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Electrostatic and aspheric influence of the fluoro-substitution of 4-bromodiphenyl ether (PBDE 3)

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Abstract

Accurate structure determinations by X-ray crystal analysis and computation using semi-empirical self-consistent field molecular orbital calculations are described and compared for 4-bromodiphenyl ether (PBDE 3), the ¹³C₆-isotopic labeled PBDE 3 (¹³C₆-PBDE 3) and its five corresponding monofluorinated analogues (F-PBDEs 3): 2-fluoro-4-bromodiphenyl ether (F-PBDE 3-2F), 2'-fluoro-4-bromodiphenyl ether (F-PBDE 3-2'F), 3-fluoro-4-bromodiphenyl ether (F-PBDE 3-3F), 3'-fluoro-4-bromodiphenyl ether (F-PBDE 3-3'F) and 4'-fluoro-4-bromodiphenyl ether (F-PBDE 3-4'F). The synthesis and full characterization by means of ¹H, ¹³C, ¹⁹F nuclear magnetic resonance spectroscopy and mass spectrometry of the F-PBDEs 3 are presented for the first time. Intermolecular interactions for PBDE 3 and the F-PBDEs 3 isomers were dominated by weak C-H(F,Br) ... π and C-H...F interactions. The bond lengths of C-F varied between 1.347(2) Å and 1.362(2) Å, C4-Br between 1.880(3) Å and 1.904(19) Å. Both correlated with electron-density differences as determined by ¹³C shifts, but not with the strength of C-F couplings. The interior ring angles at *ipso*-fluoro-substitution increased to 121.95° due to hyperconjugation by p- π -orbital overlapping, a phenomenon that was also computed. An attraction between the *vicinal* fluoro- and bromo-substituents was not determined, as seen in fluoro-substituted chlorobiphenyls. The torsion angles measured and computed for the series of PBDE 3 and F-PBDEs 3 differed strongly from each other. Since the ether linkage (an average of 2.76 Å) provides more distance and the bonds are flexible up to a certain range, the influence of a fluoro-substituent is only detectable in PBDEs with high *ortho*-substitution. A concordance of computed and measured torsion angles can be observed with increasing size and/or grade of substitution comparing *mono*- to *tetra*- fluoro-, chloro-, bromo- and methyl-substitutions in the *ortho*-positions of diphenyl ether. Differences between computational *versus* measured data demonstrates a strong need to evaluate the results against independent techniques to conclude structure receptor activity relationships of PBDEs. Any discussion of the Ah or other biological receptor activity of certain PBDEs should take this in consideration. For the first time a complete overview of known and hypothetical biological activities of PBDEs is presented.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of 209 individual congeners, distinguishable by the number and position of bromines in the rings. PBDEs are extensively in use as flame-retardants and commonly added to consumer goods *e.g.* high-impact

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polystyrene, foams, textiles, wire and cable insulation, conductors plastics, polyurethane foams and textiles (Bromine Science and Environment Forum 2003; Nordic Council of Ministers, 1998) and Christmas Goats (Zeller, 2006). PBDEs are incorporated into materials using an “additive” process and thus may slowly volatilize into the environment during the product’s lifetime (Sjödin, *et al.*, 2001). In fact, some polyurethane foam is treated with 10–30 wt % of PBDEs (Hale, *et al.*, 2002). Recent studies have shown that PBDEs are globally distributed and detected in most environmental media including air (Strandberg, *et al.*, 2001; Gouin, *et al.*, 2002; Harner, *et al.* 2002, Hoh & Hites, 2005), water (Ikonomou, *et al.*, 2002a), soil (WHO, 1994), sediment (Sellström, *et al.*, 1998; Allchin, Law & Morris, 1999; Eljarrat & Barcelo, 2004; Zhu & Hites, 2005), vegetation (Gouin, *et al.* 2002; de Boer, 2003) and biota (Ikonomou, *et al.* 2002a, b; ter Schure, *et al.*, 2002).

PBDEs are now ubiquitous contaminants and due to their lipophilic character, high bioavailability and slow elimination, they bioaccumulate in the body and biomagnify in the food web (Meironyte, Noren & Berman, 1999; Lind *et al.*, 2002; Hites, 2004; Darnerud *et al.*, 2001; Bergman *et al.*, 1999; Ryan & Patry, 2000; Johanson-Restrepo, Kannan & Raport, 2005; Hites *et al.*, 2005). The environmental levels of PBDEs are in general still lower than those of polychlorinated biphenyls (PCBs). However, while the levels of PCBs, and many other chlorinated contaminants are gradually decreasing, the levels of PBDEs are rapidly increasing. Furthermore PBDE levels found in people living in North America are currently 10 to 100 times higher than those in Europe or Japan, and are doubling every 4–6 years (Hites, 2004; Johanson-Restrepo, Kannan & Raport, 2005). As PBDE levels increase so does the public health threat; there is concern of their potential for liver toxicity, disruption of thyroid hormone homeostasis, neurotoxicity, reproductive and developmental toxicity and carcinogenicity.

Knowledge of PBDEs crystal structures and homology models to examine potential modes for ligand binding is fundamental to our understanding of the biological activity of PBDEs as agonists and antagonists. This is the basis for quantitative structure-activity relationships that can be constructed from those data to understand the ligand binding to cellular and nuclear receptors, as mediators of signaling, and gene expression. Receptor activity is of special interest since PBDEs show little metabolic activity. Currently this knowledge is extremely limited and very controversially. For the first time a complete overview of biological transcription factors activated by PBDEs is presented (see Table 1). The structural similarity of certain PBDE congeners to other polyhalogenated aromatic compounds, *e.g.* polychlorinated biphenyls (PCBs), has raised the question whether PBDEs might be active aryl hydrocarbon receptor (Ah) mediated effects. Several groups found agonistic and antagonistic activity for certain PBDEs, see Table 1. On the other hand, it is claimed that these effects result not from the PBDEs themselves, but from polybrominated dibenzofurans (PBDFs) which are present in the test compounds as impurities (Sanders *et al.*, 2005). Since the non-planar PBDEs show weak agonism compared with ‘co-planar dioxin-like’ Ah receptor ligands and steroid, heme and xenobiotic metabolism are controlled by a network of interrelated receptors, additional receptors and functions have been studied or hypothesized for PBDEs, *i.e.* constitutive androstane (CAR), pregnane $\times$ (PXR), peroxisome proliferator (PPAR), ryanodin (RyR), estrogen (ER(α , β)), androgen (AR), progesterone (PR), thyroid function (TH), glucocorticoid (GR), γ -aminobutyric acid (GABA), thyroxine (T4), insulin-like growth factor-I (IGF-I), dihydrotestosterone (DHT) and dioxin response element (DRE), see Table 1. The orphan receptors CAR and PXR activities are also of interest, since it was observed that they activate each other by “cross-talk” (Kretschmer & Baldwin, 2005). Central in the receptor ligand activity is the conformation of the ligand, *e.g.* PBDE. The conformations of diphenyl ethers are described by the torsional angles (ϕ_1 and ϕ_2) between the C1–O–C1’ plane and planes of the phenyl rings. The angles are defined as positive when the rotation is clockwise looking down the C4–C1 and C4’–C1’ axes toward the oxygen.

Conformational properties of variously substituted diphenyl ethers have previously been studied using semiempirical or *ab initio* calculations (Nevalainen & Rissanen, 1994; Hu *et al.*, 2005; Luthe *et al.* 2006). Theoretically, there are four possible types of conformations of diphenyl ethers: planar ($\phi_1 = \phi_2 = 0^\circ$), butterfly ($\phi_1 = \phi_2 = 90^\circ$), skew ($\phi_1 = 0^\circ, \phi_2 = 90^\circ$) and twist ($\phi_1, \phi_2 > 0^\circ$). A variety of experimental and theoretical studies have shown that the unsubstituted diphenyl ether itself has a twist conformation in that ϕ_1 and ϕ_2 lie in the vicinity of $25\text{--}50^\circ$ (Schaefer *et al.*, 1988). PBDE congeners prefer a skew or twist conformation depending on the number of the *ortho*-bromo-substituents (Nevalainen & Rissanen, 1994). One approach to gaining information about the three-dimensional structure of PBDEs of single crystals by X-ray analysis or solid state nuclear magnetic resonance spectroscopy, another is to compute bond lengths and angles under ideal vacuum conditions. All approaches have drawbacks in modeling the molecular structure in solution, which makes it necessary to compare and interpretate the obtained results from both approaches. Unfortunately, relatively few crystal structures of PBDEs have been reported or computed to understand quantitative structure activity relationships (QSAR) in biological systems. 4-Bromodiphenyl ether (PBDE 3) is the most fundamental PBDE and therefore ideal to study conformational changes to gain information which can be generalized.

It is our hypothesis that fluoro-tagging can be employed to study biological activity of a given PBDE congener by varying its three dimensional structure. To test this hypothesis, we have synthesized and determined the crystal structures of a series of the five possible monofluorinated isomers (F-PBDEs 3) of the fundamental PBDE 3 isomer and compared these data with semiempirical self-consistent field molecular orbital (SCF-MO) calculations. Preliminary work on monofluorinated analogues of polycyclic aromatic hydrocarbons (F-PAHs) (Luthe, Ariese & Brinkman, 2002), polychlorinated biphenyls (F-PCBs) (Luthe *et al.*, 2006a; Luthe, Swenson & Robertson, 2007) and polybrominated diphenylethers (F-PBDEs) in (Luthe *et al.*, 2006b) were very promising. The physical and chemical properties of F-containing organic compounds are related to a number of distinctive characteristics of the fluorine atom, including its radius, which is much smaller than that of the homologue bromine. The van der Waals radii of fluorine and hydrogen are comparable, especially if C–F secondary binding (hyperconjugation) is taken into account (Luthe, Ariese & Brinkman, 2002). It is our aim to explore the potential of F-PBDEs to investigate biological activity *in vitro* and *in vivo*.

2. Experimental

2.1 Synthesis and characterization

Chemicals—Phenol (99%) (**1a**) and phenol- $^{13}\text{C}_6$ (99ATM% ^{13}C) (**1b**) were purchased from Sigma Aldrich (St. Louis, MO, USA), 4-bromo-2-fluorophenol (99%) (**1c**), 3-fluorophenol (98%) (**1f**) and 4-fluorophenol (99%) (**1g**), 1,4-dibromobenzene (99%) (**2a**), bromobenzene (99%) (**2b**), copper(I)-bromide (98%), magnesium sulfate and CDCl_3 (99.8%) with TMS (0.03 %) from Acros (Morris Plains, NJ, USA), 1-fluorophenol (97%) (**1d**) from Maybridge (Morris Plains, NJ, USA) and 4-bromo-3-fluorophenol (97%) (**1e**) from Matrix Scientific (Columbia, SC, USA). Copper powder (mesh size 99.9%), potassium hydroxide (*p.a.*), methanol (*p.a.*), *n*-hexane (95%), acetonitrile, silica gel 60 Å C: C 40–63 μm were purchased from Fisher Chemical (Pittsburgh, PA, USA).

Synthesis—PBDE 3, $^{13}\text{C}_6$ -isotopic labeled PBDE 3 ($^{13}\text{C}_6$ -PBDE 3) and F-PBDEs 3, *i.e.* 2-fluoro-4-bromodiphenyl ether (F-PBDE 3-2F), 2'-fluoro-4-bromodiphenyl ether (F-PBDE 3-2'F), 3-fluoro-4-bromodiphenyl ether (F-PBDE 3-3F), 3'-fluoro-4-bromodiphenyl ether (F-PBDE 3-3'F) and 4'-fluoro-4-bromodiphenyl ether (F-PBDE 3-4'F), were synthesized by nucleophilic substitution of bromobenzenes and by phenols. In the nomenclature, the first number refers to the corresponding PBDE, the second indicates the position of the

substituend, *e.g.* fluorine, with the bromo-substituent having the highest priority. This Ballschmider-Zell-Luthe (BZL) system (Luthe, 2006a, bLuthe, 2007) corresponds easily to the broadly used BZ system (Ballschmider & Zell, 1980) of the corresponding PBDEs. *General procedure:* A mixture of a phenol (**1a–g**) (10 mmol), potassium hydroxide (0.56 g, 10 mmol), bromobenzene (**2a,b**) (12 mmol), copper bromide (1.44 g, 10 mmol) and copper powder (0.64 g, 10 mmol) was heated under refluxing at 130 °C for 2 h in acetonitril. For the reaction equation and yields, see Fig. 1.

