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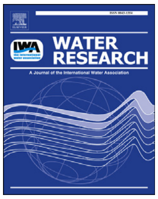

Fundamental study of the ultrasonic induced degradation of the popular antihistamine, diphenhydramine (DPH)

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ABSTRACT

Diphenhydramine (DPH) the active ingredient in Benadryl, has been detected in streams, rivers and other surface water sources. As a bioactive compound, DPH impacts human health even at low concentrations. Ultrasonic irradiation at 640 kHz leads to the rapid degradation of DPH in aqueous solution. Radical scavenging experiments and detailed product studies indicate the DPH degradation involves direct pyrolysis and degradation reactions mediated by the hydroxyl radicals produced during cavitation. The degradation can be modeled by pseudo-first order kinetics yielding rate constants k of 0.210, 0.130, 0.082, 0.050, 0.035, 0.023 min^{-1} at the initial concentrations of 2.8, 5.2, 13.9, 27.0, 61.0, 160.0 $\mu\text{mol L}^{-1}$, respectively. The degradation process follows the Langmuir-Hinshelwood (heterogeneous) model with a partition coefficient, $K_{L\text{-}H} = 0.06\ \mu\text{mol}\cdot\text{L}^{-1}$and reactivity constant $k_r = 1.96\ \mu\text{mol min}^{-1}\cdot\text{L}^{-1}$. A competition kinetic study conducted employing the hydroxyl radical trap, coumarin, illustrates that DPH was degraded primarily by hydroxyl radical mediated processes. Computational studies employing Gaussian 09 basis set provide fundamental insight into the partitioning of the reaction pathways and the degradation mechanisms. The study demonstrates the ultrasonic degradation of DPH is rapid, follows simple kinetic expressions and is accurately modeled using computational methods.

1. Introduction

One of the most widely used over the counter drugs, diphenhydramine (DPH) (2-(diphenylmethoxy)-N,N-dimethylethanamine), is the active ingredient in Benadryl. DPH has been extensively used to treat allergies, hives, itching and insomnia since 1946 and is regularly detected in natural water, treated water and wastewater effluent (Stackelber et al., 2004). DPH has also been detected in surface drinking water sources and treated water from wastewater treatment plants (WWTP) (Li et al., 2011). Kinney et al. reported DPH as one of the four most commonly detected pharmaceuticals in Colorado (Kinney et al., 2006). DPH also has high persistence in soil (Topp et al., 2012). Huerta. et.al reported the presence of DPH in fish muscles (Huerta et al., 2012). The co-occurrence of DPH and other trace amounts of pharmaceuticals in water systems can have negative impacts on aqueous organisms (Goolsby et al., 2013).

Traditional wastewater treatment processes do not effectively remove DPH(Li et al., 2011). Adsorption and ion exchange methods often require extended contact times and are often cost prohibitive for removal of DPH from drinking water sources (Li et al., 2011). UV treatment of DPH leads to only 26% degradation at fluxes of 1272 mJ cm^{-2} (Yuan et al., 2009). Photo-Fenton degradation of DPH can be effective, but requires careful preparation for optimization of the photo-catalyst (Pastrana-Martínez et al., 2012).

Advanced oxidation processes (AOPs) can effectively degrade a wide variety of pollutants (O'Shea and Dionysiou, 2012). The production of reactive species, primarily HO radicals with smaller amounts of oxidants, such as H_2O_2, $O_2^{\cdot-}$ is central to the effectiveness of AOPs. These reactive species lead to oxidative transformation and mineralization of the target pollutants. AOPs have shown tremendous promise for degradation of a wide variety of organic pollutants during water purification (Andreozzi et al., 1999; Klavarioti et al., 2009; Oller et al., 2011). Ultrasonic irradiation is a unique AOPs as it generates hydroxyl radicals directly from water molecules and thus does not require addition of catalyst or oxidant common to the majority of AOPs(Hoffmann et al., 1996; Mason and

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Tiehm, 2001). Ultrasonic irradiation can penetrate and be used to treat turbid and highly colored solutions, while the application of photochemical AOPs such as UV/peroxide is limited to relatively clear solutions which allow penetration of photons deep into the solution.

