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Photochemical Formation of Brominated Dioxins and Other Products of Concern from Hydroxylated Polybrominated Diphenyl Ethers (OH-PBDEs)

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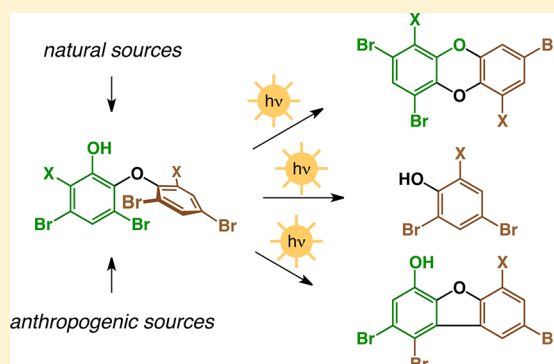
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S Supporting Information

ABSTRACT: The photochemical conversion of selected hydroxylated polybrominated diphenyl ethers (OH-PBDEs) to dioxins and other products was investigated. OH-PBDEs, which are both transformation products of polybrominated diphenyl ethers and naturally occurring compounds, undergo direct photolysis to yield a number of products that may have a higher toxicity than their parent. The compounds investigated were 6-OH-PBDE 99, 6'-OH-PBDE 100, and 6'-OH-PBDE 118. Of special interest was 6'-OH-PBDE 118, a potential transformation product of PBDE 153 that is capable of photochemically generating 2,3,7,8-tetrabromodibenzo-*p*-dioxin, the most toxic brominated dioxin congener. Photolysis experiments were conducted at two different pH values to assess the photochemical behavior of both the phenol and phenolate form of the compounds. The percent conversion to dioxin and other photoproducts was determined and the natural product, 6-OH-PBDE 99, was found to have the highest conversion to dioxin (7%). The reaction quantum yields ranged from 0.027 to 0.16 across all photolysis conditions. In addition, it is shown that all three compounds are capable of photochemically generating other compounds of concern, including brominated phenols and a dibenzofuran.



INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) have been incorporated as flame-retardants in a wide variety of consumer and industrial polymer products beginning in the 1970s. The use of PBDEs as a noncovalently bound additive allows these compounds to leach from the products into the environment. Consequently, PBDEs are now ubiquitous in both urban and pristine environments alike.^{1,2} PBDEs entering the environment have a number of potential fates, including biotic and abiotic transformation, sorption to soils/sediment, and bioconcentration. One important class of PBDE transformation products is comprised of the hydroxylated PBDEs (OH-PBDEs).

Three main routes are thought to be responsible for the environmental hydroxylation of PBDEs. The first is metabolic transformation in organisms exposed to PBDEs. OH-PBDEs have been identified as metabolites in rats and mice,^{3–5} and OH-PBDE concentrations have been shown to have a positive correlation to PBDE exposure in samples of human blood.^{6,7} Another possible path to hydroxylation is via reaction with hydroxyl radical during atmospheric transport of PBDEs. Raff et al. demonstrated that hydroxylation of PBDEs occurs in gas phase laboratory experiments,⁸ and OH-PBDEs have been detected in rain and surface waters.⁹ PBDEs may also become

hydroxylated during the oxidative stages of wastewater treatment processes,⁹ including activated sludge treatment and disinfection. The hydroxylation of PBDEs increases their toxicity, because OH-PBDEs are stronger endocrine disruptors¹⁰ and more closely resemble estrogenic compounds than PBDEs.¹¹ OH-PBDEs have been detected in a variety of freshwater¹² and marine aquatic animals, including salmon,¹³ blue mussels,¹⁴ dolphins,¹⁵ and polar bears.¹⁶ Further complicating the picture, OH-PBDEs are not only transformation products of PBDEs, but are also natural products found in marine systems. OH-PBDEs and closely related compounds have been isolated from sponges,^{17,18} tunicates,¹⁹ and red algae,^{14,20} and radiocarbon experiments have further established their natural origin.^{21,22}

In addition to the concern posed by OH-PBDEs themselves, congeners that contain both a hydroxyl group ortho to the ether linkage and an ortho bromine on the opposite ring are capable of undergoing a photochemical ring closure to form polybrominated dibenzo-*p*-dioxins (PBDDs). This ring closure