Synthesis monitoring and clean-up procedure—The reactions were monitored and the purity of all compounds was determined by gas chromatography (GC) and thin layer chromatography (TLC). A GC (Varian 3800 Palo Alto, CA, USA) equipped with a flame ionization detector (FID) was used. Separation was performed on a CP-sil 5CB column (Chrompack, Darmstadt, Germany) 20 m × 0.25 mm ID., 0.25 µm film thickness. Nitrogen was used as carrier gas. The column temperature was programmed from 50 °C to 250 °C at 5 °C/min and hold for ten minutes. For TLC ALUGRAM SIL G/UV₂₅₄, (Machery-Nagel, Düren, Germany) was used as stationary and *n*-hexane as mobile phase. After the reaction was completed the mixture was suspended in diethyl ether and the solution filtered of the employed magnesium sulfate. The solution was evaporated under reduced pressure and the crude product purified by column chromatography on a silica gel column with *n*-hexane as mobile phase. Impurities formed by brominated were removed under reduced pressure using a KUGEL-ROHR distillation. Flash chromatography was the method of choice for the purification processes. Silica gel was used as stationary and *n*-hexane as mobile phase. For 1 g of crude product ca. 300 g silica gel was used. All F-PBDEs 3 and PBDEs 3 were re-crystallized from methanol.

¹H, ¹³C and ¹⁹F NMR characterization—PBDE 3, ¹³C₆-PBDE 3 and F-PBDEs 3 were characterized by means of proton (¹H), carbon (¹³C), fluorine (¹⁹F) nuclear magnetic resonance (NMR) spectroscopy and ¹³C ¹H correlated spectroscopy (COSY). The ¹H and ¹³C NMR spectra were recorded on 300 MHz NMR spectrometer (Bruker, Billerica, MA, USA), using CDCl₃ as solvent. Chemical shifts, δ, are given in ppm relative to TMS, coupling constants, *J*, in Hz. The ¹³C NMR results are listed in Table 2, the ones of the ¹H NMR are presented in the results chapter (3.2). ¹⁹F NMR spectra were obtained with a 5 mm QNP probe, operating at 282.4 MHz. Chemical shifts were calibrated against hexafluorobenzene as standard. An overview of the shifts and couplings is given in the results. Images of the COSY spectra are attached in the supplemental materials.

GC- MS characterization—Analysis of F-PBDEs and PBDEs were carried out on a Agilent Technologies 6890N Network GC-system (Agilent, Palo Alto, CA, USA) GC with Agilent Technologies 5975 inert MS detection and autosampler (Agilent). Briefly, 1 µl was injected splitless, 1 µg absolute. The injection temperature was set to 275 °C. Separation was performed on a CP-Sil 8 capillary column (50 m × 0.25 mm I.D., 0.25 µm film thickness). Helium was used as the carrier gas at a flow of 1.2 mL/min. The split was opened after 2 min. The column temperature for the CP Sil-8 was programmed from 45 °C to 245 °C with 20 °C/min. The final temperature was held for ten minutes. Detection was based on EI-MS-mode in the full scan mode (*m/z* 50–500). Hydrogen was used as reagent gas at a flow of 3 mL/min. The ion source temperature was 230 °C. A list of the main ions is given in the results chapter (3.2).

2.2 Molecular orbital calculations

To calculate the conformation of the PBDE 3 and the corresponding F-PBDEs 3, semiempirical SCF-MO calculations using an AM1 Hamiltonian (Dewar *et al.*, 1985) with the Spartan '02 package were carried out on Quad 2.5 GHz Power Mac G5 with a PCI

express graphic card. The heats of formation were computed using a starting geometry similar to an optimized geometry. The use of symmetry constraints enhanced the convergence compared to completely unconstrained runs. The conformations of diphenyl ethers are described by the torsional angles (ϕ_1 and ϕ_2) between the C1–O–C1' plane and planes of the phenyl rings. The changes in the conformation by the introduction of a fluoro-substituent were calculated. angles are defined as positive, when the rotation is clockwise looking down the C4–C1 and C4'–C1' axes toward the oxygen. Deviation values obtained by other calculation methods are around 5–10 %. Table 3 gives an overview of the computed bond lengths, interior angles and the torsion angles.

2.3 X-ray structural determinations

Structure determinations of PBDE 3 and the five F-PBDEs 3 isomers were routine, although special handling during crystal mounting was required due to low melting points. Hydrogen atoms were located in difference maps but were constrained with the riding model (C–H = 0.95 Å, $U_{iso}(H)=1.2U_{iso,eq}(C)$). The F-PBDE 3-2F isomer showed minor disordering; details of the disorder refinements are included in the supplementary material. Experimental details are given in Table 4. Ellipsoid plots are shown in Fig. 2. Bond lengths and angles fall in the expected range, see Table 3.

2.4 Database searches

Database searches were carried out on the November 2006 version of the Cambridge Structural Database (Allen 2002, the CSD), with details in the supplementary material.

3. Results

3.1 Synthesis Aspects

In this paper we report the synthesis of PBDE 3, $^{13}C_6$ -PBDE and all five possible F-PBDEs 3 by nucleophilic substitution of the bromobenzene by a phenol under alkali conditions. The syntheses were carried out according to literature descriptions (Luthe *et al.*, 2006; Qian *et al.*, 2002; Marsh *et al.*, 2003, 1999). The applied method for the synthesis of low brominated PBDE analogues has the advantage of a one step-reaction with relatively high yields. The yields obtained are comparable to those found in literature (Luthe *et al.*, 2006; Qian *et al.*, 2002; Marsh *et al.*, 2003, 1999). The nucleophilic substitution can not be applied for the synthesis of the higher brominated analogues due to the considerable lower nucleophilicity of the phenol. As expected, we did not observe any conductive effect of the fluoro-substituent in the applied method. Best results were obtained by mixing the reactants in acetonitrile (Cristau *et al.*, 2003), evaporating of the solvent under gentle warming and re-suspension of the mixture in acetonitrile after 30 min of dryness. Extended heating under dry conditions results in de-bromination and scrambling of the bromo-substituent. The overall yields were increased by applying repeated cycles of short dryness, re-suspending in acetonitrile and refluxing.

3.2 1H , ^{13}C and ^{19}F NMR and MS characterization

4-bromodiphenyl ether (PBDE 3): 1H NMR ($CDCl_3$)— δ 7.43 (H-3/5, 2H, *m*, $^3J=9.0$ Hz), δ 7.35 (H3'/5', 2H, *m*, $^3J=8.4$ Hz, $^3J=7.4$ Hz), δ 7.13 (H4', 1H, *tt*, $^3J=7.4$ Hz, $^4J=1.1$ Hz), δ 7.00 (H2'/6', 2H, *m*), δ 6.89 (H2/6, 2H, *m*, $^3J=9.0$); **MS** (*m/z*): [M+1] $^+$: 249 (14 %), 251 (13 %), [M] $^+$: 248 (100 %), 250 (97 %), [M-1] $^+$: 247 (2 %), 249 (14 %), [M-C₂H₃] $^+$: 221 (1 %), 223 (1 %), [M-C₂H₄] $^+$: 220 (3 %), 222 (3 %), [M-C₆H₄] $^+$: 172 (3 %), 174 (3 %), [M-Br] $^+$: 169 (8 %), [M-HBr] $^+$: 168 (12 %), [M-CH₂Br] $^+$: 155 (3 %), [M-C₂Br] $^+$: 145 (8 %), [M-C₂HBr] $^+$: 144 (1 %), [M-C₂H₂Br] $^+$: 143 (8 %), [M-C₂H₃Br] $^+$: 142 (8 %), [M-C₂H₄Br] $^+$: 141 (66 %), [M-C₂H₅Br] $^+$: 140 (3 %), [M-C₂H₆Br] $^+$: 139 (12 %),

$[M]^{++}$ 124 (1 %), 125 (1 %), $[C_8H_7O]^+$ 119 (3 %), $[C_8H_5O]^+$ 117 (3 %), $[C_9H_7]^+$ 115 (28 %), $[C_6H_6O]^+$ 94 (3 %), $[C_6H_6]^+$ 78 (4 %), $[C_6H_5]^+$ 77 (57 %), $[C_6H_4]^+$ 76 (14 %), $[C_6H_3]^+$ 75 (14 %), $[C_4H_6O]^+$ 70 (6 %).

2-fluoro-4-bromodiphenyl ether (F-PBDE 3-2F): 1H NMR ($CDCl_3$)— δ 7.37 (H3, 1H, *dd*, $^3J_{H,F}=10.0$ Hz, $^4J_{H,H}=2.4$ Hz), δ 7.35 (H-3'/5', 2H, *m*, $^3J=8.4$ Hz, $^3J=7.4$ Hz), δ 7.24 (H5, 1H, *ddd*, $^3J_{H,H}=8.4$ Hz, $^4J_{H,H}=2.2$ Hz, $^5J_{H,F}=1.5$ Hz) δ 7.13 (H4', 1H, *tt*, $^3J=7.4$ Hz, $^4J=1.0$ Hz), δ 6.99 (H2'/6', 2H, *m*), δ 6.94 (H6, 1H, *dd*, $^3J_{H,H}=8.4$ Hz, $^3J_{H,F}=8.4$ Hz). ^{19}F NMR ($CDCl_3$): δ -128.05 (*ddd*, $^3J_{F,H2}=10.0$, $^4J_{F,H6}=8.4$, $^5J_{F,H5}=1.5$). **MS (m/z):** $[M+1]^+$ 267 (13 %), 269 (12 %), $[M]^+$ 266 (100 %), 268 (97 %), $[M-1]^+$ 265 (2 %), 267 (13 %), $[M-F]^+$ 247 (1 %), 249 (1 %), $[M-HF]^+$ 246 (2 %), 248 (2 %), $[M-C_2H_3]^+$ 239 (3 %), 241 (1 %), $[M-C_2H_4]^+$ 238 (11 %), 240 (11 %), $[M-C_2H_5]^+$ 237 (1 %), 239 (3 %), $[M-C_2H_4F]^+$ 219 (1 %), 221 (1 %), $[M-C_6H_4]^+$ 190 (2 %), 192 (2 %), $[M-C_6H_5]^+$ 189 (3 %), 191 (3 %), $[M-Br]^+$ 187 (3 %), $[M-HBr]^+$ 186 (5 %), $[M-C_6H_5O]^+$ 173 (1 %), 175 (1 %), $[M-C_2Br]^+$ 163 (6 %), $[M-C_2HBr]^+$ 162 (1 %), $[M-C_2H_2Br]^+$ 161 (7 %), $[M-C_2H_3Br]^+$ 160 (6 %), $[M-C_2H_4Br]^+$ 159 (49 %), $[M-C_2H_5Br]^+$ 158 (2 %), $[M-C_2H_6Br]^+$ 157 (7 %), $[C_8H_8FO]^+$ 139 (8 %), $[C_9H_6F]^+$ 133 (14 %), $[M]^{++}$ 133 (14 %), $[C_6H_6O]^+$ 94 (10 %), $[C_6H_6]^+$ 78 (4 %), $[C_6H_5]^+$ 77 (62 %), $[C_6H_4]^+$ 76 (3 %), $[C_6H_3]^+$ 75 (3 %), $[C_4H_6O]^+$ 70 (6 %).

