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# Chemically and thermally activated persulfate for theophylline degradation and application to pharmaceutical factory effluent†

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Degradation of PPCPs by AOPs has gained major interest in the past decade. In this work, theophylline (TP) oxidation was studied in thermally (TAP) and chemically (CAP) activated persulfate systems, separately and in combination (TCAP). For  $[TP]_0 = 10 \text{ mg L}^{-1}$ , (i) TAP resulted in 60% TP degradation at  $[PS]_0 = 5 \text{ mM}$  and  $T = 60 \text{ }^\circ\text{C}$  after 60 min of reaction and (ii) CAP showed slight degradation at room temperature; however, (iii) TCAP resulted in complete TP degradation for  $[PS]_0 = [Fe^{2+}]_0 = 2 \text{ mM}$  at  $T = 60 \text{ }^\circ\text{C}$  following a pseudo-first order reaction rate with calculated  $k_{obs} = 5.6 (\pm 0.4) \times 10^{-2} \text{ min}^{-1}$ . In the TCAP system, the  $[PS]_0 : [Fe^{2+}]_0$  ratio of 1 : 1 presented the best results. A positive correlation was obtained between the TP degradation rate and increasing temperature and  $[PS]_0$ , and a negative correlation was obtained with increasing pH. Both chloride and humic acid inhibited the degradation process, while nitrates enhanced it. TP dissolved in spring, sea and waste water simulating real effluents showed lower degradation rates than in DI water. Waste water caused the highest inhibition ( $k_{obs} = 2.6 (\pm 0.6) \times 10^{-4} \text{ min}^{-1}$ ). Finally, the TCAP system was tested on a real factory effluent highly charged with TP, e.g.  $[TP]_0 = 160 \text{ mg L}^{-1}$ , with successful degradation under the conditions of  $60 \text{ }^\circ\text{C}$  and  $[PS]_0 = [Fe^{2+}]_0 = 50 \text{ mM}$ .

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## 1. Introduction

Theophylline (TP), or 1,3-dimethyl-7H-purine-2,6-dione, is a crystalline compound that is used in the treatment of respiratory diseases such as asthma and wheezing; it is also found in trace amounts in normal diet foods, such as tea and cocoa beans.<sup>1,2</sup> TP belongs to the pharmaceuticals and personal care products (PPCPs) family, whose members have gained global attention in the past few decades as emerging contaminants. This increased attention is attributed to the discovery of PPCPs in ground and surface water, aided by advancements in analytical techniques which enable their detection at previously undetectable concentrations.<sup>3</sup> The presence of PPCPs in water, even at low concentrations, poses environmental hazards and possible public health risks. Among these risks are bioaccumulation, such as the accumulation of lipophilic PPCPs in aquatic organisms<sup>4,5</sup> and the development of antibiotic resistance,<sup>6</sup> in addition to uncertain synergistic/antagonist effects of long term exposure to mixtures of pharmaceuticals at low concentrations.<sup>7</sup> TP is introduced into nature by several pathways, such as from untreated pharmaceutical production plant wastewater effluents, in addition to domestic wastewater, which

can contain TP from direct disposal of the drug and from urine excretion; this contributes to the pollution of water bodies by TP.<sup>8,9</sup>

To solve the problem of water contamination by several pollutants, water treatment plants are integrated to treat wastewater discharges from domestic, agricultural and industrial sources. Conventional water treatment methods include, but are not limited to, carbon adsorption, chemical precipitation, evaporation and ion exchange.<sup>10</sup> It has been shown that conventional methods do not treat PPCPs efficiently; PPCPs are resistant to such treatment and have been detected in drinking water.<sup>11–13</sup> One of the pharmaceuticals detected in water is TP. It was found in spring water in Lebanon, possibly due to the discharge of untreated waste water.<sup>14</sup> TP degradation has been studied during the past decades by several methods, including degradation by means of ferrate(VI)<sup>15</sup> and a metal organic framework (Pd@MIL-100(Fe)) with visible light ( $\lambda \geq 420 \text{ nm}$ ),<sup>16</sup> UV/H<sub>2</sub>O<sub>2</sub>,<sup>17,18</sup> and UV/TiO<sub>2</sub> nanobelts.<sup>19</sup> Novel water treatment methods include advanced oxidation processes (AOPs), which have been proved to be significantly efficient in removing persistent organic compounds. A wide variety of techniques involving different oxidants and different methods of activation are used in AOPs; examples include Fenton,<sup>20</sup> photo-Fenton,<sup>21</sup> UV/PS,<sup>22,23</sup> Fe/PS,<sup>24,25</sup> and heat/PS<sup>26–29</sup> systems, in addition to alkaline/PS and alkaline/peroxymonosulfate<sup>30</sup> systems. PS and H<sub>2</sub>O<sub>2</sub> are the two most commonly used effective oxidants in AOPs; however, PS poses some advantages over H<sub>2</sub>O<sub>2</sub> in terms of cost, safety in handling, and ease of access in some regions. PS

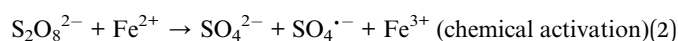
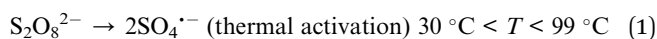
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is effective in degrading several pharmaceuticals;<sup>31–34</sup> however, to our knowledge, it has not been tested by other research groups to treat TP. The main PS activation methods are UV, chemical, and heat activation, which generate highly reactive sulfate radicals (SRs) (eqn (1)–(3)).<sup>22–29,34,35</sup> Our research group has recently studied TP degradation by UV-activated PS.<sup>36</sup>

In this study, TP degradation by thermally activated PS (TAP) and chemically activated PS (CAP) was studied separately as well as in a combined thermally and chemically activated PS (TCAP) system. The combination of activation techniques was applied, for the first time, to simulated effluents and to a real highly concentrated pharmaceutical effluent collected from a local pharmaceutical factory. The degradation process was optimized by testing several parameters in order to obtain efficient degradation within a reasonable time at an affordable cost. Finally, charge distribution and frontier orbital calculations were investigated in order to better elucidate the TP degradation mechanism by oxidative radical species in solution.



## 2. Materials and methods

### 2.1. Chemicals

Theophylline ( $\text{C}_7\text{H}_8\text{N}_4\text{O}_2$ ) ( $\text{C}_7\text{H}_8\text{N}_4\text{O}_2$ ,  $\geq 99\%$ ) and sodium persulfate (PS) ( $\text{Na}_2\text{S}_2\text{O}_8$ ,  $\geq 99.0\%$ ), were obtained from Sigma-Aldrich (China and France, respectively). Methanol (MeOH,  $\text{CH}_4\text{O}$ ) and tertiary butyl alcohol (TBA) of HPLC grade were purchased from Sigma-Aldrich (Germany). MeOH was used as the mobile phase for chromatographic analysis in combination with deionized water (DI). Ferrous chloride tetrahydrate ( $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ ), used as a chemical activator for PS, was obtained from Fluka (Switzerland). HCl (37%) was obtained from Fluka (Netherlands) and used to dissolve  $\text{FeCl}_2$  in the preparation of stock solutions. To evaluate the effects of ionic additives, sodium chloride (NaCl) was purchased from Fluka (Netherlands), and sodium nitrate ( $\text{NaNO}_3$ ) was obtained from Sigma-Aldrich (Germany). DI water was used for the preparation of all solutions in this study.

### 2.2. Chemical analysis: TP quantification and identification

High performance liquid chromatography (HPLC, Agilent 1100 series) was used for TP quantification. The HPLC was equipped with a thermo-electrically cooled autosampler unit, a quaternary pump, a vacuum degasser, and a thermally controlled column. Separation of TP from other by-products was enabled by the use of a C-18 reverse phase column (Discovery® HS, 5  $\mu\text{m}$ ; 4.6 mm internal diameter  $\times$  250 mm length) connected to a guard column (HS C-18, 5  $\mu\text{m}$ ; 4.0 mm internal diameter, 20 mm length) (Pennsylvania, USA). The temperature of the column was set at 30  $^\circ\text{C}$ , while that of the autosampler

compartment was set at 4  $^\circ\text{C}$ . A column flow rate of 0.5  $\text{mL min}^{-1}$  was used with a mobile phase consisting of water and MeOH (70 : 30 ratio) maintained in isocratic mode. The injection volume was set at 80  $\mu\text{L}$ . A diode-array detector for the quantification of TP was coupled to the HPLC. For the aforementioned conditions, the TP retention time was observed to be 12 min. All samples were filtered using 0.45  $\mu\text{m}$  PTFE 13 mm disc filters (Jaytee Biosciences Ltd., UK) before HPLC analysis. Selected TP chemical properties in addition to the calibration curve and the corresponding LINESST output are summarized in ESI Fig. 1S(a–c).† Identification of the degradation and transformation products of TP was performed on an Ultimate 3000 RSLC Thermo Scientific HPLC-MS/MS connected to a Q Exactive Orbitrap. A Hypersil GOLD C18 150 column (100  $\times$  2.1 mm, 1.9  $\mu\text{m}$ ) was used for separation. The injection volume was set as 2  $\mu\text{L}$  and the elution process was performed at a flow rate of 0.3  $\text{mL min}^{-1}$  using DI water (containing 0.1% formic acid) as eluent A and methanol as eluent B. The mass spectrometer was operated in positive ionization mode. The auxiliary gas heater temperature was set as 350  $^\circ\text{C}$  and the capillary temperature was 320  $^\circ\text{C}$ .

### 2.3. Experimental setup

The experimental setup consisted of 200 mL Erlenmeyer flasks used as reactors and immersed in a controlled-temperature water bath. The latter was equipped with an orbital shaker (Wise Bath WSB-30) and amended with a homemade Plexiglas cover plate with the capacity to hold all the Erlenmeyer flasks by their necks in order to prevent the reactors from falling (Fig. 2S†). The experimental setup could accommodate up to 12 reactors at a time, and all experiments were performed in triplicate. The reactors were efficiently submerged in the water bath to ensure that their temperatures matched that of the surrounding water. This was further guaranteed by the measurement of the inner temperature of the reactor using a thermometer. The temperatures tested were room temperature in addition to 40  $^\circ\text{C}$  to 75  $^\circ\text{C}$ . To ensure proper homogenization and heat distribution, the orbital shaker was set at 70 revolutions per minute throughout the experiments.