As ultrasonic waves pass through a solution, gas bubbles undergo local expansion and compression cycles (Colussi et al., 1998; Suslick et al., 1999). The size of the bubble increases with the number of expansion-compression cycles, leading to a pressure differential and eventually the bubbles collapse, a process referred to as cavitation (Wu et al., 2013). At collapse, three zones have been defined: the region at the center of the cavitation site referred to as the hot-spot, the gas-liquid interface and the bulk solution. The hot-spot possesses extremely high temperatures (above 5000 °K) and pressures (above 500 atm) (Colussi et al., 1998; Mason and Tiehm, 2001; Suslick et al., 1999) which leads to the pyrolysis of water vapor and produces hydroxyl radicals ($HO\cdot$) as well as other oxidative species; the gas-liquid interface has high temperatures (above 2000 °K) and high pressures (above 200 atm) leading to pyrolysis and generation of hydroxyl radicals and other oxidative species; the bulk solution possesses relatively mild conditions close to ambient temperature and pressure where target compounds are only transformed upon reaction with radical species that diffuse from the cavitation site (Kim et al., 2016; Leong et al., 2011; Peller et al., 2001; Sillanpää, 2011; Song et al., 2005).

Although the hydroxyl mediated degradation of DPH has been reported (Menachery et al., 2015), detailed studies of the ultrasonic degradation of DPH has yet to be published. Herein we report for the first time the fundamental kinetic studies, adsorption isotherms and the product studies of the ultrasonically induced decomposition of DPH. A computational method was also employed to complement product studies and established the partitioning of competing reaction pathways. This study demonstrates the ultrasonically induced degradation of DPH is rapid and the result of hydroxyl radical mediated and pyrolytic reaction pathways.

2. Chemicals

The source of DPH was diphenhydramine hydrochloride, purchased from MP Biomedicals, LLC. Acetonitrile (HPLC grade) was purchased from Burdick& Jackson, while acetonitrile (optima LC/MS), ammonium formate (99%) and formic acid (optima LC/MS) were purchased from Fisher Chemical. Coumarin was purchased from MP Biomedicals, LLC. NaH_2PO_4 (99%) was purchased from Merck & Co. Inc and 7- hydroxycoumarin (99%) purchased from Acros Organics. All aqueous solutions were prepared with millipore filtered water (18 MΩ.cm) and used at natural solution pH unless stated otherwise.

2.1. Method and experiments

Pulsed mode ultrasonic transducer UES 1.5–660 Pulsar (Ultrasonic Energy Systems Inc., Panama City, Florida) equipped with disk shaped horn attached glass reactor (500 mL) was employed for all experiments. Operating conditions were previously optimized and set at pulse duration of 0.62 s, pulse repetition of 2.5 s and frequency of 640 kHz under operational power of 396 W. Power density of the sonication was 7.9 W/cm^2 with ultrasonic horn diameter of 9 cm. Ultrasound traveled through 5 cm of water and 38 μm of the polyethylene film to reach the 500 mL solution inside reaction vessel with 9 cm diameter. The reactor was submerged in an ice bath and the monitored temperature range inside the reaction vessel was 10 ± 2 °C throughout the reaction. More details of the ultrasound equipment were described previously. (Seymour et al., 1997) (Schematic representation included in supplementary materials). The aqueous solution containing the target compound was added into the reaction vessel, saturated by gentle bubbling with O_2 for 15 min. Samples were taken at specific treatment intervals and analyzed immediately or stored in the refrigerator until analyses.

