

Synthesis and characterization of highly polybrominated diphenyl ethers

Daniel Teclechiel



Stockholm
University

Department of Environmental Chemistry
Stockholm University
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To my family:
Abby, Zion, Jazzy and Gabe

Abstract

Polybrominated diphenyl ethers (PBDEs) make up an important class of brominated flame retardants. The present production is mainly concentrated to DecaBDE but until recently also a significant production of PentaBDE and OctaBDE took place, leaving us with a large number of different PBDE congeners. The PBDEs have become widespread pollutants abiotically and in biota, particularly in high trophic level wildlife and in humans. Accordingly, pure authentic reference standards have been required to promote high quality exposure assessments of wildlife and humans and analysis of abiotic matrices, to study both chemical and physical properties of the PBDEs and to allow toxicological studies. The objective of this thesis was to develop methods for synthesis of polybrominated diphenyl ether (PBDE) congeners and to characterize them. Further, some octabrominated DEs were determined with x-ray crystallography. Main focus has been to prepare highly brominated PBDE congeners, i.e. PBDEs substituted with six to nine bromine atoms.

A total number of twenty-three PBDE congeners were synthesized via reduction of decabromodiphenyl ether receiving nonaBDEs; perbromination and bromination of mono- and diaminodiphenyl ethers followed by diazotization of the amino group(s) and reduction of the diazonium ion(s) receiving octaBDEs and nonaBDEs; selective bromination of diaminodiphenyl ethers followed by diazotization of the amino groups and insertion of bromine receiving hexaBDEs and heptaBDEs; bromination of the latter PBDEs giving octaBDEs; and an improved coupling of symmetrical diphenyliodonium salts with bromophenols yielding tetraBDEs to octaBDEs. To enable these compounds to be synthesized three hexabromodiphenyl iodonium salts were prepared: 2,2',3,3',4,4'-, 2,2',4,4',5,5'- and 2,2',4,4',6,6'-hexabromodiphenyliodonium salts. These iodonium salts are described for the first time which made it possible to synthesize PBDE congeners with 2,3,4-, 2,4,5- and 2,4,6-tribromo substitution in the phenyl rings originating from the diphenyliodonium salts. Among the PBDE congeners 18 are synthesized for the first time. The thesis includes an improved methodology for synthesis of polybromodiphenyl iodonium salts which is based on improved solubilization of both one of the reactants and the product formed. The present work on PBDE synthesis adds useful methods for synthesis of the most highly brominated diphenyl ether congeners.

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Abbreviations

CMR	Carcinogenic, mutagenic and reprotoxic
DDT	2,2-Bis(4-chlorophenyl)-1,1,1-trichloroethane
Drins	Aldrin, Dieldrin and Endrin
PCBs	Polychlorinated biphenyls
PCDDs	Polychlorinated dibenzo- <i>p</i> -dioxins
PCDFs	Polychlorinated dibenzofurans
POPs	Persistent Organic Pollutants
IFCS	International Form on Chemical Safety
UNEP	United Nations Environment Programme
HCB	Hexachlorobenzene
PentaBDE	Pentabromodiphenyl ether
OctaBDE	Octabromodiphenyl ether
HCH	Hexachlorohexane
PCAs	Polychlorinated alkanes
PFOS	Perfluorooctane sulfonate
BFRs	Brominated flame retardants
TBBPA	Tetrabromobisphenol A
PBDEs	Polybrominated diphenyl ethers
HBCDD	Hexabromocyclododecane
OH-PBDEs	Hydroxylated polybrominated diphenyl ethers
PBT	Persistent, bioaccumulative and toxic
DecaBDE	Decabromodiphenyl ether
SAICM	Strategic Approach to International Chemicals Management
NIPs	National Implementation Plans
PCQs	Polychlorinated quatrophenyls
PBBs	Polybrominated biphenyls
FRs	Flame retardants
EU	European Union
BSEF	Bromine Science and Environmental Forum
ABS	Acrylonitrile-butadiene-styrene
Log K_{OW}	Octanol-water partition coefficient
BDE	Brominated diphenyl ether
Log V_p	Subcooled liquid vapor pressure
Log K_{OA}	Octanol-Air partition coefficient
ESA	Electrophilic aromatic substitution
S_NAr	Aromatic nucleophilic substitution reaction
HPLC	High performance liquid chromatography
GC-MS	Gas chromatography-mass spectrometry
EI	Electron ionization
ECNI	Electron capture negative ionization

List of papers

This thesis is based on the following publications, which will be referred to in the text by their respective Roman numerals. The two published articles are reproduced here with the permission of the publisher. Certain unpublished results are also presented.

- Paper I** **Methods for synthesis of nonabromodiphenyl ethers and a chloro-nonabromodiphenyl ether.**
Anna Christiansson, **Daniel Teclechiel**, Johan Eriksson, Åke Bergman, Göran Marsh. *Chemosphere* **2006**, 63, 562-569
- Paper II** **Synthesis of octabrominated diphenyl ethers from aminodiphenyl ethers**
Daniel Teclechiel, Anna Christiansson, Åke Bergman, Göran Marsh. *Environ Sci Technol.* **2007**, 41, 7459-7463
- Paper III** **Synthesis of polybrominated diphenyl ethers (PBDEs) via symmetrical tetra- and hexabrominated diphenyliodonium salts.**
Daniel Teclechiel, Maria Sundström and Göran Marsh. Manuscript.
- Paper IV** **Molecular and supramolecular structure of**
2,2',3,3',4,5,5',6-OctabromoDiphenyl ether (BDE-198);
2,2',3,3',4,5',6,6'-OctabromoDiphenyl ether (BDE-201);
2,2',3,3',5,5',6,6'-OctabromoDiphenyl ether (BDE-202);
2,2',3,4,4',5,5',6-OctabromoDiphenyl ether (BDE-203) and
2,2',3,4,4',5,6,6'-OctabromoDiphenyl ether (BDE-204).
Daniel Teclechiel and Lars Eriksson. Manuscript.

1 Introduction and Aim

People, as professionals and individuals, handle or use very large and an increasing number of synthetic chemicals, a development that has been going on for a long period of time. More than 30 million chemicals have been prepared and/or characterized up to now to which, mankind is estimated to commercially produce around 240,000 chemicals. The most extensive production is limited to 20-30,000 compounds (1). Several of these chemicals still have a toxic profile that is unknown to us, while others are of intermediate toxicity, or occasionally they are of high toxicity, causing cancer, being mutagenic or reprotoxic (the so called CMR compounds). Others may damage the nervous system, the immune system or interfere with the endocrine system and functions in human and wildlife. Still, humans have benefited enormously from the chemical revolution over the last century, not least by e.g. killing crop pests, thus increasing production and to fight insect transferred diseases through improved insect control via the use of pesticides to better control deadly diseases like malaria. Large scale uses of pesticides to control vector diseases and in agriculture started after World War II. Quality of life has been improved through use of better techniques in industry, better transportation of materials and goods and all areas where there is room for further improvements in techniques by application of new chemicals.

However, the use of certain chemicals has lead to real major environmental problems, as first observed for some pesticides such as methyl mercury, DDT and “Drins”. The negative effects in agro-ecosystems, in wildlife and on human health, were first observed in the 1950s (2). Subsequently, during the 1960’s other chemicals or classes of chemicals were identified as environmental contaminants of concern, such as polychlorinated biphenyls (PCBs) (3-5), several organochlorine, nitrophenol pesticides (6) and hexachlorobenzene (7,8) . During the next decade the polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDDs/PCDFs) were identified as environmental pollutants of very high toxicity (9). In 2001 twelve of these contaminants were included in the well known Stockholm convention on Persistent Organic Pollutants (POPs) (10). POPs are chemicals that persist in the environment, accumulate in fatty tissues, are toxic and undergo long range transport (10). In 1997 the International Forum on Chemical Safety (IFCS) recommended twelve POPs to reduce the risks to human health and the environment to the UNEP Governing Council. The twelve POPs are listed in Table 1.1. In May

2001 the world's governments met in Stockholm, Sweden, to restrict and ultimately decide to stop production, use, release and storage of the 12 toxic POPs.

Table 1.1. Names and major applications of the twelve persistent organic pollutants included in the Stockholm Convention, 2001.

Name	Uses
DDT	For protection against malaria, typhus and other diseases spread by insects. General pesticide use.
Chlordane	To control termites and broad spectrum insecticide in a range of agricultural crops.
Aldrin	Pesticide applied to kill termites, grasshoppers and insect pests.
Dieldrin	Used to control termites and textile pests and broad spectrum insecticide on a range of agricultural soils.
Endrin	Insecticide for cotton and grain leaves and to control mice, voles and other rodents.
Heptachlor	Used to kill soil insects and termites and also for insects threatening cotton harvests, grasshoppers and for malaria control.
Mirex	Used to control fire ants and other types of ants and termites. It has been used as a flame retardant in plastics, rubber and electrical goods.
Toxaphene	Is used as insecticide for cotton, cereal grains, fruits, nuts and vegetables. Also been used to control ticks and mites in livestock.
Polychlorinated biphenyls (PCBs)	Main applications are as oil in transformers and capacitors. PCB has been used as a heat exchange medium and as additives in paint, carbonless copy paper and in sealants used for large constructions.
Polychlorinated dibenzo- <i>p</i> -dioxins (PCDDs)	PCDDs are by-products from industrial processes and as such present in certain chemical products. The dioxins are unintentionally formed due to incomplete combustion of waste, in automobile exhaust and in tobacco smoke. They are present in wood and coal smoke unless highly purified. By-products in some pesticides.
Polychlorinated dibenzofurans (PCDFs)	PCDFs are produced unintentionally due to incomplete combustion from a very large number of industrial processes. They are also formed during PCB manufacture and use of PCBs at high temperatures.
Hexachlorobenzene (HCB)	Applied to kill fungi that affected food crops. HCB is also an abundant by-product during manufacture of chemicals and element refining, e.g. in production of manganese.

The Stockholm Convention on Persistent Organic Pollutants entered into force and became an international law by May 17, 2004. In April 2005 over 90 countries had ratified the convention and hopefully an additional number of other countries will adopt the convention in the near future (10).

POPs are indeed a world wide problem because of their inherent properties. Even though POPs are well known in the industrialized world, the availability of information on production, import, export and uses of POPs is very poor in particular on continents in transition, such as Africa, South America and in

most countries in Asia. Even chemical analytical data for both the general environment and for human exposure are rare in these less developed parts of the world (11). The problem is becoming even more pronounced by the illegal use of POPs that may take place in these areas, particularly in the transfer of POPs and materials containing POPs from industrialized countries to those in transition. The lack of adequate resources in these countries, the lack of information on legislative measures on chemicals to the general population and unscrupulous local pesticide dealers still make these chemicals problematic. Some of the countries under transition have exceptions on the use of chemicals regulated by the Stockholm convention, e.g. some African countries may use DDT for combating malaria. Although alternative pesticides are available, they are often too expensive to find a general use. Another limiting factor may be lack of knowledge about using these alternatives. Accordingly, education is the key to improve knowledge about chemicals (10). Analytic data have shown that DDT is recently used to fight malaria mosquitoes in South Africa (12-14). The reason for this use is an estimated death of one to two million people due to malaria each year. In a rather recent study, breast milk samples were collected from April-November in 2004 in South Africa. The study showed high levels of DDT in breast milk compared to e.g. milk from Swedish mothers, a country where DDT was banned more than three decades ago. The high DDT levels in the breast milk from South Africa is interpreted as an ongoing use of DDT in that country (12,14).

The next set of POPs is knocking on the door to be added to the twelve current POPs on the present list of such compounds or classes of compounds. The new set of chemicals are listed and presented shortly in Table 1.2. It is notable that the majority of these chemicals are industrial chemicals, not pesticides.

Table 1.2. Chemicals proposed to be included in the list of POPs according to the Stockholm convention.

Name	Uses
PentaBDE and OctaBDE	These two products are commercial polybrominated diphenyl ether mixtures used as flame retardants in polymers and textiles.
α -HCH, β -HCH, γ -HCH	γ -HCH (Lindane) is a common pesticide while the other HCHs are by-products in technical production of the pesticide.
Chlordecon	An organochlorine pesticide that is chemically similar to mirex.
Short chain chlorinated paraffins (CPs) or polychlorinated alkanes (PCAs)	High temperature lubricants, cutting fluid for metals, plasticizers, flame retardants, additives in paints, rubber and sealants.
Hexabromobiphenyl	Common persistent isomers of polybrominated biphenyls (PBBs) used in the past. PBBs were applied as a flame retardant in synthetic fibers and plastics.
Pentachlorobenzene	To make pentachloronitrobenzene, a fungicide and fire retardant. A degradation product of hexachlorobenzene.
Perfluorooctane sulfonate (PFOS)	A fully fluorinated and highly acidic C8 alkyl sulfonic acid. PFOS is used in a wide variety of industrial applications and products as a surface active compound.

Brominated flame retardants (BFRs) have been used for decades to reduce risks of fire in commercial products and goods. The production of BFRs increased with decreased costs for bromine in the latter part of the 1970's. The major classes of BFRs are tetrabromobisphenol A and derivatives, polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) (15,16). The persistent PBDE congeners have reached similar concentrations as the persistent PCB congeners in at least some environmental samples and occasionally even higher than those of PCBs (17-19). As we humans are consuming products with BFRs added, we will contribute to future contamination of BFRs in our environment. The industrialized countries dump 50-80% of their electronic waste (e-waste) in the developing countries like China, India, Pakistan, Vietnam, the Philippines and in West Africa, because of their cheap labor cost and lack of stringent environment regulations (20,21). Some countries do regulate handling of e-waste but much more has to be done. Possibly the deliberate handling of waste in developing countries may influence exposure of PBDEs, e.g as seen in children and individuals working at a waste disposal site in Managua, the capital of Nicaragua. The children working and living there showed very high levels of medium brominated diphenyl ethers in their blood (19). Those children that had the highest PBDE levels also had high levels of hydroxylated metabolites (OH-PBDEs) (19). The PBDE metabolites were found to bioaccumulate in

human serum similar to hydroxylated metabolites of PCBs (22). PentaBDE and OctaBDE have been suggested as additions to the POPs list based on their PBT characteristics. Independent of the fact that DecaBDE can undergo both photolysis and reductions to yield lower brominated diphenyl ether congeners, DecaBDE is not suggested for inclusion in the list of emerging POPs (Table 1.2). DeacBDE is currently dominating the market while the PentaBDE and OctaBDE mixtures were banned within EU 2004 (23). A voluntary halt in production by the sole U.S. producer (24) was introduced on December 31, 2004. The present thesis will focus on synthesis of PBDEs and in particular the highly brominated diphenyl ethers.

Aim

The aim of this thesis was to develop methods for the synthesis of authentic individual PBDE congeners and make them available as standards for analytical, toxicological and stability/reactivity studies. These studies will form the basis of risk assessment and risk management of PBDEs. Also included in the aim was to characterize the PBDE congeners which were synthesized. The primarily highly brominated PBDE congeners which are important for the assessment of DecaBDE impact on environment and health.

The work pursued herein and in related studies should hopefully also have an impact for the work on POPs in developing countries. A work that is presently directed through Strategic Approach to International Chemicals Management (SAICM) (25). Eritrea, from where I descend, adopted the Stockholm Convention on Persistent Organic Pollutants in 2005, but no information about the use, or import/export and production of those chemical is available to the public and nothing has to my knowledge hitherto been submitted to National Implementation Plan (NIPs), pursuant to the article 7(b) of the Stockholm Convention. The deadline for submission of the NIPs was June 8, 2007 (10). Eritrea is not the only country that has missed the deadline for submission. However, the future is here, knowledge and tools are available for improvements also in these countries.

2 Background

2.1 Flame retardants (FRs)

In the 1960's PCBs and DDT were main environmental contaminants, especially after a PCB tragedy, known as the Yusho incident that occurred in the Fukuoka region in Japan. This was an accidental PCB contamination of

commercially produced rice oil, an oil that reached the market place leaving approximately two thousand individuals intoxicated (4,26). The intoxicated people developed severe chloracne, pigmentation changes and respiratory distress. After some time it was discovered that the PCB containing oil also contained polychlorinated dibenzofurans (PCDFs) and quatrophenylys (PCQs) (26). The PCDFs and PCQs were formed from PCBs subjected to the high temperatures when applied as a heat transfer medium in the process manufacturing the rice oil. Five years after the Yusho incident, 1973, polybrominated biphenyls (PBBs), the brominated analogue to PCBs, caused a major tragedy for farmers in Michigan, U.S.A. (27,28). This incident was caused by a mix up of bags containing the brominated flame retardant (BFR), Firemaster BP-6, instead of magnesium oxide to be used as a cattle feed additive. As a result numerous farmers in Michigan State fed their animals with the PBBs leading to the intoxication of over a million livestock. A total 30 000 cattle had to be slaughtered, 6000 pigs, 1500 sheep and 1.5 million chickens with symptoms of weight loss, decreased milk production, excessive salivation, diarrhea, effects on the heart function and many other symptoms were observed among the intoxicated animals (29). The mix up of the BFR and the magnesium oxide also led to the withdrawal of dairy products such as cheese, butter, milk and eggs (29). This accident lead to an investigation of BFRs that was in use at the time being. In 1979 DeCarlo et al. identified brominated diphenyl ethers in non-biological samples and in biota from New Jersey (U.S.A.) close to a bromine manufacturing facility (30). Also decabrominated diphenyl ether (decaBDE or BDE-209) was identified in environmental samples and in human hair from the surrounding of a BFR industry in Arkansas (30). However, two Swedish scientists were active earlier than that doing research in the BFR field. Sundström et al. made studies particularly oriented not only towards PBBs (31,32) but also in relation to polybrominated diphenyl ethers (PBDEs) (33). Norström et al. made a more general approach on BFRs as early as 1976 and synthesized some PBDE congeners at this point (34). In 1981 came the first article reporting on high concentrations of PBDEs in fish caught in the river Viskan, close to the west coast in southern Sweden (35). The area where the PBDE contaminated fish (pike) was sampled was in the heart of Swedish textile industry at the time. These are the events that formed the basis for future research in the BFR area in Sweden and worldwide. The history is more extensively described by Bergman in a recent review on the development of BFR research and as a topic of environmental and health concern (36).

