



Ozonation of piperidine, piperazine and morpholine: Kinetics, stoichiometry, product formation and mechanistic considerations



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ABSTRACT

Piperidine, piperazine and morpholine as archetypes for secondary heterocyclic amines, a structural unit that is often present in pharmaceuticals (e.g., ritalin, cetirizine, timolol, ciprofloxacin) were investigated in their reaction with ozone. In principle the investigated compounds can be degraded with ozone in a reasonable time, based on their high reaction rate constants with respect to ozone (1.9×10^4 – $2.4 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$). However, transformation is insufficient (13–16%), most likely due to a chain reaction, which decomposes ozone. This conclusion is based on $\cdot\text{OH}$ scavenging experiments, leading to increased compound transformation (18–27%). The investigated target compounds are similar in their kinetic and stoichiometric characteristics. However, the mechanistic considerations based on product formation indicate various reaction pathways. Piperidine reacts with ozone via a nonradical addition reaction to *N*-hydroxypiperidine (yield: 92% with and 94% without scavenging, with respect to compound transformation). However, piperazine degradation with ozone does not lead to *N*-hydroxypiperazine. In the morpholine/ozone reaction, *N*-hydroxymorpholine was identified. Additional oxidation pathways in all cases involved the formation of $\cdot\text{OH}$ with high yields. One important pathway of piperazine and morpholine by ozonation could be the formation of C-centered radicals after ozone or OH radical attack. Subsequently, O_2 addition forms unstable peroxy radicals, which in one pathway loose superoxide radicals by generating a carbon-centered cation. Subsequent hydrolysis of the carbon-centered cation leads to formaldehyde, whereby ozonation of the *N*-hydroxy products can proceed in the same way and in addition give rise to hydroxylamine. A second pathway of the short-lived peroxy radicals could be a dimerization to form short-lived tetraoxides, which cleave by forming hydrogen peroxide. All three products have been found.

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1. Introduction

Amino groups are among the most common structural units in micropollutants, since many biologically active compounds, e.g., pharmaceuticals, contain aromatic and aliphatic amino groups. Micropollutants in turn are of major concern in drinking water and wastewater (Nöthe et al., 2007; Deblonde et al., 2011; Ternes et al.,

2015). In wastewater treatment plants, they are not fully biodegraded and thus reach the environment (Huber et al., 2005; Gabet-Giraud et al., 2010). Hence, in surface water micropollutants have been found (Ternes, 1998; Benotti et al., 2009; Martínez Bueno et al., 2012). Even at low concentrations, they may be harmful to aquatic life (Huggett et al., 2002; Küster et al., 2010). Therefore, in drinking water and wastewater treatment, micropollutant abatement by ozonation is gaining importance (Ternes et al., 2002; Huber et al., 2003; Ternes and Joss, 2006; Schwarzenbach et al., 2006; Benner et al., 2008; Kim et al., 2009; Benitez et al., 2011; Zimmermann et al., 2012). The degradation of

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micropollutants with ozone is, however, in competition with the reaction of ozone with the water matrix and only micropollutants with high ozone rate constants are readily eliminated (Lee and von Gunten, 2010). This requires the determination of ozone rate constants of the micropollutants. An important degradation path involves the formation of OH radicals ($\cdot\text{OH}$) (von Gunten, 2003a,b; von Sonntag, 2007). Hence, $\cdot\text{OH}$ yield is a relevant reaction parameter. In addition, the reaction stoichiometry, the amount of ozone needed for full compound degradation, is to be determined (Nöthe et al., 2009). There is, however, now also a raising interest in the ozonation products, due to the fact that transformation products may be also toxic to aquatic life (Shang and Yu, 2001; Huber et al., 2004; Schmidt and Brauch, 2008; Boxall et al., 2014).

In the present study, the reactions of piperidine, piperazine and morpholine with ozone in aqueous solution were investigated. These compounds are archetypes for micropollutant degradation, in particular for heterocyclic amines (e.g., the pharmaceuticals: ADHD (attention deficit hyperactivity disorder) medicine ritalin, the antihistamine cetirizine, the antibiotic ciprofloxacin as well as timolol or other beta blockers). The reactions of ozone with olefins (Dowideit and von Sonntag, 1998; Theruvathu et al., 2001; Leitzke et al., 2003), aromatic compounds (Doré et al., 1980; Hoigné and Bader, 1983a,b; Beltrán et al., 1998; Mvula and von Sonntag, 2003; Naumov and von Sonntag, 2010) and some amines (Gilbert and Zinecker, 1980; Elmghari-Tabib et al., 1982; Cochechi et al., 1989; Muñoz and von Sonntag, 2000b; Flyunt et al., 2002; Sein et al., 2008; Benner and Ternes, 2009a,b) have already been investigated in detail. Thus, when considering ozone reactions some basic principles relating to amines are well established. First, it is well-known that ozone reacts strongly electrophilic. Hence the ozone-reactive site of amines is the lone electron pair at nitrogen. Protonation reduces the otherwise high ozone reactivity and so reactivity depends strongly on pH and the corresponding speciation of the amines (Tyupalo and Yakobi, 1980; von Sonntag and von Gunten, 2012). Compounds that contain two amino groups (such as EDTA), show a high rate constant, when both amino groups are deprotonated, but reaction rates drop when one of them is protonated. Obviously, protonation of one of the nitrogens also influences the electron density of the other, thereby reducing its reactivity towards ozone (Muñoz and von Sonntag, 2000b; von Sonntag and von Gunten, 2012). In addition, ozone is a highly selective reactant and its rate constants with aromatic compounds (Neta et al., 1988), nitrogen-containing compounds (von Sonntag and von Gunten, 2012), electron-rich and electron-deficient olefins (Dowideit and von Sonntag, 1998) vary by ten orders of magnitude.