2'-fluoro-4-bromodiphenyl ether (F-PBDE 3-2'F): 1H NMR ($CDCl_3$)— δ 7.43 (H-3/5, 2H, *m*, $^3J=9.0$ Hz), δ 7.22-7.12 (H3',4',5', 3H, *m*, $^3J=8.3$ Hz, $^4J=6.7$ Hz), δ 7.09 (H6', 1H, *ddd*, $^3J=7.8$ Hz, $^4J_{F,H}=7.8$ Hz, $^4J_{H,H}=2.0$ Hz), δ 6.87 (H2/6, 2H, *m*, $^3J=9.00$). ^{19}F NMR ($CDCl_3$): δ -130.68 (*m*) non-symmetrically. **MS (m/z):** $[M+1]^+$ 267 (13 %), 269 (12 %), $[M]^+$ 266 (100 %), 268 (98 %), $[M-1]^+$ 267 (13 %), $[M-F]^+$ 247 (>1%), 249 (>1 %), $[M-HF]^+$ 246 (2 %), 248 (2 %), $[M-C_2H_4]^+$ 238 (2 %), 240 (2 %), $[M-C_2H_5]^+$ 237 (>1 %), 239 (>1 %), $[M-C_2H_4F]^+$ 219 (>1 %), 221 (>1 %), $[M-Br]^+$ 187 (5 %), $[M-HBr]^+$ 186 (7 %), $[M-C_6H_3F]^+$ 172 (1 %), 174 (1 %), $[M-C_6H_4F]^+$ 171 (2 %), 173 (2 %), $[M-C_2H_2Br]^+$ 161 (1 %), $[M-C_2H_3Br]^+$ 160 (9 %), $[M-C_2H_4Br]^+$ 159 (78 %), $[M-C_2H_5Br]^+$ 158 (3 %), $[M-C_2H_6Br]^+$ 157 (18 %), $[M-C_6H_4OF]^+$ 155 (11 %), 157 (18 %), $[C_8H_8FO]^+$ 139 (8 %), $[C_9H_6F]^+$ 133 (24 %), $[M]^{++}$ 133 (24 %), $[C_8H_7O]^+$ 119 (3 %), $[C_8H_5O]^+$ 117 (3 %), $[C_6H_5F]^+$ 96 (1 %), $[C_6H_4F]^+$ 95 (8 %), $[C_6H_6O]^+$ 94 (12 %), $[C_6H_5]^+$ 77 (2 %), $[C_6H_4]^+$ 76 (21 %), $[C_6H_3]^+$ 75 (36 %).

3-fluoro-4-bromodiphenyl ether (F-PBDE 3-3F): 1H NMR ($CDCl_3$)— δ 7.45 (H5, 1H, *dd*, $^3J_{H,H}=8.0$ Hz, $^4J_{H,F}=8.7$ Hz), δ 7.38 (H-3'/5', 2H, *m*, $^3J=8.4$ Hz, $^3J=7.4$ Hz), δ 7.17 (H4', 1H, *tt*, $^3J=7.4$ Hz, $^4J=1.1$ Hz), δ 7.03 (H2'/6', 2H, *m*), δ 6.76 (H2, 1H, *dd*, $^3J_{H,F}=9.8$ Hz, $^4J_{H,H}=2.7$ Hz), δ 6.69 (H6, 1H, *ddd*, $^3J_{H,H}=8.7$ Hz, $^4J_{H,H}=2.7$ Hz $^5J_{H,F}=1.1$ Hz). ^{19}F NMR ($CDCl_3$): δ -104.64 (*ddd*, $^3J_{F,H2}=9.8$, $^4J_{F,H5}=8.7$, $^5J_{F,H6}=1.1$). **MS (m/z):** $[M+1]^+$ 267 (15 %), 269 (12 %), $[M]^+$ 266 (100 %), 268 (96 %), $[M-1]^+$ 265 (2 %), 267 (15 %), $[M-C_2H_3]^+$ 239 (2 %), 241 (1 %), $[M-C_2H_4]^+$ 238 (4 %), 240 (4 %), $[M-C_2H_5]^+$ 237 (1 %), 239 (2 %), $[M-C_6H_4]^+$ 190 (2 %), 192 (2 %), $[M-C_6H_5]^+$ 189 (1 %), 191 (1 %), $[M-Br]^+$ 187 (6 %), $[M-HBr]^+$ 186 (12 %), $[M-C_6H_5O]^+$ 173 (1 %), 175 (1 %), $[M-C_2Br]^+$ 163 (4 %), $[M-C_2HBr]^+$ 162 (1 %), $[M-C_2H_2Br]^+$ 161 (5 %), $[M-C_2H_3Br]^+$ 160 (7 %), $[M-C_2H_4Br]^+$ 159 (55 %), $[M-C_2H_5Br]^+$ 158 (2 %), $[M-C_2H_6Br]^+$ 157 (8 %), $[C_8H_8FO]^+$ 139 (6 %), $[C_9H_6F]^+$ 133 (16 %), $[M]^{++}$ 133 (16 %), $[C_6H_6O]^+$ 94 (17 %), $[C_6H_6]^+$ 78 (4 %), $[C_6H_5]^+$ 77 (56 %), $[C_6H_4]^+$ 76 (2 %), $[C_6H_3]^+$ 75 (3 %), $[C_4H_6O]^+$ 70 (6 %).

3'-fluoro-4-bromodiphenyl ether (F-PBDE 3-3'F): 1H NMR ($CDCl_3$)— δ 7.48 (H-3/5, 2H, *m*, $^3J=9.0$ Hz), δ 7.30 (H5', 1H, *ddd*, $^3J=8.3$ Hz, $^4J=6.7$ Hz), δ 6.94 (H2/6, 2H, *m*, $^3J=9.00$), δ 6.84 (H4', 1H, *dddd*, $^3J_{H,H}=^3J_{H,F}=8.3$ Hz, $^4J_{H,H}=2.4$ Hz), δ 6.79 (H6', 1H,

dd, $^3J=8.3\text{Hz}$), δ 6.72 (H2', 1H, *ddd*, $^3J_{F,H}=10.0\text{Hz}$, $^4J_{H,H}=2.4\text{Hz}$). **^{19}F NMR (CDCl_3):** δ -110.84 (*ddd*, $^3J_{F,H2'}=10.0$, $^3J_{F,H4'}=8.3$, $^4J_{F,H5}=6.6$). **MS (*m/z*):** $[\text{M}+1]^+$ 267 (13 %), 269 (12 %), $[\text{M}]^+$ 266 (100 %), 268 (95 %), $[\text{M}-1]^+$ 267 (13 %), $[\text{M}-\text{HF}]^+$ 246 (>1 %), 248 (>1 %), $[\text{M}-\text{C}_2\text{H}_3]^+$ 239 (2 %), 241 (1 %), $[\text{M}-\text{C}_2\text{H}_4]^+$ 238 (5 %), 240 (5 %), $[\text{M}-\text{C}_2\text{H}_5]^+$ 237 (1 %), 239 (2 %), $[\text{M}-\text{C}_2\text{H}_4\text{F}]^+$ 219 (1 %), 221 (1 %), $[\text{M}-\text{Br}]^+$ 187 (6 %), $[\text{M}-\text{HBr}]^+$ 186 (10 %), $[\text{M}-\text{C}_6\text{H}_3\text{F}]^+$ 172 (3 %), 174 (3 %), $[\text{M}-\text{C}_6\text{H}_4\text{F}]^+$ 171 (1 %), 173 (1 %), $[\text{M}-\text{C}_2\text{H}_2\text{Br}]^+$ 161 (1 %), $[\text{M}-\text{C}_2\text{H}_3\text{Br}]^+$ 160 (7 %), $[\text{M}-\text{C}_2\text{H}_4\text{Br}]^+$ 159 (56 %), $[\text{M}-\text{C}_2\text{H}_5\text{Br}]^+$ 158 (2 %), $[\text{M}-\text{C}_2\text{H}_6\text{Br}]^+$ 157 (12 %), $[\text{M}-\text{C}_6\text{H}_4\text{OF}]^+$ 155 (5 %), 157 (12 %), $[\text{C}_8\text{H}_8\text{FO}]^+$ 139 (5 %), $[\text{C}_9\text{H}_6\text{F}]^+$ 133 (16 %), $[\text{M}]^{++}$ 133 (16 %), $[\text{C}_8\text{H}_7\text{O}]^+$ 119 (2 %), $[\text{C}_8\text{H}_5\text{O}]^+$ 117 (2 %), $[\text{C}_6\text{H}_5\text{F}]^+$ 96 (1 %), $[\text{C}_6\text{H}_4\text{F}]^+$ 95 (10 %), $[\text{C}_6\text{H}_6\text{O}]^+$ 94 (6 %), $[\text{C}_6\text{H}_5]^+$ 77 (1 %), $[\text{C}_6\text{H}_4]^+$ 76 (8 %), $[\text{C}_6\text{H}_3]^+$ 75 (18 %).

4'-fluoro-4-bromodiphenyl ether (F-PBDE 3-4'F): ^1H NMR (CDCl_3)— δ 7.41 (H-3/5, 2H, *dt*, $^3J=9.0\text{Hz}$), δ 7.07–6.93 (H2',3',5',6', 4H, *m*), δ 6.83 (H2/6, 2H, *dt*, $^3J=9.00$). **^{19}F NMR (CDCl_3):** δ -104.64 (*dddd*, 2H $^3J_{F,H3'/5'}=8.0$, $^4J_{F,H2'/6'}=4.6$). **MS (*m/z*):** $[\text{M}+1]^+$ 267 (13 %), 269 (11 %), $[\text{M}]^+$ 266 (100 %), 268 (95 %), $[\text{M}-1]^+$ 267 (13 %), $[\text{M}-\text{C}_2\text{H}_3]^+$ 239 (1 %), 241 (>1 %), $[\text{M}-\text{C}_2\text{H}_4]^+$ 238 (1 %), 240 (1 %), $[\text{M}-\text{C}_2\text{H}_5]^+$ 237 (1 %), 239 (1 %), $[\text{M}-\text{Br}]^+$ 187 (4 %), $[\text{M}-\text{HBr}]^+$ 186 (6 %), $[\text{M}-\text{C}_6\text{H}_3\text{F}]^+$ 172 (2 %), 174 (2 %), $[\text{M}-\text{C}_6\text{H}_4\text{F}]^+$ 171 (1 %), 173 (1 %), $[\text{M}-\text{C}_2\text{H}_2\text{Br}]^+$ 161 (>1 %), $[\text{M}-\text{C}_2\text{H}_3\text{Br}]^+$ 160 (6 %), $[\text{M}-\text{C}_2\text{H}_4\text{Br}]^+$ 159 (53 %), $[\text{M}-\text{C}_2\text{H}_5\text{Br}]^+$ 158 (3 %), $[\text{M}-\text{C}_2\text{H}_6\text{Br}]^+$ 157 (12 %), $[\text{M}-\text{C}_6\text{H}_4\text{OF}]^+$ 155 (6 %), 157 (12 %), $[\text{C}_8\text{H}_8\text{FO}]^+$ 139 (4 %), $[\text{C}_9\text{H}_6\text{F}]^+$ 133 (16 %), $[\text{M}]^{++}$ 133 (16 %), $[\text{C}_8\text{H}_7\text{O}]^+$ 119 (2 %), $[\text{C}_8\text{H}_5\text{O}]^+$ 117 (2 %), $[\text{C}_6\text{H}_5\text{F}]^+$ 96 (1 %), $[\text{C}_6\text{H}_4\text{F}]^+$ 95 (8 %), $[\text{C}_6\text{H}_6\text{O}]^+$ 94 (7 %), $[\text{C}_6\text{H}_5]^+$ 77 (1 %), $[\text{C}_6\text{H}_4]^+$ 76 (10 %), $[\text{C}_6\text{H}_3]^+$ 75 (18 %).