Flame retardants are chemicals that reduce the flammability of materials. Fire is one of mankind's biggest fears when it comes to risks of life and property

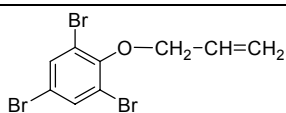
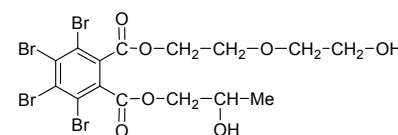
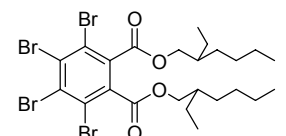
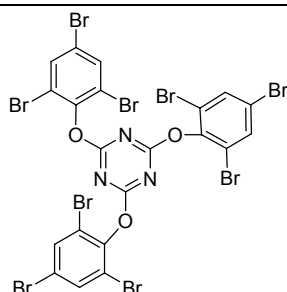
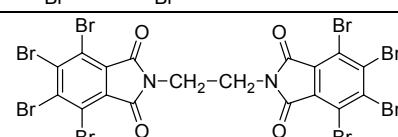
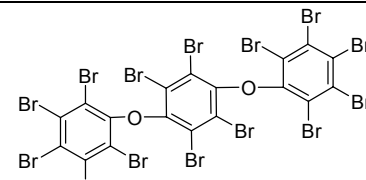
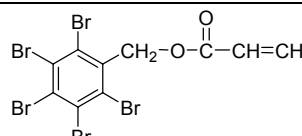
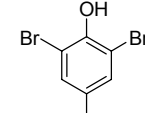
destruction. For these reasons, humans have tried to protect themselves and their property from fire. One innovative way of doing that is to use flame retardants (FRs) in materials and goods. It is not a new invention to apply chemicals as FRs; it actually goes back to around 450 BC, when the Egyptians used alum to reduce the flammability of wood, to which later the Romans used a mixture of alum and vinegar (15). Today FRs is a vast group of chemicals with hundreds of products available on the market; products that may be divided into groups of inorganic, organohalogen, organophosphorous and nitrogen-based organic flame retardants which account for 50%, 25%, 20% and approximately 5% of the annual commercial production, respectively (15,16). The main inorganic flame retardants are aluminum trioxide, magnesium hydroxide, ammonium polyphosphate and red phosphorus. The halogenated organic flame retardants are divided into three classes: aromatic, aliphatic and cycloaliphatic compounds. Brominated and chlorinated compounds are the only halogen chemicals having commercial significance as flame retardants. The reasons behind this is that fluorinated compounds are far too stable and decompose at much higher temperatures than the organic matters that burns. The reverse is true for iodinated organic compounds decomposing at too low temperatures (16). There are many different BFRs and they represent a larger number than the chlorinated flame retardants. This is likely due to the higher efficacy of BFRs than of their chlorinated counterparts. Aromatic brominated flame retardants are thermally more stable than chlorinated aliphatics, which are thermally more stable than brominated aliphatics. Organophosphorus products are primarily phosphate esters (15).

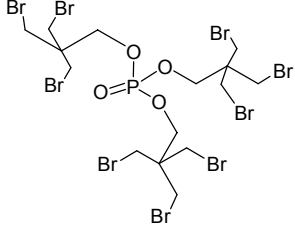
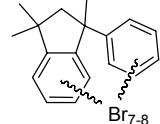
Halogenated flame retardants are either added to or reacted with the base polymer of a material. Reactive BFRs are covalently bound to the polymer and become one entity with the backbone of the polymer matrix while additive BFRs have no firm chemical bonds to the material. Additive BFRs can accordingly move within a polymer and leach out of the products during their lifetime. There are a few compounds that may be used as an additive in one application and as a reactive BFR in another; tetrabromobisphenol A (TBBPA) is such an example. Independent of how the compounds are used and independent of their commercial names and origin there is a present set of 21 different BFRs being used. This list is based on a previous list of BFRs that were commercially available and comes from three different manufacturers presented in 2004 (37). Table 2.1 presents an updated list of commercially available BFRs produced nowadays, listing chemicals or chemical classes applied as BFRs. For chemical classes only the general structures are given while the number of congeners from each class can be

represented by many more individual chemicals. Presenting the chemicals in this way I hope to avoid overlap and exaggeration of the total number of BFRs in use. Only the reactive and additive chemicals applied as BFRs are included in Table 2.1, hence leaving out all polymers that may have a defined structure but in which the reactive BFRs have been introduced.

Table 2.1. Brominated flame retardants in commercial use at the present time.

CAS no	CA name	Chemical structure	Other names
79-94-7	Phenol, 4,4'-(1-methylethylidene) bis[2,6-dibromo-		Tetrabromobisphenol A (TBBPA)
21850-44-2	Benzen, 1,1'-(1-methylethylidene) bis[3,5-dibromo-4-(2,3-dibromopropoxy)-		Tetrabromobisphenol A 2,3-dibromopropyl ether
25327-89-3	Benzen, 1,1'-(1-methylethylidene) bis[3,5-dibromo-4-(2-propenyloxy)-		Tetrabromobisphenol A bis(allyl ether)
1163-19-5	Benzene, 1,1'-oxybis[2,3,4,5,6 pentabromo-		Decabromodiphenyl ether, (DecaBDE)
3194-55-6	Cyclododecane, 1,2,5,6,9,10-hexabromo-		Hexabromocyclododecane, (HBCDD or HBCD)
84852-53-9	Benzene, 1,1'-[1,2-ethanediylbis] bis[2,3,4,5,6-pentabromo-		Decabromodiphenyl ethane
37853-59-1	Benzene, 1,1'-[1,2-ethanediylbis(oxy)] bis[2,4,6-tribromo-		1,2-Bis(2,4,6-tribromophenoxy) ethane
637-79-1	1,3-Isobenzofurandione, 4,5,6,7-tetrabromo-		Tetrabromophthalic anhydride

CAS no	CA name	Chemical structure	Other names
3278-89-5	Benzene, 1,3,5-tribromo-2-(2-propenyloxy)-		2,4,6-Tribromophenyl allyl ether
20566-35-2	1,2-Bezenedicarboxylic acid, 3,4,5,6-tetrabromo-,2-(2-hydroxyethoxy) ethyl 2-hydroxypropyl ether		2-(2-Hydroxyethoxy) ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate
26040-51-7	1,2-Bezenedicarboxylic acid, 3,4,5,6-tetrabromo-,bis (2-ethylhexyl) ester		Di (2-ethylhexyl) tetrabromophthalate
25713-60-4	1,3,5-Triazine, 2,4,6-tris (2,4,6-tribromophenoxy)		2,4,6-Tris (2,4,6-tribromophenoxy)-1,3,5-triazine
32588-76-4	1H-Isoindole-1,3(2H)-dione, 2,2'-(1,2-ethanediyl)bis [4,5,6,7-tetrabromo-		1,2-Bis (tetrabromophthalimido) ethane
58965-66-5	Benzene, 1,2,4,5-tetrabromo-3,6-bis (pentabromophenoxy)-		1,4-Bis (pentabromophenoxy) tetrabromobenzene
59447-55-1	2-Propenoic acid, (pentabromophenyl) methyl ester		2,3,4,5,6-pentabromobenzyl acrylate
118-79-6	2,4,6-tribromophenol		Tribromophenol

CAS no	CA name	Chemical structure	Other names
3296-90-0	1,3-Propanediol, 2,2-bis (bromomethyl)-	$\begin{array}{c} \text{CH}_2\text{Br} \\ \\ \text{HO}-\text{C}-\text{C}-\text{CH}_2-\text{OH} \\ \\ \text{CH}_2\text{Br} \end{array}$	Pentaerythritol dibromide
36483-57-5	1-Proanol, 3-bromo-2,2-bis (bromomethyl)-	$\begin{array}{c} \text{CH}_2\text{Br} \\ \\ \text{BrH}_2\text{C}-\text{C}-\text{CH}_2-\text{OH} \\ \\ \text{CH}_2\text{Br} \end{array}$	Tribromoneopentyl alcohol
79-27-6	1,1,2,2-tetrabromoethane	$\begin{array}{c} \text{Br} \quad \text{Br} \\ \quad \\ \text{H}-\text{C}-\text{C}-\text{H} \\ \quad \\ \text{Br} \quad \text{Br} \end{array}$	tetrabromoethane
19186-97-1	1-Propanol, 3-bromo-2,2-bis (bromomethyl)-phosphate		Tris[3-bromo-2,2-bis (bromomethyl) propyl] phosphate
155613-93-7	1H-Indane, 2,3-dihydro-1,1,3-trimethyl-3-phenyl-octabromo derive.		Brominated Trimethylphenyl Indane

2.2 Production

The brominated flame retardants have commercial significance and they are used in a variety of materials and goods. TBBPA is produced in the largest volume of any of the BFRs in use today followed by decabromodiphenyl ether and hexabromocyclododecane (HBCDD). Production volumes for the dominating BFRs in 2001 are presented in Table 2.2. It is unfortunate that no updated information is available for BFR production since major changes have been implemented between 2001 and today, i.e. PentaBDE and OctaBDE have been banned by the EU from 2004 (23) and their production has been ceased by the Great Lakes Chemical Cooperation in the U.S.A. from 2005 (24). BFRs are produced in China but it is yet unknown what the production volumes are.

Table 2.2. Total production volumes of different BFRs by region 2001 (BSEF 2005). The volumes are presented in metric tons.

	America	Europe	Asia	The rest of the world	Total market demand
TBBPA	18 000	11 600	89 400	600	119 600
HBCDD	2800	9500	3900	500	16 700
DecaBDE	24 500	7600	23 000	1050	56 150
OctaBDE	1500	610	1500	180	3790
PentaBDE	7100	150	150	100	7500
Total	53 900	29 460	117 950	2430	203 790

The PBDEs (PentaBDE, OctaBDE and DecaBDE) will be further discussed in Chapter 3 since the thesis is focused on this class of BFRs. Tetrabromobisphenol A (TBBPA) is mainly used as a reactive flame retardant and it is the largest volume BFR on the market. TBBPA (structure in Figure 2.1) is a white crystalline powder containing 59% bromine by weight. The reactive TBBPA main uses are in epoxy resins of printed circuit boards, polycarbonate resins, as additive in acrylonitrile-butadiene-styrene (ABS) resin and high-impact polystyrene (16). TBBPA is also a starting material for a set of derivatives applied either as reactive or as additive BFRs. TBBPA is constituted of one compound with possibly traces of a tribrominated analogue. This is unusual among technical BFRs but relates to the method for its production, bromination of bisphenol A, a simple reaction leading to *ortho*-substitution relative to the phenol groups in bisphenol A.

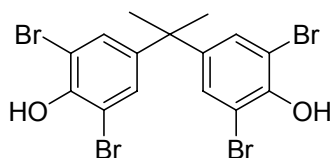


Figure 2.1. Structure of tetrabromobisphenol A (TBBPA).

Hexabromocyclododecanes are aliphatic cyclic hydrocarbons used as additive BFRs in high impact polystyrene foams, thermal insulation in buildings, textiles and electronic equipments (38). HBCDD consists primarily of three isomers (α , β and γ) and six chiral carbons; each carbon can be R or S, which gives $2^6 = 64$ possible enantiomers. However due to symmetry only 16 enantiomers really exists, (38). The commercial mixtures consist of γ -HBCDD (75-89%), α -HBCDD (10-13%) and β -HBCDD (1-12%) and each one of them are chiral (Figure 2.2). HBCDD has replaced PentaBDE and the OctaBDE in some applications but is most well known as additive in Styrofoam products.

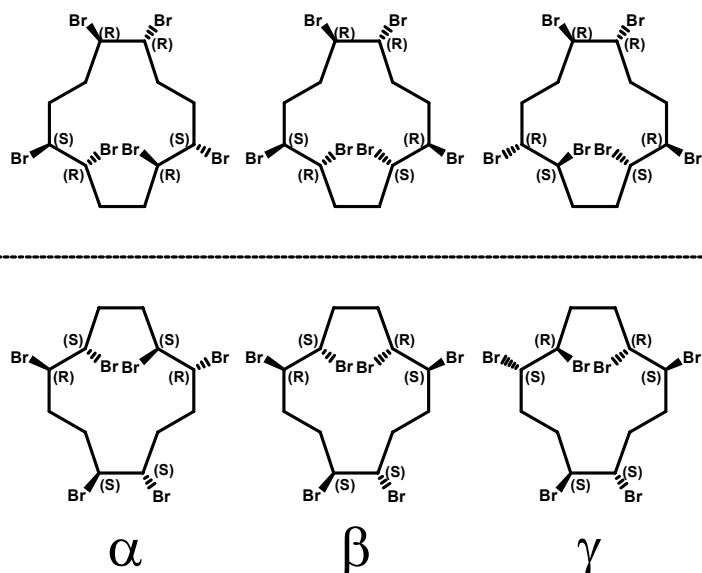
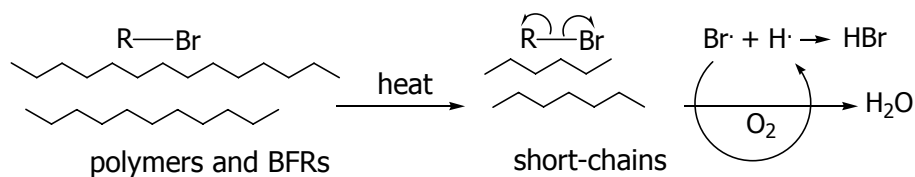


Figure 2.2. Structure of α , RR SR RS (left), β , RR RS RS (middle) and γ , RS SS SR (right) hexabromocyclododecane (HBCCD).

2.3 Mechanism of action

Flame retardants should inhibit or suppress the initial phase in a combustion process, acting chemically or physically in the solid, liquid or gas phase depending on their nature. FRs interfere with combustion during a particular stage of this process, i.e. during heating, decomposition, ignition or flame spread. Halogen containing FRs act primarily by chemical interference with the radical chain taking place in the gas phase during combustion. BFRs contain different numbers of bromine atoms which are released from the polymer it is set to protect, by heat. The neutralized energy-rich radicals produced during the combustion process are inhibiting the process of combustion to continue. The bromine radicals from the BFRs react with high-energy OH and H radicals released from the polymers in the initial phase of the combustion. The fire is inhibited since reaction with oxygen is prevented. The flame retardant has to decompose approximately 50°C below the polymer to be an efficient flame retardant and this is one critical factor when selecting a flame retardant to be applied in the protection of the material (17,39). The mechanism of BFR action is described schematically in Scheme 2.1.



Scheme 2.1.

2.4 BFRs and the environment

TBBPA is a lipophilic compound with $\log k_{ow}$ 5.9 and with low water solubility, 0.24 mg/L at 25°C. Additional data on physico-chemical parameters on TBBPA is available from a variety of sources (40,41). TBBPA has been assessed in a large number of sediments in Europe (42) and occasionally in other matrices (43). It is present in the non-biological environment at sometimes high concentrations but much less research has been conducted on TBBPA and wildlife/humans. More data on TBBPA have been reviewed and presented in publications (40,43-46). TBBPA was a priority compound in a recent EU R&D program, FIRE, including a large number of studies reviewed in the final report from the program (47).

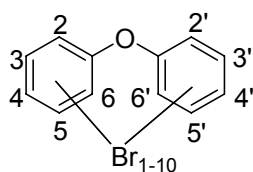
HBCDD has a high $\log K_{ow}$, 5.6 at 25°C, and water solubility of only 0.066 mg/L at 20°C. Additional data on physico-chemical parameters have been presented elsewhere (38,40). HBCDD contaminations have reached the environment and humans by leaching from the products or disposal of the products and emission during production. HBCDD was first detected in fish and sediment from the River Viskan in Sweden (48), where the first fish contaminated with PBDEs was detected. Several reviews have summarized environmental levels of HBCDD and concentrations in humans (38,40,46,49) to which I prefer to refer to, since they are far more comprehensive than I have room for in this thesis focusing on PBDEs. Also HBCDD was part of the FIRE program (47).

PBDEs concentrations in the environment and in humans will be discussed in Chapter 3.

3 Polybrominated diphenyl ethers

Brominated flame retardants have been increasingly used for at least the last 40 years. It is yet unknown to me when BFR production exactly started but a driving force may very well have been the decreasing price of bromine in the 1980's due to increased use of unleaded gasoline. Leaded gasoline required addition of dibromoethane (50). The production of PBDEs dates back to at least the 1970's. PBDEs were manufactured as three technical mixtures; the PentaBDE, OctaBDE and DecaBDE as discussed in Chapter 2. PBDEs are used in a variety of products; such as in plastic materials, television and computer cabinets, cables, building materials, coatings, wall to wall carpets and textile products (51).

There are theoretically 209 PBDE congeners and the number of isomers for mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona- and decaBDEs are 3, 12, 24, 42, 46, 42, 24, 12, 3 and 1, respectively, just as for PCBs and PBBs. Hence PBDEs are numbered for convenience as proposed for the polychlorinated biphenyls (PCBs) (52), just changing the abbreviation letters CB (chlorinated biphenyl) for BDE (brominated diphenyl ether).



Scheme 3.1. General structure of PBDEs.

Commercial PBDEs are synthesized by bromination of diphenyl ether with a Lewis acid, aluminium tribromide (AlBr_3), or iron as a catalyst. The products contain mixtures of PBDE homologues and isomers, as discussed above. The commercial decabromodiphenyl ether product (DecaBDE) contains mainly decaBDE (BDE-209) and trace levels of nonaBDE isomers. The OctaBDE is a mixture of hexa-, hepta-, octa- and nona-BDE isomers, potentially containing traces of (BDE-209). PentaBDE is a mixture of tri-, tetra-, penta-, and hexa-BDE isomers. The relative amounts of the different homologues are presented in Table 3.1, below (53).