Received: April 23, 2012

Revised: July 3, 2012

Accepted: July 5, 2012

Published: July 5, 2012

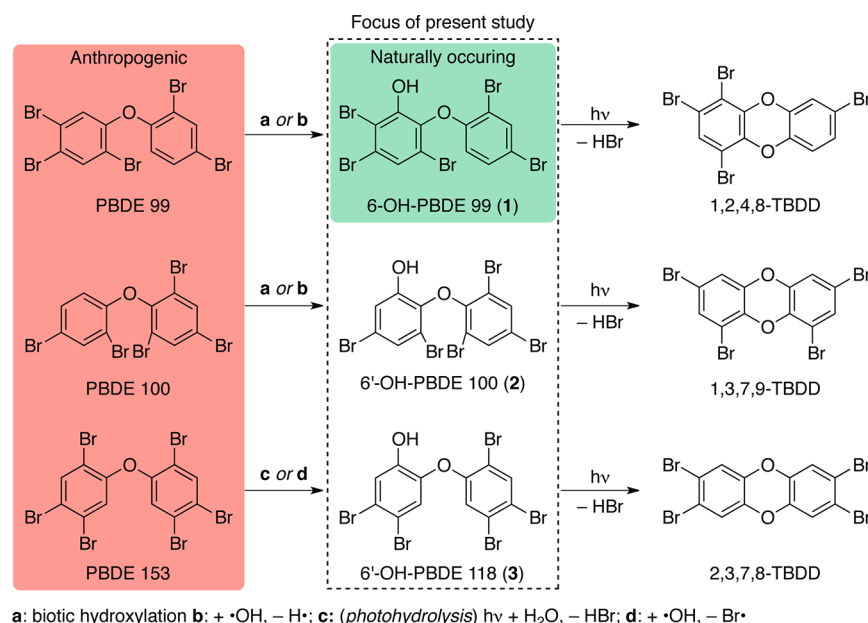


Figure 1. Transformation scheme illustrating possible routes from PBDEs to OH-PBDEs (outside the scope of this study) and from OH-PBDEs to TBDDs.

