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Identification of reaction products from reactions of free chlorine with the lipid-regulator gemfibrozil

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ABSTRACT

High global consumption rates have led to the occurrence of pharmaceutically active compounds (PhACs) in wastewater. The use of chlorine to disinfect wastewater prior to release into the environment may convert PhACs into uncharacterized chlorinated by-products. In this investigation, chlorination of a common pharmaceutical, the antihyperlipidemic agent gemfibrozil, was documented. Gemfibrozil (2,2-dimethyl-5-(2,5-dimethylphenoxy)pentanoic acid) was reacted with sodium hypochlorite and product formation was monitored by gas chromatography-mass spectrometry (GC-MS). The incorporation of one, two or three chlorine atoms into the aromatic region of gemfibrozil was demonstrated using negative-ion electrospray ionization mass spectrometry (ESI-MS) and tandem mass spectrometry (ESI-MS/MS). Further analysis using ^{1}H nuclear magnetic resonance (NMR) spectroscopy identified the reaction products as 4′-ClGem (5-(4-chloro-2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid) 4′,6′-diClGem (5-(4,6-dichloro-2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid), and 3′,4′,6′-triClGem (5-(3,4,6-trichloro-2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid), products consistent with electrophilic aromatic substitution reactions. The rapid reaction of gemfibrozil with free chlorine at pH conditions relevant to water treatment indicates that a mixture of chlorinated gemfibrozils is likely to be found in wastewater disinfected with chlorine.

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1. Introduction

Pharmaceutically active compounds (PhACs) enter the environment through a variety of pathways, including human orli-vestock excretion (treated or untreated), PhAC manufacturing discharge, or improper disposal of unused prescriptions into sewers or landfill sites (Ternes, 1998). Typically 12–20% of people in the United Kingdom dispose of unfinished prescriptions in household liquid wastes (Bound et al., 2006; Slack et al., 2005). In North America, PhAC concentrations in surface and ground waters have been quantified in the ng/L–μg/L range (Boyd et al., 2005; Brun et al., 2006; Kolpin et al., 2002; Metcalfe et al., 2003a,b), and two Canadian surveys of wastewater treatment plants (WWTPs) detected gemfibrozil (a lipid regulating drug) in 7 out of 8 (Brun et al., 2006) and 3 out of 18 (Metcalfe et al., 2003a) WWTP effluents. Furthermore, literature reports have shown that PhACs are not fully degraded or removed through conventional WWTPs (Brun et al., 2006; Miao et al., 2002; Thomas and Foster, 2005).

A survey (CWWA, 2001) by the Canadian Water and Wastewater Association indicated that 184 of 738 Canadian WWTPs used chlorine for disinfection. Free chlorine is a strong, non-specific oxidant, that reacts with most organic material (Sirivedhin and Gray, 2005; Pinkston and Sedlak,

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2004) to form disinfection by-products (DBPs) (Sirivedhin and Gray, 2005). The reactions of natural organic matter and dissolved organic carbon with free chlorine to produce trihalomethanes (THMs) and haloacetic acids (HAAs) through drinking water treatment are well-documented (Inaba et al., 2006; Kanokkantapong et al., 2006; Westerhoff et al., 2004). THMs, such as chloroform ($CHCl_3$), containing only one carbon atom, correspond to the final degradation products resulting from the chlorination of complex organic molecules when exposed to free chlorine. Chloroform is used in the water industry as a generic indicator for DBPs, and signifies the current or past presence of other chlorinated by-products in the sample (Singer, 2006).

The use of chlorine as a disinfectant also could lead to reactions with organic matter that form other chlorinated products. Reactions of chlorine with PhACs have been indicated by several studies (Benotti et al., 2009; Gibs et al., 2007; and Pinkston and Sedlak, 2004), while other investigations have provided evidence for the formation of chlorinated products from PhACs, such as acetominophen, gemfibrozil, naproxen and trimethoprim (Boyd et al., 2005; Bedner and MacCrehan, 2006a,b; Dodd and Huang, 2007; Glassmeyer and Shoemaker, 2005; Quintana et al., 2010 and Xagoraraki et al., 2008). These reports suggest that PhAC contaminants in the waste stream may not be fully oxidized to carbon dioxide and water during chlorine disinfection. The disinfection by-products may have greater adverse human and ecosystem effects than the parent compounds (e.g., Boyd et al., 2005; Vogna et al., 2004), and their formation will result in the discharge of a mixture of unknown toxicity into the environment.

