Dual roles of hydroxyl radicals and effects of competition on ozonation kinetics of two phenazone-type pollutants

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Abstract
Ozonation has been proved to be a promising approach for eliminating emerging pollutants in wastewater. In previous studies, emerging pollutants including diverse pharmaceuticals were found to exhibit significantly different ozonation reactivity. However, how the structural differences of emerging pollutants determine ozonation reactivity and mechanisms are still ambiguous. In this work, ozonation of dimethylaminophenazone (DMP) and acetylaminophenazone (AAA) with the same parent structure of phenazone but different substitution groups was investigated, in order to probe influencing mechanisms of structural differences on ozonation reactivity. Results show that DMP reacts with ozone and HO/C15 almost 2 and 1 order of magnitude faster than AAA, respectively. At pH 8, HO/C15 accelerates ozonation of DMP, but decreases ozonation of AAA. Competition simultaneously decreases degradation rate of the two phenazines, but effects on AAA are more significant than that on DMP. According to theoretical calculation results, differences in ozonation reactivity and mechanisms of the two phenazines can be mainly attributed to different substitution groups. The dimethylamino group in the structure of DMP increases the ozonation reactivity of phenazone by increasing reaction orbital energies and altering reaction sites, while the acetylamino group in the structure of AAA decreases the reaction orbital energy and therefore lowers the reactivity.

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1. Introduction
The occurrence of a huge number of pharmaceuticals and their active metabolites in aquatic environments becomes an issue of increasing concerns, as these pollutants potentially cause ecological risks to aquatic organisms and humans. Among the pharmaceuticals the most commonly detected in aquatic environments are analgesics [1]. Phenazone-type drugs including phenazone and derivatives like dipyrone are frequently prescribed analgesics. According to Chinese statistical data, several thousand tons of dipyrone were produced in 2011 [2]. In other countries, phenazone-type drugs are also widely used, and often detected in wastewater effluents and surface waters [1,3–5]. An environmental risk assessment using hazard indexes shows that phenazone-type pollutants rank among the most relevant pharmaceuticals for invertebrates and algae [6]. In aquatic environments, some dipyrone metabolites can transform to persistent and toxic photolytic products [7]. Conventional wastewater treatment plants were found to remove only up to 30% of phenazone and less than 40% of acetylaminophenazone (AAA) [8], which is a final metabolite of dipyrone and frequently detected in wastewater and environmental waters [4,9,10]. Some widely used phenazines, e.g.

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phenazone, propyphenazone and dimethylaminophenazone (DMP), degrade fast through chlorination [11–13]. Unfortunately, chlorinated products were formed [11] and a high N-nitrosodimethyamine formation potential was observed for DMP [14], raising concerns on potential ecotoxicity. In a previous work, polychlorinated products were formed [11] and a high

than direct O3 oxidation [19]. These indicate that the ozonation reacting slowly with O3, H2O

many antibiotics at a neutral pH range [18]. But for ibuprofen

molecule (O3) and/or its hydrolytic product, hydroxyl radicals (HO•)

emerging organic pollutants, e.g. pharmaceuticals and personal

wastewater were usually predicted by considering in

coexisting PPCPs, as PPCPs show diverse reactivity in ozonation

Due to structurally differences, the reactivity of PPCPs reacting

that the substitution groups in

that the substitution groups determine electrophilic reac-
tivity and reacting sites of DMP and AAA.

show that the substitution groups related with ozonation. The calculation results

Second-order reaction rate constants of the phenazones with O3

and HO• (kHO•) were determined with competitive kinetic experiments employing MC and pCBA as reference compounds, respectively. Experiments were performed at equal concentrations of reference and target compounds, i.e. 0.01 mM. For determining kO3, t-BuOH was added to scavenge HO•. For determining kHO•, H2O2 (10% v/v) was added for improving HO• generation. kO3 and kHO• values are calculated according to equations (1) and (2), respectively.

\[ k_{O3,p} = \frac{\ln \frac{C_{0,MC}}{C_{t,MC}}}{\ln \frac{C_{0,p}}{C_{t,p}}} \]  

(1)

\[ k_{HO•,p} = \frac{\ln \frac{C_{0,MC}}{C_{t,MC}}}{\ln \frac{C_{0,p}}{C_{t,p}}} \]  

(2)

where, kO3,p and kHO•,p are second-order reaction rate constants of the phenazones; kO3, MC and kHO•, pCBA are second-order reaction rate constants of the reference compounds.