4-bromodiphenyl ether $^{13}\text{C}_6$ (PBDE 3): ^1H NMR (CDCl_3)— δ 7.43 (H-3/5, 2H, *m*, $^3J=9.0\text{Hz}$), δ 7.35 (H3'/5', 2H, *m*, $^3J=8.4\text{Hz}$, $^3J=7.4\text{Hz}$), δ 7.13 (H4', 1H, *tt*, $^3J=7.4\text{Hz}$, $^4J=1.1\text{Hz}$), δ 7.00 (H2'/6', 2H, *m*), δ 6.89 (H2/6, 2H, *m*, $^3J=9.00$); **MS (*m/z*):** $[\text{M}+1]^+$ 255 (14 %), 257 (13 %), $[\text{M}]^+$ 254 (100 %), 256 (97 %), $[\text{M}-1]^+$ 253 (2 %), 255 (14 %), $[\text{M}-\text{C}_2\text{H}_3]^+$ 221 (1 %), 223 (1 %), $[\text{M}-\text{C}_2\text{H}_4]^+$ 220 (3 %), 222 (3 %), $[\text{M}-\text{Br}]^+$ 175 (7 %), $[\text{M}-\text{HBr}]^+$ 174 (14 %), $[\text{M}-\text{C}_6\text{H}_4]^+$ 172 (3 %), 174 (14 %), $[\text{M}-\text{C}_6\text{H}_5]^+$ 171 (1 %), 173 (1 %), $[\text{M}-\text{C}_2\text{H}_2\text{Br}]^+$ 148 (1 %), 147 (24 %), 146 (25 %), 145 (12 %), 144 (5 %), 143 (5 %), ($x=13,12.5,12;y=1-6$), $[\text{M}-\text{CH}_2\text{Br}]^+$ 155 (2 %), $[\text{M}-\text{C}_2\text{Br}]^+$ 145 (8 %), $[\text{M}-\text{C}_2\text{HBr}]^+$ 144 (1 %), $[\text{M}-\text{C}_2\text{H}_2\text{Br}]^+$ 143 (8 %), $[\text{M}-\text{C}_2\text{H}_3\text{Br}]^+$ 142 (8 %), $[\text{M}-\text{C}_2\text{H}_4\text{Br}]^+$ 141 (66 %), $[\text{M}-\text{C}_2\text{H}_5\text{Br}]^+$ 140 (3 %), $[\text{M}-\text{C}_2\text{H}_6\text{Br}]^+$ 139 (12 %), $[\text{M}]^{++}$ 127 (1 %), 128 (1 %), $[\text{C}_8\text{H}_7\text{O}]^+$ 119 (3 %), $[\text{C}_8\text{H}_5\text{O}]^+$ 117 (3 %), $[\text{C}_9\text{H}_7]^+$ 115 (28 %), $[\text{C}_6\text{H}_6\text{O}]^+$ 100 (2 %), $[\text{C}_6\text{H}_4\text{O}]^+$ 92 (2 %), $[\text{C}_6\text{H}_5]^+$ 83 (31 %), $[\text{C}_6\text{H}_4]^+$ 82 (3 %), $[\text{C}_6\text{H}_3]^+$ 81 (2 %), $[\text{C}_6\text{H}_5]^+$ 77 (2 %), $[\text{C}_6\text{H}_4]^+$ 76 (8 %), $[\text{C}_6\text{H}_3]^+$ 75 (8 %).

3.3 C-F and C4-Br bond length and angles

In general, the measured and computed bond lengths and angles of C-F and C4-Br are of similar magnitude. There is an interesting trend of C4-Br bond lengths. While the C4-Br bond lengths of PBDE 3 and F-PBDE 3-2F are 1.896(3) and 1.897(2) Å, for F-PBDE 3-2'F, 3-3'F and 3-4'F which do not carry the fluoro-substituent on the same ring as the bromo-substituent, the C-Br bond increases to 1.904(19) Å. The shortest C4-Br bond length with 1.880(3) Å are shown in the *vicinal* position for F-PBDE 3-3F. The C-F bond lengths of the *ortho*-substituted F-PBDEs 3-2F and 3-2'F are the shortest with 1.3488(13) Å and 1.347(2) Å, while F-PBDE 3-3'F has the longest C-F bond of 1.362(2) Å. The Br-C4-C3 and Br-C4-C5 bond angles are widened for one to two degrees up to 121.0(2)° and 121.1(2)° in F-PBDE 3-3F isomer with the *vicinal* fluoro-substituent. This effect was not seen in the computed model. The repulsion of bromine and fluorine-substituents determined by the bond angles of F-C3-C2 (117.7(2)°) and F-C3-C4 (119.1(3)°) of the F-PBDE 3-3F isomer are smaller than computed with 118.6° and 120.7°.

3.4 C-C and C-O bond lengths and angles

The computed and by measured C-C bond lengths and interior angles are generally in good agreement and of similar magnitude, see Table 3. However, we observed a change by fluorosubstitution in the C-C bond lengths and the interior angles of the phenyl rings by X-ray determination, not found by computation. The fluoro-*ipso* bond angles are widened from 120.2(2)° (PBDE 3) to 121.95(10)° in F-PBDE 3-2F (C3-C2-C1), 121.9(2)° for F-PBDE 3-2'F (C3'-C2'-C1'), 122.9(2)° for F-PBDE 3-3F (C2-C3-C4), 124.0(2)° for F-PBDE 3-3'F (C4'-C3'-C2') and 122.2(3)° for F-PBDE 3-4'F (C3'-C4'-C5'). The other interior angles were diminished. The computational model did not predict this effect, see Table 3.

The X-ray determination shows, that fluorine effects the C1-O and C1'-O bond lengths, depending on the steric and electronic influence. In the two influenced *ortho*-fluoro-substituted F-PBDE isomers 3-2F and 3-2'F the bond lengths are slightly increased from 1.376(3) Å and 1.386(3) Å (PBDE 3) to 1.389(2) Å and 1.400(2) Å (F-PBDE 3-2F) and 1.386(2) Å and 1.389(2) Å (F-PBDE 3-2'F). In the *meta*- and *para*-substituted F-PBDEs 3, the C-O is shortest on the ring carrying the fluorine, *i.e.* 1.364(3) Å (C1-O) to 1.410(3) Å (C1'-O) in F-PBDE 3-3F, 1.384(3) Å (C1'-O) to 1.393(2) Å (C1-O) in F-PBDE 3-3'F and 1.384(3) Å (C1'-O) to 1.395(4) Å (C1-O) in F-PBDE 3-4'. The bond angles C6-C1-O, C2-C1-O, C6'-C1'-O and C2'-C1'-O follow the distortion of the aromatic ring by fluoro-substitution. The X-ray measurements show as well that the C1'-O bond length is longer, 1.386(3) Å compared with the one carrying the bromo-substituent 1.376(3) Å. Both effects are apparently not taken into account in the computational model, giving for all isomers the same C1-O and C1'-O bond lengths of 1.376 Å.

3.5 Torsion and C-O-C bond angles

In general, the torsion angles C1'-O-C1-C6(2) and C2'(6')-C1'-O-C1 measured and computed for the series of PBDE 3 and F-PBDEs 3 differ strongly from each other, except that PBDE 3 and F-PBDEs 3 have a twisted conformation, see Table 3. Comparing diphenyl ethers from *mono*- to *tetra* with fluoro-, chloro-, bromo- and methyl-substitutions in the *ortho*-positions, we observed a general alignment of computed and determined data, see Table 3 and Fig. 2. This is the case for the torsion angles of methyl-diphenyl ether (determined: 145.48°, -36.23°; computed: 141.3°, -42.1°) dibromodiphenyl ether (determined: 78.70°, -107.05°; computed: 92.1°, 92.1°) and dimethylether (determined: 93.08°, -91.22°; computed: 91.9°, 91.9°) with *ortho*-substitutions on one ring, but not with the one on two rings. With four fluoro-substituents in *ortho*-positions the fit of computed and measured torsion angles is in agreement (measured: 57.71°, -127.97°; computed: 49.4°, -134.2°).

We determined that the C1-O-C1' bond angle in F-PBDE 3-2F displays the smallest value (115.96(12)°), and the broadest for PBDE (121.09(18)°) and F-PBDE 3-3F (120.9(2)°), see Table 5 and Fig. 2. Comparing diphenyl ethers from *mono* to *tetra* with fluoro, chloro, bromo- and methyl-substitutions in the *ortho*-positions, we observed a trend of alignment in the computed data, resulting in increased angles with higher substitution and increasing volume of the substituent, see Table 5. This trend was not seen in the data of measured compounds. This might be due to the limited resource of data for these types of compounds.

3.6 Packing of the PBDE 3 and F-PBDEs 3 isomers

The intermolecular interactions of BDE3 and the F-BDE3 isomers are weak and dominated by C-H(F, Br)⋯ π with some C-H⋯F interactions.

Packing of the 4-bromodiphenyl ether (PBDE 3)—The molecules stack parallel to the unit cell c-axis forming columns. The columns are interconnected via C-H⋯ π

interactions to form sheets perpendicular to the a-axis ($H2 \cdots X1a^{(i)} = 2.880 \text{ \AA}$, $H5 \cdots X1a^{(ii)} = 2.745 \text{ \AA}$, $H2' \cdots X1b^{(iii)} = 2.939 \text{ \AA}$, $H5' \cdots X1b^{(iv)} = 2.863 \text{ \AA}$; (i) = x, 2-y, -0.5+z; (ii) = x, 1-y, 0.5+z; (iii) = x, 1-y, -0.5+z; (iv) = x, 2-y, 0.5+z). The sheets interact via general van der Waals forces with a close $C3'-H3' \cdots Br^{(v)}$ contact ($0.95 \text{ \AA}$, $3.00 \text{ \AA}$, $3.566 \text{ \AA}$, 145° ; (v) = 0.5+x, 1.5-y, -0.5+z).

Packing of the 2-fluoro-4-bromodiphenyl ether (F-PBDE 3-2F)—The molecules stack parallel to the unit cell a-axis. $C-H \cdots \pi$ ($H4' \cdots X1a^{(i)} = 2.936 \text{ \AA}$, $H5 \cdots X1b^{(ii)} = 2.875 \text{ \AA}$; (i) = x, -1+y, z; (ii) = 1-x, 0.5+y, 1.5-z) and $C-Br \cdots \pi$ ($Br1 \cdots X1a^{(iii)} = 3.761 \text{ \AA}$, (iii) = 2-x, 0.5+y, 1.5-z) interactions connect these stacks into bi-layers with the F atoms on the 'exterior' of the bi-layers. $C-H \cdots \pi$ interactions ($H2' \cdots X1b^{(iv)} = 3.001 \text{ \AA}$, (iv) = -0.5+x, 0.5-y, 2-z) connect the bi-layers. General van der Waals forces hold the bi-layer together.

Packing of the 2'-fluoro-4-bromodiphenyl ether (F-PBDE 3-2'F)—The molecules stack parallel to the unit cell b-axis to form columns. $C-H \cdots \pi$, $C-F \cdots \pi$ and $C-H \cdots F$ interactions connect the molecules in the columns ($H2 \cdots X1a^{(i)} = 3.384 \text{ \AA}$, $H5 \cdots X1a^{(ii)} = 3.386 \text{ \AA}$, $H5' \cdots X1b^{(ii)} = 3.498 \text{ \AA}$, $F1 \cdots X1b^{(i)} = 3.473 \text{ \AA}$ and $C6-H6 \cdots F1^{(iii)}$ ($0.95 \text{ \AA}$, $2.43 \text{ \AA}$, $3.256(3) \text{ \AA}$, 145°); (i) = x, -1+y, z; (ii) = x, 1+y, z; (iii) = x, 1+y, z) and interconnect neighboring columns ($C5-H5 \cdots F1^{(iv)}$ ($0.95 \text{ \AA}$, $2.48 \text{ \AA}$, $3.375(3) \text{ \AA}$, 157° ; (iv) = 1-x, 1+y, 0.5-z) to double the column. The doubled columns are held together via general van der Waals forces.