Table 3.1. Product composition of commercial PBDE products

	PBDE homologue %							
Technical product	Tri	Tetra	Penta	Hexa	Hepta	Octa	Nona	Deca
DecaBDE							0.3-3	97-99
OctaBDE				10-12	43-44	31-35	9-11	0-1
PentaBDE	0-1	24-38	50-62	4-8				

The European Union (EU) has banned the use of PentaBDE and OctaBDE products since 2004 (23). There has been a voluntary halt in production of PentaBDE and OctaBDE by the only producer in the USA. (24). The DecaBDE production is still ongoing but DecaBDE is not allowed to be used in Swedish manufacturing processes (54) and it is banned in Norway (55) and a few states in the U.S.A. (51). DecaBDE is not yet regulated within the EU as a whole.

PBDE congeners having 4 - 6 or 10 bromine atoms are generally the most common environmental PBDE contaminants. The PBDE congeners with 4-6 bromines are persistent, bioaccumulative and toxic (PBT). They are widely distributed in abiotic environments, in wildlife and humans, even in matrices from remote areas (45). The perbrominated diphenyl ether, BDE-209, has also been found in humans and in remote areas (45,56-58).

PentaBDE is a viscous liquid used in textile, as additive in polyurethane foam and also in phenolic resins, polyesters and epoxy resins. The composition of the PentaBDE products on the market depend on the manufacturer as shown by differences in the relative amounts of the major PBDE congeners. OctaBDE is used in polymers for use in plastic housing and office equipment. DecaBDE is used in high-impact polystyrene, textile and electronic equipment. (51). The PentaBDE and OctaBDE are classified as PBT products. OctaBDE fulfils these criteria since it contains brominated diphenyl ether congeners with an intermediate number of bromines. Since this Chapter does not include a review of PBDE toxicity and ecotoxicity I like to refer to a few review articles that in a good way address these issues. The most extensive documentation is the EU risk assessment documents on PBDEs, subdivided into documents on PentaBDE, OctaBDE and DecaBDE (59). Several reviews have been published in the scientific literature over the last few years on PBDE in general and accordingly including the toxicological/ecotoxicological aspects of PBDEs (43,60-64).

3.1 Physicochemical properties

PBDEs are lipophilic compounds with low water solubilities and low vapour pressures, the latter decreases with increasing bromine content. Table 3.2 shows physicochemical data of PBDEs that are frequently found in the environment. The molecule masses of PBDEs range from 249.11 g/mol for monoBDEs, 406.90 g/mol for triBDEs, 643.59 g/mol for hexaBDEs and 959.16 g/mol for the fully brominated diphenyl ether, BDE-209.

Table 3.2. A summary of some physicochemical characteristics of PBDEs.

	BDE-47	BDE-99	BDE-153	BDE-183	BDE-209
Log V_p (Pa, (25°C))	-3.7 ^a	-4.8 ^a	-5.7 ^a	-6.3 ^a	-8.4 ^b
Log K_{OA} (25°C)	10.5 ^c	11.3 ^c	11.8 ^c	12 ^c	15.3 ^b
Log K_{OW}	6.8 ± 0.08 ^d	7.3 ± 0.14 ^d	7.9 ± 0.14 ^d	8.3 ± 0.26 ^d	10 ^e
Water solubility (nmol/L)	30.9 ^a	16.6 ^a	1.4 ^a	2.1 ^a	20.9-31.3 ^f

^aTittlemier et al.(65), ^bWang et al. (predicted value) (66), ^cHarner et al. (67), ^dBraekvelt et al. (68), ^ede Wit et al. (43) and ^fWHO (53)

3.2 Chemical reactivity

The chemical reactivity of individual PBDEs have been studied in some detail showing large variations among the congeners but over all the intermediate brominated diphenyl ethers are the most stable (69,70). PBDE congeners have been tested versus photolysis, hse (hydrolysis-substitution-elimination), oxidation and reduction.

As early as 1987, Watanabe and coworkers reported debromination of decaBDE subjected to UV light (71). Numerous subsequent studies have come to similar results. When subjecting DecaBDE to UV light while dissolved in toluene, methanol or tetrahydrofuran, adsorbed to silica gel, sand, sediment or soil, BDE-209 is transformed to lower brominated diphenyl ether congeners, primarily hexaBDEs – nonaBDEs, and to low brominated dibenzofurans. Only very recently a more quantitative approach has been taken to assess the relative amounts of PBDE and PBDF congeners formed (72-74). The half life of DecaBDE dissolved in or adsorbed on different materials is presented in Table 3.3 (75).

Table 3.3. Half-life (h) for BDE-209 on different matrices as determined by Söderström and coworkers (75).

	UV-light	Discontinuous sunlight	Continuous sunlight (calculated)
Toluene	< 0.25		
Silica gel	< 0.25		
Sand	12	37	13
Sediment	40-60	80	30
Soil	150-200		

The rate of photolysis of PBDEs is depending on the degree of bromination as presented by Eriksson et al 2004. The decomposition rates for each one of 15 PBDE congeners were measured in methanol/water showing increasing half lives with decreasing number of bromine substituents (Table 3.4).

Table 3.4. Half-life (h) of 15 PBDE congeners when subjected to UV light dissolved in methanol:water (80:20) as extracted from Eriksson and coworkers (69).

PBDE no.	Half-life (h)
209	0.5
208	1.1
207	1.0
206	2.3
203	5.0
190	6.4
183	29
181	6.0
155	47
154	58
139	48
138	31
99	64
77	340
47	290

It is evident that decaBDE to octaBDE isomers have the fastest transformation rates. This type of reactivity has been an important reason for synthesis of nonaBDEs and octaBDEs as presented in this thesis, both for testing purposes and for identification of transformation products.

PBDEs may undergo hydrolysis with sodium methoxide in a mixture of dimethylformamide (DMF) and methanol (70). BDE-209 was rapidly undergoing nucleophilic aromatic substitution (NAS) with methoxide as nucleophile. The reaction rates for the less brominated diphenyl ethers tetra-

and tri-BDE are decreased by one order of magnitude, due to the decrease of bromine substituents (70). The methoxylated PBDEs that are formed under these conditions require other authentic standards for their identification and so far no such identification work has, to my knowledge, been pursued.

Even oxidative transformations of the PBDEs can occur but then only at a very slow rate, far slower than oxidation of OH-PBDEs (76). PBDE congeners are metabolized via oxidations and formation of OH-PBDEs, but this requires Cytochrome P450 catalysis (64,77).

Particularly the highest brominated diphenyl ethers may undergo reductive debromination (78). Hence also this route is leading to highly brominated diphenyl ethers for which authentic reference standards are required.

3.3 Exposure

Polybrominated diphenyl ethers are found in all non-biological compartments and in biota, i.e. wildlife and humans. Exposure data are presented in all major review articles (45,79-83). However, a brief expose of PBDE levels in different matrices are given below.

In abiotic media the more volatile PBDE congeners dominate in the vapor phase, while the BDE-209 typically predominates bound to particles. PBDE congeners are found in remote areas confirming long-range transport, especially for the more volatile congeners. Only a few examples of external exposure data are shown in this thesis but still a summary is presented in Table 3.5. The Table includes scattered data on PBDEs in air, dust, soils, sediments and in biosolids. A comprehensive study was recently published by Hale and coworkers on PBDEs in abiotic matrices (84).

Table 3.5. Some published data on Σ PBDEs concentrations in non-biological matrices from around the world.

Compartment	Location	Mean/median	Min-Max	Ref
Air	Canadian Arctic	7.7 pg/m ³	0.4-47	(85)
	Baltic Sea	8.6	0.4-79	(86)
	Canada		3.0-30	(87)
Indoor dust	USA	1.9 µg/g	0.59-34	(88)
	Singapore	1.2	0.11-13	(89)
	USA (17 houses)		0.78-30	(90)
Soil	China	1.0 ng/g dw	0.1-3.8	(91)
	Spain		21	(92)
	Sweden (5 sites)		0.03-1.9	(93)
	China		305	(94)
Amended soil	Spain (6 sites)	ng/g dw	30-690	(92)
	Sweden (2 sites) low dose		0.58-1.2	(93)
	Sweden (2 sites) high dose		0.84-2.1	(93)
	Sweden (2 sites) sludge applied		0.063-3900	(93)
Sediment	China	ng/g dw	4434-16088	(95)
	Spain (3 sites)		30-14395	(96)
	USA (3 sites)		1.7-4	(97)
	Australia (35 sites)	0.30		(98)
Sewage sludge	Sweden (50 STPs) *	µg/kg dw	18-260	(46)
	Danmark	238± 23		(46)
	Spain (6 STPs)		844-18100	(46)
	Spain (5 STPs)		197-1185	(92)
	Germany (11 STPs)	108	13-288	(99)

* Sewage treatment plants (STPs)

PBDEs are ubiquitous contaminants in wildlife and humans with PBDEs substituted with 4-6 bromines being the most abundant congeners (100) and these have been reported in biota at high trophic levels in variable concentrations and congener patterns (45,56). BDE-209 and other highly brominated diphenyl ethers have been reported in wildlife (45). A few examples of wildlife PBDE concentration are summarized in Table 3.6.

Table 3.6. Some selected data on ΣPBDEs concentrations (ng/g fat) in wildlife from around the globe, including references.

Species	Location	Mean/median	Min-Max	Ref
Terrestrial				
Red Fox (muscle)	Belgium	3.4	1.0-44	(101)
Birds				
Kestrel (muscle)	China	12300 ± 5540	279-31700	(102)
Guillemot (egg)	Baltic Sea	77		(103)
Sparrowhawk (liver)	Belgium	4900	280-26000	(104)
Fish				
Brown trout (liver)	Switzerland		16-7400	(105)
Brown trout (fillet)	Norway		21-1215	(106)
Burbot (liver)	Norway		125-915	(106)
Lake trout (whole fish)	USA		1395 ± 56	(107)
Marine mammal				
Beluga whale (female)	Canadian arctic	540	300-1060	(108)
Pilot whale (male, young)	Faroe Islands		3160	(100)
Harbor seal (male)	USA	5100	1900-8300	(108)
Ringed seal (male)	Canadian arctic	4600	2900-6300	(108)
Bottlenose dolphins	USA	5860± 4285	429-22783	(109)
Arctic species				
Polar bear	E-Greenland	70	22-192	(110)
Polar bear (female)	Svalbard	50	27-114	(111)
Polar bear (female)	Alaska	6.7	4.6-11	(111)
Walrus (male)	Svalbard	15	9-27	(112)
Penguin (egg)	Antarctica	3.1		(113)

Humans are exposed to both lower and the higher brominated diphenyl ether congeners, via food, indoor air and possibly through dermal uptake (100). In Sweden, a human milk time-related study from 1972-1997 was made, showing that concentrations of PBDEs in human milk had increased over the past two decades (114). This trend peaked in 1997 possibly due to the voluntary ban on the production and use of the PentaBDE in Europe as early as the 1990's (114). Human milk from Sweden, Japan, Canada and USA have been compared, it demonstrated large differences between the concentrations from Sweden and Japan with median levels of 3.2 and 1.4 ng/g fat, respectively, compared to 25 and 41 ng/g fat in milk from Canada and the USA, respectively. The concentrations from Canada and the USA are 10 times higher than those from Sweden and Japan. This could be a result of a more abundant use of PentaBDE in North America than in Europe and Asia (44). However, also high concentration of PBDEs in human from Nicaragua and the Faroe Island have been reported (19,115). Human serum/plasma concentrations of PBDEs, in different part of the world, are presented in Table 3.7, including levels of BDE-47, 99, 153, 183 and 209.

Table 3.7. Human serum PBDE concentrations (ng/g fat) from different parts of the world are presented.

Location	Year	N	BDE-47		BDE-99		BDE-153		BDE-183		BDE-209		ref
			median	min-max	median	min-max	median	min-max	median	min-max	median	min-max	
Sweden*	2000	17 (M) ^a	1.2	<LOQ ^b -6.3	1.9	1.1-3.7	<LOQ	<LOQ	2.4	0.88-9.3	(58)		
Sweden	2000	50 (F) ^c	0.91	0.27-8.1	1.1	0.29-4.7	0.46	<LOQ-3.3	(116)				
Norway	1977-03	20 (M)	1.3 ^d	0.3 ^d	1.3 ^d	0.18 ^d	<10 ^d	(117)					
Norway	1977-03	20 (F)	1.6 ^d	0.35 ^d	0.8 ^d	<0.1 ^d	<10 ^d	(117)					
Faroe Islands	1994-95	57 (F)	1.3	<LOQ-11	1.0	0.26-7.1	0.77	<LOQ-3.6	(118)				
UK	2003	154 ^e	0.82	<0.30-180	1.7	<0.26-87	0.30	<0.14-1.8	<15	<15-240	(119)		
Spain	2003-04	61 (F)	2.4	0.30-9.0	2.6	1.4-6.9	0.86	<LOQ-2.5	0.47	<LOQ-2.3	1.1	<LOQ-20	(120)
Spain	2003-04	51 (M)	2.3	0.34-7.3	2.3	1.4-5.3	0.81	<LOQ-3.2	0.60	<LOQ-2.6	1.1	<LOQ-59	(120)
Belgium	1999-04	11 ^f	1.17	0.2-3.07	0.20	0.20-1.02	1.55	0.99-3.07	0.21	0.10-0.41	11.1	3.6-33.1	(121)
Netherlands	2001-02	114 (F)	0.8	0.04-6	0.2	ND ^g -2.1	1.6	0.3-20					(122)
New Zealand	2001	23 ^h	3.17	0.76-12.7	0.88	0.32-2.34	1.02	0.43-2.31	0.23	0.06-0.97			(123)
Korea	2001	10 (M)	5.74 ^d	2.20-12.12	2.68 ^d	1.46-5.39	4.69 ^d	2.78-7.74	2.04 ^d	0.51-4.86			(124)
Korea	2001	12 (F)	4.49 ^d	1.84-7.74	2.29 ^d	1.11-4.92	2.99 ^d	1.64-7.48	2.10 ^d	0.59-5.85			(124)
China	2006	21 (F)	1.0	0.36-3.6	0.36	0.08-7.4	1.4	0.36-6.4	0.31	0.0-1.3			(125)
China,	2007	20 (F)	1.1	0.5-3.6	0.4	0.1-7.4	1.3	0.4-6.4	0.3	ND-1.3	5.7	ND-63.2	(126)
USA	1999-01	24 (F)	11	2.5-205	2.9	0.5-54	1.5	0.4-35	0.1	0.1-39			(127)
USA	2001	12 (F)	28	9.2-310	5.7	2.4-68	2.9	1.0-83	0	0.0-2.7			(128)
Nicaragua	2002	11 ⁱ	218 ^j	119 ^j	20 ^j	1.7 ^j	8.9 ^j						(19)
Mexico	2004	5 (F)	9.0 ^d	3.0-14.5	2.0 ^d	0.6-3.6	3.9 ^d	0.9-6.6	9.5 ^d	4.8-14.6			(129)

^aMale. ^bLimit of quantification. ^cFemale. ^dMean. ^e50/154 M, 104/154 F. ^fUnknown gender. ^gNot Detected. ^h10/23 M, 13/23 F. ⁱChildren. ^jPooled samples

*Referents, abattoir workers

N is number of sample

3.4 The importance of standards

The importance of pure reference standards for quantifying the analyte in biological samples plays a key roll for any assessment of the compound. In 1981, tri- to hexabrominated diphenyl ethers were found in pike from Sweden (35). In the same area, fish were caught in 1977 but no PBDEs were found, indicating that they were most likely new pollutants. The quantifications that were made in 1981 were based on a technical PBDE product, Bromkal 70-5 DE, as a standard due to the lack of pure authentic reference standards. Identification of the Bromkal 70-5 DE started in 1976 (Table 3.8) and two major structures were identified, BDE-47 and BDE-99 (33). Also Norström and coworkers identified at the same time BDE-47 in Bromkal 70-5DE (34). In 1998 there were more than 30 PBDE congeners available and 11 PBDE congeners were identified in the Bromkal 70-5 DE, including BDE-47 and BDE-99 (130). At present there are a large number of PBDE congeners on the market that make the quantification of PBDEs in environmental samples far easier. Accordingly, identification of PBDE congeners in commercial PBDEs increased and most recently Korytar et al. have identified in total 18 PBDE congeners in Bromkal 70-50 DE (Table 3.8) (131). Table 3.9 is similarly describing the development of the identification work of PBDE congeners in the PentaBDE mixture, DE-71. A total 25 PBDE congeners have now been identified in DE-71, according to Konstantinov et al. (132) and La Guardia et al. (133).

The development of identification of PBDE congeners in OctaBDE products are shown in Table 3.10 and Table 3.11 for Bromkal 79-8 DE and for DE-79, respectively. In total 19 PBDE congeners have been identified in Bromkal 79-8 DE by different researchers. Konstantinov et al. (132) have identified 24 PBDE congeners in the OctaBDE mixture (DE-79) and La Guardia et al. (133) have confirmed 18 of them and additionally one i.e. BDE-144. A total of 25 PBDE congeners have been identified in the OctaBDE mixture (DE-79), taken both these articles in consideration. As mentioned before in this Chapter, Table 3.1, DecaBDE consist most exclusively of BDE-209 and trace of the three nonaBDE congeners, i.e. BDE-206, 207 and 208 (53).

Table 3.8. Identified PBDE congeners present in the PentaBDE mixture Bromkal 70-50 DE as presented by different researchers and time.

The composition of PentaBDE mixture (Bromkal 70-5 DE) through time				
	1976 ¹	1998 ²	2005 ³	2006 ⁴
PBDE congeners	47, 99	17, 28, 47, 66, 85, 99, 100, 138, 153, 154, 183	17, 28, 47, 49, 66, 74, 85, 99, 100, 101, 97/118, 138, 139, 140, 153, 154, 155, 183	17, 28/33, 47 ^a /74, 49, 66/42, 85, 99, 100, 97/118, 138, 139, 140, 153, 154, 126/155 ^a , 175/183 ^a

¹Sundström et al. (33), ²Sjödin et al. (130), ³Korytar et al. (131) and ⁴La Guardia et al. (133).