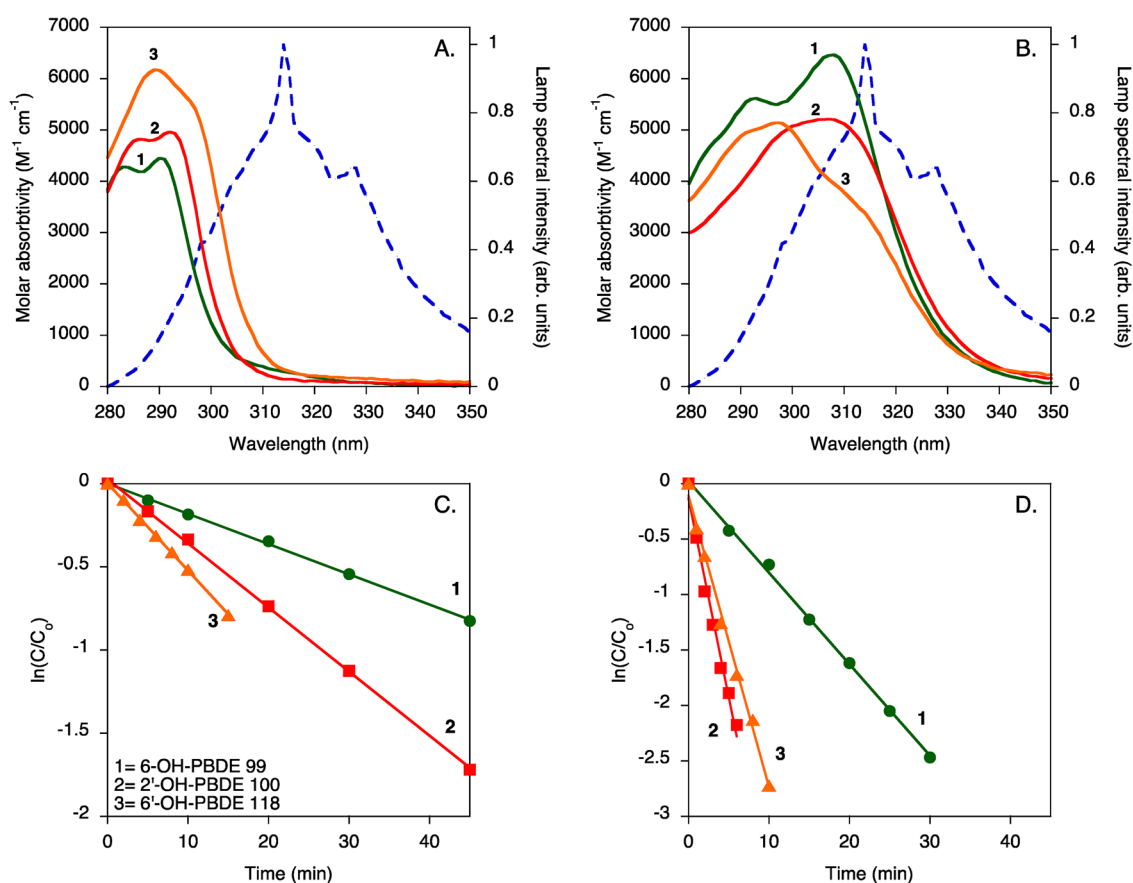


Figure 2. The absorbance spectra for the phenol and phenolate forms of compounds 1–3 along with the lamp spectrum are shown in panels (A) and (B), respectively. Panels (C) and (D) show kinetic traces for the photodegradation of 1–3 at pH 4 and 10, respectively.

has been previously observed for triclosan,^{23,24} some of its chlorinated derivatives,²⁵ as well as OH-PBDEs.^{26,27} PBDDs are structurally analogous to their better-studied chlorinated counterparts and share the same route of toxicity. Previous work has established that PBDDs are at least as toxic as

chlorinated dioxins and thus are a cause for concern.^{28–30} Alongside OH-PBDEs and other halogenated compounds found in marine environments, there is some uncertainty as to the origin of PBDDs, which in some places have been detected in increasing concentrations.³¹ One possible source

for these dioxins may be photochemical formation from OH-PBDEs (Figure 1).

The aim of this work was to investigate the photochemical degradation of three different OH-PBDEs: 6-OH-PBDE 99 (1), 6'-OH-PBDE 100 (2) and 6'-OH-PBDE 118 (3). Compound 1 was chosen because it is known to be a natural product, and has been found in a variety of biota.^{20,32} Compounds 2 and 3 were chosen because they represent transformation products of two congeners present in the industrial Penta mixture. Compound 3 is of particular interest since it is set up to undergo a photochemical transformation to 2,3,7,8-TBDD, the most toxic dioxin congener. It is also worth noting that 1 is a possible transformation product of BDE 99, which is also one of the main components of the Penta mixture. Here we report that compounds 1–3 are each photochemically transformed under environmentally relevant conditions to polybrominated dioxins. In addition, we also report other photoproducts that are concerning from a toxicity standpoint, including brominated phenols, a dibenzofuran, and dihydroxybiphenyls.

EXPERIMENTAL SECTION

Chemicals. Compounds 1–3 were synthesized as described in the Supporting Information. The preparation of 6-OH PBDE 47 has been described previously.²⁷ Pyridine (Py; 99.9%), *p*-nitro anisole (PNA; 97%), NaOH, HCl, acetic acid, and sodium acetate were all purchased from Sigma Aldrich. Sodium tetraborate decahydrate ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$) was purchased from Merck. The standards used were 1,2,4,8-/1,2,4,7-tetrabromodibenzo-*p*-dioxin (10 $\mu\text{g}/\text{mL}$ in toluene, AccuStandard), 2,3,7,8-tetrabromodibenzo-*p*-dioxin (50 $\mu\text{g}/\text{mL}$ in toluene, Wellington Laboratories), 2,4-dibromophenol (neat, Supelco), 2,4,5-tribromophenol (1 mg/mL in isopropanol, Chiron AS), and 2,4,6-tribromophenol (neat, Sigma Aldrich). All compounds were used as received with the exception of *p*-nitro anisole (PNA), which was first recrystallized from *n*-hexane. Ultrapure water (18 $\text{M}\Omega \cdot \text{cm}$) was obtained from a Barnstead Nanopure Diamond system. All solvents were of chromatography grade.

pK_a Value Determinations. pK_a values were measured by spectrophotometric titration. Because the water solubility of these compounds is very low when they are in the protonated form, titrations had to be performed in methanol:water mixtures. Solutions of 1–3 (15 mL, approximately 50 μM) in various methanol/water mixtures were brought to a pH value between 10 and 11 with NaOH. These solutions were then titrated to a pH value near 4 with a maximum of 200 μL of 0.1 M HCl, so that the change in OH-PBDE concentration was negligible. Absorbance measurements were taken with a Cary 100 Bio (Varian) UV/Visible spectrophotometer in 1.00 cm quartz cuvettes. Plots of the absorbance at ~ 310 nm vs pH were fit using a nonlinear regression (Kaleidograph, version 4.04, Synergy Software) to determine the pK_a values.