### 2.4. Experimental procedure

The stock solutions were prepared as follows: TP (100  $\text{mg L}^{-1}$ ) was prepared by dissolving 100 mg of dry TP powder in 1 L of DI water; PS (100 mM) was prepared by dissolving 2.38 g of sodium persulfate in 100 mL of DI;  $\text{FeCl}_2$  (80 mM) was prepared by dissolving 3.1808 g of  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  in concentrated HCl (37%) in a 250 mL volumetric flask, followed by the addition of DI. The stock solutions were prepared weekly and stored in the dark at 4  $^\circ\text{C}$ . The water bath was turned on before the experiments to attain the required temperature. The reactors outside the water bath were each filled with predetermined amounts of prepared concentrated stock solutions of TP and matrix solution when required, in addition to DI water. Each obtained solution was mixed and preheated in the water bath to reach the desired temperature. Finally, the experiment was initiated by adding  $\text{FeCl}_2$  (20 mM) and PS (100 mM) stock solutions, reaching a final



reactor volume of 200 mL. Samples were withdrawn using a clean 1 mL syringe from every reactor, then filtered using a 0.45  $\mu\text{m}$  PTFE 13 mm disc filter and stored in 2 mL HPLC vials. To quench any further oxidation reactions after sample withdrawal, vials were placed in an ice bath to prevent further thermal activation of PS<sup>26</sup> and spiked with 0.5 mL of methanol to prevent further chemical activation of PS.<sup>34</sup> Waste water used in real water sample experiments was pre-filtered using a 1  $\mu\text{m}$  ashless glass fiber filter.

## 2.5. Calculation of charge distributions and frontier orbitals

The theoretical calculations were performed using the Gaussian 09 program<sup>37</sup> with density functional theory. The Becke 3-parameter Lee–Yang–Parr (B3LYP)<sup>38,39</sup> functional was used with the 6-311++(2d,2p) basis set. First, the molecular parameters of theophylline molecule were optimized using the mentioned level of theory. Second, at the same level of theory, the frontier electron densities and Mulliken charge distributions were obtained utilizing the optimized parameters.

## 3. Results and discussion

### 3.1. Thermal activation of PS (TAP system)

**3.1.1. Thermal stability of TP and effects of [PS]<sub>0</sub>.** To test the stability and behaviour of TP molecules under thermal stress, control experiments were conducted in a PS-free medium with [TP]<sub>0</sub> = 10 mg L<sup>-1</sup> at different temperatures (40–75 °C) for a total reaction time of 60 min.

As can be noted in Fig. 3S,† heat did not significantly affect the stability of TP in aqueous solutions. In fact, a slight decline in the concentration of TP was observed, with a maximum of about 5% for  $T = 40\text{--}75$  °C, demonstrating the thermal stability of TP.

Thermal activation was tested by spiking a [TP]<sub>0</sub> = 10 mg L<sup>-1</sup> solution with different concentrations of PS at 60 °C. Table 1 and Fig. 4S† show that the TP degradation increased from 3% to 60% with increasing [PS]<sub>0</sub> from 0.25 mM to 5 mM, respectively, after a period of 60 min. This increase in the % degradation is attributed to the production of more SO<sub>4</sub><sup>•-</sup> in the more PS-concentrated solution, as per eqn (1).

**3.1.2. Effects of temperature and determination of activation energy.** The effects of temperature on TP degradation by the TAP system were studied under the following conditions: [TP]<sub>0</sub> = 10 mg L<sup>-1</sup>, [PS]<sub>0</sub> = 2 mM and  $T = 55\text{--}75$  °C. Fig. 1a shows that increasing the temperature resulted in improved TP degradation. For example, when temperature increased from 55 °C to 75 °C, the % TP degradation increased from 10% to 100% at  $t = 40$  min. This observed trend has been found in several studies of TAP systems.<sup>26,28</sup> This can be explained by the increase in the energy provided to the system upon heating, which in its turn favors increasing numbers of collisions between the reacting TP and SRs.

The observed degradation rate constant ( $k_{\text{obs}}$ ) was calculated according to the pseudo-first order kinetics model using eqn (4), which showed good fit (Text S2†). Additionally, the activation energy ( $E_A$ ) of the TP degradation reaction in the TAP system was determined using the Arrhenius equation (eqn (5)), where  $T$  is the temperature in K,  $k_{\text{obs}}$  is the observed degradation rate constant calculated at different temperatures in min<sup>-1</sup>,  $A$  is the Arrhenius constant, and  $R$  is the gas constant (8.314 J mol<sup>-1</sup> K<sup>-1</sup>). eqn (5) was plotted, and the slope obtained represents  $\frac{E_A}{R}$  (Fig. 1b).  $E_A$  and  $\ln(A)$  were determined to be 154 ( $\pm 16$ ) kJ mol<sup>-1</sup> and 50 ( $\pm 5$ ) kJ mol<sup>-1</sup>, respectively. The  $E_A$  value is close to those reported by Ghauch *et al.* for ibuprofen,  $E_A = 168$  ( $\pm 9$ ) kJ mol<sup>-1</sup>, and naproxen,  $E_A = 155.03$  ( $\pm 26.4$ ) kJ mol<sup>-1</sup>, both using a TAP

**Table 1** % TP degradation in the TAP system at  $T = 55\text{--}75$  °C and different [PS]<sub>0</sub>, and in the CAP system at room temperature. Experimental conditions: [PS]<sub>0</sub> = 0.25–5 mM, [PS]<sub>0</sub> : [Fe<sup>2+</sup>]<sub>0</sub> ratios = 1 : 10, 1 : 5 and 1 : 1, and [TP]<sub>0</sub> = 10 mg L<sup>-1</sup> for all studied cases

Activation method	[TP] <sub>0</sub> (mg L <sup>-1</sup> )	$T$ (°C)	[PS] <sub>0</sub> (mM)	[Fe <sup>2+</sup> ] <sub>0</sub> (mM)	% degradation at $t = 60$ min	pH <sub>i</sub> /pH <sub>f</sub>		
TA <sup>a</sup>	10	55	2	—	14	3.83/3.69		
			0.25	3	4.30/4.56			
		60	1	12	3.87/3.75			
			2	28	3.83/3.58			
			5	60	3.41/3.05			
			2	45	3.57/3.46			
			70	100	3.57/3.22			
			75	100	3.50/3.22			
		CA <sup>b</sup>	10	20	0.25	0.025	0.5	3.48/3.83
						0.125	—	2.97/2.84
0.25	5				2.81/2.54			
1	0.1				4	2.96/3.18		
	0.05				—	2.43/2.30		
	1				2	2.23/2.12		
5	0.5				4	2.59/2.76		
	0.25				1	1.84/1.79		
	5	2	1.65/1.54					

<sup>a</sup> Check Fig. 4S, Fig. 1a. <sup>b</sup> Check Fig. 5S



system; however, they used half the  $[PS]_0$  used in this work, *e.g.* 1 mM.<sup>26,28</sup> The uncertainties reported for  $\ln(A)$  and  $E_A$  were determined using the LINEST function of Microsoft Excel.

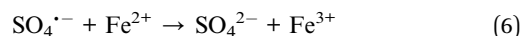
$$\ln \frac{[TP]}{[TP]_0} = -k_{\text{obs}}t \quad (4)$$

$$\ln(k_{\text{obs}}) = \ln(A) - \frac{E_A}{RT} \quad (5)$$

### 3.2. Chemical activation of PS (CAP system)

To test the effectiveness of CAP for TP degradation at room temperature, a solution of  $[TP]_0 = 10 \text{ mg L}^{-1}$  was subjected to  $[PS]_0 = 0.25, 1$  and  $5 \text{ mM}$  activated by  $Fe^{2+}$  with  $[PS]_0 : [Fe^{2+}]_0$  ratios of 10 : 1, 2 : 1 and 1 : 1 at favorable acidic pH to ensure  $Fe^{2+}$  solubility. Under all conditions tested, only negligible degradation of TP was observed (Fig. 5S†), with a maximum of

5% TP degradation noted at 60 min for the case of  $[PS]_0 = 0.25 \text{ mM}$  and a  $[PS]_0 : [Fe^{2+}]_0$  ratio of 1 : 1, as summarized in Table 1. Thus, TP is demonstrated to be relatively resistant to the CAP system at room temperature compared to other organic contaminants. For example, Oh *et al.* obtained incomplete degradation of polyvinyl alcohol utilizing  $Fe^{2+}$ -based CAP at room temperature and used a higher reaction temperature to secure significant degradation of the contaminant.<sup>40</sup> This can be explained by the common scavenging effect of  $SO_4^{\cdot-}$  by  $Fe^{2+}$  to form the less effective  $Fe^{3+}$  ion (eqn (6))<sup>24,41</sup> in addition to the recalcitrant character of the TP molecule.



### 3.3. Combined thermal and chemical activation of PS (TCAP system)

Because both TAP and CAP systems showed low to negligible performance in degrading TP in aqueous solutions, both activation methods were combined into a thermally and chemically activated PS (TCAP) system. This system was tested for different  $[PS]_0 : [Fe^{2+}]_0$  ratios,  $[PS]_0$  values and temperatures in order to positively or negatively confirm any synergistic effect that can be obtained upon combination of both PS activation techniques.

**3.3.1. Effects of  $[PS]_0 : [Fe^{2+}]_0$  ratio and  $[PS]_0$ .** TP degradation was studied at different  $[PS]_0 : [Fe^{2+}]_0$  ratios and  $[PS]_0$  values.  $[PS]_0 : [Fe^{2+}]_0$  ratios of 10 : 1, 2 : 1 and 1 : 1 were tested at  $[PS]_0 = 0.25, 1$  and  $5 \text{ mM}$ ,  $[TP]_0 = 10 \text{ mg L}^{-1}$  and  $T = 60^\circ \text{C}$ .  $k_{\text{obs}}$  was calculated for the pseudo-first order kinetics model according to eqn (4), as demonstrated in previous work (Text S3,† Table 3). In fact, the reaction at the early stage can be considered to be zero order in the first five minutes;<sup>25</sup> however, as the reaction proceeds, degradation by-products form and the reaction follows pseudo-first order kinetics. As depicted in Fig. 2 and Table 2, the 1 : 1  $[PS]_0 : [Fe^{2+}]_0$  ratio showed the highest degradation rate in the three tested  $[PS]_0$  conditions, followed by the 2 : 1 and 10 : 1 ratios.