^aMajor PBDE congener of the co-eluting pair.

Table 3.9. PBDE congeners identified in the pentaBDE mixture DE-71 as determined by the authors indicated and time.

The composition of PentaBDE mixture (DE-71) through time		
	2005 ¹	2006 ²
PBDE congeners	17, 28, 42, 47, 48, 49, 51, 66, 85, 91, 99, 100, 102, 119, 138, 139, 140, 153, 154, 155, 156, 183	17, 28/33, 47 ^a /74, 48/71, 49, 51, 66/42, 75, 85, 99, 100, 102, 97/118, 138, 139, 140, 153, 154, 126/155 ^a , 175/183 ^a , 184

¹Konstantinov et al. (132) and ²La Guardia et al. (133)

^aMajor PBDE congener of the co-eluting pair.

Table 3.10. Shows the identified PBDE congeners in the OctaBDE mixture Bromkal 79-8 DE as identified by different authors and time.

The composition of OctaBDE mixture (Bromkal 79-8 DE) through time				
	2000 ¹	2003 ²	2005 ³	2006 ⁴
PBDE congeners	153, 154, 183	183, 196, 197, 203, 206, 207, 208, 209	173/190, 181, 183, 191, 196, 197, 203, 204, 205, 206, 207, 208, 209	144, 153, 154, 171, 175/183 ^a , 184, 196, 197, 201, 203, 206, 207, 208, 209

¹Sjödin et al. (134), ²Björklund et al. (135), ³Korytar et al. (131) and ⁴La Guardia et al. (133)

^aMajor PBDE congener of the co-eluting pair.

Table 3.11. The OctaBDE mixture DE-79 content of PBDE congeners are shown as determined by different authors.

The composition of OctaBDE mixture (DE-79) through time		
	2006 ¹	2006 ²
PBDE congeners	99, 119, 128, 138, 139, 140, 149, 153, 154, 171, 180, 182, 183, 184, 191, 194, 196, 197, 201, 203, 206, 207, 208, 209	138, 140, 144, 153, 154, 171, 180, 175/183 ^a , 184, 191, 194, 196, 197, 201, 203, 206, 207, 208, 209

¹Konstantinov A et al. (136) and ²La Guardia et al. (133).

^aMajor congener of the co-eluting pair.

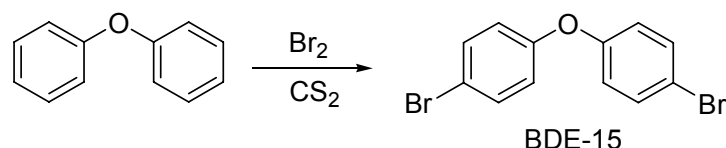
The availability of authentic reference standards has greatly improved the identification of environmentally present PBDE congeners. An additional number of PBDE congeners are formed abiotically and through metabolism making the analysis even more of a challenge when assessing them in samples from any of the abiotic environments or samples from wildlife or humans.

4 Synthesis of polybrominated diphenyl ethers (PBDEs)

Chapter 4 summarizes methods for the preparation of single PBDE congeners, which have been published in the past and integrating the work pursued in this thesis, i.e. related to the two published articles, Papers I and II, and to the manuscript, Paper III.

4.1 Synthesis of PBDEs by bromination of diphenyl ether

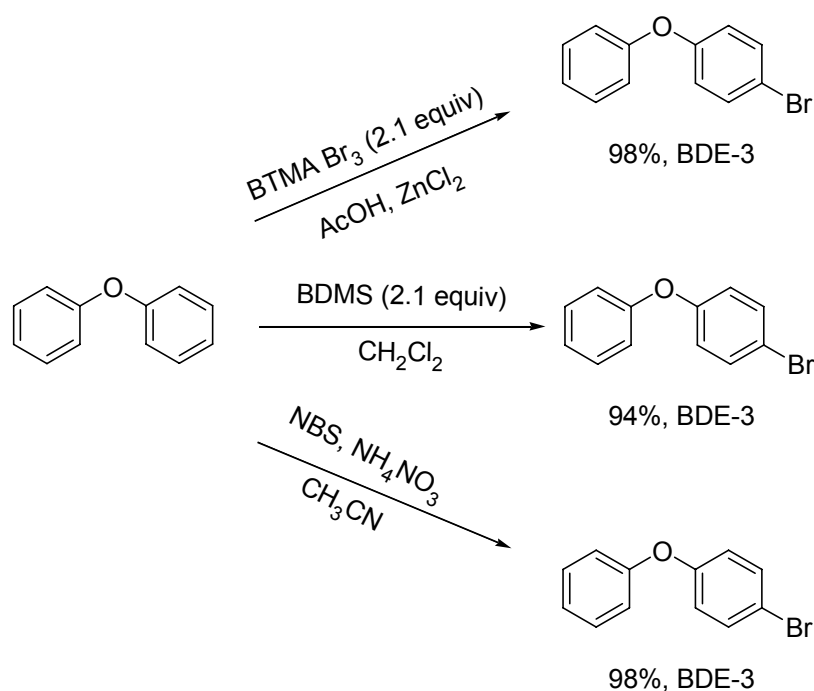
The first original paper describing the synthesis and characterizing a PBDE congener was presented by Hoffmeister et al 1871 (137), who synthesized 4,4'-dibromodiphenyl ether (BDE-15) by bromination of diphenyl ether using bromine in carbon disulfide (CS₂) (Scheme 4.1). Since then, a number of scientific articles have reported on synthesis of individual PBDE congeners including Paper I, II and III from this thesis. The most important synthetic pathways are summarized in the present Chapter.



Scheme 4.1.

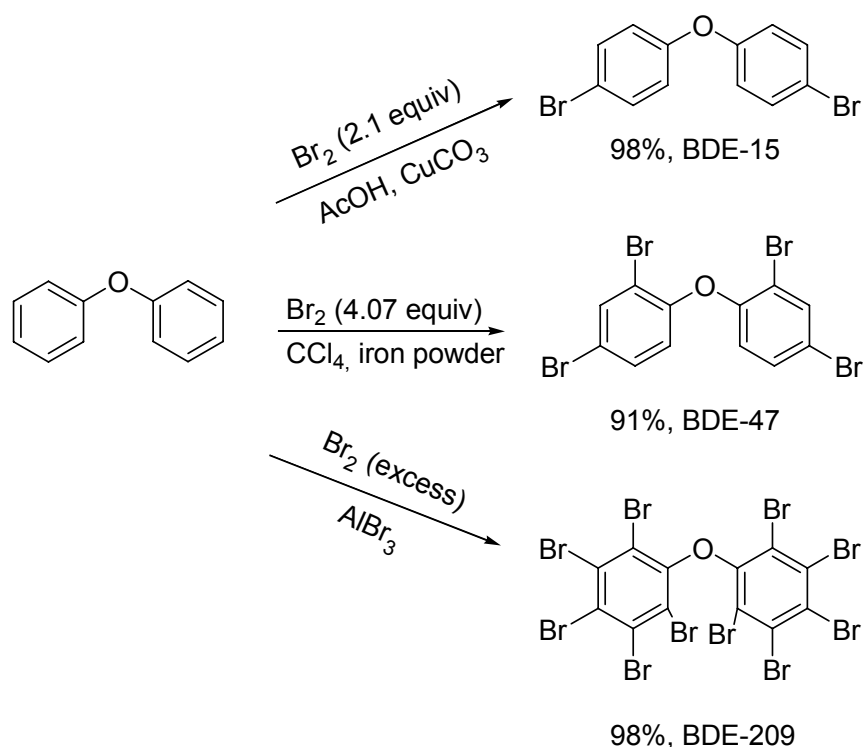
Commercial PBDE product mixtures are synthesized by the bromination of diphenyl ether in the presence of a Lewis acid. Bromine is used as the bromination reagent and aluminium bromide (AlBr₃) or iron (Fe) as catalysts (53). The bromine atoms are attached to the aromatic rings via an electrophilic aromatic substitution (EAS) mechanism. This procedure gives mixtures of PBDE congeners which are present in the commercial PentaBDE, OctaBDE and DecaBDE products; details of these three industrial PBDE products are presented in Chapter 3. However, it is possible to prepare four PBDE congeners by direct bromination of diphenyl ether in a rather selective

manner, i.e. 4-bromodiphenyl ether (BDE-3), BDE-15, 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) and 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (BDE-209). Bromination of diphenyl ether with bromodimethylsulfonium bromide (BDMS) in dichloromethane (CH_2Cl_2) (138), *N*-bromosuccinimide (NBS) in acetonitrile (CH_3CN) with a weak acid ammonium nitrate (NH_4NO_3) (139) or benzyltrimethylammonium tribromide (BTMA Br_3) in acetic acid (AcOH) with zinc chloride (ZnCl_2) as a catalyst (140) gave the monobrominated BDE-3 (Scheme 4.2). Despite an excess of the brominating agent in the latter case, only BDE-3 was formed.



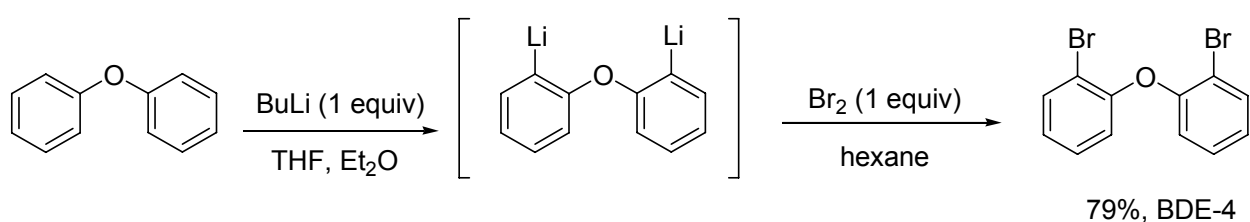
Scheme 4.2.

Bromination of diphenyl ether with 2.1 equivalents of bromine in AcOH with copper carbonate (CuCO_3) as catalyst gave BDE-15 in 98% yield (141). Norström et al. (34) received BDE-47 in 91% yield using 4.1 equivalents of bromine in tetrachloromethane (CCl_4) in the presence of iron powder. BDE-209 has been isolated in over 90% yield by perbromination of diphenyl ether, using AlBr_3 and an excess of bromine (Scheme 4.3) (142).



Scheme 4.3.

2,2'-Dibromodiphenyl ether (BDE-4) has also been prepared from diphenyl ether using bromine (141). However, in this case diphenyl ether in tetrahydrofuran (THF) was first treated with butyllithium (BuLi) in diethyl ether (Et_2O) and thereafter bromine in hexane to introduce bromine in two of the *ortho* positions to the ether oxygen, one in each phenyl ring, as shown in Scheme 4.4.

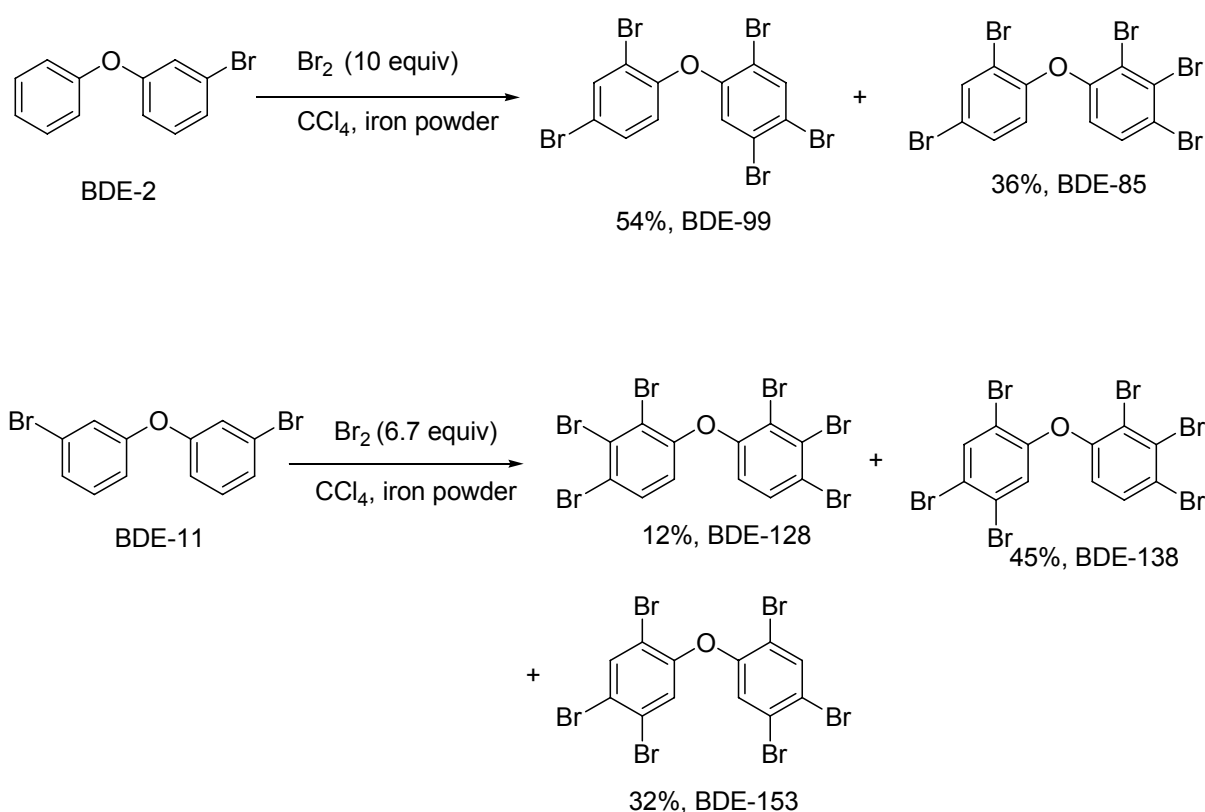


Scheme 4.4.

4.2 Synthesis of PBDEs by bromination of other PBDEs

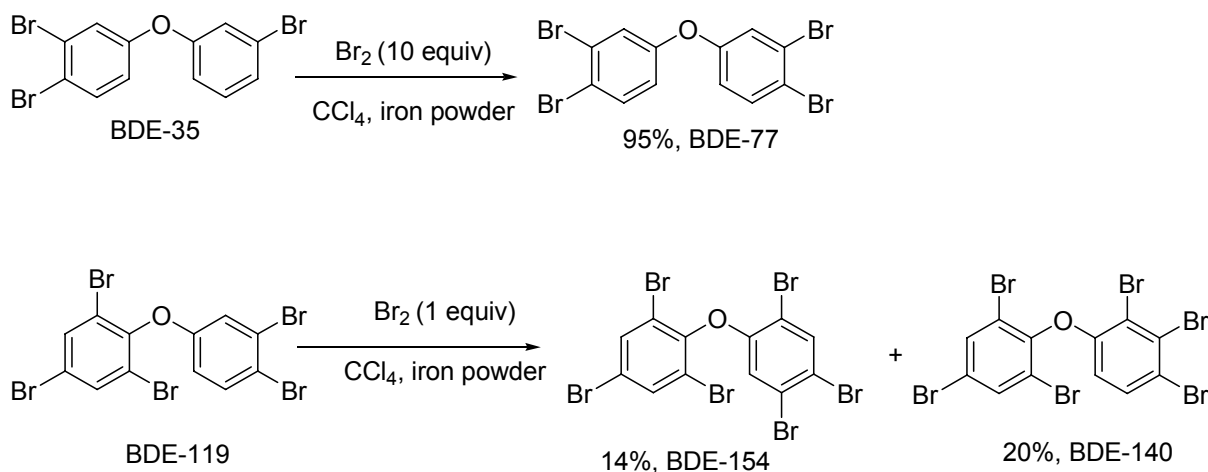
The bromination of an existing PBDE congener has been used to synthesize PBDEs substituted with 2-8 bromine atoms as described in the literature (141,143-145) and in Paper II. Two pentaBDEs and three hexaBDEs were prepared using two different PBDE congeners as shown in Scheme 4.5 (145). Bromine and iron powder in CCl_4 were used in the bromination of the PBDE

congener 3-bromodiphenyl ether (BDE-2) which yielded 2,2',4,4',5-pentabromodiphenyl ether (BDE-99) and 2,2',3,4,4'-pentabromodiphenyl ether (BDE-85). The PBDE congener 3,3'-dibromodiphenyl ether (BDE-11) was prepared similarly and yielded 2,2',3,3',4,4'-hexabromodiphenyl ether (BDE-128), 2,2',3,4,4',5'-hexabromodiphenyl ether (BDE-138) and 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153). 3,3',4,4',5,5'-Hexabromodiphenyl ether (BDE-169) and 2,3,3',4,4',5',6-heptabromodiphenyl ether (BDE-191) were brominated similar as above to yield 2,2',3,3',4,4',5,5'-octabromodiphenyl ether (BDE-194) and 2,2',3,3',4,4',5',6-octabromodiphenyl ether (BDE-196), respectively in Paper II.



Scheme 4.5.