Photolysis Experiments. Samples of 1–3 in 1 mM pH 4 acetate buffer with 30% methanol or 1 mM pH 10 borate buffer with an initial concentration of 10 μM were placed in a merry-go-round sample holder of a Rayonet photoreactor containing two 300 nm bulbs (spectrum from within a test tube shown in Figure 2). The irradiation intensity in the range of 280–400 nm was about 40% of natural sunlight. For all photolysis experiments, triplicate 10 mL samples were irradiated in borosilicate glass test tubes. At set intervals, 150 μL aliquots were taken for analysis by either high-pressure liquid chromatography (HPLC) for kinetics and photoproduct

quantification or liquid chromatography-mass spectrometry (LC-MS) for photoproduct identification. Dark controls showed no loss of parent compound over 2 h irradiation time. To determine accurate polychromatic apparent reaction quantum yield values (Φ_r), a PNA-Py chemical actinometer system³³ was irradiated alongside the samples in borosilicate glass test tubes. Φ_r values for 1–3 were calculated according to eq 1.

$$\Phi_r = \frac{k_{\text{deg}} \sum \epsilon_{a,\lambda} I_{\lambda}}{k_a \sum \epsilon_{a,\lambda} I_{\lambda}} \Phi_a \quad (1)$$

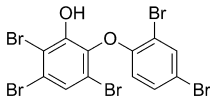
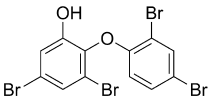

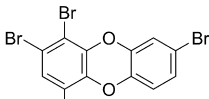
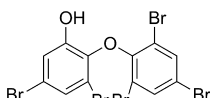
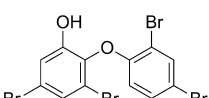
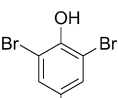
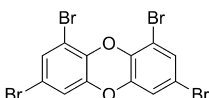
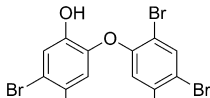
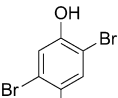
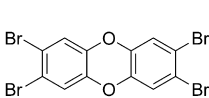
First-order rate constants of degradation (k_{deg}) were compared to that of a PNA-Py chemical actinometer with a known Φ_a . Molar absorptivities (ϵ) as a function of wavelength were measured for each compound at pH 4 and 10, and the lamp spectrum was measured from inside a borosilicate test tube using a fiber optic coupled to a calibrated radiometer (Ocean Optics Jaz).

The percent conversion is defined as the rate constant of formation of a given photoproduct (k_p) divided by the overall rate constant of degradation (k_{deg}) of the parent compound multiplied by 100. It is not possible to measure k_p directly from the growth of product, because product appearance is kinetically bound to the rate constant of starting material loss k_{deg} . For a photostable product, the ratio k_p/k_{deg} is equal to the final product concentration $[P]_{\infty}$ divided by the starting concentration of the parent compound $[A]_0$. Dioxin percent conversion values were calculated in this manner because of their negligible photodegradation over the course of the experiments. For the bromophenols, which were photolabile, the kinetic profiles were fit to eq 2. The term $f[A]_0$ refers to the fraction of A that goes to form photoproduct P (i.e., the percent conversion or k_p/k_{deg}), and the percent conversion values were calculated based on the $f[A]_0$ fit parameter. The term k_{-p} is the first-order degradation rate constant of photoproduct P.

$$[P] = \frac{k_{\text{deg}} f A_0}{k_{-p} - k_{\text{deg}}} (e^{-k_{\text{deg}} t} - e^{-k_{-p} t}) \quad (2)$$