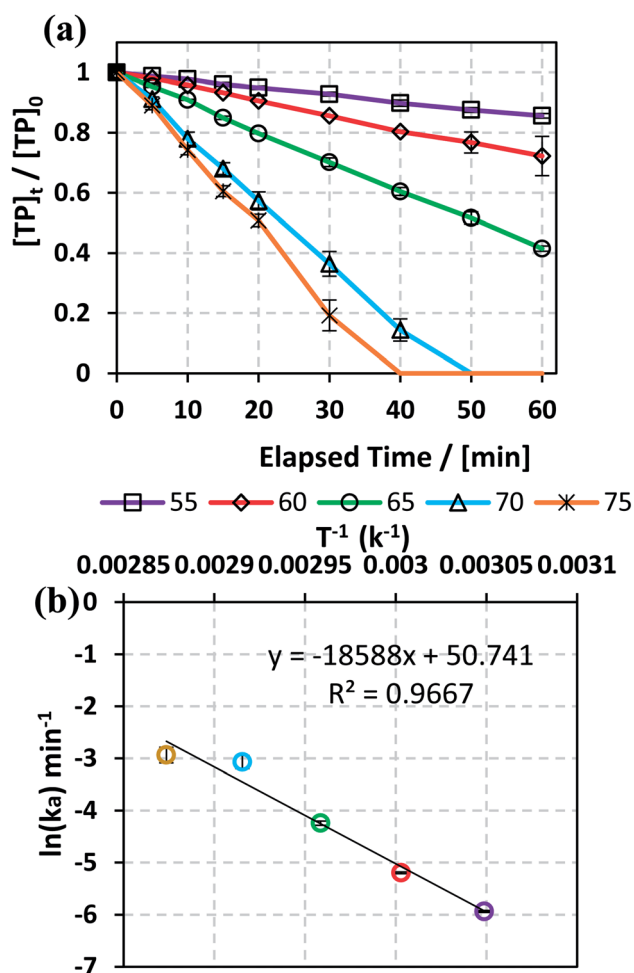


Fig. 1 (a) Effects of temperature on TP degradation in a TAP system. (b) The corresponding Arrhenius plot of  $\ln(k_a)$  vs.  $(1/T)$ , showing the equation for linear best fit. Experimental conditions:  $[TP]_0 = 10 \text{ mg L}^{-1}$ ,  $[PS]_0 = 2 \text{ mM}$  and  $T = 55\text{--}75^\circ \text{C}$ . Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.

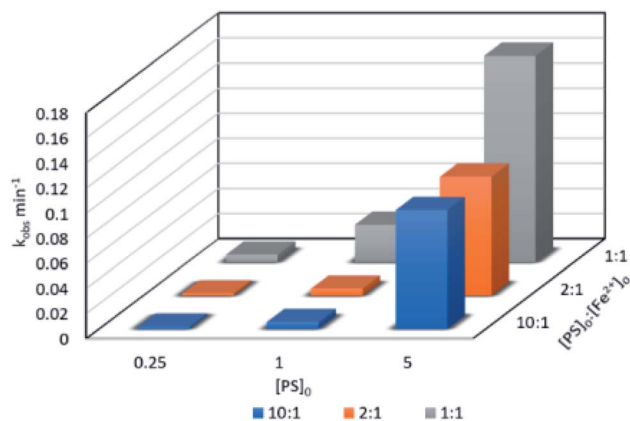


Fig. 2 Effects of the  $[PS]_0 : [Fe^{2+}]_0$  ratio on TP degradation in a TCAP system. Experimental conditions:  $[PS]_0 = 0.25, 1$  and  $5 \text{ mM}$ ,  $[PS]_0 : [Fe^{2+}]_0$  ratios of 1 : 1, 2 : 1 and 10 : 1, and  $T = 60^\circ \text{C}$ .





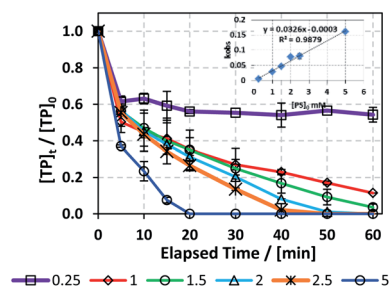
**Table 2** Effects of the  $[PS]_0 : [Fe^{2+}]_0$  ratio on TP degradation in a TCAP system. Initial and final pH values are presented for every case. Experimental conditions:  $[PS]_0 = 0.25, 1$  and  $5$  mM,  $[PS]_0 : [Fe^{2+}]_0$  ratios of  $1 : 1, 2 : 1$  and  $10 : 1$ , and  $T = 60$  °C

$[PS]_0 : [Fe^{2+}]_0$	$[PS]_0$ mM	$[Fe^{2+}]_0$ mM	pH <sub>i</sub> /pH <sub>f</sub>
10 : 1	0.25	0.025	3.50/3.30
	1	0.1	2.79/2.7
	5	0.5	2.19/2.07
2 : 1	0.25	0.125	2.97/2.85
	1	0.5	2.53/2.9
	5	0.25	1.84/1.79
1 : 1	0.25	0.25	2.81/2.54
	1	1	2.23/2.12
	5	5	1.63/1.54

Different studies have showed the effectiveness of different  $[PS]_0 : [Fe^{2+}]_0$  ratios. The optimum ratio obtained varies depending on different parameters, such as the target analyte, the method of iron addition, and the state/morphology of the added iron.<sup>42</sup> For example, a study by Oh *et al.* showed that  $1 : 1$   $[PS]_0 : [Fe^{2+}]_0$  was the optimum ratio for the degradation of polyvinyl alcohol by CAP.<sup>40</sup> Also, Naim and Ghauch (2016) showed that  $1 : 1$   $[PS]_0 : [Fe^{2+}]_0$  was the most effective ratio to yield full ranitidine degradation in almost 10 min.<sup>24</sup> On the other hand, Shang *et al.* obtained  $10 : 1$   $[PS]_0 : [Fe^{2+}]_0$  as the optimum ratio for degrading diatrizoate in a CAP system.<sup>43</sup>

In order to study the effects of  $[PS]_0$  on TP degradation, different  $[PS]_0$  concentrations were used (0.25 to 5 mM) while maintaining a constant  $[PS]_0 : [Fe^{2+}]_0$  ratio of  $1 : 1$  and  $[TP]_0 = 10$  mg L<sup>-1</sup> at  $T = 60$  °C. Fig. 3 and Table 3 show that the higher the  $[PS]_0$ , the greater the observed rate constant  $k_{obs}$ . For example,  $k_{obs}$  increased by 32 fold when  $[PS]_0$  increased from 0.25 mM to 5.0 mM with good correlation ( $R^2 = 0.9879$ ), as shown in the inset of Fig. 3. This observation can be explained by the production of a greater amount of  $SO_4^{\cdot-}$  upon increasing  $[PS]_0$  (Fig. 3).

**3.3.2. Effects of temperature and determination of the activation energy.** To study the effects of temperature on TP degradation in TCAP systems, the same conditions as before



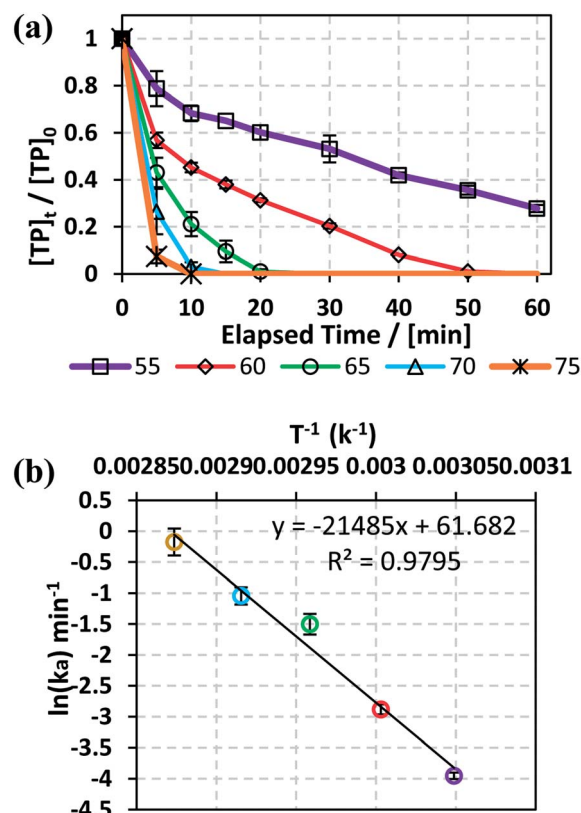
**Fig. 3** Optimization of reaction conditions for the TCAP system: effects of  $[PS]_0 = 0.25$ – $5$  mM on the degradation of TP at a  $[PS]_0 : [Fe^{2+}]_0$  ratio of  $1 : 1$ .  $[TP]_0 = 10$  mg L<sup>-1</sup> for all experiments and  $T = 60$  °C. Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.

**Table 3** Optimization of  $[PS]_0$  for the TCAP system. The  $k_{obs}$  values and linearity constants of the pseudo-first order equation plot are presented.  $[TP]_0 = 10$  mg L<sup>-1</sup> for all experiments and  $T = 60$  °C

$[PS]_0$ (mM)	$[Fe^{2+}]_0$ (mM)	$k_{obs} \times 10^{-1}$ (min <sup>-1</sup> )	$R^2$
0.25	0.25	0.05 ( $\pm 0.02$ )	0.41
1	1	0.29 ( $\pm 0.02$ )	0.93
1.5	1.5	0.47 ( $\pm 0.03$ )	0.96
2	2	0.56 ( $\pm 0.04$ )	0.96
2.5	1.5	0.8 ( $\pm 0.1$ )	0.93
5	5	1.6 ( $\pm 0.1$ )	0.98

(Section 3.3.1) were adopted; however, in addition to the temperature reaction variation:  $[TP]_0 = 10$  mg L<sup>-1</sup>,  $[PS]_0 = [Fe^{2+}]_0 = 2$  mM and  $T = 55$  °C to  $75$  °C. As can be noted in Fig. 4a, complete TP degradation occurred in only 10 min at  $75$  °C, while up to 50 min were required at  $60$  °C. However, at  $55$  °C, only partial TP degradation, e.g. 83%, was obtained after 1 h of reaction. The results also showed that as the temperature increased from  $55$  °C to  $75$  °C,  $k_{obs}$  increased by 44 fold from  $1.9 (\pm 0.1) \times 10^{-2}$  min<sup>-1</sup> to  $8.3 (\pm 0.1) \times 10^{-1}$  min<sup>-1</sup>.