The lipid-regulator gemfibrozil (Fig. 1) is frequently detected in drinking water, surface water and wastewater in the ng/L to low μg/L range (Batt et al., 2008; Benotti et al., 2009; Bueno et al., 2007; Gibs et al., 2007; Gros et al., 2006; Miao et al., 2002; Mompelat et al., 2009; Wu et al., 2009). Glassmeyer and Shoemaker (2005) indicated that gemfibrozil was susceptible to chlorination and in their liquid chromatography-mass spectrometry (LC-MS) analysis of a 48-h reaction mixture containing gemfibrozil and free chlorine (1:2 Molar ratio) showed the formation of a product at longer retention time. The presence of chlorine in the product was inferred by comparing *m/z* values of fragment ions formed from the product and gemfibrozil in the particle beam interface. The present investigation was conducted to identify the structure of this product as well as others formed upon reaction of gemfibrozil with free chlorine. The structures of three of the four possible ring chlorinated reaction products (Fig. 1) were assigned using direct evidence collected by electrospray ionization mass spectrometry (ESI-MS) and ^1H nuclear magnetic resonance (NMR) spectroscopy.

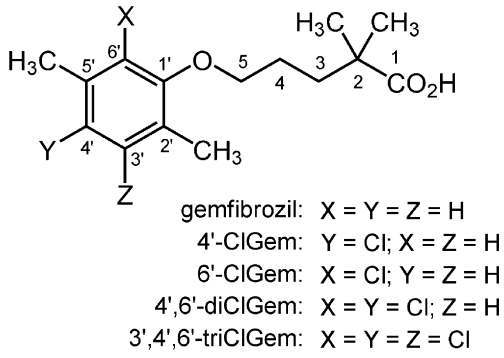

Fig. 1 – Structure of gemfibrozil and the structures deduced for the gemfibrozil-HOCl reaction products.

2. Materials and methods

2.1. Standards and reagents

Gemfibrozil (2,2-dimethyl-5-(2,5-dimethylphenoxy)pentanoic acid; Fig. 1), the surrogate standard meclofenamic acid (2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid) and the derivatization agent BSTFA + TMCS, 99:1 (*N,O-bis*-[trimethylsilyl] trifluoroacetamide with 1% trimethylchlorosilane) and 5% dichlorodimethylsilane (DCDMS) in toluene used for glassware silylation were obtained from Sigma–Aldrich. Acetone, ethyl acetate, and toluene (all > 99.9%), and ascorbic acid and sodium thiosulphate used for quenching chlorine were purchased from Fisher Scientific. Aqueous 6% sodium hypochlorite (NaOCl) was purchased from VWR and diluted as necessary. The free chlorine concentration of stock solutions was determined prior to use by the *N,N*-diethyl-*p*-phenylenediamine (DPD) colorimetric method (APHA, AWWA, WEF, 1999). Stock solutions of gemfibrozil and the surrogate standard in methanol (0.8 g/L) were stored in amber flasks at −18 °C and diluted as necessary for working solutions. Ultra Pure water was obtained from a Milli-Q water generator (Millipore, USA).

2.2. Analytical methods

Samples were analyzed on a Varian CP-3800 GC and Saturn 2200 Ion Trap Mass Spectrometer (MS) with CP-8400 autosampler. Syringe fill speed was 2.0 μL/s and injection speed was 0.5 μL/s. Pre-injection delay was 6.0 s, and the post-injection delay was 0.5 s. The CP-1177 injector was held constant at 250 °C (523 K). Helium of >99.999% purity was used as the carrier gas. The capillary column was a Varian Factor Four™ VF-5ms, with 29.5 m length × 0.25 mm internal diameter × 0.25 μm film thickness, preceded by a 5 m × 0.25 mm deactivated fused silica guard column. The guard column and Deactivated Universal Press Tight connectors were purchased from Chromatographic Specialties (division of Restek). The GC temperature ramping program was as follows: 120 °C [2 min] → (20 °C/min) 215 °C [2 min] → (2 °C/min) 230 °C [0 min] → (30 °C/min) 290 °C [2 min]. The total time for the method was 20.25 min. Retention times were 8.9 min for gemfibrozil, 10.9 min for the postulated 6′-ClGem, 11.5 min for 4′-ClGem, 14.0 min for 4′,6′-diClGem, and 17.5 min for 3′,4′,6′-triClGem. A constant column flow of 1.0 mL/min was used. The ion trap was kept at a temperature of 185 °C, and the transfer line was at 200 °C. Electron ionization conditions of 70 eV were employed.

Negative-ion electrospray ionization mass spectroscopy (ESI-MS and ESI-MS/MS) was performed on a Thermo-Finnigan LCQ Duo ion trap using flow-injection analysis (20 μL/min) as described by Grossert et al. (2006). Collision energies for MS/MS are given in parentheses in the arbitrary units (%) supplied by the software. Solutions of gemfibrozil and the

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