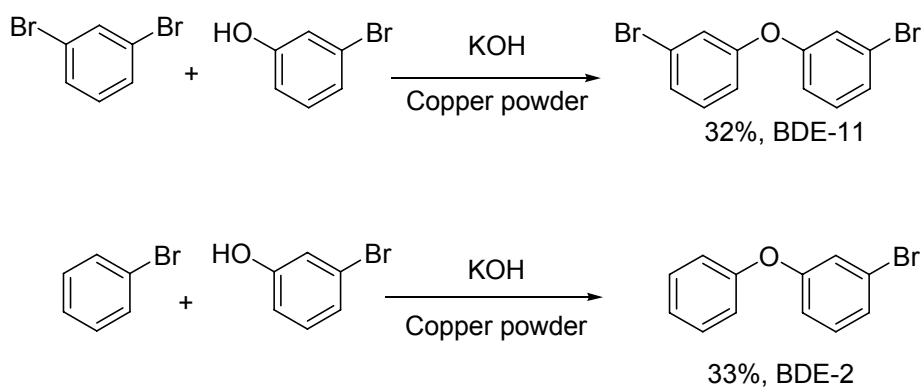
Also Marsh et al. (143) used bromine and iron powder in CCl₄ in the bromination of 3,3',4-tribromodiphenyl ether (BDE-35) which gave 3,3',4,4'-tetrabromodiphenyl ether (BDE-77), and 2,3',4,4',6-pentabromodiphenyl ether (BDE-119) was brominated to give two hexaBDEs, 2,2',3,4,4',6'-hexabromodiphenyl ether (BDE-140) and 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE-154), see Scheme 4.6.



Scheme 4.6.

4.3 Ullmann diphenyl ether synthesis

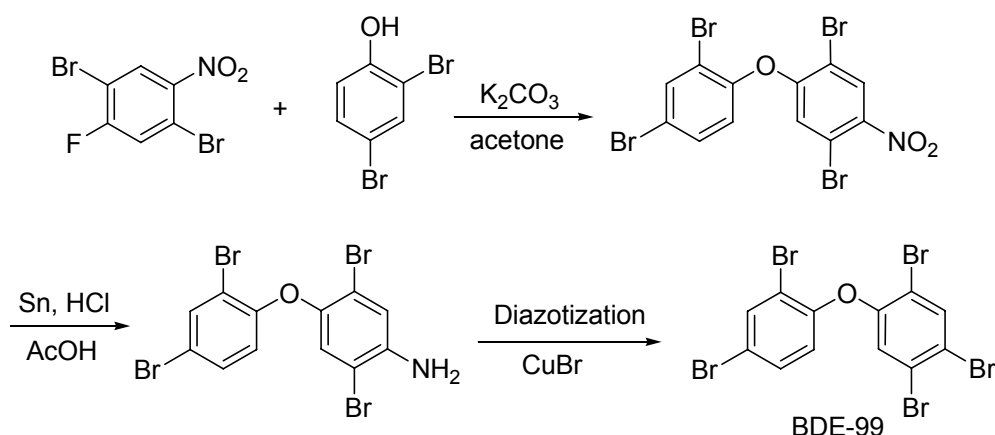
When a phenolate ion is coupled with a halobenzene in the presence of copper powder and a base, this is known as the original Ullmann diphenyl ether coupling reaction (146). Synthesis of low brominated diphenyl ethers containing 1-2 bromine atoms have been prepared by this method (145) as shown in Scheme 4.7. Accordingly an excess of bromobenzene was mixed with the bromophenol and potassium hydroxide (KOH), and then heated at 170 °C. These PBDE products served as precursors for the penta- and hexabrominated DE products, 3-bromodiphenyl ether (BDE-2) and (BDE-11) as showed in Scheme 4.5.



Scheme 4.7.

4.4 S_NAr based reactions for synthesis of PBDEs

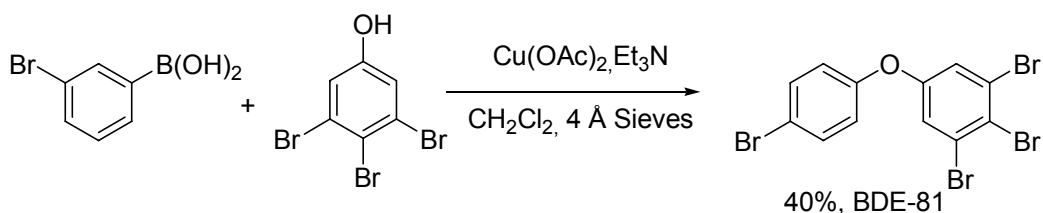
Several activated aromatic nucleophilic substitution reactions (S_NAr) with fluorine as the leaving group and with a nitro group in the *para* position to the fluorine have generated PBDE congeners e.g. BDE-99, BDE-153, BDE-154 and 2,2',3,4,4',5,5'-heptabromodiphenyl ether (BDE-183) after reduction of the nitro group with tin and hydrochloric acid in acetic acid (Sn/HCl/HOAc) followed by diazotization in a Sandmeyer type reaction using copper bromide (CuBr) (147). The preparation of (BDE-99) via this route is shown in Scheme 4.8. All these PBDE products have a 2,4,5-tribromo substitution pattern in one of the phenyl rings.



Scheme 4.8.

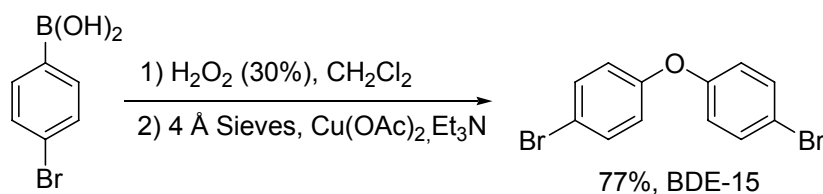
4.5 PBDEs synthesis via Suzuki type coupling

Phenols can be coupled with aryl boronic acids in presence of copper (II) under mild conditions to give diphenyl ethers as first reported by Chan et al. 1998 (148) and Evans et al. 1998 (149). The aryl boronic acid is associated with the well known Suzuki biphenyl synthesis. Chen et al. (147) used this method for synthesis of 3,4,4',5-tetrabromodiphenyl ether (BDE-81) as shown in Scheme 4.9. Consequently, the bromophenol was coupled with the bromoaryl boronic acid in CH₂Cl₂ using copper acetate (Cu(OAc)₂) as a catalyst and triethylamine as the base.



Scheme 4.9.

In this reaction, powdered molecular sieves 4 Å was added to remove the water that is formed from the boronic acid group. If water is not removed, it reacts with the boronic acid group in side-reactions and forms for example the corresponding phenols. It should here be mentioned that Simon et al. (150) converted arylboronic acids to phenols in water and hydrogen peroxide. Also, Simon and coworkers (150) synthesized symmetrical diphenyl ethers including BDE-15 by adding 0.25 equiv. hydrogen peroxide to the Suzuki based diphenyl ether synthesis as shown in Scheme 4.10. Thus, the bromophenol was generated in situ and thereafter deprotonated and coupled with the arylboronic acid to obtain the PBDE product.



Scheme 4.10.

4.6 Reductive debromination of decabromodiphenyl ether (BDE-209)

Reductive debromination of BDE-209 with sodium borohydride (NaBH_4) in THF has generated all three theoretical nonabBDEs, i.e. 2,2',3,3',4,4',5,5',6-nonabromodiphenyl ether (BDE-206), 2,2',3,3',4,4',5,6,6'-nonabromodiphenyl ether (BDE-207) and 2,2',3,3',4,5,5',6,6'-nonabromodiphenyl ether (BDE-208) of which BDE-206, reductive debromination in the *ortho* position to the diphenyl ether oxygen, is the major product (see. Paper I). An HPLC chromatogram of the starting compound and the product mixture is shown in Figure 4.1. BDE-206 was isolated using high performance liquid chromatography (HPLC) with a preparative C18 column and with $\text{CH}_3\text{CN}/\text{MeOH}$ (8:2) as the mobile phase. BDE-207 and BDE-208 were co-eluting on this column and had to be separated on a HPLC semi-preparative phenyl column with $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (76:24) as the mobile phase (Figure 4.2). Thus, on the phenyl column, separations of the two isomers were performed by collecting first eluting part of BDE-208 and the last part of BDE-207 (see. Figure 4.2 for the chromatography).

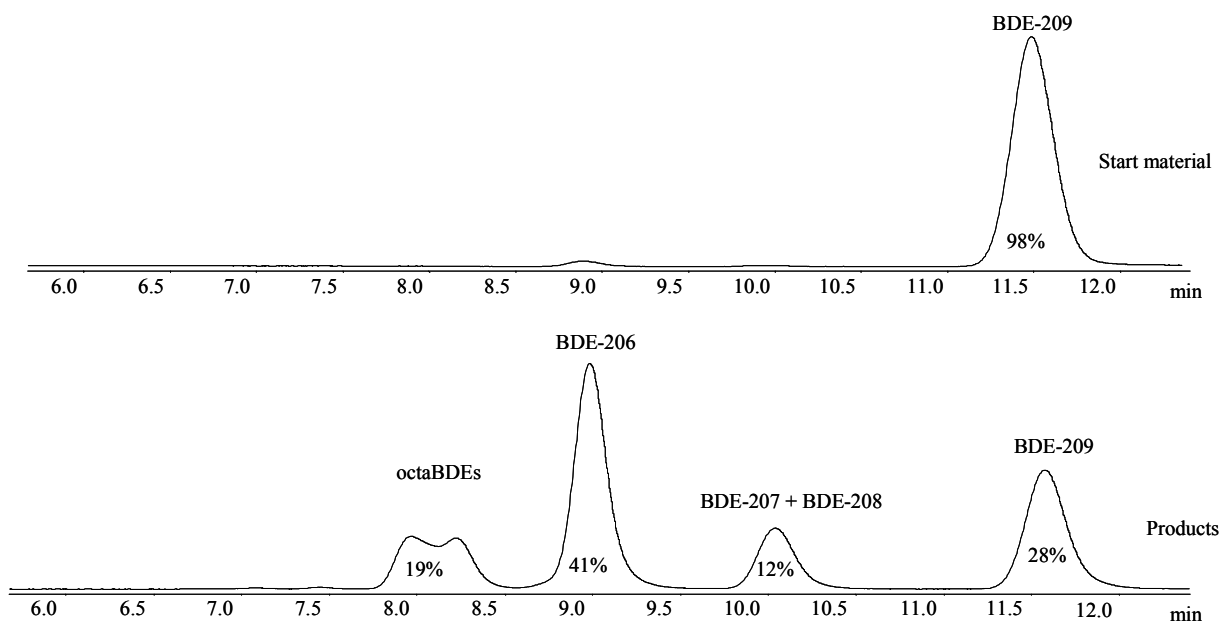


Figure 4.1. Reduction of BDE-209 and separation on a preparative HPLC applying a C18 derivatized silica column. The products obtained in the synthesis are shown in the chromatogram.

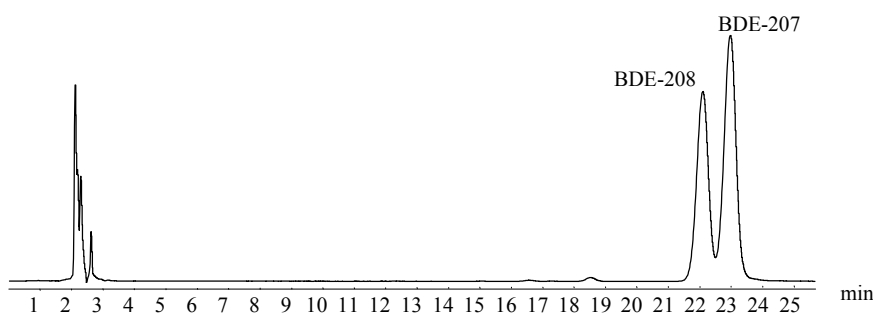
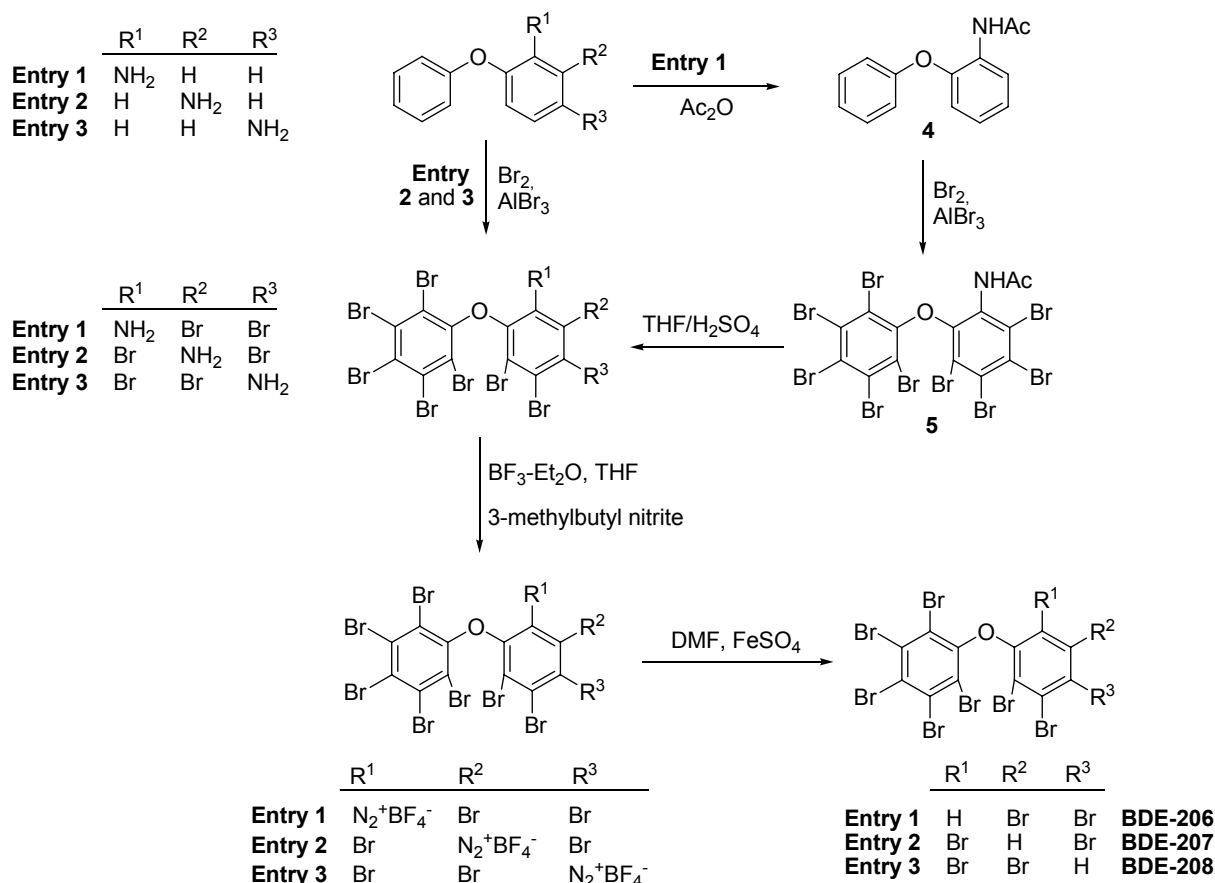


Figure 4.2. The co-eluted BDE-207 and BDE-208 in the first step were separated with semi-preparative phenyl HPLC column (shown in Figure 4.1).

4.7 Aminodiphenyl ethers for synthesis of PBDEs

In Papers I and II, octaBDE and nonaBDE congeners were prepared by perbromination of monoamino- and diaminodiphenyl ethers using bromine and AlBr_3 followed by diazotization with 3-methylbutyl nitrite and borontrifluoridetherate in THF and reduction of the diazonium ion with iron (II) sulfate (FeSO_4) in dimethylformamide (DMF). Two nonaBDEs i.e. BDE-207 and BDE-208 were synthesized, as described in Paper I, via this pathway starting from 3-phenoxyaniline and 4-phenoxyaniline, respectively (see Entry

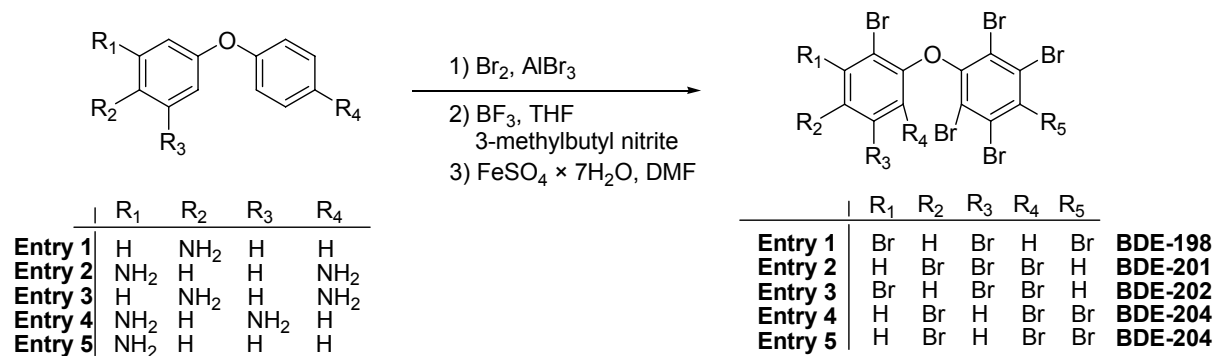
2 and 3 in Scheme 4.11). However, the starting compound for the nona-brominated BDE-206, i.e. 2-phenoxyaniline, had to be protected with an acetyl group by acetic acid anhydride (Ac₂O) before perbromination. Unless the compound is protected, this reaction will yield tetrabromo- and pentabromodibenzofuranes as well as a pentabromodiphenyl ether and a tetrabromodiphenyl ether, but no desired product (see Paper I and Entry 1 in Scheme 4.11). Consequently, the acetyl group was removed (acid catalyzed hydrolysis) prior to diazotization (Entry 1 in Scheme 4.11).



Scheme 4.11.