The TCAP system, like the investigated TAP system (Section 3.1.2), showed excellent fitting with the Arrhenius equation,



**Fig. 4** (a) Effects of temperature on TP degradation in TCAP systems. (b) The corresponding Arrhenius plot of  $\ln(k_a)$  vs.  $1/T$ , showing the equation of linear best fit. Experimental conditions:  $[TP]_0 = 10$  mg L<sup>-1</sup>,  $[PS]_0 = [Fe^{2+}]_0 = 2$  mM and  $T = 50$ – $75$  °C. Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.



where the calculated  $\ln(A)$  and the apparent activation energy  $E_A$  were greater than those calculated in the absence of  $\text{Fe}^{2+}$ , e.g.  $61 (\pm 5) \text{ kJ mol}^{-1}$  and  $178 (\pm 14) \text{ kJ mol}^{-1}$ , respectively (Fig. 4b). This should not be surprising, as one might expect a lower activation energy in the presence of  $\text{Fe}^{2+}$ . In fact,  $\text{Fe}^{2+}$  does not play the role of a catalyst to decrease  $E_A$ , nor is it involved in the TP degradation reaction directly. Rather, it plays the role of speeding the production of  $\text{SO}_4^{\cdot-}$  from PS upon the chemical activation process (eqn (2)). Additional experiments were carried out at a  $10 : 1$   $[\text{PS}]_0 : [\text{Fe}^{2+}]_0$  ratio at different temperatures ( $40^\circ\text{C}$ ,  $50^\circ\text{C}$  and  $60^\circ\text{C}$ ), and the obtained results showed the same outputs. For example, as the reaction temperature increased from  $40^\circ\text{C}$  to  $50^\circ\text{C}$  and  $60^\circ\text{C}$ , the % degradation of TP improved from 29% to 45% and 100%, respectively, at 60 min for  $[\text{PS}]_0 = 5 \text{ mM}$  (Fig. 6S<sup>†</sup>). A similar trend was observed for aniline degradation, where  $[\text{PS}]_0 = 2.5 \text{ mM}$  and zero valent iron  $[\text{ZVI}]_0 = 0.3 \text{ g L}^{-1}$  resulted in the total elimination of  $[\text{aniline}]_0 = 0.05 \text{ mM}$  in periods of 1 and 2 h at  $T = 80^\circ\text{C}$  and  $60^\circ\text{C}$ , respectively.<sup>44</sup>

### 3.4. Effects of pH adjustment of the TCAP system

To study the effects of pH on the TP degradation process in the TCAP system, the initial pH ( $\text{pH}_i$ ) was adjusted to values of around 3, 5 and 7 using NaOH solution before the addition of PS. The subsequent PS addition caused a further decrease in pH ( $\text{pH}_{\text{PS}}$ ) (Fig. 5 and Table 4). The use of a buffer solution was not possible because an organic buffer would compete with TP on the PS present in the solution; on the other hand, an inorganic buffer, such as phosphate buffer, would cause interference by complexing with  $\text{Fe}^{2+}$ .<sup>25,34</sup> The effect of initial pH is important to study because the effluent to be treated may contain traces of acid or base from the reactor cleaning process; however, most pharmaceutical production plants use deionized water for preliminary washing of their equipment, so the effluent should contain the highest [TP] at acidic pH.

It should be noted that the decrease in pH in the case of the un-adjusted solution is due to two main factors. First, the added  $\text{Fe}^{2+}$  solution contains HCl, which was used to increase its

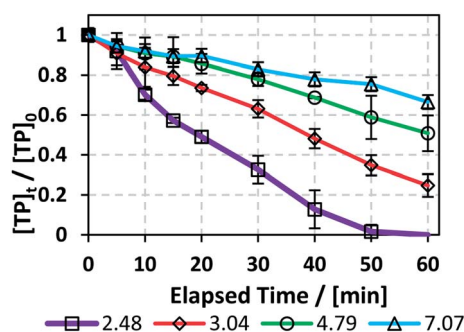


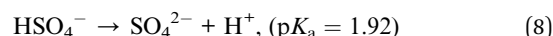
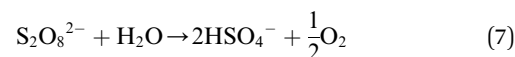
Fig. 5 Effects of pH adjustment on the degradation of TP in the TCAP system. The pH values adjusted before PS addition are presented. Experimental conditions:  $[\text{TP}]_0 = 10 \text{ mg L}^{-1}$ ,  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 2 \text{ mM}$  and  $T = 60^\circ\text{C}$ . Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.

Table 4 Effects of pH adjustment on the degradation of TP in the TCAP system.  $\text{pH}_i$  represents the pH adjusted before PS addition, i.e. the pH value of the solution before treatment,  $\text{pH}_{\text{PS}}$  is the pH after PS addition, and  $\text{pH}_f$  is final pH at  $t = 60 \text{ min}$ .  $k_{\text{obs}}$  is calculated from the pseudo-first order equation plot. Experimental conditions:  $[\text{TP}]_0 = 10 \text{ mg L}^{-1}$ ,  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 2 \text{ mM}$  and  $T = 60^\circ\text{C}$

pH adjustment	$\text{pH}_i^a$	$\text{pH}_{\text{PS}}^b$	$\text{pH}_f$	$k_{\text{obs}} (\text{min}^{-1})$
–	2.48	2.01	2.20	$4.9 (\pm 0.4) \times 10^{-2}$
+	3.04	2.19	2.39	$1.7 (\pm 0.1) \times 10^{-2}$
+	4.79	2.23	2.93	$1.09 (\pm 0.6) \times 10^{-2}$
+	7.07	2.81	5.06	$6.0 (\pm 0.3) \times 10^{-3}$

<sup>a</sup>  $\text{pH}_i$  is measured before PS addition. <sup>b</sup>  $\text{pH}_{\text{PS}}$  is measured after PS addition.

solubility. Second, PS causes acidification of the medium, as per eqn (7) and (8):<sup>25</sup>



The results showed that the initial pH value significantly impacts the degradation process, where  $k_{\text{obs}}$  decreased with increasing  $\text{pH}_i$  from  $4.9 (\pm 0.4) \times 10^{-2} \text{ min}^{-1}$  in the case of  $\text{pH}_i = 2.48$  to  $6.0 (\pm 0.3) \times 10^{-3} \text{ min}^{-1}$  for  $\text{pH}_i = 7.07$  (Fig. 5 and Table 4). This can be explained by the fact that at increasing pH, e.g. pH above 4, the free iron species in the solution decrease, probably as a result of the formation of  $\text{Fe}(\text{II})$  complexes.<sup>45</sup> This was proved experimentally by the formation of a visible precipitate upon pH increase, e.g. formation of  $\text{Fe}(\text{OH})_2$  precipitate. As a result, a decrease in the amount of soluble  $\text{Fe}^{2+}$  occurs, thereby decreasing the reaction rate between  $\text{Fe}^{2+}$  and PS for  $\text{SO}_4^{\cdot-}$  production. This was further clarified by comparing the case of  $\text{pH}_i$  adjusted to pH 7 in the TCAP system to that of the TAP system at the same  $[\text{PS}]_0 = 2 \text{ mM}$ . In fact,  $k_{\text{obs}}$  is  $6.0 (\pm 0.3) \times 10^{-3}$  for the former and  $5.52 (\pm 0.08) \times 10^{-3} \text{ min}^{-1}$  for the latter (Table 1S<sup>†</sup>). These values can be explained by the insignificant effects of  $\text{Fe}^{2+}$  in the TCAP system adjusted initially to neutral pH. Thus, the studied TCAP system is very sensitive to pH variations. These results can be compared to a solar/ $\text{Fe}^{2+}$ /PS system investigated by Nie *et al.*<sup>46</sup> In fact, the authors found a decrease in the degradation rate of chloramphenicol by around 70% when the reaction pH increased from 3 to 9.

### 3.5. Additive and matrix effects in the TCAP system

In order to test the effects of  $\text{Cl}^-$ ,  $\text{NO}_3^-$ , and HA additives on the degradation rate of TP, the experimental conditions that yielded full TP degradation in 1 h at  $60^\circ\text{C}$  were chosen as previously determined (Fig. 3).