Photoproduct Identification and Quantification. When photoproducts of 1–3 were commercially available, these compounds were used to create calibration curves for the HPLC and LC-MS (except for dioxins, which were only quantified by HPLC). All calibration curves used for quantification had an R^2 of 0.999 or better. Only photoproducts for which an authentic standard was available were quantified and a percent conversion reported, with the exception of 1,3,7,9-TBDD, which was quantified using the calibration curve for 2,3,7,8-TBDD. This was deemed reasonable because the slopes of the calibration curves for the other two tetrabrominated congener standards, 1,2,4,8- and 2,3,7,8-TBDD were within 2% of one another. The identity of 1,3,7,9-TBDD was inferred from the precursor structure reaction scheme in Figure 1 and on the basis of a photoproduct with an elution time and UV-vis spectrum that were similar to the two standards that were available. Photoproducts for which no authentic standards were available were identified and classified only by their general structure using exact mass measurements and relative retention time data. Products observed by LC-MS alone could not be quantified because the MS instrument response strongly depends on the ionization efficiency of the compound.

Table 1. pK_a Values, Reaction Quantum Yields, And Quantified Photoproducts

Parent compound	pK_a	Φ pH 4 pH 10	Debromination ^c (% conversion)	C-O cleavage ^c (% conversion)	Dioxin ^c (% conversion)
 6-OH-BDE 99 (1)	5.81 ^a	0.027 0.031	 6-OH-BDE 47 (<1%)	 2,4-dibromo-phenol (8%)	 1,2,4,8-TBDD (7%)
 6'-OH-BDE 100 (2)	8.39 ^a	0.063 0.16	 6-OH-BDE 47 (<1%)	 2,4,6-tribromo-phenol (11%)	 1,3,7,9-TBDD (1.1%)
 6'-OH-BDE 118 (3)	7.39 ^b	0.057 0.13	n.q. ^d	 2,4,5-tribromo-phenol (13%)	 2,3,7,8-TBDD (0.5%)

^aEstimated pure aqueous pK_a value determined from a series of titration of solutions with different methanol:water compositions. pK_a value given is the extrapolated value. ^bEstimated pK_a value using the slope from the other compounds extrapolation (both lines have the same slope) and the pK_a value determined in a 50% methanol solution. ^cQuantification is reported for pH 10 experiments. Photoproduct for which no standard was available were not quantified.

HPLC Analysis. Compounds 1–3 and actinometer samples were analyzed using a Dionex P680 HPLC with a PDA-100 photodiode array UV-vis detector. Injection volumes of 100 μ L were used for all samples. The column was a Supelco Discovery C16 RP amide (15 cm \times 4.6 mm, 5 μ m diameter particles). For analysis of 1–3, the mobile phase was 85:13.5:1.5 methanol:pH 3 phosphate buffer:acetonitrile at a flow rate of 1 mL/min. All compounds were quantified at a wavelength of 210 nm except for the dioxins, which were quantified at 230 nm. Sample run times were 35 min. For the actinometer, the mobile phase was 65:31.5:3.5 methanol:pH 3 phosphate buffer:acetonitrile at a flow rate of 1 mL/min. PNA was quantified at a wavelength of 314 nm. Sample run times were 7 min.

LC-MS Analysis. Photoproducts of 1–3 were identified using a Waters NanoAquity UPLC interfaced to a Thermo Exactive Orbitrap high-resolution mass spectrometer. Injections (1 μ L) were made onto a Waters Atlantis dC18 Nano Ease column (15 cm \times 300 μ m, 3 μ m diameter particles) held at 40 $^{\circ}$ C with a flow rate of 17 μ L min⁻¹ and a mobile phase composition of 60:40 acetonitrile:water. All samples were analyzed by electrospray ionization MS in negative mode and were scanned from 100 to 600 m/z . Sample run times were 15 min.

RESULTS AND DISCUSSION

pK_a Values. The pK_a values for the phenolic groups of 1–3 were 5.81, 8.39, and 7.39, respectively (Table 1). The pK_a value for 1, which contains three bromo substituents on the phenol ring, is significantly lower than that for 2 and 3, which each only contain two bromo substituents on the phenol ring. A series of titrations for compounds 1 and 2 in different methanol:water compositions demonstrated linear relationships with the solvent composition that could be used to extrapolate to the

pure aqueous pK_a values. Compound 3 was titrated only in 50:50 methanol:water because of material limitations. A reasonable prediction of the aqueous pK_a value was made for 3 using the common slope from the extrapolation plots for 1 and 2. The titration plots and extrapolations are provided in the Supporting Information.