In Paper II, a similar methodology as for synthesis of the nonaBDEs (BDE-207 and BDE-208) was applied for the synthesis of the octaBDEs, 2,2',3,3',4,5',6,6'-octabromodiphenyl ether (BDE-201), 2,2',3,3',5,5',6,6'-octabromodiphenyl ether (BDE-202) and 2,2',3,4,4',5,6,6'-octabromodiphenyl ether (BDE-204) (see Entry 2-4 in Scheme 4.12). Thus, all aromatic hydrogens were replaced with bromines and the amino groups were exchanged for hydrogens of the diaminodiphenyl ethers used as precursors when this pathway was applied. In addition, two octaBDE congeners were synthesized from monoaminodiphenyl ethers (Paper II and Entry 1 and 5 in Scheme 4.12),

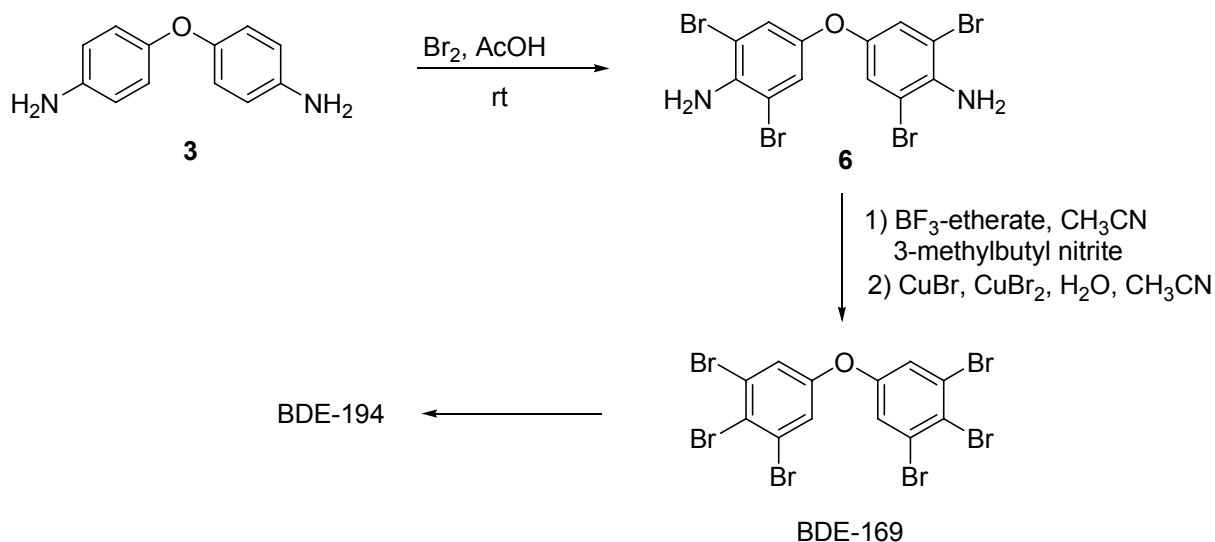
since it was noted that it was possible to stop the reaction at an octa-brominated level during the work with the perbrominations in Paper I. Accordingly, the octaBDEs, 2,2',3,3',4,5,5',6-octabromodiphenyl ether (BDE-198) and BDE-204 were both prepared via this route (Paper II).



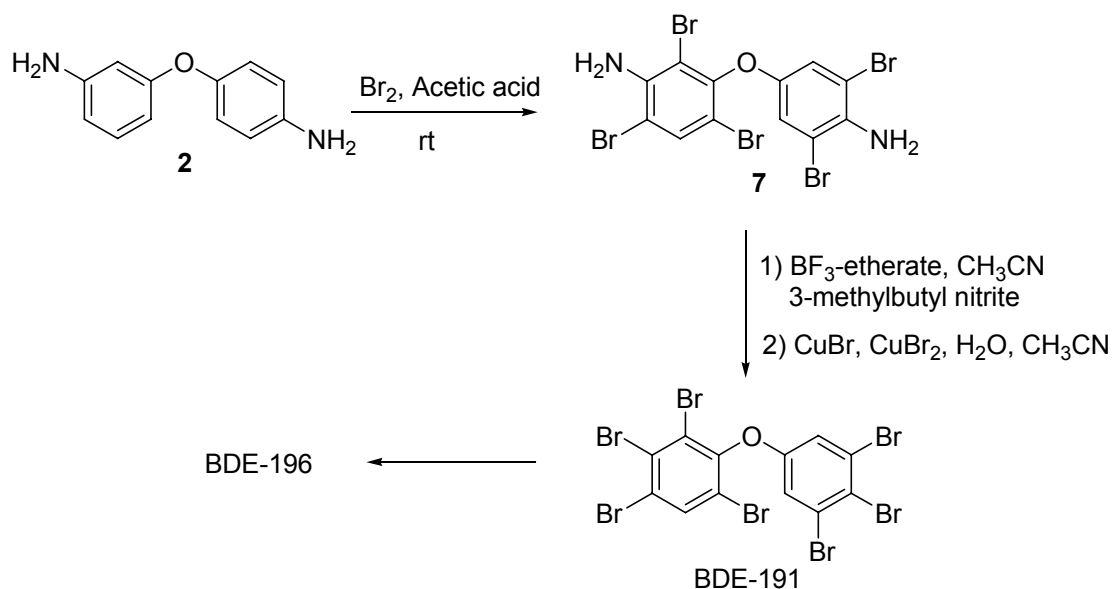
Scheme 4.12.

4.8 Selective bromination of aminodiphenyl ethers for synthesis of PBDEs

Two diaminodiphenyl ethers, 3,4'-diaminodiphenyl ether and 4,4'-diaminodiphenyl ether were used in Paper II as starting material for the preparation of BDE-194 and BDE-196. The route for synthesis includes four steps i.e. i) selective bromination *ortho* and *para* to the amino groups using bromine in AcOH, ii) diazotization of the amino groups with the treatment of borontrifluoridetherate and 3-methylbutyl nitrite in CH₃CN, iii) the amino group was exchanged for a bromine via a Sandmeyer type of reaction using a mixture of copper (I) bromide and copper (II) bromide in water and iv) bromination of PBDE congeners as mentioned in Section 4.2 (Schemes 4.13 and 4.14). Consequently, BDE-169 and BDE-191 were obtained before the fourth step was carried out.



Scheme 4.13.

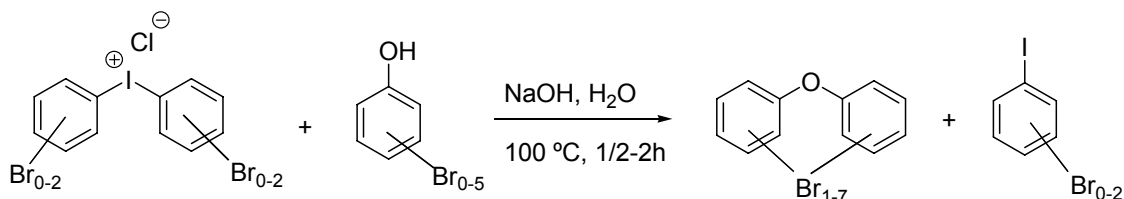


Scheme 4.14.

4.9 Synthesis of PBDEs via diphenyliodonium salts

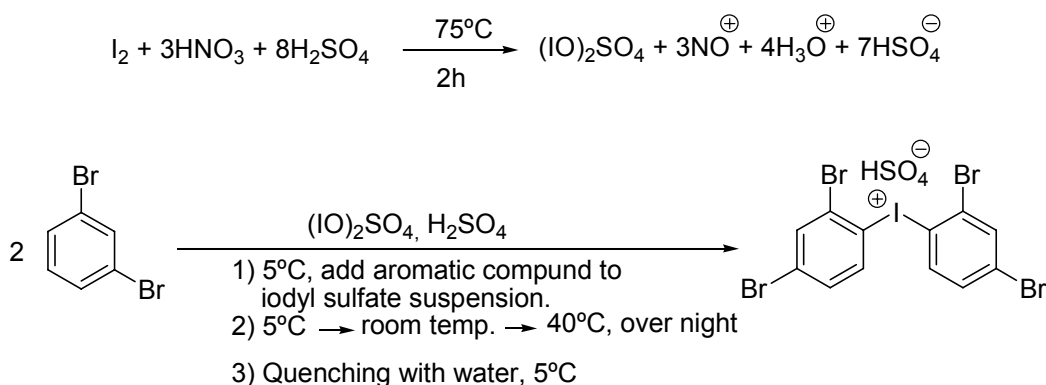
The coupling of bromophenolate and a bromodiphenyliodonium salt is the synthetic method that has generated the largest number of PBDE congeners according to the scientific literature (143,147,151-153) and Paper III. This methodology is also known to have generated many congeners of polychlorinated diphenyl ethers (PCDE) (151,153-156). Traditionally, in PBDE synthesis, the coupling of the diphenyliodonium salt (as the chloride) and the phenol has been carried out in refluxing aqueous NaOH as the general

formula is outlined in Scheme 4.15 (143,147,152). This reaction was based on methodology previously published by Crowder et al. (157).



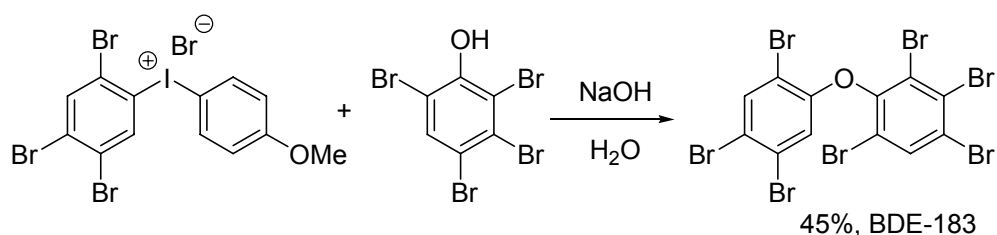
Scheme 4.15.

Thus, the diphenyliodonium salts were prepared by oxidizing iodine with fuming nitric acid in sulfuric acid giving iodyl sulfate as shown in Scheme 4.16. Thereafter, the bromobenzene was added to the iodyl sulfate suspension to yield the diphenyliodonium salt (Scheme 4.16). This reaction methodology was originally developed by Beringer et al. (158).



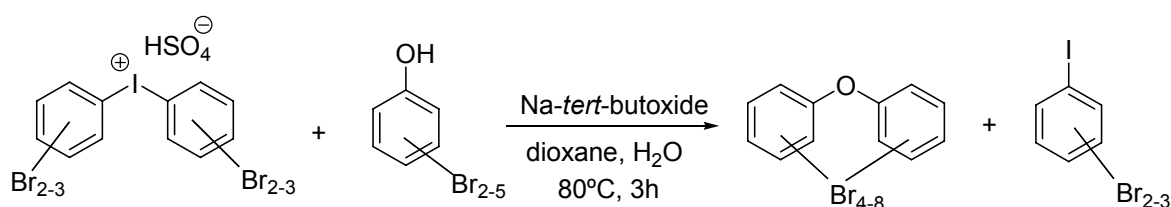
Scheme 4.16.

The diphenyliodonium salts used in those articles were symmetrical to give non-bromo-, 4-bromo-, 2,4- and 3,4-dibromo substitution in one of the phenyl rings of the PBDE products (143,147,152) as well as a 2,4,5-tribromo-substitution of the PBDEs for the unsymmetrical iodonium salt (147).



Scheme 4.17.

However, in Paper III, methods for the preparation of three symmetrical hexabrominated diphenyliodonium salts; 2,2',3,3',4,4'-hexabromodiphenyliodonium sulfate, 2,2',4,4',5,5'-hexabromodiphenyliodonium sulfate and 2,2',4,4',6,6'-hexabromodiphenyliodonium sulfate were developed. This gave me the opportunity to synthesize PBDE congeners with 2,3,4-tribromo, 2,4,5-tribromo and 2,4,6-tribromo substitution pattern in one of the phenyl rings. The synthesis of hexabrominated diphenyliodonium salts has previously failed (147,154), but extended reaction times and above all, the addition of more solvent (sulfuric acid) were sufficient modifications to obtain the desired product. The preparation of hexabrominated diphenyliodonium salts made it possible to synthesize PBDEs at an octabromo level, by reactions with pentabromophenol. In addition to the synthesis of new symmetrical hexabrominated diphenyliodonium salts, also the iodonium salt coupling was modified as described in detail in Paper III (Scheme 4.18), resulting in higher yields, especially for PBDE products substituted with six or more bromine atoms. Briefly, the modifications which gave better yields of the desired product and less by-products was the selection of 1,4-dioxane as a co-solvent, a new base (tert-butyloxy instead of hydroxid ion), a slight excess of the base and the diphenyliodonium salt (instead of equimolar amounts) and lower temperature (80°C instead of refluxing water mixture). With this modified method were tetra- to octaBDE congeners synthesized (Scheme 4.18 and Paper III).

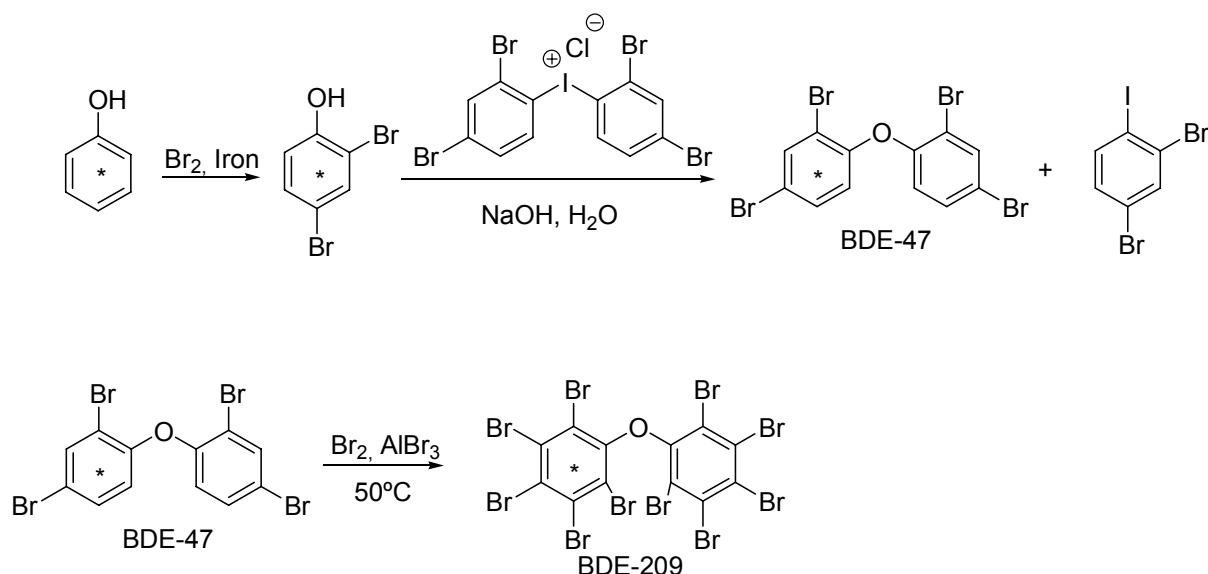


Scheme 4.18.

4.10 Synthesis of ¹⁴C-labeled PBDEs

A few ¹⁴C-labeled PBDEs have been described in scientific articles in the past (145,159,160). Bromination of ¹⁴C labelled phenol with 2.4 equivalents of bromine in CCl₄ with iron as a catalyst at room temperature gave ¹⁴C-labelled 2,4-dibromophenol. The ¹⁴C-labeled 2,4-dibromophenol was coupled with 2,2',4,4',5,5'-hexabromodiphenyliodonium chloride salt and 2,2',4,4'-tetrabromodiphenyliodonium chloride in aqueous NaOH to generate (BDE-99) and (BDE-47), respectively (160). ¹⁴C-labeled BDE-47, BDE-85 and

BDE-99 were synthesized by an Ullmann-coupling of ^{14}C -phenol (145,161) as in Scheme 4.7. Perbromination of ^{14}C -labelled BDE-47, using AlBr_3 as a catalyst and an excess of bromine gave ^{14}C -labelled BDE-209 (159) as shown in Scheme 4.19. The methods described above for synthesis of unlabeled PBDE congeners can preferentially be applied for new labeled compounds in those cases when it is possible to use a labeled polybromophenol as coupling agent. Other routes are most likely too tedious and laborious to be used for this purpose.



Scheme 4.19.

4.11 Comments on synthesis of PBDE congeners

This thesis has concentrated on the development of methods for synthesis of the highly brominated DEs. Hence it is now possible to basically synthesize any of the highest brominated DEs as well as most other PBDE congeners. It is obvious from 4.1-4.10 above, that there is a need for different methods depending on the desired structure of the final PBDE product. Still the iodonium salt pathway is the most ubiquitous method but if this method is to be applied it may require the synthesis of polybromophenols as coupling agents since there is a lack of such phenols from commercial sources. Significant contributions from the present work are the synthesis of hexabrominated diphenyl iodonium salts, the improvements made to increase the yields of PBDEs via the iodonium salt pathway (Paper III) and the synthesis of octaBDEs and nonaBDEs from aminodiphenyl ethers (Paper I and II).

5 Characterization of PBDEs

The present thesis has included characterization of the PBDE congeners synthesized as presented in Papers I-III. Below are a presentation and discussion on selected compounds and their features in relation to GC-MS, NMR and X-ray.

5.1 GC-MS

Gas chromatography-mass spectrometry (GC-MS) characterization of PBDE congeners was performed on an ion trap mass spectrometer operating in the electron ionization mode. Detailed parameters of the GC-MS performance are reported in Paper I, II and III. Mass spectra of PBDEs, recorded in electron ionization mass spectrometry (EIMS) mode, consist generally of the $[M]^+$ (molecular ion), $[M - 2Br]^+$, $[M - nBr - CO]^+$ ($n = 1-5$) and double charged ions of the fragment ion $[M - 2Br]^{2+}$. $[M - 2Br]^+$ ions are the most abundant ones for PBDEs substituted with at least one bromine atom in the *ortho* position to the diphenyl ether bond (Figures 5.1-5.5). The high abundance of the $[M - 2Br]^+$ ion is probably due to the formation of the more stable dibenzofuran ion (162) (Figure 5.6). The $[M]^+$ ion was the most abundant fragment ion for PBDEs with no bromine substituted in the *ortho* position (Figures 5.7 and 5.8). However, those PBDEs without bromine substituted in the *ortho* position, do also form distinct dibenzofuran ions through rearrangement of bromine in the phenyl rings after initial ionization (162), but with less intensity compared to $[M - 2Br]^+$. In some PBDEs with *ortho* bromine atoms, the difference between $[M - 2Br]^+$ and $[M]^+$ is less pronounced. For example, the abundance of the ions $[M]^+$ and $[M - 2Br]^+$ were about the same range 93% and 100%, respectively for BDE-47 as shown in Figure 5.9. Thus, when bromine is substituted in *ortho* and *para* position (but not in *meta* position) the abundance of the $[M]^+$ ion increase in relation to the $[M - 2Br]^+$ ion. This may be due to that bromine substituted in *ortho* and *para* position stabilizes the $[M]^+$ ion through conjugation. Other examples are e.g. BDE-75 and BDE-100, which lack bromines in the *meta* position. Thus, generally non-*ortho*-PBDEs have $[M]^+$ as the base peak whereas *ortho* PBDEs have the $[M - 2Br]^+$ as the base peak, and the number of bromine atoms in the *meta* position decrease the intensity of the $[M]^+$ ion in *ortho* substituted PBDEs in relation to the $[M - 2Br]^+$ ion. These fragment ion observations are based on the PBDEs synthesized by Marsh et al. (143) and the PBDEs that have been synthesized in Paper I, II and III. Eljarrat et al. (163), Larrazabal et al. (164) and Ackerman et al. (165) have also observed the same fragment ions as described in this Chapter.