2.3. Analytical methods

A HPLC-UV system (Waters, USA) employing a reverse-phase TC-C18 column (150 mm × 4.6 mm, 5 μm, Agilent, USA) was used for analyzing target and reference compounds. Mobile phases and detected wavelengths are methanol:H2O (3:7), 254 nm for AAA, acetonitrile:H2O (4:6), 254 nm for DMP, methanol:H2O (4:6) with 0.1% H3PO4, 287 nm for MC, and methanol:H2O (7:3) with 0.5% H2PO4, 236 nm for pCBA.

2.4. Calculation methods

Geometries of target compounds and phenazone were optimized based on density functional theory (DFT) at the B3LYP/6-31+G(d,p) level. Frequency analysis was performed at the same level to characterize the stationary points. FMO were calculated at the B3LYP/6-311+G(3df,2p) level for characterizing electrophilic reactivity and electrophile preferring attack sites. The integral equation formalism polarized continuum model (IEF-PCM) was employed in all calculations including geometry optimization. All DFT calculations were performed with Gaussian 09 software package [25].
ference observed between pH range studied in this work. This explains the insigni-

\[ \text{Addition of } \text{BuOH leads to rate increase for AAA but rate decrease for DMP.} \]

3. Results and discussion

3.1. pH-dependence and roles of HO•

Apparent degradation kinetic constants \( k_{\text{obs}} \) of AAA and DMP determined at different pH conditions and in the presence of t-BuOH are shown in Fig. 1. No significant pH change was observed before and after the ozonation experiments. Ozonation of the two compounds was found to follow pseudo-first-order kinetics. \( k_{\text{obs}} \) of AAA shows slight difference at pH 3 and 8, but decreases at pH 10. \( k_{\text{obs}} \) of DMP at pH 8 is the highest, followed by that at pH 10 and 3. Addition of t-BuOH leads to rate increase for AAA but rate decrease for DMP, implying HO• may play different roles in their degradation.

The pH influence on ozonation of ionizable pollutants is usually related to deprotonation. For example, deprotonated \( N \) is ozone preferred but protonated \( N \) reacts slowly with ozone [26]. As the dimethylamino group of DMP has a \( pK_a \) value of 5.0 for an \( N \) protonated form transforming to an unprotonated form [27], the increase in \( k_{\text{obs}} \) from pH 3 to 8 can be attributed to an increase percentage of the unprotonated form, which is well known to show a higher reactivity to ozone than the \( N \) protonated form. No exact dissociation constant \( (pK_a) \) was found for AAA, but as indicated by a negative acid dissociation constant reported for \( N \)-acetylaniline [28], AAA was inferred to exist mainly as a neutral form within the pH range studied in this work. This explains the insignificant difference observed between \( k_{\text{obs}} \) values of pH 3 and 8. However, the \( k_{\text{obs}} \) changes from pH 8 to 10 for the two compounds are unlikely induced by deprotonation, as neither of them deprotonates in this pH range.

HO• was proposed to be responsible for the \( k_{\text{obs}} \) changes of AAA and DMP at high pH values, as increased pH artificially accelerate ozone decomposition to form HO• [16]. Moreover, the \( k_{\text{obs}} \) values of the two target compounds change significantly after t-BuOH addition, which is a strong HO• scavenger and can save \( O_3 \) from decomposition through radical chain reactions. The addition of t-BuOH is expected to inhibit HO• formation and elongate life of \( O_3 \), thus increasing stable-state concentrations of \( O_3 \). AAA degrades fast after adding t-BuOH, implying that HO• plays a negative role in AAA degradation. As HO• is a strong oxidant that can oxidize almost all organic pollutants non-selectively, the target compounds are supposed to undergo HO• induced oxidation besides reacting with ozone. It can be inferred that the potential HO• oxidation for AAA cannot compensate a rate decrease due to loss of ozone from radical chain reactions. Therefore, \( k_{\text{obs}} \) of AAA increased significantly when radical chain reactions were stopped by t-BuOH. The \( k_{\text{obs}} \) decrease observed for AAA at pH 10 can be attributed to a similar reason, as increased pH accelerates HO• formation. For DMP, HO• plays a positive role in the ozonation at pH 8, as decreased \( k_{\text{obs}} \) after t-BuOH addition. But when pH increases to 10, HO• formation rate increases significantly, and the excess HO• consumes \( O_3 \) fast, resulting in a decreased rate for DMP.

In order to confirm the role of HO• in ozonation of the target compounds in wastewaters, influence of some HO• scavengers ubiquitous present in wastewaters was investigated. As shown in Fig. 2, acceleration of AAA degradation and decrease of DMP degradation were observed, though not as significant as that in the presence of t-BuOH. This is consistent with the conclusions stated above.