Packing of the 3-fluoro-4-bromodiphenyl ether (F-PBDE 3-3F)—The molecules stack parallel to the unit cell c-axis forming columns. The columns are interconnected via $C-H \cdots \pi$ and $C-H \cdots F$ interactions to form a three dimensional network ($H2 \cdots X1a^{(i)} = 2.710 \text{ \AA}$, $H5 \cdots X1a^{(ii)} = 2.839 \text{ \AA}$, $H5' \cdots X1b^{(iii)} = 2.943 \text{ \AA}$, $H2' \cdots X1b^{(iv)} = 3.380 \text{ \AA}$ and $C4'-H4' \cdots F1^{(v)}$ ($0.95 \text{ \AA}$, $2.42 \text{ \AA}$, $3.239(3) \text{ \AA}$, 145°); (i) = -x, 1-y, -0.5+z; (ii) = 0.5-x, y, 0.5+z; (iii) = -x, 2-y, 0.5+z; (iv) = 0.5-x, y, -0.5+z; (v) = x, 1+y, z).

Packing of the 3'-fluoro-4-bromodiphenyl ether (F-PBDE 3-3'F)—The molecules stack parallel to the unit cell a-axis forming columns. The columns are interconnected via $C-H \cdots \pi$ and $C-Br \cdots \pi$ interactions to form a three dimensional network ($H4' \cdots X1a^{(i)} = 3.064 \text{ \AA}$, $Br1 \cdots X1a^{(ii)} = 3.714 \text{ \AA}$, $H2 \cdots X1b^{(iii)} = 2.732 \text{ \AA}$, $H5 \cdots X1b^{(iv)} = 2.890 \text{ \AA}$; (i) = x, -1-y, z; (ii) = 0.5-x, 0.5+y, 1.5-z; (iii) = 1-x, 1-y, 1-z; (iv) = 1.5-x, 0.5+y, 1.5-z; (v) = x, 1+y, z).

Packing of the 4'-fluoro-4-bromodiphenyl ether (F-PBDE 3-4'F)—The molecules stack parallel to the unit cell a-axis forming columns. The columns are interconnected via $C-H \cdots \pi$, $C-F \cdots \pi$ and $C-Br \cdots \pi$ interactions to form a three dimensional network ($H5 \cdots X1a^{(i)} = 3.243 \text{ \AA}$, $Br1 \cdots X1a^{(ii)} = 3.735 \text{ \AA}$, $Br1 \cdots X1b^{(iii)} = 3.461 \text{ \AA}$, $F1 \cdots X1b^{(iv)} = 3.469 \text{ \AA}$; (i) = x, -y, -0.5+z; (ii) = 0.5+x, 0.5+y, z; (iii) = -0.5+x, 0.5+y, z; (iv) = 0.5+x, 0.5-y, -0.5+z).

4. Discussion

4.1 Synthesis Aspects

Several pathways to obtain the desired PBDE 3 and analogues are described in literature, *i.e.* coupling of diphenyl iodyl salts with phenols (Luthe *et al.*, 2006, Marsh *et al.*, 2003, 1999), coupling of arylboronic acids with phenols (Chouteau *et al.*), ether synthesis by Ullmann-coupling (Luthe *et al.*, 2006a; Qian *et al.*, 2002, Cristau *et al.*, 2003) and direct substitution of the diphenyl ether molecule or its derivatives (Luthe *et al.*, 2006a). PBDE 3 was synthesized by several methods independently. The highest yield of 98% was obtained by Kiyoshi *et al.* (2003) using N-bromo-succinimide and ammonium nitrate in acetonitrile. The five F-PBDEs 3 have not been synthesized before and are presented here for the first time.

Due to the commercial availability of the starting materials, the short pathway of a single step reaction, the high purity of the products and the relatively high yields (>90%, Cristau *et al.*, 2003), we employed the Ullmann-coupling. Aside these advantages, the fluorosubstituent has no conductive influence on the reaction, like in a direct coupling with diphenyl iodyl salts (Luthe *et al.*, 2006). The yields obtained are competitive: PBDE 3 (59%), $^{13}\text{C}_6$ -PBDE 3 (60%), F-PBDE 3 2-F (54%), F-PBDE 3 3-F (55%), F-PBDE 3 2'-F (59%), F-PBDE 3 3'-F (60%) and F-PBDE 3 4'-F (58%). The synthesis conditions are responsible for the somewhat lower yields for the congeners F-PBDEs 3 2-F and 3 3-F. With a high excess of the bromobenzene, the side reaction of a self-attack could be reduced, resulting in a higher product yield. We observed that the solvent volume was critical for the successful reaction. This should be kept as low as possible (only supporting the blend stirring) to keep the temperature high.

4.2 ^1H , ^{13}C and ^{19}F NMR and MS characterization

The ^1H NMR spectra of the PBDE 3 and F-PBDEs 3 are of higher spin order. For a defined determination of the shifts and couplings, we employed ^1H ^{13}C COSY NMR, see supplement. The PBDE 3 carrying the bromine is a A,A',X,X' and a A,A',X,X',Z system (prime side); F-PBDE 3-2F is a A, B, Z and a A,A',X,X',Z system (prime side); F-PBDE 3-2'F is a A,A',X,X' and A, B, X, Z (prime side); F-PBDE 3-3F is a A, X, Z and A,A',X,X',Z system (prime side); F-PBDE 3-3'F is a A,A',X,X' and A, B, X, Z system (prime side) and F-PBDE 3-4'F is a A,A',X,X' and A, A', Z, Z' (prime side). The chemical shifts are between $\delta = 6.69$ ppm (F-PBDE 3-3F) and 7.77 ppm (F-PBDE 3-3'F). Vicinal protons to the fluoro-substitution are shifted to higher δ values, and ones in *meta*-position to lower. Fluoro-substitution influenced as well the electron density on the ring not carrying a fluorine and changed slightly the ^1H chemical shifts., *i.e.* from 6.89 ppm for H2/6 to 6.87 ppm (PBDE 3-2'F), 6.94 ppm (F-PBDE 3-3'F) and 6.83 ppm (F-PBDE 3-4'F), for H3/5 from 7.43 ppm to 7.48 ppm (F-PBDE 3-3'F) and 7.41 ppm (F-PBDE 3-4'F), for H2'/6' from 7.00 ppm to 7.03 ppm (F-PBDE 3-3F). The J_{HH} couplings are between $^3J_{\text{HH}}$ 7.4 Hz – 9.00 Hz, $^4J_{\text{HH}}$ 1.0 Hz – 2.4 Hz. Bromo-substitution, as well as the oxygen substitution increased the coupling strength, *e.g.* compare $^4J_{\text{H}_3\text{H}_5'}$ 1.0 Hz with $^4J_{\text{H}_3\text{H}_5}$ 2.2 Hz *via* bromine in F-PBDE 3-2F and $^4J_{\text{H}_3\text{H}_5'}$ 1.0 Hz with $^4J_{\text{H}_2\text{H}_6}$ 2.7 Hz *via* oxygen in F-PBDE 3-3F. Fluoro-substitution influenced the coupling strength of its neighbor's protons as well, but not in *ortho*-position like the bromo-substituent, but in *meta*-position. For example, F-PBDE 3-2'F showed a coupling of $^4J_{\text{H,H}}$ 2.4 Hz versus 2.0 Hz in a non-substituted ring.

^{13}C NMR spectra, see Table 2, show shifts to highest values on C1/1' due to the -I effect of oxygen and on carbons with *ipso*-substitution, ranging from 154.0 – 163.7 ppm. The lowest shifts of 154.0 ppm (F-PBDE 3-2'F) and 154.3 ppm (F-PBDE 3-2F) were found in the *ortho*-positions C2/2' due to electron density increasing on these positions by the influence of oxygen. Comparing the shifts induced by a *meta*-fluoro-substitution in C3/3' shows the electron density increasing by *ortho*-bromo-substitution resulting in a lower shift of 159.7 ppm (F-PBDE 3-3F) *versus* 163.7 ppm (F-PBDE 3-3'F). The $^1J_{\text{CF}}$ couplings ranged from 242.28 Hz–253.60 Hz. The strength of the coupling is reflecting the strength of the C-F bond. The C2/2' positions have the highest electron density based on ^{13}C NMR shift assumption, and the $^1J_{\text{CF}}$ of the *ortho*-fluoro-substituents is the strongest, with 253.6 Hz (F-PBDE 3-2F) and 249.07 Hz (F-PBDE 3-2'F). Similar conclusions can be drawn based on electron density of the F-C bonds for $^2J_{\text{CF}}$ couplings. Aside from the electron density of the carbon, buttressing effects, electron donation and withdrawing over space; steric effects play a major role. To determine the change in electron density by fluoro-substitution, the difference between the ^{13}C NMR shifts of a given substituted compound (F-PBDEs 3) and the corresponding parent compounds (PBDE 3) can be formed, see Fig. 4. Positive values

indicate an increase of electron density, negative a decrease. This information is critical to understand shape and reactivity and is therefore of fundamental importance.

The ^{19}F NMR spectra are of first order and can be explained on the basis of direct coupling with its neighboring hydrogens. The chemical shifts in ^{19}F NMR are the highest for the positions C3, 5 and 4' with -104.64 ppm, followed by C3' and 5' with -110.84 ppm, C2 and 6 with -128.05 ppm and finally C2 and 6' with -130.68 ppm. This trend is in comparison with electron density of PBDE 3, determined by ^{13}C NMR shifts. Aside the C4 (^{13}C δ 115.8 ppm) what has due to the bromo-substituent the highest electron density, followed by C2' and 6' (^{13}C δ 119.2 ppm), C2 and 6 (^{13}C δ 120.6 ppm), C3' and 5' (^{13}C δ 130.1 ppm), C3 and 5 (^{13}C δ 132.9 ppm), see Table 2. The ^{19}F NMR δ shift -119.55 ppm of C4' can not be explained on the basis of electron density alone, since the ^{13}C δ 123.9 ppm should result in a ^{19}F δ around -125 ppm. We explain this anomaly on the basis of the anisotropy effect of the torsion energy, the so called 'Ringstrom'. The J_{FH} couplings are between $^3J_{\text{FH}}$ 8.0 Hz – 10.00 Hz, $^4J_{\text{FH}}$ 4.6 Hz – 8.4 Hz, $^5J_{\text{FH}}$ 1.1 Hz – 1.5 Hz and are by this very strong. F-PBDE 3-2'F showed a non-symmetrical spectra. Since ^1H - ^{19}F coupled spin systems can not lead to spectra of second or higher order, this observation can be explained on the basis of signal carryover and more than one signal coincidentally resonate at the same frequency. The proton coupling partners are not magnetically equivalent.

The parent ion peak $[\text{M}]^+$ is the main signal in MS for PBDE 3 and the corresponding F-PBDEs 3. Major fragments are $[\text{M}-\text{Br}]^+$, $[\text{M}-\text{HBr}]^+$, $[\text{M}-\text{C}_2\text{Br}]^+$, $[\text{M}-\text{C}_2\text{H}_2\text{Br}]^+$ and $[\text{M}-\text{C}_2\text{H}_4\text{Br}]^+$. Fluorine loss is around 1% and refelects the strong C-F bond, especially in an aromatic system due to hyperconjugation. The $[\text{M}]^{++}$ reflects the potential to stabilize a second positive charge of the molecule by delocalization or resonance. While for PBDE 3 the abundance of the $[\text{M}]^{++}$ is only 1 %, it increases by a monofluorination to 14% (F-PBDE 3-2F), 16 % (F-PBDEs 3-3F, 3-3'F and 3-4'F) and even 24% (F-PBDE 3-2'F). A similar observation could be made comparing monofluorinated polycyclic aromatic hydrocarbons with their non-fluorinated parent compounds (Luthe *et al.*, 2003). The electron density in the σ -bond-system diminishes by fluorosubstitution, but increases by hyperconjugation in the π -system since fluorine is too hard to retain the charge and pushes it back *via* p- π -orbital overlap. This results in a stabilization of the additional charge. Additionally, reinforced by the negative inductive effect of fluorine, the removal of a second electron should lead to a less energetic atomic orbital $1s^2 2s^2 2p^4$, with two unpaired electrons for fluorine.