In ozone reactions, mechanistic considerations are of growing interest and this includes product studies. The investigated amines in this study could refer to more complex micropollutants. In the literature several primary ozone reactions with miscellaneous compounds have been discussed (Muñoz et al., 2001; von Sonntag, 2008; von Gunten et al., 2010; von Sonntag and von Gunten, 2012), so that on the basis of these studies four conceivable primary processes (presented in Scheme 1) are feasible for the three investigated amines in aqueous solution: Addition (reaction (1)), electron transfer (reaction (4)), H-abstraction (reaction (7)) and insertion (reaction (9)). Piperidine is exemplarily shown in Scheme 1 but all reactions are applicable to morpholine and piperazine as well.

The initial step of the ozone addition to the lone electron pair of the nitrogen atom is well-established (Muñoz and von Sonntag, 2000b) and leads to the formation of an ozonide ammonium zwitterion (reaction (1)). This zwitterion subsequently can eliminate singlet oxygen ($^1\text{O}_2$, see Supporting Information Text S8, Muñoz et al., 2001) by yielding *N*-hydroxy products (similar to

propranolol, Benner and Ternes, 2009b) (shown in Scheme 1, reaction (2)–(3)). In competition with the singlet oxygen elimination, the initially formed ozonide ammonium zwitterion may also separate by forming different radicals through reactions such as electron transfer, H-abstraction and insertion (von Sonntag and von Gunten, 2012). In principle, these radical processes could also proceed via a direct reaction pathway without adduct as intermediate (von Sonntag and von Gunten, 2012). However, in experiments the direct pathway and the adduct pathway cannot be distinguished. From the electron transfer reaction an amine radical cation (reaction (4)), (which is in equilibrium with an amine radical (reaction (5)) (von Sonntag and von Gunten, 2012) and an ozonide radical anion, $\text{O}_3^{\bullet-}$ (adduct of the hydrated electron to ozone, Elliot and McCracken, 1989; see reaction therein) are formed. The ozonide radical anion, $\text{O}_3^{\bullet-}$ reacts with water giving rise to $\cdot\text{OH}$ (reaction (6), Bühler et al., 1984). In the H-abstraction process an amine radical and hydrotrioxyl radical, HO_3^{\bullet} (reaction (7)) are formed and the latter likewise decomposes to $\cdot\text{OH}$ and oxygen (reaction (8), Bühler et al., 1984). One further radical pathway is after insertion (reaction (9)) the subsequent formation of a nitroxyl radical and a hydroperoxyl radical, HO_2^{\bullet} (reaction (10)). The latter is in equilibrium with its conjugate base, the superoxide radical anion, $\text{O}_2^{\bullet-}$ (equilibrium reaction 11, $\text{pK}_a(\text{HO}_2^{\bullet}) = 4.8$) which dominates even in slightly acid solution (Bielski et al., 1985; Ragnar et al., 1999). $\text{O}_2^{\bullet-}$ can react with ozone to the ozonide radical anion, $\text{O}_3^{\bullet-}$ (reaction (12)), the precursor of $\cdot\text{OH}$ (Sehested et al., 1983; Staehelin et al., 1984). Under alkaline experimental conditions the hydrotrioxyl radical ($\text{pK}_a(\text{HO}_3^{\bullet}) = -2$, (Naumov & von Sonntag, 2011b) and hydroperoxyl radical (HO_2^{\bullet} , pK_a see above and in Scheme 1 the equilibrium reaction (11)) exist mostly as their conjugated bases, $\text{O}_3^{\bullet-}$ and $\text{O}_2^{\bullet-}$, respectively. Which of the above mentioned primary reactions take place preferentially, can be inferred from products that are formed in the ozone/compound reactions.

Some previous studies have investigated ozone reactions with tertiary (Muñoz and von Sonntag, 2000b; Zimmermann et al., 2012) and secondary amines (Benner and Ternes, 2009a,b). A study about the ozonation of pyrrolidine, piperidine, morpholine and piperazine has already reported rate constants determined from the decrease of the amine concentration vs. the reaction time at pH 7.0 (Pietsch et al., 1999). One study investigating the regioselective oxidation of *N*-phenylmorpholine by ozone in dichloromethane or acetonitrile has reported the formation of lactam and a diformyl derivative (Suarez-Bertoa et al., 2012). However, these studies and even the most comprehensive textbook (von Sonntag and von Gunten, 2012) have not included details on the kinetics, stoichiometry and products of the ozonation of secondary heterocyclic amines. Thus, the objectives of the present work are kinetic studies and stoichiometry in the reaction of ozone with piperidine, piperazine and morpholine. These compounds should be archetypes for secondary heterocyclic amines, a structural unit that is often present in pharmaceuticals in aqueous solution. Furthermore, the most abundant primary pathways of Scheme 1 as well as advanced mechanistic considerations are provided as a result of product yields.

2. Experimental part

2.1. Chemicals and materials

All chemicals were commercially available in high purity (>97%). Further information on chemicals is given in Supporting Information Text S1. Ozone stock solutions (max. 1×10^{-3} M) were freshly prepared by bubbling ozone-containing gas from an ozonator (Sander, Uetze-Eltze, Germany) fed with oxygen (6.0 from

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