Direct Photolysis. The loss of compounds 1–3 during irradiation followed first-order kinetics under all experimental conditions tested. The starting concentration for all photolysis samples was low enough that self-screening was unimportant, making it unnecessary to correct kinetic data used to calculate Φ_r values. Figure 2 shows the absorption spectra and degradation plots for 1–3. In the phenol form, all of the compounds have a broad absorbance band with a maximum near 290 nm, tailing off to approximately zero absorbance at around 310 nm. In the phenolate form, the absorbance maximum red-shifts for each compound differently, but they all display a maximum between 300 and 310 nm and a tailing off to near zero absorbance around 340 nm. All compounds degraded faster under basic conditions due mostly to the greater light absorption of the phenolate species.

For the phenol forms of 1–3, Φ_r values ranged from 0.027 to 0.063, while the values for the phenolate forms ranged between 0.031 and 0.16 (Table 1). Our results are in good agreement with earlier work with halogenated phenoxyphenols.^{23–27} Under both acidic and basic conditions, 2 and 3 had noticeably larger Φ_r values than 1. One possible contributing factor to this observation is the bromine in the 3 position of 1, ortho to the hydroxyl group. While the origin of this “ortho effect” on quantum yield is not understood, it is noteworthy, particularly in light of our previous work which showed the same effect for chlorinated triclosan derivatives.²⁵

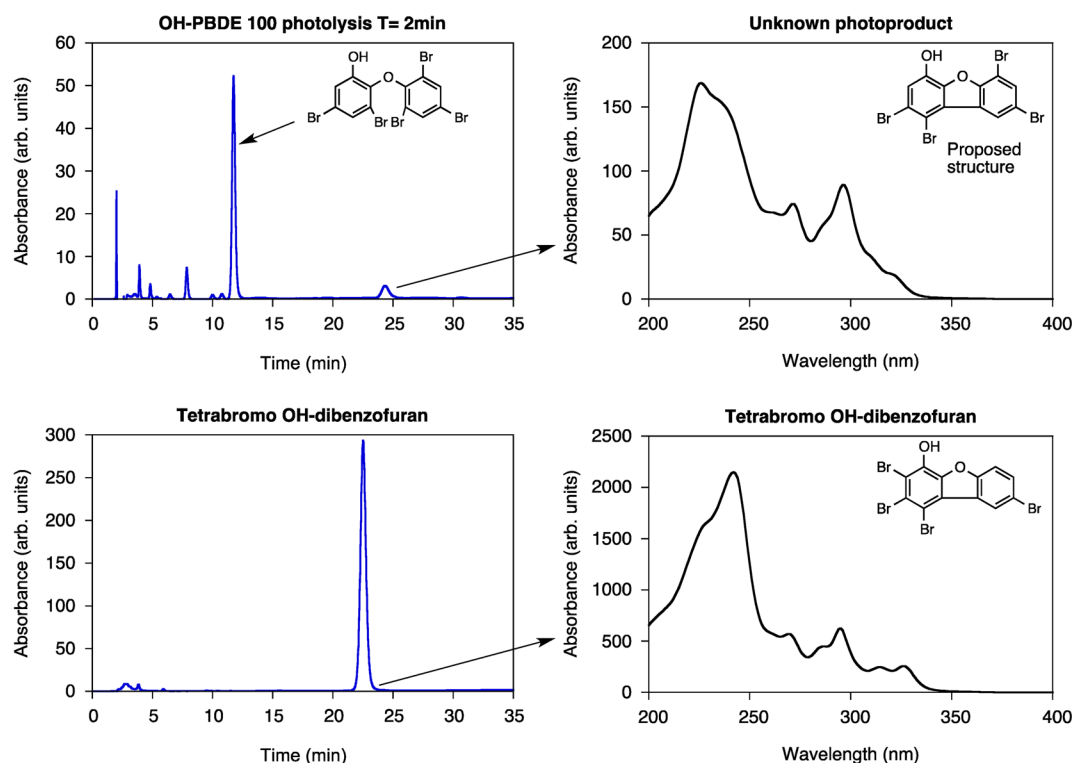


Figure 3. (Top panels) The HPLC-UV (diode array) chromatogram of the product mixture resulting from the photolysis of **2** and the UV absorbance spectrum corresponding to the indicated peak. The peak eluting at 11.7 min is of the starting compound **2**. (Bottom panels) The HPLC-UV chromatogram is of the synthesized OH-TBDF and the UV absorbance spectrum of the indicated peak. See text for assignment of the dibenzofuran structures.