3.2. Bimolecular rate constants of reacting with \( O_3 \) and HO•

Curves of \( \ln(c_{t, p}/c_{0, p}) \) vs \( \ln(c_{t, MC}/c_{0, MC}) \) and \( \ln(c_{t, pCA}/c_{0, pCA}) \) are shown in Fig. 3. According to equations (1) and (2), \( k_{O_3} \) and \( k_{HO•} \) values of AAA and DMP were calculated with known \( k_{O_3, MC} \) \( (6.8 \times 10^4 \ M^{-1} \ s^{-1} [29]) \), \( k_{HO•, pCA} \) \( (5.2 \times 10^8 \ M^{-1} \ s^{-1} [30]) \) values and slopes (Table 1).

The \( k_{O_3} \) value of DMP is almost 2 orders of magnitude higher than that of AAA. This is consistent with the result that DMP degrades faster than AAA in the presence of an equal import amount of \( O_3 \). Nevertheless, adding t-BuOH that saves \( O_3 \) from decomposition to form HO• results in a decreased rate for DMP but an increase for AAA. This can be attributed to a significantly higher \( k_{HO•} \) value of DMP than that of AAA. As \( k_{HO•} \) of DMP \( (9.1 \pm 2.3 \times 10^8 \ M^{-1} \ s^{-1}) \)
10^10 \text{ M}^{-1}\text{ s}^{-1} \) is almost 2 orders of magnitude higher than that of ozone \((1 \times 10^8 – 2 \times 10^7 \text{ M}^{-1}\text{ s}^{-1})\), it can be inferred that most HO^• formed due to O3 alkaline decomposition reacts with DMP at pH 8 rather than inducing radical chain reactions. However, O3 alkaline decomposition was accelerated at pH 10, and there was enough HO^• formed due to O3 alkaline decomposition reacts with DMP at pH 8 to cause considerable ozone decomposition. Therefore, the fast loss of O3 at the alkaline pH results in degradation decreased of DMP.

### 3.3. Competitive ozonation of AAA and DMP

As AAA and DMP can represent emerging organic pollutants exhibiting significantly different ozonation reactivity, competition of the two compounds in ozonation was investigated. Competitive \(k_{obs}^\text{fi} \text{ values (C-}k_{obs}^\text{fi})\) determined at pH 8 are listed in Table 2. Competitive ozonation of the two phenazones was found to follow pseudo-first-order kinetics. For AAA, C-\(k_{obs}^\text{fi}\) value \((3.0 \pm 0.15 \text{ s}^{-1})\) is close to the individual \(k_{obs}^\text{fi}\) value \((3.1 \pm 0.56 \text{ s}^{-1})\). For DMP, C-\(k_{obs}^\text{fi}\) value \((7.5 \pm 0.82 \text{ s}^{-1})\) is lower than the individual \(k_{obs}^\text{fi}\) value \((9.2 \pm 0.95 \text{ s}^{-1})\), but the difference is statistically insignificant \((p > 0.05)\) as tested by t-test. As the initial concentrations of the two compounds are halved in the competitive ozonation experiments, the steady-state concentration of O3 or HO^• is close to that in the individual experiments. The slight decrease in degradation of DMP can be attributed to the competition effect of AAA.

In a WWEf sample, the competition of AAA and DMP was found to be more significant than that in the buffer solution. The C-\(k_{obs}^\text{fi}\) value of DMP in WWEf solution decreased by 20% compared with that in the pH 8 solution, while that of AAA decreased by 70% (Table 2). As shown in Fig. 2, ubiquitous anions slightly reduce DMP degradation but accelerate AAA degradation, which cannot explain the large rate decrease observed for AAA. Dissolved organic matters were found to scavenge either O3 or HO^• [31]. Therefore, O3 or HO^• in the WWEf solution with TOC of 12 mg L\(^{-1}\) is lower than that in the pH 8 solution. This means that the competition between AAA and DMP is stronger in the WWEf solution, where O3 or HO^• is less abundant. As DMP reacts with O3 or HO^• much faster than AAA, the decreased C-\(k_{obs}^\text{fi}\) observed for AAA is more significant than that observed for DMP. Accordingly, the decrease of ozonation rates for coexisting pollutants is not only dependent on wastewaster matrix but also vary with pollutants.