4.3 C-F and C4-Br bond lengths

The differences in C-F and C-Br bond lengths may be explained on the basis of differences in electron density and orbital overlap. Many factors, *e.g.* mesomeric, inductive, steric and/or direct electric field effects, may alter the electron density. Substituent-induced chemical shifts in ^{13}C NMR reflect the actual distribution of electron charges at the C atom between the carbon and the fluoro-substituent, see Fig. 4. The approach of ^{13}C NMR measurements had been used previously (Luthe *et al.*, 2007). Therefore, instead of using semi-empirical SFC-MO calculations, we have relied on substituent-induced chemical shifts and couplings. Fig. 4 gives an overview of the change of electron density for the C positions 1 to 6, and 1' to 6'. Higher shift values indicate a reduction in electron density, lower ones increase at the carbon position. A lower electron density results in a less strong C-F bond and a lengthening of the bond. In the non substituted ring, C3' has the highest ^{13}C NMR shift δ of 130.1 ppm resulting in the longest C-F bond of 1.362 Å, followed by C4' δ 123.9 ppm and C-F bond length 1.354 Å and C2' δ 119.2 ppm and C-F bond length 1.347 Å. Comparing the shifts for C1'-C6' in PBDE 3 with C1-C6 in diphenyl ether demonstrates that the bromine has a negligible effect on the non-bromo-substituted ring in PBDE 3. The following ^{13}C NMR shifts, δ [ppm], in diphenyl ether were determined 156.9 (C1), 119.2 (C2, C6), 130.1 (C3, C5) and 123.9 (C4). The highest ^{13}C NMR shift δ of 132.9 ppm results in the longest C-F

bond of 1.357 Å at C3 position, followed by δ of 120.6 ppm results in the longest C-F bond of 1.349 Å at the C2 position. The strength of the J_{CF} couplings does not follow the trend of the C-F bond lengths, see Fig. 5. We found in general that a strong coupling results in a shorter bond. But the values determined for the specific isomers do not reflect the trend of bond length. Aside from the electron density of the carbon, buttressing effects, electron donation and withdrawing over space; steric effects play a major role. By computation with SCF-MO the differences in the C-F bond lengths can not be determined.

There is a trend of C4-Br bond lengths. While the C-Br bond lengths of PBDE 3 and F-PBDEs 3-2F are 1.896(3) and 1.897(2) Å, for F-PBDEs 3-2'F, 3-3'F and 3-4'F (which do not carry the fluoro-substituent on the same ring as the bromo-substituent), the C-Br bond increases to 1.903(2), 1.904(2) and 1.897(3) Å. The shortest C-Br bond length with 1.880(3) Å are determined in the *vicinal* position in F-PBDE 3-3F. This can not be explained on the basis of electron density determined by ^{13}C NMR measured in PBDE 3. The C4-Br bond lengths result from the additive influences of fluoro- and bromo-substituents. Therefore we determine the change of electron density in the F-PBDEs 3 at the various positions by comparing the ^{13}C NMR shifts of the F-PBDEs 3 with the corresponding PBDE 3, see Fig. 4. The *vicinal* fluoro-substituent in F-PBDE 3-3F results in the highest electron increase in the C4 position of $\Delta\delta$ 13.7 ppm by *ortho*-induction, giving the shortest C4-Br bond lengths of 1.880(3) Å. On the other hand, the strongest reduction of electron density by fluorine substitution at C4 was determined to be $\Delta\delta$ -0.9 ppm for F-PBDE 3-3'F, resulting in the longest C4-Br bond with 1.904(2) Å. Again, the differences in the C4-Br bond lengths can not be determined by computation with SCF-M.

4.4 Influence of fluoro-substitution on aromatic interior bond angles

All three, X-ray analysis, microwave spectroscopy and SCF-MO computation show a distorted ring in fluorobenzene. As discussed earlier (Luthe et al., 2007), this is caused by hyperconjugation of the 2p orbitals of the fluoro substituent with the aromatic π system. In chloro- and bromobenzene this effect was not observed, since the 3p and 4p orbitals are too big to result in a good overlap with the aromatic π system. The fluoro-*ipso*-bond angle is widened to 122.9(2)° (F-PBDE 3-3F) and the aligned angles are narrowed down to 117.75(13)° and 117.9(2)° (F-PBDE 3-2F, 3-3F). The other angles are just slightly affected and show the common angles of 120.2°. This observation could be partly computed. The broadening of the interior angle at the *ipso*-substitution can be simulated with a lower amplitude, but the narrowing is averaged over all other angles, which is not correct. In our study of F-PCBs (Luthe et al., 2007a), we could observe an attraction of the fluoro to the chloro substituent in F-PCB 3-3F. This appeared on the surface to be very unusual, since one might expect that chloro and fluoro substituents should display repulsive behavior towards each other. If the chlorine functions as an electron donor for the more electronegative electron acceptor fluorine, this would create a *vicinal* coupling through space. However, this was not the case with the bromo-substituent in F-PBDE 3-3F. We explain this on the basis that the overlap of the 2p and the 4p orbitals of the fluoro- and the bromo- are much less due to their different size. A more detailed study regarding this aspect is in progress.

4.5 Influence of fluoro-substitution on the torsion angles

We compared the torsion C1'-O-C1-C6(2) and C2'(6')-C1'-O-C1 and the bond C1-O-C1' angles in diphenyl ether affected by fluoro-, chloro-, bromo- and methyl- and no substituents in the *ortho*-positions, see Table 5. There we observed that in general there is a trend of alignment of computed and determined data. The strength depends on the size of the substituent, grade of substitution and the position. So there is a comparison for the torsion angles of methyldiphenyl ether (determined: 145.48°, -36.23°; computed: 141.3°, -42.1°) dibromodiphenyl ether (determined: 78.70°, -107.05°; computed: 92.1°, 92.1°) and

dimethyl ether (determined: 93.08°, -91.22°; computed: 91.9°, 91.9°) with *ortho*-substitutions on one ring, but not with the one on two rings. With four fluoro-substituents in *ortho*-positions the fit of computed and determined torsion angles is in alignment (determined: 57.71°, -127.97°; computed: 49.4°, -134.2°). Since the average distance of the ether linkage is 2.76 Å, compared with 1.48 Å in PCBs (Luthe *et al.*, 2007a) the steric interaction of the *ortho*-substituents is much weaker. Both, the ether bond and the angle of the C1-O-C1' bond attribute high flexibility to the substituted diphenyl ethers minimizing the steric interaction. Therefore the interaction must be strong enough by size of the substituent, grade and pattern of substitution to emphasise the intramolecular interaction versus energy gaining by weak intermolecular interactions in solid state, *e.g.* stacking effects and C-H(F, Br) ... π interactions. Therefore the computed values, calculated under ideal circumstances in the vacuum, differ strongly from the ones determined by X-ray for small substituents and low grade of substitution. We observed this effect as well in our series of F-PBDEs 3 and PBDE 3, where the computed and determined torsion and ether bond angles differ strongly. The steric interaction is too weak in solid state for this series to give a clear picture of the intramolecular interactions. Even that the intermolecular interactions of PBDE 3 and the F-PBDE 3 isomers are weak and only dominated by C-H(F,Br) ... π and C-H...F interactions. The interpretation of X-ray data for receptor activity of PBDEs as shown in Table 1 should be evaluated carefully against this finding and it is advisable to use computed data comprehensive for these studies. This result might be contribute to the scientific discussion around the AhR activity of PBDEs or PBDF impurities from a QSAR point of view.

4.6 Packing of the F-PBDEs 3 isomers

The intermolecular interactions for PBDE 3 and all five F-PBDE 3 isomers were dominated by weak C-H(F,Br) ... π and C-H...F interactions, whereas the F-PCBs 3 were dominated by π ... π stackings. This leads to crystal packings built up by columns which are interconnected via C-H... π interactions, C-H...F(Br) close contacts and van der Waals forces. The F-PBDEs 3-3'F and 3-4'F have very similar crystal packing interactions. The F-PBDE 3-2F isomer connects stacks into bi-layers with the F-atoms on the 'exterior' of the bi-layers.. There are no linear halo ... halo interactions, *e.g.* F...Br, as could be found for the F...Cl in F-PCBs. This is due to the big difference of the orbital sizes.

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PBDE/F-PBDE					pattern starting materials	
no.	BZ/BZL-no.	Pattern	Yield[%]	Purity [%]	phenol	bromobenzene
(3a)	PBDE 3	R1-7,9,10=H; R8=Br	59	99.5	(1a) R1-5=H	(2a) R6,7,9,10=H; R8=Br
(3b)	¹³ C ₆ -PBDE 3	R1-7,R9R10=H; R8=Br	60	99.5	(1b) R1-5=H (¹³ C)	(2a) R6,7,9,10=H; R8=Br
(3c)	F-PBDE 3-2'F	R1=F; R2,4-10=H; R3=Br	54	99.9	(1c) R1=F; R2,4,5=H; R3=Br	(2b) R6-10=H
(3d)	F-PBDE 3-2'F	R1=F; R2-7,9,10=H; R8=Br	59	99.5	(1d) R1=F; R2-5=H	(2a) R6,7,9,10=H; R8=Br
(3e)	F-PBDE 3-3'F	R1,4-10=H; R2=F; R3=Br	55	99.9	(1e) R1,4,5=H; R2=F; R3=Br	(2b) R6-10=H
(3f)	F-PBDE 3-3'F	R1,3-7,9,10=H; R2=F; R8=Br	60	99.2	(1f) R1,3-5=H; R2=F	(2a) R6,7,9,10=H; R8=Br
(3g)	F-PBDE 3-4'F	R1,2,4-7,9,10=H; R3=F; R8=Br	58	99.9	(1g) R1,2,4,5=H; R3=F	(2a) R6,7,9,10=H; R8=Br

Fig. 1.

Synthesis of the PBDE 3, ¹³C₆-PBDE 3 and F-PBDEs 3 (**3a–g**) by nucleophilic substitution of bromobenzenes (**2a–b**) and phenols (**1a–g**). For details, see Experimental section.

Fig. 2. Ellipsoid plots (50 % level) showing PBDE 3 and F-PBDEs 3: a) 4-bromodiphenyl ether (PBDE 3), b) 2-fluoro-4-bromodiphenyl ether (3-2F), c) 2'-fluoro-4-bromodiphenyl ether (3-2'F), d) 3-fluoro-4-bromodiphenyl ether (3-3F), e) 3'-fluoro-4-bromodiphenyl ether (3-3'F) and f) 4'-fluoro-4-bromodiphenyl ether (3-4'F).

(a)

(b)

(c)

(d)

Fig. 3. Stereo diagrams of unit cell contents showing intermolecular interactions (dotted lines). Atoms are shown as spheres of arbitrary size with the highest atomic number having the largest radius and the lowest the smallest. a) 2-fluoro-4-bromodiphenyl ether (3-2F), b) 2'-fluoro-4-bromodiphenyl ether (3-2'F), c) 3-fluoro-4-bromodiphenyl ether (3-3F), d) 3'-fluoro-4-bromodiphenyl ether (3-3'F), e) 4'-fluoro-4-bromodiphenyl ether (3-4'F) and f) 4-bromodiphenyl ether (PBDE 3).