Brominated Dioxins. Dioxin formation was observed for **1–3** under all conditions. The percent conversion to dioxin for **1–3** at pH 10 was found to be 7, 1.1, and 0.5%, respectively. In all cases, the dioxin photoproducts were relatively photostable under the experimental conditions, and were seen to photodegrade on the order of 100 times slower than the parent compounds during our experiments. The factors that control the wide range in dioxin conversion yields are not understood. Nevertheless, it is a happy circumstance that compound **3**, which forms the most toxic dioxin congener, 2,3,7,8-TBDD, had the lowest dioxin yield of 0.5%. By contrast, compound **1**, the natural product, was found to have an order of magnitude higher dioxin conversion of 7%.

Bromophenols. Compounds **1–3** all generated a bromophenol photoproduct from the cleavage of the ether linkage where the bridging oxygen atom remains with the nonphenolic ring. Interestingly, these were the only C–O cleavage products observed above trace levels in any of our experiments. The percent conversion values ranged from 8 to 13%. The amount of bromophenol photoproduct is not controlled by steric crowding around the ether linkage. Indeed, compound **3**, the least sterically crowded congener, showed the highest bromophenol conversion. Noting that the higher conversion yields are associated with a greater number of bromo substituents on the departing phenol, the bromophenol production may instead be a function of the resulting bromophenolate's leaving group ability. A study with a wider range of structural analogs will be needed to more rigorously test this hypothesis.

Debromination and di-OH-PBB Formation. Hydrodebromination is one of the predominant degradation pathways for PBDEs,^{34,35} therefore we expected to observe a number of

transformation products corresponding to reductive debromination. Instead, we observed only small amounts of debromination products. This conclusion was based on two sets of observations. First, we quantified the production of 6-OH-PBDE **47**, the only debromination product standard that we had available. For **1** to form 6-OH-PBDE **47** it must lose the bromine ortho to the hydroxy group, whereas **2** must lose one of its two bromo substituents ortho to the ether linkage on the nonhydroxylated ring. In both cases, 6-OH-PBDE **47** is formed in less than 1% yield. Second, we examined LC-MS ion chromatograms for each of the hydrodebromination product masses. We observed a group of photoproducts with the same formula (and thus exact mass) as the reductive debromination products, which are believed to belong to another compound class. Based on their poor retention on the HPLC column (ca. 3 min), which is similar to bromophenols, and literature precedent for diphenyl ether to hydroxy biphenyl photoconversion,³⁴ we tentatively assign these early eluting products as dihydroxylated polybrominated biphenyls (di-OH-PBBs). The analogous photochemical formation of OH-PBBs from a PBDE has been reported from the photolysis of BDE-153 in 20% yield.³⁴ Due to a lack of authentic standards and an inability to collect enough material for structural identification by NMR, a firm assignment could not be made. Tentatively assigned debromination products, which have retention times near the parent OH-PBDEs and di-OH-PBBs, were observed in varying amounts for **1–3**, but all compounds produced at least one of each.

Dihydroxy-PBDEs and Hydroxydibenzofuran. The last two types of photoproducts that were identified were products arising from the replacement of bromine with a hydroxyl group to form di-OH-PBDEs, and products that had formally lost

HBr to form a hydroxylated polybrominated dibenzofuran (OH-PBDF).

The di-OH-PBDEs are isobaric with tri-OH-PBBs and thus difficult to distinguish by MS. Furthermore, both compound types are expected to elute early in reverse phase LC. Indeed, the peaks assigned as di-OH-PBDEs had early retention times in the LC-MS chromatogram, similar to bromophenols. We favor the assignment of di-OH-PBDEs (versus tri-OH-PBBs) due to their kinetic behavior. Specifically, the plot of their appearance vs time (Supporting Information Figure S8) does not show any lag in initial production, as would be expected for a second-generation transformation product (i.e., arising from hydroxy-debromination of di-OH-PBBs).