**3.5.1. Effects of sodium chloride.** Different concentrations of saline solutions spiked with TP were investigated in the TCAP system. The resulting TP solutions had NaCl concentrations of 0, 200, 2000 and 20 000  $\text{mg L}^{-1}$  to mimic the conditions of



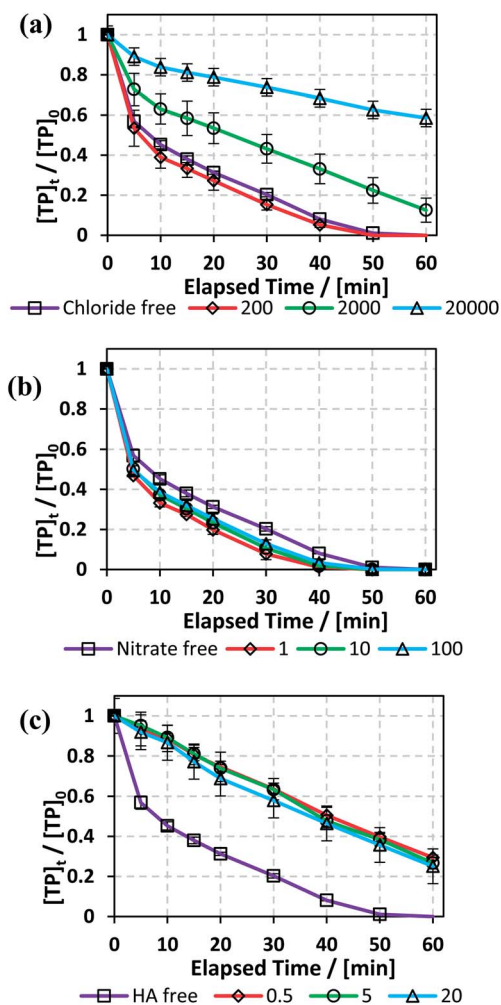


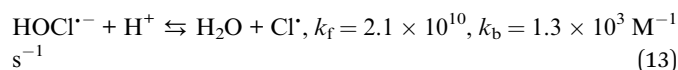
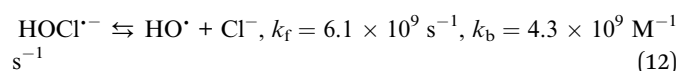
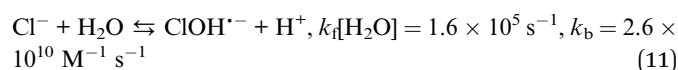
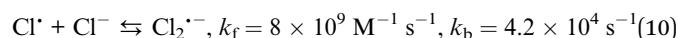
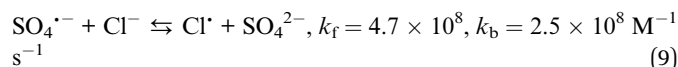
Fig. 6 Effects of (a)  $[\text{NaCl}] = 200\text{--}20\,000\text{ mg L}^{-1}$ , (b)  $[\text{NO}_3^-] = 1\text{--}100\text{ mg L}^{-1}$ , and (c)  $[\text{HA}] = 0.5\text{--}20\text{ mg L}^{-1}$  on TP degradation in the TCAP system. Experimental conditions:  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 2\text{ mM}$  and  $[\text{TP}]_0 = 10\text{ mg L}^{-1}$  for all conditions tested. Error bars are calculated as  $\frac{ts}{\sqrt{n}}$  where absent bars fall within the symbols.

distilled, fresh, brackish and saline water, respectively, according to Gorrell *et al.* and EPA data.<sup>47,48</sup> It should be noted that chloride was present in all solutions at a concentration of 4 mM from  $\text{FeCl}_2$  ( $\text{Fe}^{2+}$  source) because  $\text{FeCl}_2$  was used as a source of  $\text{Fe}^{2+}$ .

As can be noted from Fig. 6, the calculated  $k_{\text{obs}}$  for the cases of DI and fresh water were almost equal, showing a very slight positive effect of low  $[\text{NaCl}]_0$  in solution. However, the results also showed that higher  $[\text{NaCl}]_0$  caused inhibition of the degradation process, where  $k_{\text{obs}}$  decreased from  $5.6 (\pm 0.4) \times 10^{-2}\text{ min}^{-1}$  in the case of DI water to  $3.0 (\pm 0.2) \times 10^{-2}\text{ min}^{-1}$  and  $8.0 (\pm 0.5) \times 10^{-3}\text{ min}^{-1}$  in the cases of brackish and saline water, respectively (Fig. 6a and Table 5). Moreover, although a decrease in  $k_{\text{obs}}$  was noticed for fresh water, almost complete TP degradation was achieved in 60 min. The decrease in  $k_{\text{obs}}$  is attributed to the quenching of  $\text{SO}_4^{\cdot-}$  ( $E^\circ = 2.437 (\pm 0.019)\text{ V}$ ) by  $\text{Cl}^-$  to produce  $\text{Cl}^\cdot$  ( $E^\circ = 2.432 (\pm 0.018)\text{ V}$ ), which in turn reacts to produce  $\text{Cl}_2^{\cdot-}$  ( $E^\circ = 2.126 (\pm 0.017)\text{ V}$ ) (eqn (9) and (10)). The

latter radical formed has lower redox potential and is thus less effective in terms of oxidation of TP and its transformation products compared to  $\text{SO}_4^{\cdot-}$ .<sup>49–51</sup>

Different studies have showed varied effects of  $\text{Cl}^-$  on degradation processes. For example, Fan *et al.* observed enhancement in the degradation of sulfamethazine,<sup>52</sup> whereas Norzaee *et al.* observed inhibition of penicillin G degradation,<sup>53</sup> both in TAP systems. Wang *et al.* observed inhibition of acetaminophen degradation at low chloride concentrations and enhancement at high concentrations, while Amasha *et al.* noted inhibition of ketoprofen degradation, both in  $\text{Fe}^{2+}/\text{PS}$  systems.<sup>34,54</sup> The increased degradation in the presence of  $\text{Cl}^-$  can be explained by the formation of  $\text{Cl}^\cdot$ , which has a redox potential close to that of  $\text{SO}_4^{\cdot-}$ , in addition to the formation of reactive  $\text{HO}^\cdot$  (eqn (9) and (11)–(13)).<sup>50,51</sup>



**3.5.2. Effects of nitrates.** Nitrate is one of the most commonly present ions in different water bodies, such as groundwater, due to the excessive use of fertilizers.<sup>55</sup> Accordingly, the effects of  $[\text{NO}_3^-] = 1, 10$  and  $100\text{ mg L}^{-1}$  on TP degradation in the TCAP system were tested. The results showed that the reaction rate increased in the presence of  $[\text{NO}_3^-]$ , where  $k_{\text{obs}}$  increased by 6 fold from  $5.6 (\pm 0.4) \times 10^{-2}\text{ min}^{-1}$  to  $1.0 (\pm 0.1) \times 10^{-1}\text{ min}^{-1}$  in DI media and  $[\text{NO}_3^-] = 1\text{ mg L}^{-1}$ , respectively, and then slightly decreased for  $[\text{NO}_3^-] = 10$  and

Table 5 Effects of  $[\text{NaCl}] = 200\text{--}20\,000\text{ mg L}^{-1}$ ,  $[\text{NO}_3^-] = 1\text{--}100\text{ mg L}^{-1}$ , and  $[\text{HA}] = 0.5\text{--}20\text{ mg L}^{-1}$  on TP degradation in a TCAP system. Experimental conditions:  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 2\text{ mM}$  and  $[\text{TP}]_0 = 10\text{ mg L}^{-1}$  for all conditions tested.  $k_{\text{obs}}$  is obtained as per the pseudo-first order reaction rate model

Matrix	Unit	$k_{\text{obs}} \times 10^{-2} (\text{min}^{-1})$	pH <sub>i</sub> /pH <sub>f</sub>
No additive	$\text{mg L}^{-1}$	5.6 ( $\pm 0.4$ )	1.85/1.53
$[\text{NaCl}] = 200$		6.5 ( $\pm 0.5$ )	1.85/1.56
$[\text{NaCl}] = 2000$		3.0 ( $\pm 0.2$ )	1.81/1.62
$[\text{NaCl}] = 20\,000$		0.8 ( $\pm 0.05$ )	1.78/1.56
$[\text{NO}_3^-] = 1$		10.0 ( $\pm 0.1$ )	1.81/1.71
$[\text{NO}_3^-] = 10$		9.0 ( $\pm 0.1$ )	1.79/1.71
$[\text{NO}_3^-] = 100$		7.6 ( $\pm 0.7$ )	1.78/1.70
$[\text{HA}] = 0.5$		1.68 ( $\pm 0.07$ )	1.84/1.97
$[\text{HA}] = 5$		2.1 ( $\pm 0.1$ )	1.83/1.95
$[\text{HA}] = 20$		2.2 ( $\pm 0.1$ )	1.81/1.94



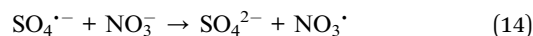
**Table 6** Physical parameters of the natural water matrices used before and after treatment in the TCAP system. Experimental conditions:  $[TP]_0 = 10 \text{ mg L}^{-1}$ ,  $[PS]_0 = 5 \text{ mM}$  and  $[Fe^{2+}]_0 = 0.5 \text{ mM}$

Parameters	Units	Spring water		Sea water		Waste water	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
pH	—	7	3.14	8	2.84	8.2	4.12
Total coliforms	CFU <sup>a</sup>	NA	NA	76	NA	TNTC <sup>c</sup>	NA
Fecal coliforms	NA	NA	NA	4	NA	TNTC	NA
Turbidity	NTU <sup>b</sup>	0.63	8.52	1	6.9	9.5	4.68
TSS	mg L <sup>-1</sup>	9	3	88	125	425	15
TDS		350	1460	32 500	32 400	4400	6140
Sulfate		16	300	3500	3300	420	590
Chloride		42.6	450	25 250	21 500	3375	2265

<sup>a</sup> Colony forming unit. <sup>b</sup> Nephelometric turbidity unit. <sup>c</sup> Too numerous to count.

100 mg L<sup>-1</sup> to values of  $9.0 (\pm 0.1) \times 10^{-2} \text{ min}^{-1}$  and  $7.6 (\pm 0.7) \times 10^{-2} \text{ min}^{-1}$ , respectively (Fig. 6b and Table 5).