Fig. 4. Changes in the ^{13}C NMR shifts, δ [ppm], by fluorine substitution relative to PBDE 3 (4-bromodiphenyl ether). ^{13}C NMR shifts indicate a change in electron density at the carbon atom. Positive values indicate increase of electron density, negative values an decrease. For more details see Experimental Section.

Fig. 5. Direct carbon-fluorine couplings, J_{CF} [Hz] in all F-PBDEs 3. Stronger couplings relates to a higher electron density in the C-F bond.

Table 1
Receptor/enzyme interactions of PBDEs. For a more complete review see Luthe et al. (2007b)

Please note that direct binding of the PBDEs themselves may not have been demonstrated, but is inferred by effect. Also note that the levels of the receptors themselves might be influenced by the PBDEs themselves.

Receptor abbreviation	Gene or function affected	PBDEs		Response and references
		Ligands		
Aryl hydrocarbon (AhR)	CYP 1A	PBDEs 3, 15, 17, 28, 47, 49, 66, 71, 75, 77, 85, 99, 100, 119, 126, 152, 153, 154, 183, 6-OH-PBDE 47 47, PBDE mixture (D-71) PBDF impurities		agonists, weak to moderate (Wang et al., 2006; Chen & Bruce, 2003; Peters et al., 2006a; Peters et al., 2006b; Germer et al., 2006;) antagonist in fish, weak (Kuiper et al., 2004) no Ah activity by PBDEs, but from PBDFs impurity (Sanders et al., 2005)
Constitutive androstane (CAR)	CYP 2B	PBDE mixtures DE-71, PBDE 79		weak (Kretschmer & Baldwin, 2005; Carlson, 1980; Sanders et al. 2005; Germer et al., 2006)
Pregnane X (PXR)	CYP 3A	PBDE mixture D-71		(Germer et al., 2006)
Peroxisome proliferator (PPAR)	CYP 4A	Ah active PBDEs and potentially PBDFs		suggested repression in analogy to PCBs (Ariyoshi et al., 1998)
Ryanodin (RyR)	Ca ²⁺ channel	Non co-planar PBDEs and OH-PBDEs		Suggested agonist in analogy to the findings in PCBs (Pessah et al., 2006)
Estrogen (ER)	Estrogen	OH-PBDE Di-OH-PBDE PBDE 99		(Kretschmer & Baldwin, 2005; Stoker et al., 2004; Meerts et al., 2001; Ceccatelli et al., 2006)
Androgen (AR)	Androgen	PBDE mixture DE-71, PBDEs 100 PBDEs 47, 99, 100, 153, 154		Suppression and inhibition (Stoker et al., 2005) competitive anti-androgenic (Stoker et al., 2005)
Progesterone (PR)	Progesterone	PBDE 99		suppression (Ceccatelli et al., 2006)
Dihydro-testosterone (DHT)	Dihydrotestosterone	PBDE 47, 100		Inhibitor transcriptional activation (Stoker et al., 2005)
Thyroid function (TH)	Thyroid hormone	OH-PBDEs PBDE 47 PBDE mixtures DE-71, 79		Agonist (Kretschmer & Baldwin, 2005; Eslami et al., 2006; Hallgren, Damerud, 2002; Zhou et al., 2002) disruptor (Kretschmer & Baldwin, 2005)
Thyroxine (T4)	Thyroxine	PBDEs 71, 73, 125		reducing serum T4 level (Kretschmer & Baldwin, 2005; Stoker et al., 2004; Hooper & McDonald, 2000; Zhou et al., 2002; Eslami et al., 2006)
Triiodothyronine (T3)		4'OH-PBDE 27		
Glucocorticoid (GR)	Glucocorticoid	MeSO ₂ -PBDE		suggested repression by competitive antagonism in analogy to MeSO ₂ -PCBs (Johansson, Nilsson & Lund, 1998)
Insulin-like growth factor (IGF)	Insulin-like growth factor	PBDE 99		agonist, weak (Ceccatelli et al., 2006)

Table 2

^{13}C chemical shifts δ [ppm] relative to TMS, the $^{13}\text{C}^{19}\text{F}$ couplings J [Hz] over n bindings of all carbons in PBDE 3 and F-PBDE 3 F congeners. Numbering is according to the BZ, or the BZL systems.

BZ/BZL no.	coupling	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
3		156.8	120.6	132.9	115.8	132.9	120.6	156.9	119.2	130.1	123.9	130.1	119.2
3-2F		143.5	154.3	120.8	116.2	128.0	122.9	157.0	117.7	130.0	123.8	130.0	117.7
3-3F	$^nJ(\text{C},\text{F})$	11.32 (n=2)	253.60 (n=1)	21.13 (n=2)	8.30 (n=3)	3.77 (n=4)	1.51 (n=3)						
		158.5	107.1	159.7	102.1	133.9	115.3	156.0	119.8	130.3	124.7	130.3	119.8
3-2F	$^nJ(\text{C},\text{F})$	9.81 (n=3)	25.66 (n=2)	247.56 (n=1)	21.13 (n=2)	1.51 (n=3)	3.77 (n=4)						
		156.8	119.0	132.8	115.7	132.8	119.0	143.3	154.0	117.4	125.6	122.3	125.0
3-3F	$^nJ(\text{C},\text{F})$							11.32 (n=2)	249.07 (n=1)	18.11 (n=2)	6.79 (n=3)	0.75 (n=4)	3.77 (n=3)
		155.7	121.7	133.7	116.7	133.7	121.7	158.5	106.4	163.7	110.5	130.8	114.2
3-4F	$^nJ(\text{C},\text{F})$							10.57 (n=3)	24.91 (n=2)	247.56 (n=1)	21.13 (n=2)	9.81 (n=3)	3.02 (n=4)
		157.1	120.0	132.9	115.7	132.9	120.0	152.5	120.9	116.7	159.2	116.7	120.9
	$^nJ(\text{C},\text{F})$							2.26 (n=4)	8.30 (n=3)	23.40 (n=2)	242.28 (n=1)	23.40 (n=2)	8.30 (n=3)

Table 3

Bond lengths [Å], bond angles [deg] and torsion angles [deg] measured by X-ray compared to computed values by semi empirical self consistent field molecular orbital calculation (italics).

Structure specifications	PBDE 3 and F-PBDEs 3						
	3	3-2F	3-2'F	3-3F	3-3'F	3-4'F	
Br-C4	1.896(3) <i>1.891</i>	1.8965(17) <i>1.890</i>	1.903(2) <i>1.891</i>	1.880(3) <i>1.891</i>	1.9041(19) <i>1.891</i>	1.897(3) <i>1.890</i>	
F-C	-	1.3488(13) <i>1.341</i>	1.347(2) <i>1.341</i>	1.357(3) <i>1.341</i>	1.362(2) <i>1.340</i>	1.354(3) <i>1.339</i>	
C1-C2	1.401(4) <i>1.398</i>	1.3782(14) <i>1.396</i>	1.384(3) <i>1.398</i>	1.392(3) <i>1.396</i>	1.382(3) <i>1.398</i>	1.383(4) <i>1.398</i>	
C1-C6	1.396(3) <i>1.396</i>	1.385(2) <i>1.396</i>	1.379(3) <i>1.396</i>	1.400(4) <i>1.399</i>	1.379(3) <i>1.396</i>	1.379(4) <i>1.396</i>	
C2-C3	1.377(4) <i>1.397</i>	1.3827(14) <i>1.391</i>	1.381(3) <i>1.397</i>	1.377(4) <i>1.392</i>	1.386(3) <i>1.396</i>	1.392(4) <i>1.396</i>	
C3-C4	1.389(3) <i>1.395</i>	1.383(2) <i>1.393</i>	1.383(3) <i>1.395</i>	1.374(4) <i>1.394</i>	1.382(3) <i>1.395</i>	1.390(4) <i>1.395</i>	
C4-C5	1.393(4) <i>1.395</i>	1.382(3) <i>1.397</i>	1.378(3) <i>1.394</i>	1.397(4) <i>1.395</i>	1.376(3) <i>1.395</i>	1.374(4) <i>1.395</i>	
C5-C6	1.385(4) <i>1.396</i>	1.391(3) <i>1.398</i>	1.392(3) <i>1.396</i>	1.376(4) <i>1.398</i>	1.384(3) <i>1.396</i>	1.386(4) <i>1.396</i>	
C1'-C6'	1.396(3) <i>1.397</i>	1.378(2) <i>1.398</i>	1.380(3) <i>1.397</i>	1.380(4) <i>1.397</i>	1.384(3) <i>1.399</i>	1.388(4) <i>1.399</i>	
C1'-C2'	1.386(4) <i>1.395</i>	1.385(2) <i>1.395</i>	1.381(3) <i>1.395</i>	1.373(4) <i>1.395</i>	1.391(3) <i>1.394</i>	1.381(4) <i>1.397</i>	
C2'-C3'	1.392(4) <i>1.395</i>	1.389(3) <i>1.395</i>	1.375(3) <i>1.392</i>	1.396(5) <i>1.395</i>	1.377(3) <i>1.390</i>	1.385(4) <i>1.395</i>	
C3'-C4'	1.395(4) <i>1.395</i>	1.389(3) <i>1.395</i>	1.383(3) <i>1.396</i>	1.379(5) <i>1.395</i>	1.371(3) <i>1.392</i>	1.376(4) <i>1.391</i>	
C4'-C5'	1.389(4) <i>1.396</i>	1.376(3) <i>1.395</i>	1.385(4) <i>1.397</i>	1.382(5) <i>1.396</i>	1.385(3) <i>1.395</i>	1.376(4) <i>1.391</i>	
C5'-C6'	1.388(4) <i>1.395</i>	1.395(2) <i>1.390</i>	1.390(3) <i>1.385</i>	1.385(4) <i>1.397</i>	1.397(3) <i>1.395</i>	1.395(4) <i>1.395</i>	

Structure specifications		PBDE 3 and F-PBDEs 3					
bond lengths [Å]		3	3-2F	3-2F	3-3F	3-3F	3-4F
C1-O		1.396	1.396	1.397	1.395	1.397	1.396
		1.376(3)	1.3889(18)	1.386(2)	1.364(3)	1.393(2)	1.395(4)
		1.376	1.375	1.377	1.377	1.376	1.376
C1'-O		1.386(3)	1.400(2)	1.389(2)	1.410(3)	1.384(3)	1.384(3)
		1.376	1.376	1.376	1.376	1.377	1.377
bond angles [deg]							
C2-C1-C6		120.1(2)	119.24(13)	120.87(18)	119.5(2)	121.24(19)	121.3(3)
		120.3	119.7	120.3	120.3	120.3	120.3
C6-C1-O		124.4(2)	120.80(14)	123.96(17)	126.3(2)	118.8(2)	121.1(3)
		116.9	117.4	116.7	116.7	117.1	117.0
			122.6	117.0	122.8		
C2-C1-O		115.4(2)	119.93(13)	115.16(17)	114.2(2)	119.88(18)	117.5(3)
		122.8	122.7	123.0	123.0	122.5	122.6
C3-C2-C1		120.2(2)	121.95(10)	119.80(19)	118.8(2)	119.45(19)	119.3(3)
		119.8	120.7	119.8	119.3	119.8	119.8
			121.0		119.5		
C2-C3-C4		119.5(2)	117.75(13)	119.43(18)	122.9(2)	119.0(2)	118.8(3)
		119.7	119.2	119.7	120.7	119.7	119.7
C5-C4-C3		120.8(2)	121.95(16)	120.92(19)	117.9(2)	121.63(19)	121.7(3)
		120.6	120.7	120.6	119.9	120.6	120.6
C4-C5-C6		119.9(2)	118.88(17)	119.7(2)	120.9(2)	119.29(19)	119.3(3)
		119.6	119.8	119.6	119.7	119.7	119.7
C5-C6-C1		119.5(2)	120.23(16)	119.29(18)	120.1(2)	119.4(2)	119.6(3)
		119.9	119.8	120.0	120.1	119.9	119.9
C6'-C1'-C2'		120.8(2)	121.65(15)	119.11(19)	122.1(3)	121.35(19)	120.9(3)
		120.2	120.2	119.7	120.3	120.3	120.4
C6'-C1'-O		122.8(2)	122.46(16)	119.48(18)	121.8(3)	123.73(18)	122.7(3)
		122.6	123.1	117.3	122.3	116.8	122.6
			122.4	117.9		122.7	