Finally, we observed the formation of a photoproduct with a retention time similar to that of the dioxin products during HPLC analysis, and with a mass corresponding to the loss of HBr for compound **2**. We propose that this product is a hydroxy-substituted polybrominated dibenzofuran (OH-PBDF). The large peak in the HPLC chromatogram suggests that a significant amount of the dibenzofuran photoproduct was formed. It is also worth noting that the photochemical formation of hydroxylated polychlorinated dibenzofurans has been previously observed from triclosan and its chlorinated derivatives.^{36,37}

Because no authentic standards for OH-PBDFs are commercially available, we synthesized a tetrabrominated OH-PBDF to judge whether the UV-vis absorbance spectrum and HPLC retention time was similar to that of the suspected OH-PBDF. The choice of the synthetic standard was constrained by its synthetic accessibility. While not a match to our proposed product, the standard was helpful due to the similarity of dibenzofuran retention times and absorbance spectra for congeners of the same degree of halogenation. The details of the synthesis can be found in the Supporting Information. Our synthesized OH-PBDF had an HPLC retention time of 23.5 min and the suspected OH-PBDF produced by **2** had a retention time of 24.3 min, respectively (Figure 3). A comparison of their UV-vis spectra shows three similar spectral features and an absorbance tailing to zero near 330 nm. Based on this comparison and the exact mass match, we favor the assignment of the unknown as a tetrabrominated OH-PBDF, but cannot definitively assign the structure. Based on our proposed transformation mechanism (discussed below), we propose that 1,2,6,8-tetrabromo-4-hydroxydibenzofuran is the specific congener formed from **2**.

At first glance, the formation of OH-PBDF from **2** seems unlikely, because it does not have any hydrogen atoms ortho to the ether linkage to eliminate during cyclization. Our hypothesis is that furan formation proceeds via a photochemical electrocyclic ring closure to form the ring system skeleton,³⁸ followed by a 1,3-migration of a bromine atom from the nonphenolic ring to the phenolic ring (Supporting Information Figure S9). Subsequent elimination and tautomerization would yield the proposed product (Figures 3 and S9).

Environmental Significance. The presence of OH-PBDEs in the environment is now well established, and while the largest share of OH-PBDEs comes from natural sources, the possibility of anthropogenic sources remain. Our results show that **1–3** all photodegrade to generate transformation products that are themselves priority pollutants. While bromophenol production was seen for all compounds, the anthropogenically derived compounds, **2** and **3**, produced the largest amounts. In addition to generating bromophenols, the previously unre-

ported formation of di-OH-PBBs and OH-PBDFs from OH-PBDEs also could be of concern. Compound **1** is a known natural product, and has been isolated from biotic sources in the Baltic Sea.¹⁴ Our results show that **1** is readily capable of transforming into a TBDD under environmental conditions, and may be a major source of natural tetrabrominated dioxin in the Baltic Sea, a possibility that has been previously discussed.³⁹ While **1** produced more dioxin than **2** and **3**, the toxicity of the resulting dioxin is likely much higher for **2** and certainly for **3**. The scarcity of toxicity data and lack of accepted toxic equivalent factors (TEFs) for the dioxins formed by **1** and **2** complicates the comparison of their relative dioxin toxicity. If we conservatively assume a TEF of 0.001 (the actual TEF is likely much lower) for 1,2,4,8-TBDD, then at the dioxin production rates from our experiments, compound **3** will produce 70 times the toxicity as the natural product **1** from the same starting concentrations.

Our work confirms that OH-PBDEs of both natural and anthropogenic origin are capable of being converted photochemically to a variety of other brominated compounds, including brominated dioxins. While the actual production rates for the anthropogenic OH-PBDEs remain unknown, this work supports the hypothesis that these compounds, whether natural or anthropogenic, are a source of brominated dioxins in the environment. Further work will be required to better constrain any estimates about the share of dioxin toxicity attributable to the various OH-PBDE sources.

■ ASSOCIATED CONTENT

● Supporting Information

Figures S1–S12, synthesis of compounds **1–3**, synthesis of dibenzofuran derivatives, and additional references. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. P. J. Alaimo (Seattle University) for the helpful discussions. We gratefully acknowledge support of the U.S. National Science Foundation (CBET-0967163).

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