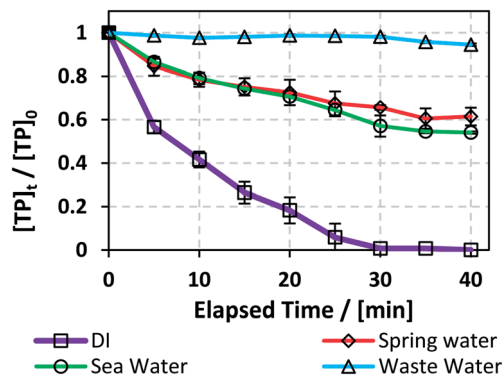
The increase in TP degradation in the presence of nitrates can be attributed to the formation of  $\text{NO}_3^{\cdot-}$ , which is considered to have significant oxidation redox potential ( $E_{1/2}^{\text{red}} = 2.50 \text{ V}$ ) and can react with TP.<sup>22</sup> Therefore, although nitrates react with  $\text{SO}_4^{\cdot-}$  and quench them, the formation of  $\text{NO}_3^{\cdot-}$  appears to compensate for the decrease in  $[\text{SO}_4^{\cdot-}]$  (eqn (14)). However, the increase in  $[\text{NO}_3^-]$  also results in an increase of  $[\text{NO}_3^{\cdot-}]$ , which can subsequently undergo self-quenching reactions; this decreases  $[\text{NO}_3^{\cdot-}]$  and, as a result, decreases the degradation rate. Ghanch *et al.* also noted an increase in the naproxen degradation rate by 154.3% in the presence of  $[\text{NO}_3^-] = 5 \text{ mg L}^{-1}$  in a TAP system.<sup>26</sup>



**3.5.3. Effects of humic acid (HA).** One widely present type of natural organic matter (NOM) is humic acid (HA).<sup>45</sup> TP degradation in the TCAP system was studied in the presence of  $[\text{HA}]_0 = 0.5, 5$  and  $20 \text{ mg L}^{-1}$ , which are in the typical naturally existing range.<sup>56</sup> The results show that HA inhibited the degradation rate, where  $k_{\text{obs}}$  decreased by almost 3 fold when  $[\text{HA}]_0 = 0.5 \text{ mg L}^{-1}$  compared to HA-free medium. After that, the increase in  $[\text{HA}]_0$  caused no significant change in  $k_{\text{obs}}$  (Fig. 6c and Table 5). The inhibition in TP degradation can be explained by the competitiveness of active radicals, where NOM quenches  $\text{SO}_4^{\cdot-}$  due to the presence of electron-rich sites.<sup>57</sup> Liu *et al.* noted a significant decrease in reaction rate with increasing  $[\text{HA}]$  during sulfachloropyridazine degradation in a TAP system.<sup>57</sup> Amasha *et al.* noted enhanced ketoprofen degradation in a CAP system at  $[\text{HA}]_0 = 0.5$ , which was explained by the possible reductive ability of HA towards transition metals which, in the case of a CAP system, can regenerate  $\text{Fe}^{2+}$  from  $\text{Fe}^{3+}$ .<sup>34,58</sup> Thus, for the case of TP degradation in the TCAP system, the cease in the decrease in  $k_{\text{obs}}$  with increasing  $[\text{HA}]_0$  can be explained by the counter effects of HA; at higher concentrations, HA contributes more to the re-generation of  $\text{Fe}^{2+}$ , which counteracts its radical-quenching properties.

### 3.6. Case of natural water matrices: spring, sea, and waste water in the TCAP system

The degradation of TP was studied in media of natural sea, spring and waste water (SW, SpW and WW) obtained from locations at coordinates of  $33^\circ 44' 17.9'' \text{N}$   $35^\circ 34' 12.5'' \text{E}$ ,  $33^\circ 54' 11.1'' \text{N}$   $35^\circ 28' 44.8'' \text{E}$  and  $33^\circ 54' 08.2'' \text{N}$   $35^\circ 29' 05.0'' \text{E}$ , respectively. The experimental conditions are as follows:  $[PS]_0 = 5 \text{ mM}$ ,  $[Fe^{2+}]_0 = 0.5 \text{ mM}$ , and TP were added in adequate amounts to each water medium so that  $[TP]_0 = 10 \text{ mg L}^{-1}$ . A  $[PS]_0 : [Fe^{2+}]_0$  ratio of 10 : 1 was used instead of the optimum obtained ratio of 1 : 1 in order to decrease the use of  $\text{Fe}^{2+}$ , *e.g.*  $\text{Fe}(\text{OH})_2$  in neutral media.<sup>45</sup> These conditions were adopted because natural water matrices are buffered to around neutral pH (Table 6), mainly because of the presence of bicarbonate. The results showed that TP degradation was inhibited in the three tested cases compared to the DI matrix case, where  $k_{\text{obs}} = 1.5 (\pm 0.1) \times 10^{-1} \text{ min}^{-1}$ , with WW showing  $\sim 570$  fold inhibition in terms of  $k_{\text{obs}} = 2.6 (\pm 0.6) \times 10^{-4} \text{ min}^{-1}$ , followed by SpW  $\sim 14$  fold and SW  $\sim 10$  fold,  $k_{\text{obs}} = 1.1 (\pm 0.1) \times 10^{-2}$  and  $1.54 (\pm 0.09) \times 10^{-2} \text{ min}^{-1}$ , respectively (Fig. 7).



**Fig. 7** Degradation of TP in real water samples: spring, sea and waste water. Experimental conditions:  $[TP]_0 = 10 \text{ mg L}^{-1}$ ,  $[PS]_0 = 5 \text{ mM}$  and  $[Fe^{2+}]_0 = 0.5 \text{ mM}$ . Error bars are calculated as  $\frac{ts}{\sqrt{n}}$  where absent bars fall within the symbols.





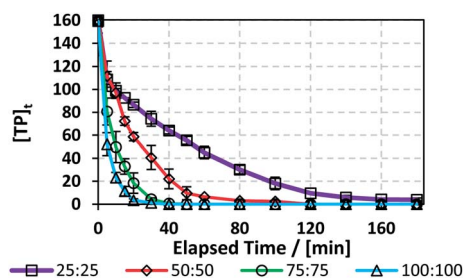


Fig. 8 Degradation of TP by TCAP in real pharmaceutical effluent containing  $[TP]_0 = 160 \text{ mg L}^{-1}$ . Experimental conditions:  $[PS]_0 = 25, 50, 75$  and  $100 \text{ mM}$ ,  $[PS]_0 : [Fe^{2+}]_0$  ratio of  $1 : 1$ , and  $T = 60 \text{ }^\circ\text{C}$ . Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.

One reason for the inhibition of the degradation of TP in the three investigated cases is the neutral to slightly basic pH values (7 to 8.2); this pH range causes the complexation and precipitation of  $Fe^{2+}$ , e.g. as  $Fe(OH)_2$ , where natural water media act as buffer solutions compared to DI medium, which becomes acidic ( $pH_i \approx 2$ ) immediately after the addition of PS and  $Fe^{2+}$  solutions. The inhibition was the highest in the case of the WW matrix, where WW possessed the highest values of total and fecal coliforms, chlorides, turbidity and total suspended and dissolved solids among the three studied matrices. The organic and inorganic material present in WW competes with TP in reacting with  $SO_4^{4-}$ , thus inhibiting TP degradation. Additionally, chlorides acted as quenchers in the studied TCAP system (Section 3.5.1), and WW showed the highest  $[Cl^-]$ . It should be noted that total elimination of coliforms was observed in the WW and SW (Table 6) systems; this is probably due to the heat factor in addition to the activity of the  $SO_4^{4-}$  present. Effluents of pharmaceutical production plants, after discharge, may be mixed with several water matrices with different properties. In addition, the water used for initial cleaning operations may be of natural origin and not DI water. The results presented in this section show that it is crucial to clean mixing reactors in pharmaceutical production facilities with distilled water whenever possible and to treat the effluent mixture before its release into the environment. A great decrease in degradation rates in waste water was also observed by Ghauch's research group upon degradation of chloramphenicol and ketoprofen in UV/PS systems.<sup>22,34</sup>

### 3.7. Case study: real factory effluent

**3.7.1. Effects of  $[PS]_0$ .** The efficiency of the TCAP system was tested on a real pharmaceutical factory effluent solution containing TP in addition to other excipients. The effluent samples were collected from a local production facility that produces a syrup containing TP. The production process consists of mixing TP and other excipients in a 1000 L 316 SS container, after which the mixture is pumped through a filter press into 100 L 316 SS containers. Waste water samples were collected by washing the SS reactor and the filter press with distilled water. The resulting factory effluent solution contained  $[TP]_0 = 160 \text{ mg L}^{-1}$  (Fig. 8S†). To account for the high  $[TP]_0$

effluent content,  $[PS]_0$  was tested at 25, 50, 75 and 100 mM utilizing the optimum  $[PS]_0 : [Fe^{2+}]_0$  ratio of  $1 : 1$  and  $T = 60 \text{ }^\circ\text{C}$ .

The results showed that a higher  $[PS]_0$  caused faster degradation, where total TP elimination was observed within 40 min in the case of  $[PS]_0 = [Fe^{2+}]_0 = 100 \text{ mM}$  and within 180 min for  $[PS]_0 = [Fe^{2+}]_0 = 25 \text{ mM}$  (Fig. 8 and Table 7). To compare the degradation of TP in DI and in the factory effluent mixture,  $k_{obs}$  can be compared in cases of similar  $[PS]_0/[TP]_0$  molar ratios. As such, for the case of  $[TP]_0 = 10 \text{ mg L}^{-1}$  ( $0.0555 \text{ mM}$ ) and  $[PS]_0 = [Fe^{2+}]_0 = 1.5 \text{ mM}$  in DI,  $[PS]_0/[TP]_0 = 27$ , while for the case of  $[TP]_0 = 160 \text{ mg L}^{-1}$  and  $[PS]_0 = [Fe^{2+}]_0 = 25 \text{ mM}$  in factory effluent,  $[PS]_0/[TP]_0 = 28$ . The corresponding  $k_{obs}$  decreased by 2 fold from  $0.29 (\pm 0.02) 10^{-1}$  to  $1.4 (\pm 0.1) \times 10^{-2} \text{ min}^{-1}$ . Thus, the TP degradation in factory effluent is less efficient than in DI medium. This can be attributed to the presence of excipients, such as potassium sorbate, sorbitol, ethanol, vanillin and saccharine, as provided by the manufacturer. Those can compete with TP in reacting with the active SRs. It should be noted that the efficiency of the TCAP system would have decreased if natural water was used to rinse the mixing reactor instead of DI water (Section 3.3.5); thus, it is crucial for industries to utilize adequate amounts of distilled (DI) water in rinsing apparatuses and tools used during syntheses and mixing processes for efficient and cost-effective effluent treatment.