EI can be used for the analysis of PBDEs in environmental samples using a ion trap tandem mass spectrometry detection (ITD-MS-MS) as reported by Gómara et al. (166).

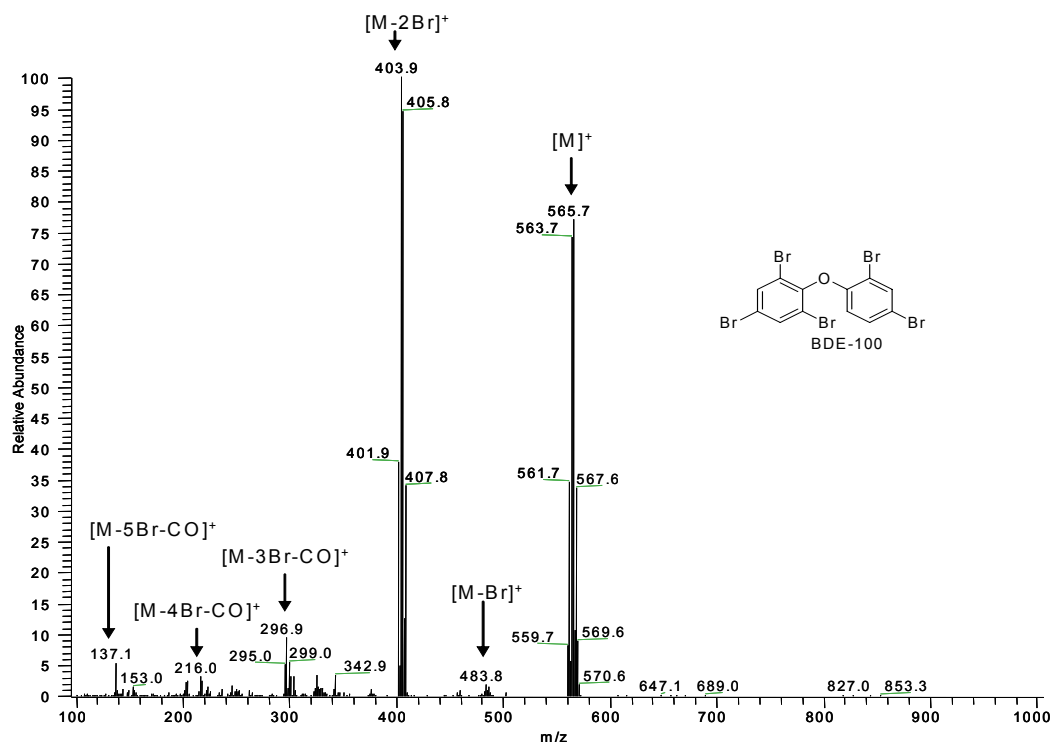


Figure 5.1. Electron ionization mass spectra of 2,2',4,4',6-pentaBDE (BDE-100).

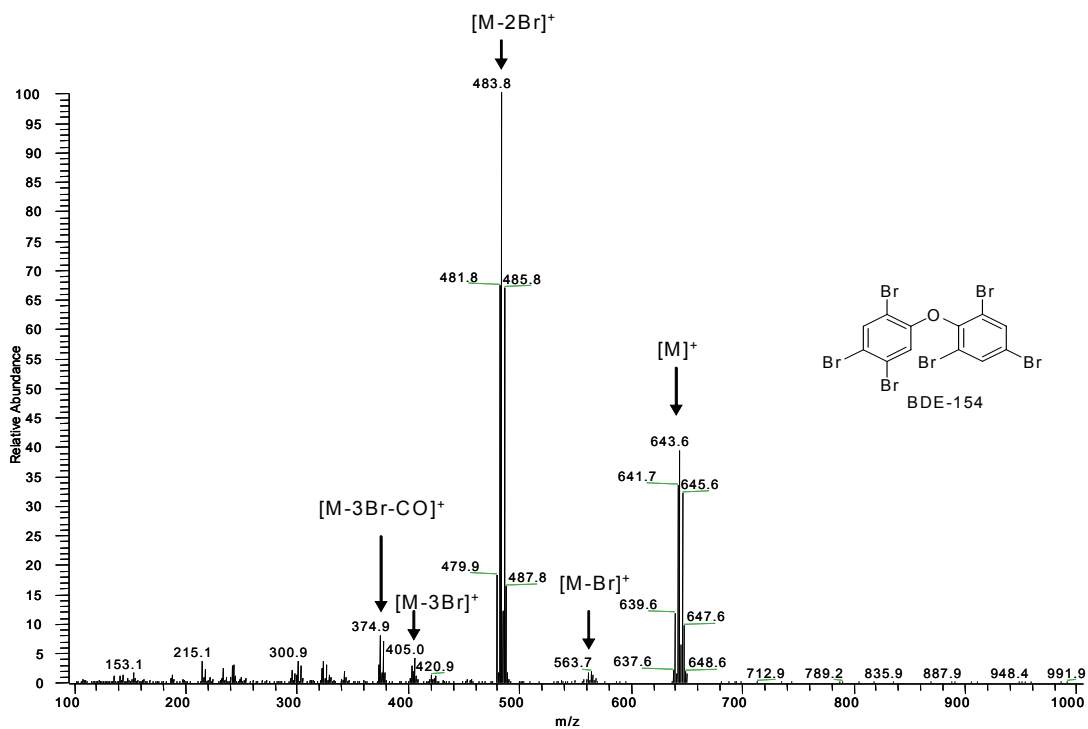


Figure 5.2. Electron ionization mass spectrum of 2,2',4,4',5,6'-hexabDE (BDE-154).

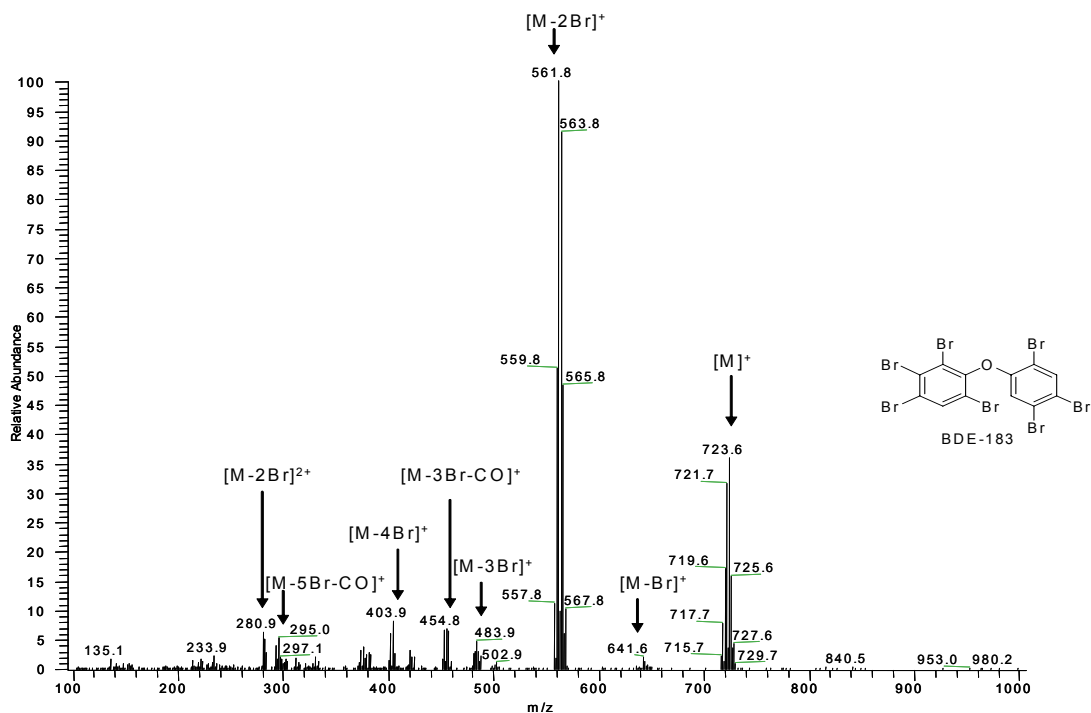


Figure 5.3. Electron ionization mass spectra of 2,2',3,4,4',5',6'-heptaBDE (BDE-183).

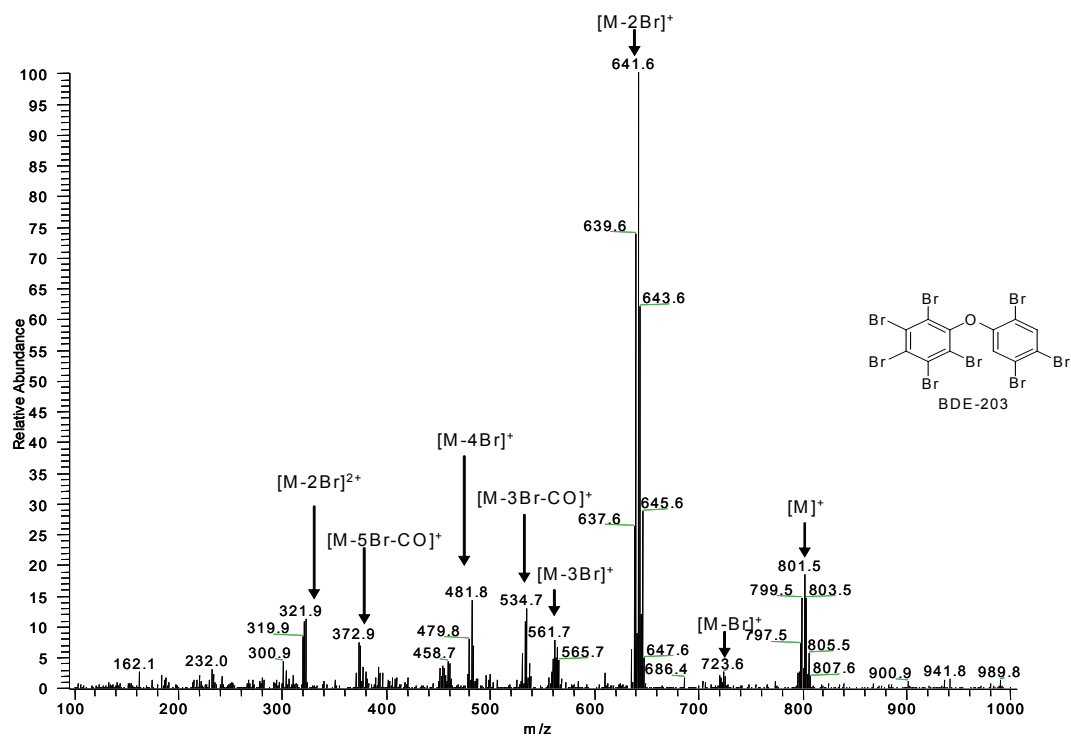


Figure 5.4. Electron ionization mass spectrum of 2,2',3,4,4',5,5',6-octaBDE (BDE-203).

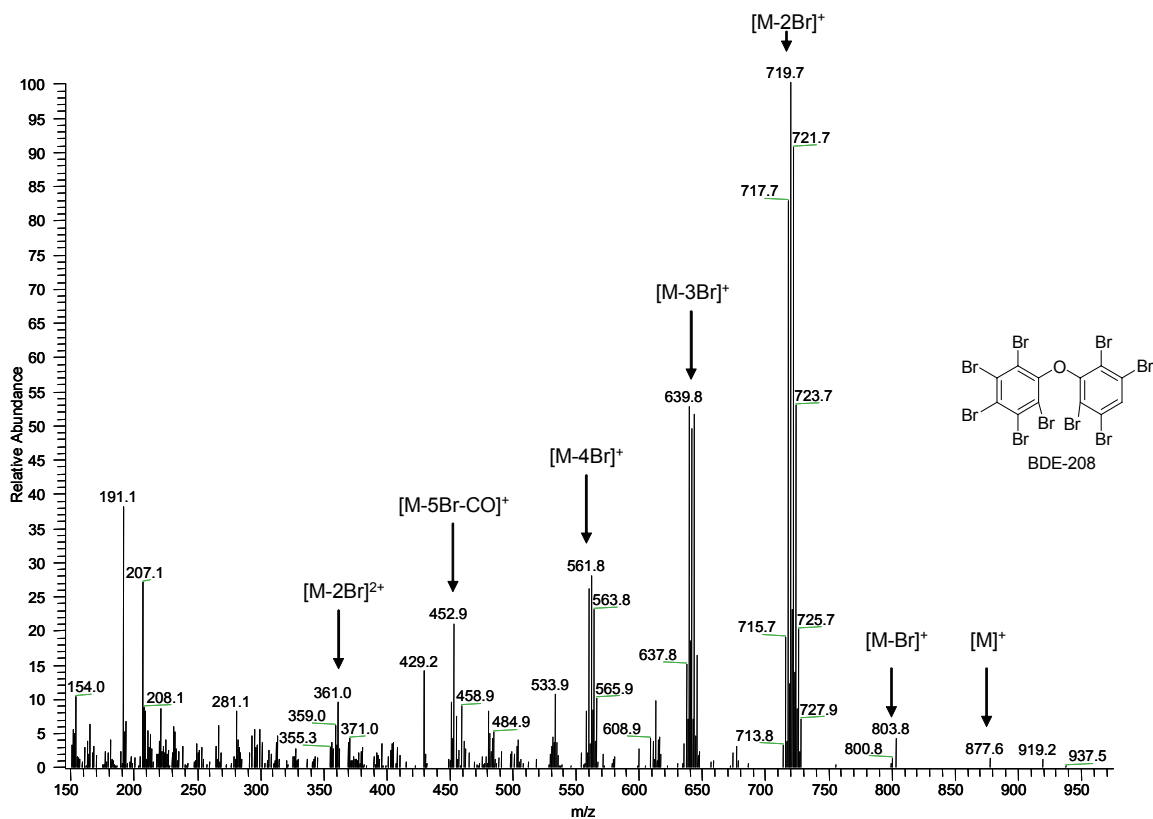


Figure 5.5. Electron ionization mass spectrum of 2,2',3,3',4,5,5',6,6'-nonaBDE (BDE-208).

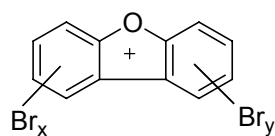


Figure 5.6. The $[M - 2Br]^+$ fragment ion of PBDE congeners can most likely be explained by the formation of a stable dibenzofuran ion.

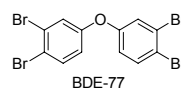
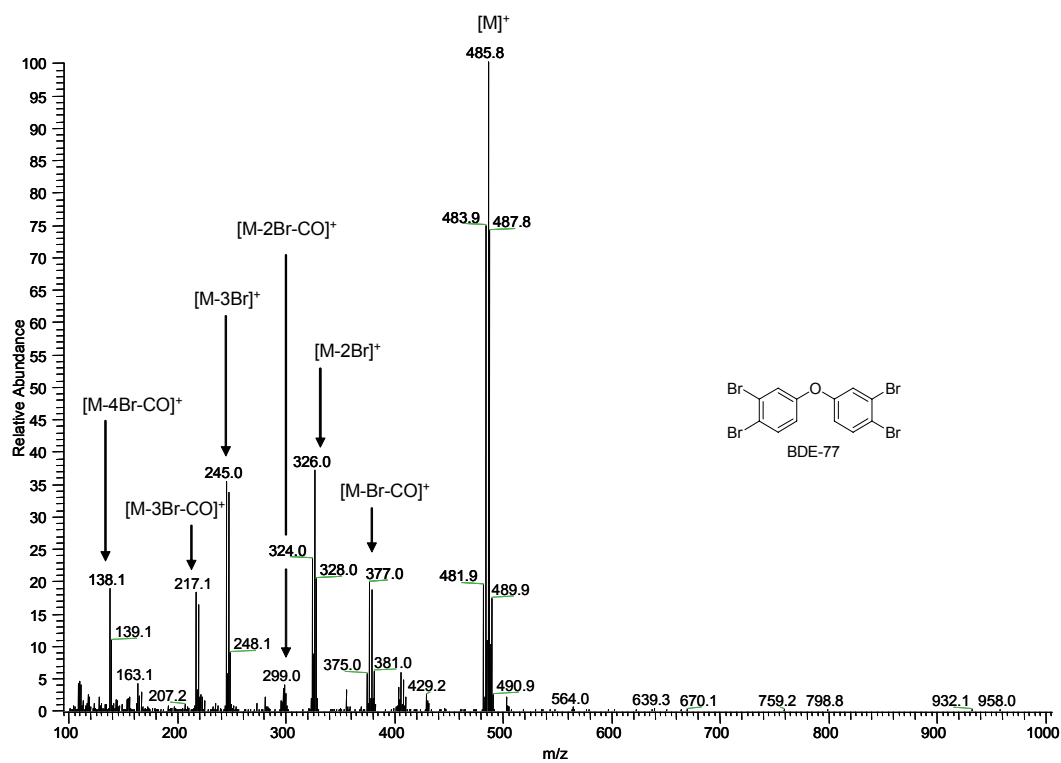


Figure 5.7. Electron ionization mass spectrum of 3,3',4,4'-tetraBDE (BDE-77) with no bromines in the *ortho* positions of the diphenyl ether.