A Varian Pro star 210 HPLC with a diode array detector was employed to monitor the concentration of DPH. A 250 × 4.60 mm 5 μ C18 column (S.N.410920–29) using mobile phase A (acetonitrile (ACN)) and B (water, 20 mM NaH_2PO_4 at pH = 2.8) (40:60 (v/v)) at a flow rate of 1 ml/min with the detection wavelength of 219 nm was used to monitor the concentration of DPH. Carefully prepared standards were employed to confirm the retention times and calibrate the HPLC. Agilent 6530 Accurate mass spectrometer equipped with an Agilent Infinity 1290 Infinity Binary Pump equipped with a 3.0 × 100 mm 1.8 μ C18 column was used for the product studies. The mobile phase for the LC-MS product study was composed of solvent A (water, 5 mM ammonia formate, 0.1% (v/v) formic acid) and solvent B (acetonitrile/water, 0.1% (v/v) formic acid 90:10 (v/v)) with a flow rate of 0.4 ml/min and a gradient program 0–1 min: 95% A; 1–10 min: from 95 to 5% A. The column temperature was 30 °C.

To monitor the concentration of DPH accurately, a calibration curve was carefully developed from 2 to 2000 $\mu mol\ L^{-1}$. A 1000 mg/L stock solution was prepared using volumetric flasks and stored in the refrigerator. Different concentration solutions were obtained from the dilution of stock solution employing adjustable pipettes and volumetric flasks. The DPH degradation was monitored over a range of initial DPH concentrations of 2.8, 5.2, 14.0, 27.0, 62.0 and 160.0 $\mu mol\ L^{-1}$. The sampling times were adjusted according to the extent of degradation at different initial concentrations. For $[DPH]_0 = 2.8$ and 5.2 $\mu mol\ L^{-1}$, samples were taken at 0, 1, 2, 3, 4, 6 and 8 min of the treatment; $[DPH]_0 = 14.0$ and 27.0 $\mu mol\ L^{-1}$, samples were taken at 0, 2, 4, 6, 8 and 10 min; for the 62.0 $\mu mol\ L^{-1}$, samples were taken at 0, 4, 8, 12 and 16 min while for $[DPH]_0 = 160.0$ $\mu mol\ L^{-1}$, samples were analyzed at 0, 5,10, 20 and 30 min. Samples for the product studies using LC-MS were taken at 0 and 30 min for the 14.0 $\mu mol\ L^{-1}$ DPH solution.

3. Results and discussion

3.1. Degradation kinetics

The ultrasonically induced degradation of DPH was effective over a range of initial concentrations, from 2.8 to 160.0 $\mu mol\ L^{-1}$ under O_2 saturation at ~5 °C. The degradations of DPH as a function of treatment time at different initial concentrations are illustrated in S. Fig. 1. The extent of degradation decreases with increasing initial concentration. The treatment time required to degrade 50% of the initial concentration varied from 3.9 to 33.3 min for the initial DPH concentrations of 2.8–160.0 $\mu mol\ L^{-1}$, respectively.

Previous studies have established that the ultrasonic mediated degradation of a variety of organic compounds follows pseudo-first kinetics at a given initial concentration (Cui et al., 2017; Hua et al., 1995; Kim et al., 2012; Song et al., 2009; Taylor et al., 2014). Pseudo-first-order kinetics are represented by the mathematical equation $\ln\frac{C_t}{C_0} = -kt$ (k (min^{-1}) where C_t and C_0 ($\mu mol\cdot L^{-1}$) are the concentration at treatment time t and the initial concentration, respectively. The pseudo-first-order kinetic plot (Fig. 1) of the degradation of DPH yields rate constants of 0.21, 0.13, 0.082, 0.050, 0.035 and 0.023 min^{-1} corresponding to the initial concentrations of 2.8, 5.2, 14.0, 27.0, 61.0 and 160.0 $\mu mol\ L^{-1}$, respectively. The observed rate constants decreased by approximately 10-fold as the initial concentration increased by about 80 times. The rate constant does not change significantly with initial concentration for a true