**3.7.2. Economic study.** The cost of factory effluent treatment utilizing the TCAP system was estimated. The electric energy required to heat the solution in addition to the reagent price were considered to be the main contributors to the total cost of operation (eqn (15)).

$$\text{Total system cost (\$ per m}^3\text{)} = \text{electrical energy cost} + \text{reagent cost} \quad (15)$$

Electric energy per order ( $E_{EO}$ ) was defined as the electric energy required to degrade contaminants by one order of magnitude, for example from  $10 \text{ mg L}^{-1}$  to  $1 \text{ mg L}^{-1}$ , in one cubic meter of contaminated water or air; this was calculated using eqn (16) for a batch system.<sup>59</sup>

$$E_{EO} = \frac{P \times t \times 1000}{V \times \log\left(\frac{C_i}{C_f}\right)} \quad (16)$$

where  $P$  is the power supplied to the system in kW,  $t$  is the duration of the treatment in hours,  $V$  is the volume treated in L,  $C_i$  and  $C_f$  are the initial and final concentrations, respectively,

Table 7 Degradation of TP by TCAP in real pharmaceutical effluent containing  $[TP]_0 = 160 \text{ mg L}^{-1}$ . Experimental conditions:  $[PS]_0 = 25\text{--}100 \text{ mM}$ ,  $[PS]_0 : [Fe^{2+}]_0$  ratio of  $1 : 1$ , and  $T = 60 \text{ }^\circ\text{C}$ .  $k_{obs}$  is calculated for the pseudo-first order reaction rate

$[PS]_0$ mM	$[Fe^{2+}]_0$ mM	$T$ $^\circ\text{C}$	$k_{obs}$ $\text{min}^{-1}$	$pH_i/pH_f$
25	25	60	$1.4 (\pm 0.1) \times 10^{-2}$	1.17/1.08
50	50		$4.5 (\pm 0.2) \times 10^{-2}$	0.85/0.78
75	75		$1.16 (\pm 0.05) \times 10^{-1}$	0.67/0.60
100	100		$1.65 (\pm 0.09) \times 10^{-1}$	0.58/0.48



**Table 8** Treatment costs of pharmaceutical effluent contaminated with TP using a TCAP system. The calculations of total system cost for different TP degradation conditions in pharmaceutical effluent are based on electricity price rates in the US and in Lebanon. Experimental conditions:  $[TP]_0 = 160 \text{ mg L}^{-1}$ ,  $[PS]_0 = 25, 50, 75 \text{ and } 100 \text{ mM}$ ,  $[PS]_0 : [Fe^{2+}]_0$  ratio of 1 : 1, and  $T = 60 \text{ }^\circ\text{C}$

$[PS]_0$ , mM	$k_{\text{obs}}$ , $\text{min}^{-1}$	$E_{\text{EO}}$ , kW h per $\text{m}^3$ per order	Electricity cost (US), \$ per $\text{m}^3$ per order	Electricity cost (Lebanon), \$ per $\text{m}^3$ per order	Reagent cost <sup>a</sup> , \$ per $\text{m}^3$	Total cost (US), \$ $\text{m}^{-3}$	Total cost (Lebanon), \$ per $\text{m}^3$
25	$1.4 (\pm 0.1) \times 10^{-2}$	558	39.6	94.4	22.2	61.8	116.6
50	$4.5 (\pm 0.2) \times 10^{-2}$	174	12.3	29.4	44.5	56.8	73.8
75	$1.16 (\pm 0.05) \times 10^{-1}$	67.4	4.8	11.4	66.7	71.5	78.1
100	$1.65 (\pm 0.09) \times 10^{-1}$	47.4	3.4	8.0	88.9	92.3	96.9

<sup>a</sup> Check Table 1S.

and 1000 is a conversion factor from L to  $\text{m}^3$ . Thus,  $E_{\text{EO}}$  is obtained in kW h per  $\text{m}^3$  per order. Additionally, eqn (16) was simplified by substituting the first-order reaction rate eqn (17) in eqn (16) and changing the unit of time. Thus, the following simplification was performed (eqn (16)–(19)):

$$\log \frac{C_i}{C_f} = 0.4343 \times k_{\text{obs}} \times t \quad (17)$$

$$E_{\text{EO}} = \frac{P \times t \times 1000}{V \times 0.4343 \times k_{\text{obs}} \times t \times 60} \quad (18)$$

$$E_{\text{EO}} = \frac{38.4 \times P}{V \times k_{\text{obs}}} \quad (19)$$

The resulting simplified eqn (19) shows  $P$  in kW,  $V$  in L, and  $k_{\text{obs}}$  in  $\text{min}^{-1}$ .<sup>59</sup> Power was calculated based on the energy and time needed to heat the reactors. The energy required for this heating was calculated using eqn (20), where  $Q$  is the energy in J,  $m$  is the mass of water in g (200 g),  $C$  is the specific heat capacity of water ( $4.186 \text{ J g}^{-1} \text{ }^\circ\text{C}^{-1}$ ), and  $\Delta T$  ( $35 \text{ }^\circ\text{C}$ ) is the temperature difference for heating from  $25 \text{ }^\circ\text{C}$  to  $60 \text{ }^\circ\text{C}$ .  $Q$  was found to be 29.3 kJ.

$$Q = mC\Delta T \quad (20)$$

Power was calculated utilizing eqn (21), where  $t$  is the time in seconds needed to heat the solution to the desired temperature. Experimentally, 12 min were required to heat the 200 mL reactor from room temperature to  $60 \text{ }^\circ\text{C}$ . Thus,  $P = 0.122 \text{ kW}$ .

$$P = \frac{Q}{t} \quad (21)$$

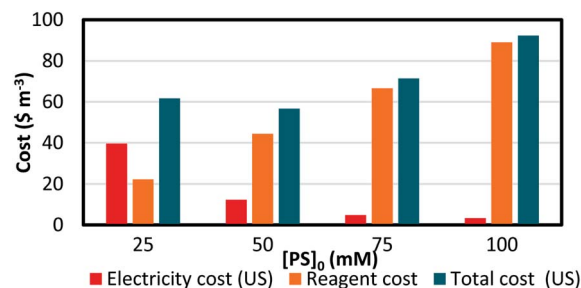
The  $E_{\text{EO}}$  was calculated for each of the four different  $[PS]_0$  values, and the results are presented in Table 8. The electrical energy cost was estimated utilizing electricity cost rates in Lebanon, with the Electricit  du Liban (EDL) average rate of 255 LBP per kW per h equivalent to 0.169 \$ per kW per h at the current conversion rate,<sup>60,61</sup> as well as in the US, where the average electricity cost rate for the industrial sector is 0.0709 \$ per kW per h. The costs of the reagents were calculated using

wholesale prices in every case (Table S1†). The total system cost can thus be obtained (eqn (15)) and is presented in detail in Fig. 9. It was observed that as  $[PS]_0$  increases, the reagent cost increases, while the electric cost due to heating decreases. Consequently, the choice of  $[PS]_0$  for the treatment of factory effluent can be based on the estimated total cost, where the case of  $[PS]_0 = 50 \text{ mM}$  gave the lowest total cost of 56.8 and 73.8 \$ per  $\text{m}^3$  based on electricity prices in the US and in Lebanon, respectively (Fig. 9 and Table 8).

Amasha *et al.* obtained a total cost of 44.414 \$ per  $\text{m}^3$  for degradation of ketoprofen ( $7.87 \text{ } \mu\text{M}$ ,  $2.00 \text{ mg L}^{-1}$ ) in a TAP system, with  $[PS]_0 = 1 \text{ mM}$  and  $T = 60 \text{ }^\circ\text{C}$ .<sup>34</sup> The lower total cost obtained by the mentioned study can be attributed to the fact that no  $\text{Fe}^{2+}$  was used, so the reagent price was lower; in addition, the degradation was performed in DI and not in factory effluent, where competitive reactions take place between  $\text{SO}_4^{\cdot-}$  and the excipients present (Section 3.7.1).

### 3.8. Effects of MeOH and TBA quenchers

Radical scavenging by methanol (MeOH) and *tert*-butyl-alcohol (TBA) was tested in the TCAP system to determine the effectiveness of the produced  $\text{SO}_4^{\cdot-}$  and  $\text{HO}^\cdot$  in the degradation of TP. Different concentrations of MeOH and TBA (400, 800 mM) were added separately to reactors containing  $[TP]_0 = 10 \text{ mg L}^{-1}$



**Fig. 9** Treatment cost of pharmaceutical effluent contaminated with TP using a TCAP system. The electricity, reagent and total costs are presented (based on US electricity cost). Experimental conditions:  $[TP]_0 = 160 \text{ mg L}^{-1}$ ,  $[PS]_0 = 25\text{--}100 \text{ mM}$ ,  $[PS]_0 : [Fe^{2+}]_0$  ratio of 1 : 1 and  $T = 60 \text{ }^\circ\text{C}$ .



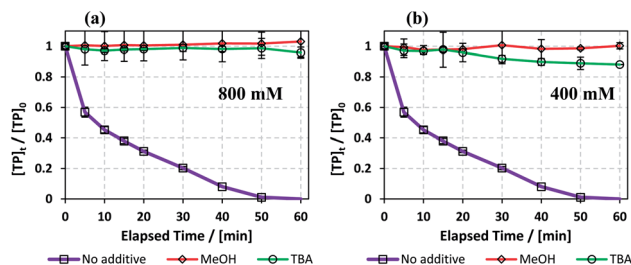


Fig. 10 (a) Effects of MeOH and TBA quenchers on TP degradation in the TCAP system. Experimental conditions:  $[TP]_0 = 10 \text{ mg L}^{-1}$ ,  $[PS]_0 = [Fe^{2+}]_0 = 2 \text{ mM}$ ,  $[MeOH] = [TBA] =$  (a) 800 and (b) 400 mM and  $T = 60 \text{ }^\circ\text{C}$ . Error bars are calculated as  $\frac{ts}{\sqrt{n}}$ , where absent bars fall within the symbols.

and  $[PS]_0 = [Fe^{2+}]_0 = 2 \text{ mM}$ . The experiments were conducted in tight reactors using rubber stoppers in order to prevent substantial loss of MeOH ( $k_H^\circ = 230 \text{ mol kg}^{-1} \text{ bar}^{-1}$ ) and TBA ( $k_H^\circ = 83 \text{ mol kg}^{-1} \text{ bar}^{-1}$ ) from the reactor due to heat.<sup>62</sup> It is

known that MeOH quenches both  $SO_4^{\bullet-}$  and  $HO^\bullet$  radicals, whereas TBA mainly quenches  $OH^\bullet$ .<sup>22</sup>

Fig. 10 shows that MeOH and TBA caused increased inhibition as their concentrations increased. This is due to the increase in competition between the quenchers and TP to react with the radicals present in the medium. Wang *et al.* also obtained a positive correlation between inhibition extent and the concentrations of TBA and MeOH used in a TAP system.<sup>63</sup> In the case of 800 mM quenchers used (quencher/PS: 400/1), TBA and MeOH caused almost total quenching due to their high concentrations. However, when 400 mM quenchers were used (Quencher/PS: 200/1), MeOH caused slightly more quenching than TBA. We can deduce that  $HO^\bullet$  is the major reactive species when degrading TP in a TCAP system.