Structure specifications		PBDE 3 and F-PBDEs 3						
bond lengths [Å]		3	3-2F	3-2F	3-3F	3-3F	3-3F	3-4F
C2'-C1'-O		116.1(2)	115.88(16)	121.24(19)	115.8(3)	114.91(17)	116.3(3)	
		117.1	116.7	122.8	117.2	122.8	116.9	
C3'-C2'-C1'			117.2	122.4		117.0		
		119.5(2)	118.77(16)	121.9(2)	118.6(3)	117.2(2)	120.1(3)	
C4'-C3'-C2'		119.9	120.0	120.5	119.8	119.1	119.8	
		120.5(2)	120.46(16)	118.8(2)	120.2(3)	124.0(2)	118.7(3)	
C3'-C4'-C5'		120.0	120.0	119.7	120.0	121.2	119.5	
		119.1(3)	119.67(15)	120.2(2)	120.1(2)	117.3(2)	122.2(3)	
C4'-C5'-C6'		120.1	120.1	120.0	120.1	119.6	121.1	
		121.2(2)	120.77(16)	120.2(2)	120.4(3)	121.4(2)	119.1(3)	
C5'-C6'-C1'		120.0	120.1	120.2	120.0	119.8	119.6	
		118.9(2)	118.67(16)	119.8(2)	118.6(3)	118.7(2)	119.0(3)	
F-C-C		119.7	119.8	119.8	119.7	120.1	119.7	
			F-C2-C1	F-C2'-C1'	F-C3-C2	F-C3'-C2'	F-C4'-C3'	
F-C-C			118.85(11)	118.56(19)	117.7(2)	117.15(19)	119.1(3)	
			120.7	120.8	118.6	119.4	119.4	
Br-C4-C3			F-C2-C3	F-C2'-C3'	F-C3-C4	F-C3'-C4'	F-C4'-C5'	
			119.19(12)	119.52(19)	119.4(2)	118.82(19)	118.7(3)	
Br-C4-C5			118.7	118.8	120.7	119.4	119.4	
		120.3(2)	119.12(12)	119.85(15)	121.0(2)	119.35(16)	119.4(2)	
C1'-O-C1-C6(2)		119.7	119.7	119.7	120.6	119.7	119.7	
		118.90(18)	118.92(13)	119.22(16)	121.1(2)	119.01(15)	118.8(2)	
		119.7	119.7	119.7	119.4	119.7	119.7	
		-25.9(3)	-102.7(2)	-4.1(3)	172.2(2)	94.9(2)	55.9(4)	
		158.7(2)	79.5(3)	175.13(18)	-8.9(4)	-88.1(2)	-127.9(3)	
			71(2) (C")					
			-109(2) (C")					
		-47.3	(-58.8)	-45.2	(-44.8)	-50.2	-49.0	
		136.3	124.8	138.3	138.7	133.4	134.6	
			-47.3	-49.6	-46.1	-49.2		

Structure specifications		PBDE 3 and F-PBDEs 3					
bond lengths [Å]		3	3-2F	3-2'F	3-3F	3-3'F	3-4'F
C2(6)-C1'-O-C1			136.2	133.9	(137.5)	134.4	
		142.6(2)	21.3(4)	-108.7(2)	130.0(3)	6.6(3)	-154.5(3)
		-42.9(3)	-160.1(3)	76.1(3)	-55.2(4)	-173.55(18)	29.2(4)
			28(5) (C ^m)				
			-157(4) (C ^m)				
C1-O-C1'		-49.6	-44.9	-57.2	-52.4	-47.0	-48.3
		134.0	138.7	(126.4)	131.1	(136.5)	135.2
			-52.1	(-50.0)	-51.4	(-48.3)	
			131.3	133.6	132.1	135.3	
		121.09(18)	115.96(12)	118.93(15)	120.9(2)	118.05(15)	118.1(2)
		117.3	117.0	117.1	117.3	117.3	117.3

Table 4

Experimental details for PBDE 3 and the five F-PBDE 3 isomers.

Experim. details	PBDE 3 and F-PBDEs 3				
	3	3-2F	3-2F	3-3F	3-4F
Crystal data					
Chemical formula	C ₁₂ H ₉ BrO	C ₁₂ H ₉ BrFO	C ₁₂ H ₈ BrFO	C ₁₂ H ₈ BrFO	C ₁₂ H ₈ BrFO
<i>M_r</i>	249.10	267.09	267.09	267.09	267.09
Cell setting, space group	Monoclinic, <i>Cc</i>	Orthorhombic, <i>P2₁2₁2₁</i>	Monoclinic, <i>C2/c</i>	Orthorhombic, <i>Pca2₁</i>	Monoclinic, <i>Cc</i>
Temperature (K)	150 (2)	150 (2)	150 (2)	150 (2)	150 (2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	23.628 (3), 7.5461 (9), 5.8066 (7)	5.8708 (7), 9.0974 (10), 19.396 (2)	23.752 (3), 4.3622 (5), 21.357 (3)	14.9203 (16), 11.6841 (13), 5.8727 (7)	5.9477 (7), 9.0635 (10), 19.481 (2)
<i>α</i> , <i>β</i> , <i>γ</i> (°)	90.00, 97.919 (5), 90.00	90.00, 90.00, 90.00	90.00, 110.762 (5), 90.00	90.00, 90.00, 90.00	90.00, 94.030 (5), 90.00
<i>V</i> (Å ³)	1025.4 (2)	1035.9 (2)	2069.1 (5)	1023.8 (2)	1034.3 (2)
<i>Z</i>	4	4	8	4	4
<i>D_x</i> (Mg m ⁻³)	1.614	1.713	1.715	1.733	1.715
Radiation type	Mo <i>Kα</i>	Mo <i>Kα</i>	Mo <i>Kα</i>	Mo <i>Kα</i>	Mo <i>Kα</i>
<i>μ</i> (mm ⁻¹)	3.97	3.95	3.95	4.00	3.96
Crystal form, colour	Plate, colorless	Irregular prism, colorless	Plate, colorless	Plate, colorless	Plate, colorless
Crystal size (mm)	0.36 × 0.24 × 0.07	0.34 × 0.31 × 0.19	0.19 × 0.16 × 0.06	0.45 × 0.44 × 0.08	0.38 × 0.08 × 0.07
Melting point (°C)	17	5	-10	-5	20
Data collection					
Diffractometer	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD
Data collection method	CCD phi and ω scans	CCD phi and ω scans	CCD phi and ω scans	CCD phi and ω scans	CCD phi and ω scans
Absorption correction	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)
<i>T_{min}</i>	0.329	0.315	0.520	0.267	0.355
<i>T_{max}</i>	0.769	0.473	0.797	0.741	0.891
No. of measured, independent and observed reflections	11708, 2310, 2216	21969, 2373, 2293	19505, 2367, 2029	15796, 2327, 2190	21638, 2390, 1891
Criterion for observed reflections	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)	<i>I</i> > 2σ(<i>I</i>)

Experim. details	PBDE 3 and F-PBDEs 3				
	3	3-2F	3-2'F	3-3F	3-4'F
R_{int}	0.027	0.022	0.039	0.051	0.022
θ_{max} (°)	27.4	27.5	27.5	27.4	27.5
Refinement					
Refinement on F^2		F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.024, 0.063, 1.08	0.016, 0.038, 1.03	0.028, 0.070, 1.05	0.029, 0.077, 1.12	0.027, 0.065, 1.02
No. of reflections	2310 reflections	2373 reflections	2367 reflections	2327 reflections	2289 reflections
No. of parameters	127	170	136	136	136
H-atom treatment	Constrained to parent site	Constrained to parent site	Constrained to parent site	Constrained to parent site	Constrained to parent site
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0391P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0168P)^2 + 0.2751P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0358P)^2 + 1.6942P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.1087P]$ where $P = (F_o^2 + 2F_c^2)/3$	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0435P)^2 + 0.0519P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\text{max}}$	0.001	0.002	0.001	<0.0001	0.001
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.28, -0.36	0.17, -0.20	0.67, -0.46	0.44, -0.32	0.38, -0.73
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881	Flack H D (1983), Acta Cryst. A39, 876-881	Flack H D (1983), Acta Cryst. A39, 876-881	Flack H D (1983), Acta Cryst. A39, 876-881	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.010 (8)	-0.003 (7)		0.021 (11)	0.013 (10)

Table 5

Torsion angles [$^{\circ}$] ranges of mono-, di-, tri- and tetra-substituted diphenyl ethers by fluorine, chlorine, bromine and methyl in the *ortho*-positions X_i ($i = 1-4$). The torsion angles are determined by averaging of structures found in the Cambridge Structural Database and computed by semi empirical self-consistent field molecular orbital calculation (*italics*). Note: values in parentheses are number of structures found with the particular *ortho*-substitution pattern.

Torsion angles and bond angles of x _i substituted diphenyl ethers												
C1'-O-Cl-C6				C2'-Cl'-O-Cl				Cl-O-Cl'				
Substitution pattern												
None	fluoro	chloro	bromo	methyl	fluoro	chloro	bromo	methyl	fluoro	chloro	bromo	methyl
	4.85				4.85				118.27			
	-175.02				-175.02							
	48.2				48.2				117.3			
X ₁	-135.4				-135.4							
	11.25	1.86	96.69	113.16	78.03	99.10	8.45	145.48	119.77	119.03	117.93	117.82
	-48.1	-55.7	-56.8	-56.5	-108.38	-85.13	-172.72	-36.23	117.1	117.0	117.1	117.3
X ₁ X ₂												
	105.21	105.90	78.70	93.08	163.67	172.32	26.16	179.22	118.57	119.38	117.32	118.65
	-80.55	-78.56	-107.05	-91.22	-18.23	-10.32	-155.55	-0.13				
	123.3	101.4	92.1	91.9	134.14	163.4	0.0	0.0	116.4	117.9	118.3	118.2
X ₁ X ₃	-60.4	-82.7	-92.1	-91.9	-9.4	-18.0	180.0	180.0				
	--	-34.19	27.78	--	--	-34.19	50.0	--	--	119.94	118.58	--
	-131.2	-128.1	-129.8	-128.7	52.5	56.1	54.5	55.6	116.8	118.4	119.2	118.6
	-131.2	-128.1	-129.8	-128.7	52.5	56.1	54.5	55.6

Torsion angles and bond angles of x _i substituted diphenyl ethers											
	Cl'-O-Cl-C6				C2'-Cl'-O-Cl				Cl-O-Cl'			
	Substitution pattern											
	fluoro	chloro	bromo	methyl	fluoro	chloro	bromo	methyl	fluoro	chloro	bromo	methyl
X ₁ X ₂ X ₃	--	100.32	77.97	--	--	-5.09	26.30	--	--	118.81	115.67	--
		-83.26	-104.58									
	53.9	57.7	56.8	54.0	46.2	49.7	48.7	50.6	117.3	119.0	119.8	119.4
	-129.8	-126.8	-127.9	-130.5								
X ₁ X ₂ X ₃ X ₄	57.71	--	146.41	--	57.71	--	146.41	--	117.69	--	120.94	--
	-127.71		-38.96		-127.97		-38.96					
	49.4	53.1	52.1	50.6	49.4	53.1	52.1	50.6	117.4	119.5	120.4	120.1
	-134.2	-131.0	-132.2	-133.7	-134.2	-131.0	-132.2	-133.7				