural surface water systems (Huang & Mabury 2000b; Canonica *et al.* 2005). In addition, the existence of  $\text{HCO}_3^-$  has been reported to induce a higher generation rate of reactive species during the photolysis of  $\text{NO}_3^-$  (Vione *et al.* 2009). Previous studies have also demonstrated that  $\cdot\text{CO}_3^-$  has an affinity for reacting with compounds that contain electron-rich moieties (e.g. aromatic anilines, amino acids, phenols, nitrogen-containing and sulfur-containing organics) through the reactions of electron transfer and hydrogen abstraction (Neta *et al.* 1988; Huang & Mabury 2000a; Wang & Lin 2012; Liu *et al.* 2016).

### Photolysis byproducts ( $\text{NO}_3^-$ system versus $\text{NO}_3^- + \text{HCO}_3^-$ system)

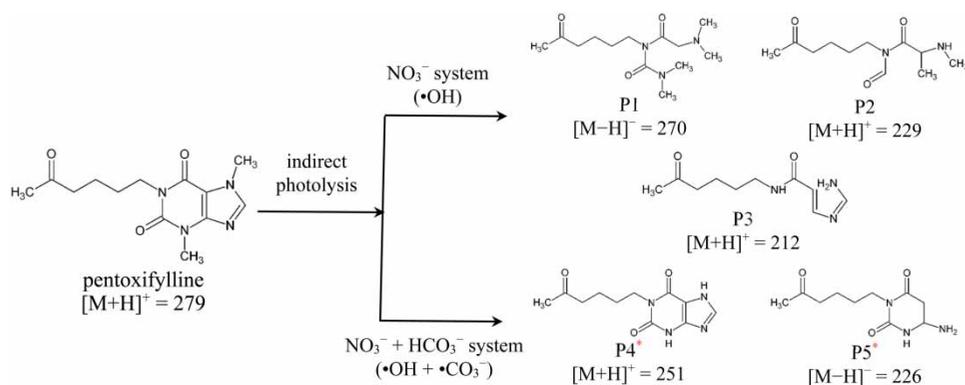
To further understand the photolytic mechanism of pentoxifylline in the  $\text{NO}_3^-$  system and the  $\text{NO}_3^- + \text{HCO}_3^-$  system, the TOC and photolytic byproducts produced during the reaction were studied; the results are shown in Figure 5. Although the target compound pentoxifylline was degraded, the TOC remained constant, indicating that pentoxifylline was merely transformed to byproducts and no mineralization occurred. In the byproduct analysis, five byproducts (P1–P5) that have not been previously reported are



**Figure 5** | The indirect photolysis byproducts of pentoxifylline in (a) the  $\text{NO}_3^-$  system and (b) the  $\text{NO}_3^- + \text{HCO}_3^-$  system. The numbers are m/z, as determined by LC-MS/MS. The solid symbols represent byproducts found in a positive mode  $[\text{M} + \text{H}]^+$ , and the hollow symbols represent byproducts found in a negative mode  $[\text{M} - \text{H}]^-$ .

proposed according to the HPLC–MS/MS and ACD MS fragmenter; detailed information regarding the retention times and the mass spectroscopy parameters are provided in Tables S3 and S4 (available with the online version of this paper). The numbers of the observed byproduct types in the two systems ( $\text{NO}_3^-$  system and  $\text{NO}_3^- + \text{HCO}_3^-$  system) were different. Three byproducts (P1–P3) were detected in the first system; however, in the  $\text{NO}_3^- + \text{HCO}_3^-$  system, in addition to P1–P3, byproducts P4 and P5 were also observed. The proposed structures of the photolytic byproducts are shown in Figure 6.

In the photolysis of  $\text{NO}_3^-$ ,  $\cdot\text{OH}$  was generated. Because pentoxifylline is unable to undergo direct photolysis (Figure 1(b)), byproducts P1–P3 were produced through a  $\cdot\text{OH}$  attack on pentoxifylline. In addition, in the presence of both  $\text{NO}_3^-$  and  $\text{HCO}_3^-$ ,  $\cdot\text{OH}$  and  $\cdot\text{CO}_3^-$  were produced



**Figure 6** | The proposed indirect photolysis byproducts and degradation pathways of pentoxifylline. (The "\*" symbol indicates that the compound was only observed in the  $\text{NO}_3^- + \text{HCO}_3^-$  system.).

and further reacted with the target compound pentoxifylline. Therefore,  $\cdot\text{CO}_3^-$  may be involved in the generation of byproducts P4 and P5. P4 is the demethylation product of pentoxifylline. The role of  $\cdot\text{CO}_3^-$  in the degradation of oxytetracycline by a UV-based advanced oxidation process has been investigated, and it has been reported that  $\cdot\text{CO}_3^-$  proceeds the demethylation reaction (Liu *et al.* 2016). A similar phenomenon was also noted in another study (Mazellier *et al.* 2007), which demonstrated the demethylation byproduct of fenuron by UV photolysis of  $\text{Co}(\text{NH}_3)_5\text{CO}_3^+$  in the presence of  $\cdot\text{CO}_3^-$ . In summary, different types of byproducts were formed in the two systems ( $\text{NO}_3^-$  system and  $\text{NO}_3^- + \text{HCO}_3^-$  system), which implies that different photodegradation pathways occurred.

## CONCLUSIONS

This study provides the first comprehensive investigation of the photochemical fate of pentoxifylline in surface waters. The results indicated that pentoxifylline is fairly persistent in the aquatic environment once it is released to the environment, and sunlight photolysis is very likely the predominant attenuation process. In waters such as the Jingmei river ( $t_{1/2} = 34.7 \pm 2.2$  h), it would take approximately 5–7 days for the concentration of pentoxifylline to decrease by half (assuming 5–7 h of bright sunlight a day). However, the presence of DOM,  $\text{NO}_3^-$  and  $\text{HCO}_3^-$  greatly affects the photolysis rate of pentoxifylline. During the photolysis of  $\text{NO}_3^-$ , the presence of  $\text{HCO}_3^-$  contributes to photodegradation of pentoxifylline due to the participation of  $\cdot\text{CO}_3^-$ . Despite the fact

that pentoxifylline was photodegraded through indirect sunlight photolysis, TOC data (no mineralization) indicated that pentoxifylline was only photo-transformed into degradation byproducts. Five photodegradation byproducts (P1–P5) of pentoxifylline, which have not been reported previously, are proposed for the first time in this work; among the degradation byproducts, byproducts P4 and P5 were only observed in the  $\text{NO}_3^-$  and  $\text{HCO}_3^-$  system. This finding implies that compared to  $\cdot\text{OH}$ ,  $\cdot\text{CO}_3^-$  likely leads to a different degradation pathway. Given that  $\text{HCO}_3^-$  is abundant in natural waters (approximately 1–3 mM), the involvement of  $\text{HCO}_3^-$  in the photochemical fate should not be neglected. An additional toxicity assessment of the photodegradation byproducts is also essential to understand their risk toward ecosystems and humans.

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