### 3.4. Computational interpretations on different ozonation reactivity

FMO energy and electron distributions of AAA, DMP and phenazone are shown in Fig. 4. As either ozone or HO^• acts mainly as electrophiles, preferring to attack the highest occupied molecular orbitals (HOMO) of organic pollutants, ozonation reactivity of the phenazones is expected to be related with HOMO energies \(E_{\text{HOMO}}\) and distributions. The order of \(k_{O3}\) or \(k_{HO^•}\): DMP > phenazone \((k_{O3} = 6.2 \times 10^7 \text{ M}^{-1}\text{ s}^{-1}, \text{pH} = 7 [17]; k_{HO^•} = 4.86 \times 10^7 \text{ M}^{-1}\text{ s}^{-1} [32]) > AAA, was found to be consistent with the order of \(E_{\text{HOMO}}\): DMP (-5.63 eV) > phenazone (-6.17 eV) > AAA (-6.27 eV). Moreover, a positive linear correlation was found between \(E_{\text{HOMO}}\) and \(k_{O3}\) values: \(k_{O3} = 1 \times 10^8 E_{\text{HOMO}} + 3 \times 10^7\) \((R^2 = 0.99)\). Therefore, the HOMO characteristics were vital influencing parameters for determining the ozonation reactivity of the phenazones.

As shown in Fig. 4, AAA and DMP have the same phenazone parent structure, but different substituted R groups, that is, CH\(_3\)CON(H)– for AAA, (CH\(_3\))\(_2\)N– for DMP. Either CH\(_3\)CON(H)– or (CH\(_3\))\(_2\)N– exhibits an electron donating conjugative effect, however, it causes opposite influence on the reactivity of phenazone. The amino group in sulfamethoxazole almost resists to ozone after acetylation, implying low reactivity of the CH\(_3\)CON(H)– group to ozone [18]. Moreover, the presence of CH\(_3\)CON(H)– group decreases reactivity of other reaction sites in ozonation as indicated by \(k_{O3}, k_{HO^•}\) and \(E_{\text{HOMO}}\) of phenazone and AAA. DMP has a higher \(E_{\text{HOMO}}\) value than AAA and phenazone, therefore, showing higher reactivity with electrophiles. As shown by the HOMO profile (Fig. 4), AAA and phenazone have similar HOMO electron distributions while that of DMP is significantly different. For AAA and phenazone, ozone or HO^• prefers to attack the benzene ring and the pyrazol ring. But for DMP, electrophilic attacks mainly occur on the (CH\(_3\))\(_2\)N– group and the pyrazol ring. As tertiary N atoms usually react 1 or 2 orders

![Fig. 3. Curves of ln(cﬁ/cco) vs ln(cﬁ/c0) for AAA and DMP in pH 8 and 10 solutions and in a WWEf sample.](image)

### Table 1

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>(k_{O3}) (M(^{-1}\text{ s}^{-1}))</th>
<th>(k_{HO^•}) (M(^{-1}\text{ s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>5.3 ± 0.3 \times 10^4</td>
<td>8.4 ± 0.7 \times 10^6</td>
</tr>
<tr>
<td>DMP</td>
<td>3.0 ± 0.3 \times 10^6</td>
<td>9.1 ± 2.3 \times 10^6</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Solution</th>
<th>(k_{obs}^\text{fi} \times 10^7) (s(^{-1})) of AAA</th>
<th>(k_{obs}^\text{fi} \times 10^7) (s(^{-1})) of DMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual</td>
<td>Competitive</td>
</tr>
<tr>
<td>pH8</td>
<td>3.1 ± 0.6 (0.99)</td>
<td>3.0 ± 0.2 (0.99)</td>
</tr>
<tr>
<td>WWEf</td>
<td>0.9 ± 0.1 (0.96)</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) Average \(R^2\) \((n = 3)\). 
\(^b\) Not determined.
of magnitude faster than the benzene ring with ozone [31], the different reactivity of AAA and DMP can be attributed to different electrophilic reacting sites caused by substitution effects.

4. Conclusions

In this work, the ozonation of two phenazone-type pollutants was investigated. The results show that HO\(^\cdot\) exhibits dual roles in the ozonation of the two phenazines. At pH 8, HO\(^\cdot\) accelerates DMP degradation, but decreases AAA degradation. Competition in a WWEF solution is stronger than that in pH 8 buffer solutions, and results in unequal rate decreases for DMP and AAA, i.e. 20% and 70% respectively. Accordingly, \(k_{\text{obs}}\) values obtained in ozonation experiments of individual pollutant or employing unreal wastewater cannot be arbitrarily used for predicting degradation rate of coexisting pollutants in real wastewater, especially the pollutants exhibits significantly different ozonation reactivity. The dual roles of HO\(^\cdot\) and the significant competitive effects can be mainly attributed to different ozonation reactivity of the two phenazines, as DMP reacts with O\(_3\) or HO\(^\cdot\) more than one order of magnitude faster than AAA. As indicated by DFT calculations, the different reactivity is mainly related with \(E_{\text{HOMO}}\) values and different reaction sites determined by substitution groups.

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