### 3.9. Suggested degradation pathway

A theoretical study of the degradation pathway utilizing frontier orbitals and charge distribution was conducted. Frontier molecular orbital theory shows that electrophilic reactions are more likely to occur for atoms with higher values of the highest

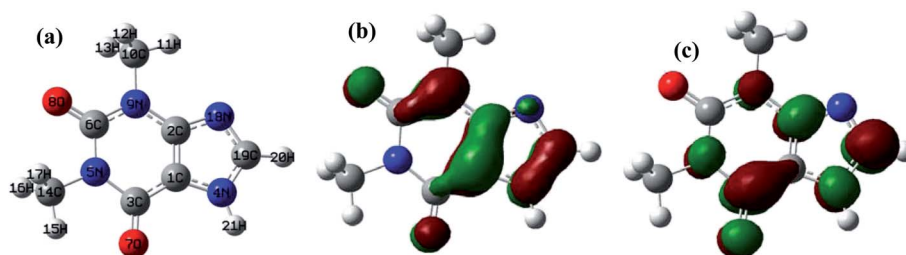
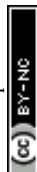


Fig. 11 (a) TP atomic labeling and numbering. Isodensity surfaces of the (b) HOMO and (c) LUMO of TP with isovalues of 0.05.

Table 9 The computed values of the FEDs for the HOMO and LUMO in addition to the Mulliken charge distributions

Atom	$FED_{HOMO^2} + FED_{LUMO^2}$	$2FED_{HOMO^2}$	$2FED_{LUMO^2}$	Mulliken charge
1C	0.27	0.45	0.08	0.35
2C	0.23	0.19	0.27	0.11
3C	0.38	0.17	0.58	0.25
4N	0.17	0.13	0.21	-0.21
5N	0.05	0.01	0.10	-0.25
6C	0.02	0.04	0.01	0.56
7O	0.18	0.17	0.19	-0.66
8O	0.10	0.20	0.00	-0.67
9N	0.25	0.38	0.11	-0.26
10C	0.01	0.01	0.01	-0.21
11H	0.00	0.00	0.00	0.14
12H	0.01	0.02	0.00	0.14
13H	0.01	0.02	0.00	0.14
14C	0.00	0.00	0.00	-0.15
15H	0.00	0.00	0.00	0.15
16H	0.01	0.00	0.02	0.14
17H	0.01	0.00	0.02	0.14
18N	0.01	0.01	0.01	-0.47
19C	0.28	0.19	0.36	0.29
20H	0.00	0.00	0.00	0.23
21H	0.00	0.00	0.00	0.25
22H	—	—	—	—



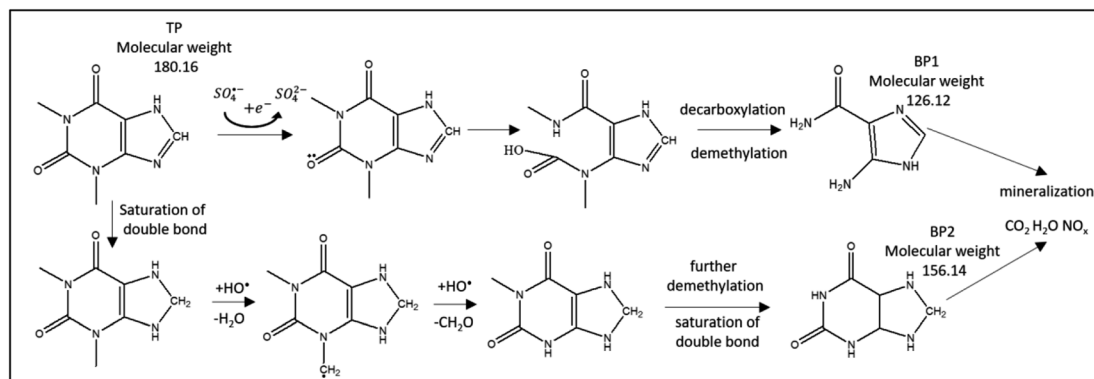


Fig. 12 Suggested TP degradation pathway by  $\text{SO}_4^{\bullet-}$  and  $\text{HO}^\bullet$ . Two detected by-products, BP1 and BP2, are included.

occupied molecular orbital (HOMO), while nucleophilic reactions are prone to occur for atoms with higher values of the lowest unoccupied molecular orbital (LUMO).<sup>64</sup> Consequently, several studies suggest that atoms with a higher  $2\text{FED}_{\text{HOMO}^2}$  are more easily oxidized, and those with a higher  $\text{FED}_{\text{HOMO}^2} + \text{FED}_{\text{LUMO}^2}$  are more susceptible to addition reactions.<sup>65–67</sup> The  $2\text{FED}_{\text{HOMO}^2}$ ,  $2\text{FED}_{\text{LUMO}^2}$ , and Mulliken charge distributions were calculated for TP and are presented along with the atom numbering and the isodensity surfaces of frontier molecular orbital theory in Fig. 11 and Table 9. For TP, 1C showed the highest  $2\text{FED}_{\text{HOMO}^2}$ , followed by 9N, 8O, 2C, 19C, 3C and 7O. Therefore, attack by oxidants is expected to occur readily on 1C, 9N and 8O. Also, 3C showed the highest  $\text{FED}_{\text{HOMO}^2} + \text{FED}_{\text{LUMO}^2}$ , followed by 19C, 1C, 9N, 2C, 7O and 4N. Thus, addition reactions will mostly take place at 1C, 19C and 3C; however, it was noted that 19C is the least sterically hindered of the three atoms. Thus, addition reactions are expected to occur more readily at 19C, such as the formation of hydroxylated products at this site. It is known that  $\text{HO}^\bullet$  performs H abstraction and  $\text{SO}_4^{\bullet-}$  acts selectively as an electron transfer reactant.<sup>68</sup> According to the obtained Mulliken charge distributions, electrons are mostly abstracted from 7O and 8O because they show the most negative charges (Table 9). These results were used to suggest a degradation mechanism (Fig. 12).

LC/MS/MS was used to identify the by-products of TP degradation. Fig. 8S† shows two identified by-products termed BP1 (molecular weight  $126.12 \text{ g mol}^{-1}$ ) and BP2 (molecular weight  $156.14 \text{ g mol}^{-1}$ ). The extracted ion chromatograms of BP1 and BP2 showed that the intensities of their peaks constantly increased with time, which proves that these by-products are formed throughout the degradation reaction (Fig. 8S†). It was noted that the intensity of BP1 is higher, which suggests that it is more prevalent than BP2.

Fig. 12 presents the suggested degradation pathway based on the results obtained from theoretical studies and LC/MS/MS results. Electron abstraction is expected on the oxygen group (8O, Fig. 11) by  $\text{SO}_4^{\bullet-}$ . Attack of  $\text{SO}_4^{\bullet-}$  and  $\text{HO}^\bullet$  is expected on the 6-membered ring, where ring opening occurs with the formation of carboxylic groups. This is followed by loss of  $\text{CO}_2$  and de-methylation on the 5N and 9N sites. As a result, BP1 is obtained.

Demethylation is initiated by hydrogen abstraction at 10C and 14C, which is followed by  $\text{HO}^\bullet$  attack. BP2 is formed through demethylation and saturation of double bonds. Ultimately, mineralization is expected, which was obtained in similar AOP studies.<sup>69,70</sup>

## 4. Conclusions

In this study, TP degradation was tested in systems of TAP, CAP and TCAP. TAP resulted in incomplete (60%) TP degradation at  $t = 60 \text{ min}$  for  $[\text{PS}]_0 = 5 \text{ mM}$  and  $T = 60^\circ \text{C}$ . The CAP system was not effective at room temperature, where a maximum of 5% TP degradation was observed at  $t = 60 \text{ min}$  for  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 0.25 \text{ mM}$ . To obtain better efficiency, the two methods of PS activation were combined in a TCAP system, which resulted in complete TP degradation at  $T = 60^\circ \text{C}$  and  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 2 \text{ mM}$ . The reaction followed a pseudo-first order reaction rate, with  $k_{\text{obs}} = 5.6 (\pm 0.4) \times 10^{-2} \text{ min}^{-1}$ . The effects of  $[\text{PS}]_0 : [\text{Fe}^{2+}]_0$  ratio,  $[\text{PS}]_0$  and temperature were tested, where the 1 : 1 ratio gave optimum results, and the degradation rate increased with increasing  $[\text{PS}]_0$  and temperature. Salinity inhibited the degradation process, while nitrates slightly enhanced the process. The presence of HAs inhibited TP degradation. TP was dissolved in real water samples of spring, sea and waste water, which showed lower degradation rates in comparison with DI water medium. Real factory effluent containing TP was obtained and showed total degradation of  $[\text{TP}]_0 = 160 \text{ mg L}^{-1}$  within 180 and 40 min for  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 25$  and 100 mM, respectively. The degradation cost was estimated to  $56.8 \text{ \$ per m}^3$ , for electricity price rates in the US at  $[\text{PS}]_0 = [\text{Fe}^{2+}]_0 = 50 \text{ mM}$ . A degradation mechanism involving *in situ* evolved reactive oxidative species, mainly sulfate and hydroxyl radicals, was also suggested based on LC/MS/MS HRAM analyses supported by frontier molecular orbital theory calculations.

## Conflicts of interest

There are no conflicts to declare.





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