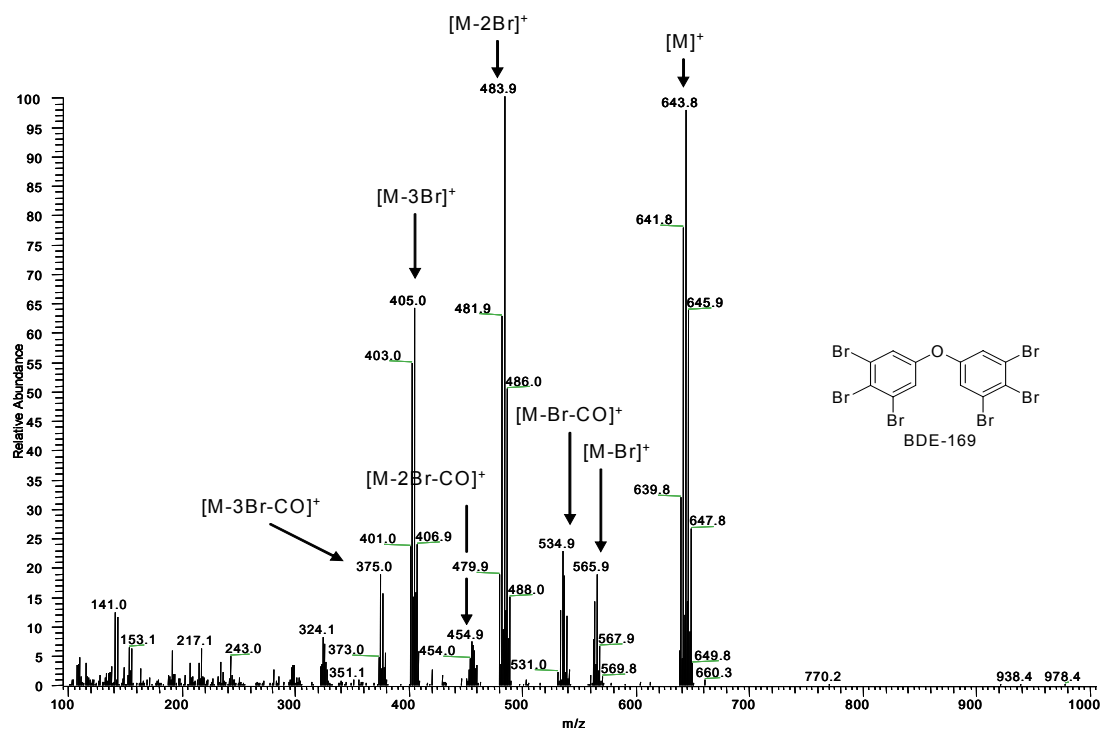


Figure 5.8. Electron ionization mass spectra of 3,3',4,4',5,5'-hexaBDE (BDE-169).

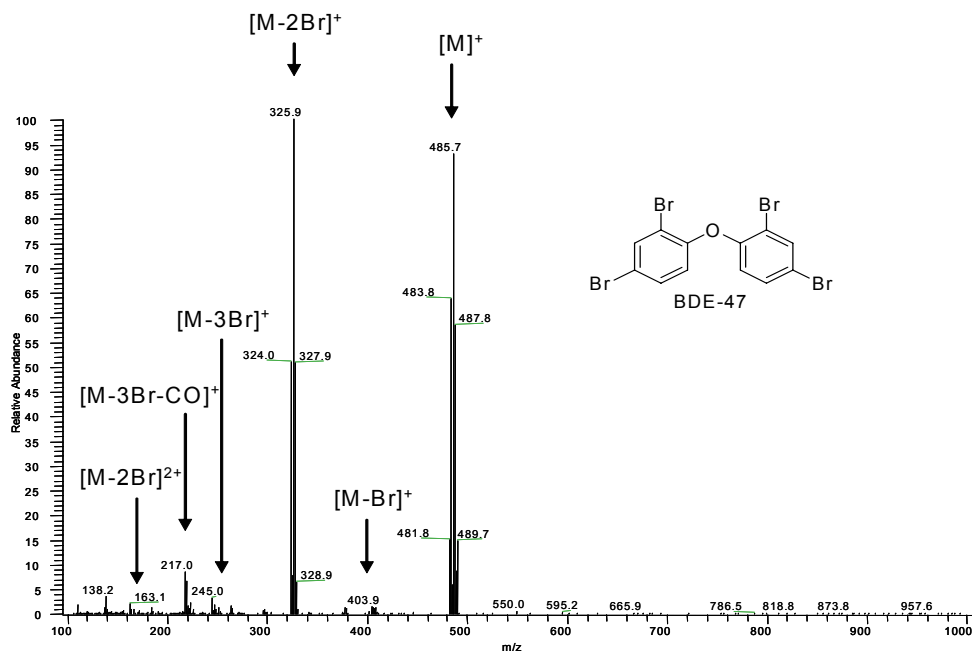


Figure 5.9. Electron ionization mass spectra of 2,2',4,4'-tetraBDE (BDE-47).

Electron capture negative ionization (ECNI) is another useful tool for characterization and analysis of PBDE congeners that are widely used for PBDE analysis measuring m/z 79, 81. This method can supply us with particular structure information of the PBDE congeners analyzed.

For example, an octabrominated DE can be substituted with four bromines in each phenyl ring or with three bromines in one of the phenyl rings and accordingly five bromines in the other phenyl ring. ECNI will cleave the diphenyl ether bridge resulting in phenoxide ions. In the first case above, the phenoxide ion contain four bromine atoms and in the second case three and five bromine atoms depending on how the molecule fragment. It is therefore possible to distinguish between 2,2',3,3',4,4',6,6'-octabromodiphenyl ether (BDE-197) and 2,2',3,4,4',5,6,6'-octabromodiphenyl ether (BDE-204) which co-elute on non-polar GC-columns. Thus, BDE-197 only forms the tetrabrominated phenoxide ions $[C_6Br_4HO]^-$ whereas BDE-204 gives both tri- $[C_6Br_3H_2O]^-$ and pentabrominated phenoxide ions $[C_6Br_5O]^-$ (133). This diphenyl ether bond cleavage occurs for PBDEs with seven or more bromines, and tri-, tetra- or pentabromophenoxide ions are the dominating fragment ions. This is in contrast to PBDEs with seven or less bromine substituents for which fragment ions are dominated by $[Br]^-$ and $[HBr_2]^-$ ions (133). It is observed that the diphenyl ether cleavage for some heptabrominated DEs with three bromines on one phenyl ring and four on the other phenyl ring, but not for heptabrominated DEs with two bromines in one of the phenyl rings and five bromines in the other phenyl ring (133). The pentaphenoxide ion may be used for the analysis of BDE-209 (167).

Differences in the abundance of the fragment ions of PBDEs as well as possible different fragment ions may be observed depending on which instrument and temperature is used. It is important that the researchers understand how their instruments behave from time to time regarding MS in both EI and ENCI mode.

5.2 NMR

The synthesized compounds were characterized by 1H NMR and ^{13}C NMR, for instruments and performance see Papers I, II and III. Table 5.1 summarize the 1H NMR chemical shifts of PBDE congeners that previously have been reported (143,145,147) as well as reported in the Papers I, II and III.

A diphenyl ether may have four possible types of conformations, the planar ($\varphi_1 = \varphi_2 = 0^\circ$), butterfly ($\varphi_1 = \varphi_2 = 90^\circ$), skew ($\varphi_1 = 0^\circ, \varphi_2 = 90^\circ$) and twist ($0^\circ < \varphi_1 = \varphi_2 < 90^\circ$) (151) see Figure 5.11. The conformations of PBDEs exist in twist to skew conformations according to 1H NMR (143,168,169) and by X-ray measurements (170-173). The higher the number of bromine atoms

substituted *ortho* to the diphenyl ether linkage is, the more skewed is the conformation of the PBDE.

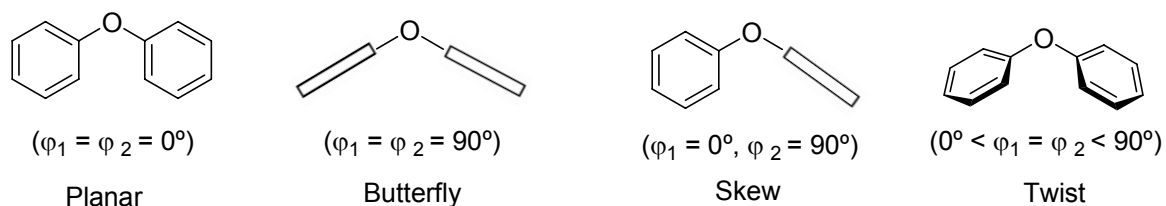


Figure 5.11. General conformations of diphenyl ethers, planar, butterfly, skew and twist.

For PBDEs, ^1H NMR chemical shifts in CDCl_3 are in the range of 6.24 to 7.27 for *ortho*-protons, 7.18 to 8.08 for *meta*-protons and 7.01-7.29 for *para*-protons, 6.59-7.59 in DMSO-d_6 for *ortho*-protons, 7.47-8.37 for *meta*-protons and 7.82-8.19 for *para*-protons and 6.97-7.49 in THF-d_8 for *ortho*-protons, 7.85-8.50 for *meta*-protons and 8.01-8.07 for *para*-protons (Table 5.1). *Meta*-protons surrounded by bromine have the highest chemical shifts (8.50) whereas the ^1H NMR chemical shifts for *ortho*-protons surrounded with tri-*ortho* bromines were considerably more upfield (6.24). This can be described as an inter-ring effect, caused by the magnetic ring current in the neighboring phenyl (ring). This type of PBDEs are forced into a skew or near skew conformation by bulky *ortho* bromines (143,169). Examples of PBDE congeners with the latter effect are BDE-51, -100, -140 and -206.

Table 5.1. ^1H NMR chemical shifts of 58 individual PBDE congeners.

	Solvent	1	2	3	4	5	6	7	8	9	10
BDE-1	CDCl_3	-	7.63	7.01	7.25	6.96	6.97	7.34	7.11	7.34	6.97
BDE-2	CDCl_3	7.14	-	7.22	7.18	6.93	7.02	7.36	7.15	7.36	7.02
BDE-3	CDCl_3	6.88	7.43	-	7.43	6.88	7.00	7.35	7.12	7.35	7.00
BDE-7	CDCl_3	-	7.77	-	7.36	6.81	6.96	7.35	7.12	7.35	6.96
BDE-8	CDCl_3	-	7.64	7.05	7.28	6.98	6.83	7.43	-	7.43	6.83
BDE-10	CDCl_3	-	7.61	7.01	7.61	-	6.81	7.30	7.05	7.30	6.81
BDE-12	CDCl_3	7.25	-	-	7.53	6.83	7.01	7.38	7.17	7.38	7.01
BDE-13	CDCl_3	7.13	-	7.24	7.19	6.93	6.90	7.46	-	7.46	6.90
BBD-15	CDCl_3	6.88	7.44	-	7.44	6.88	6.88	7.44	-	7.44	6.88
BDE-17	CDCl_3	-	7.78	-	7.34	6.66	-	7.64	7.06	7.28	6.89
BDE-25	CDCl_3	-	7.79	-	7.41	6.87	7.09	-	7.25	7.19	6.88

	Solvent	1	2	3	4	5	6	7	8	9	10
BDE-28	CDCl ₃	-	7.78	-	7.39	6.84	6.83	7.44	-	7.44	6.83
BDE-30	CDCl ₃	-	7.76	-	7.76	-	6.80	7.30	7.06	7.30	6.80
BDE-32	CDCl ₃	-	7.61	7.03	7.61	-	6.70	7.40	-	7.40	6.80
BDE-33	CDCl ₃	7.19	-	-	7.53	6.77	-	7.64	7.10	7.32	7.03
BDE-35	CDCl ₃	7.27	-	-	7.57	6.84	7.16	-	7.29	7.22	6.94
BDE-37	CDCl ₃	7.24	-	-	7.55	6.82	6.90	7.47	-	7.47	6.90
BDE-47	CDCl ₃	-	7.79	-	7.38	6.71	-	7.79	-	7.38	6.71
BDE-49	CDCl ₃	-	7.80	-	7.41	6.78	-	7.50	7.17	-	6.91
BDE-51	CDCl ₃	-	7.78	-	7.25	6.26	-	7.62	7.05	7.62	-
BDE-66	CDCl ₃	-	7.80	-	7.43	6.89	7.19	-	-	7.55	6.77
BDE-71	CDCl ₃	-	7.62	7.05	7.62	-	7.09	-	-	7.51	6.65
BDE-75	CDCl ₃	-	7.76	-	7.76	-	6.69	7.40	-	7.40	6.69
BDE-77	CDCl ₃	7.27	-	-	7.58	6.84	7.27	-	-	7.58	6.84
BDE-81 ^a	Not given	7.80	-	-	-	7.80	6.71	7.42	-	7.42	6.71
BDE-85 ^b	CDCl ₃	-	-	-	7.54	6.76	-	7.79	-	7.40	6.64
BDE-99 ^b	CDCl ₃	-	7.87	-	-	6.99	-	7.79	-	7.41	6.80
BDE-100	CDCl ₃	-	7.77	-	7.77	-	-	7.78	-	7.26	6.27
BDE-116	CDCl ₃	-	-	-	-	-	6.79	7.32	7.09	7.32	6.79
BDE-119	CDCl ₃	-	7.77	-	7.77	-	7.08	-	-	7.52	6.64
BDE-126 ^a	Not given	7.27	-	-	-	7.27	7.32	-	-	7.64	6.90
BDE-128 ^b	CDCl ₃	-	-	-	7.60	6.70	-	-	-	7.60	6.70
BDE-138 ^b	CDCl ₃	-	-	-	7.60	6.74	-	7.89	-	-	7.04
BDE-139 ^c	DMSO-d ₆	-	-	-	8.36	-	-	8.00	-	7.47	6.59
BDE-140	CDCl ₃	-	-	-	7.45	6.24	-	7.78	-	7.78	-
BDE-153 ^b	CDCl ₃	-	8.08	-	-	7.26	-	8.08	-	-	7.26
BDE-154	CDCl ₃	-	7.88	-	-	6.58	-	7.79	-	7.79	-
BDE-155	DMSO-d ₆	-	7.99	-	7.99	-	-	7.99	-	7.99	-
BDE-166	CDCl ₃	-	-	-	-	-	6.68	7.42	-	7.42	6.68
BDE-169 ^d	THF-d ₈	7.48	-	-	-	7.48	7.48	-	-	-	7.48
BDE-180 ^c	DMSO-d ₆	7.59	-	-	-	-	7.56	-	-	8.20	-
BDE-181 ^c	CDCl ₃	-	-	-	-	-	-	7.80	-	7.27	6.25
BDE-182 ^c	DMSO-d ₆	7.05	-	-	-	-	-	8.12	-	8.15	-
BDE-183 ^c	CDCl ₃	-	-	-	7.98	-	-	7.89	-	-	6.57
BDE-184 ^c	DMSO-d ₆	-	8.22	-	-	-	-	7.99	-	7.99	-
BDE-190	CDCl ₃	-	-	-	-	-	7.09	-	-	7.53	6.62
BDE-191 ^d	THF-d ₈	-	-	-	8.19	-	7.27	-	-	-	7.27
BDE-194 ^d	THF-d ₈	7.47	-	-	-	-	7.47	-	-	-	-
BDE-195 ^c	THF-d ₈	-	-	-	-	-	7.49	8.50	-	-	-
BDE-196 ^d	THF-d ₈	-	-	-	8.21	-	-	-	-	-	6.97
BDE-198 ^d	DMSO-d ₆	-	-	-	-	-	-	-	7.82	-	7.15
BDE-201 ^d	THF-d ₈	-	-	-	8.10	-	-	-	8.07	-	-
BDE-202 ^d	DMSO-d ₆	-	-	8.19	-	-	-	-	8.19	-	-
BDE-203 ^c	THF-d ₈	-	-	-	-	-	-	8.01	-	-	7.01
BDE-204 ^c	THF-d ₈	-	-	-	-	-	-	7.85	-	7.85	-
BDE-206 ^e	THF-d ₈	-	-	-	-	-	7.10	-	-	-	-
BDE-207 ^e	THF-d ₈	-	-	-	-	-	-	8.05	-	-	-
BDE-208 ^e	THF-d ₈	-	-	-	-	-	-	-	8.01	-	-

^{a)}Chen et al 2001, ^{b)}Örn et al 1996, ^{c)}Paper III, ^{d)}Paper II, ^{e)}Paper I

¹³C NMR data are published by Hu et al. (169), Liu et al. (152) and in Paper I, II and III. ¹³C NMR data can be calculated by an equation that is described by Hu et al. (169). No particular characteristics have been extracted from collected data which is the reason for no further discussion herein.

5.3 X-ray

The structures of seven of the octaBDEs in Paper IV have also been verified by X-ray crystallographic measurements (174). The X-ray studies have been of key importance for unambiguous identification of several of the PBDE congeners. The structures were solved by standard direct methods using the program SHELXS and refined with full matrix least square calculations using the program SHELXL. All non-hydrogen atoms were refined with anisotropic displacement parameters. Severe problems with absorption effects causing systematic error in the diffraction data occurred. A major part of these systematic errors were corrected using traditional absorption correction methods but also through the use of averaging data from several different crystals. The packing structure of the different compounds are both composed of π - π stacking with more or less parallel π -systems interacting with each other and also some C-Br... π interactions making a packing pattern similar to the traditional herring bone pattern, often found in structures of aromatic compounds.

A few details of the crystal structure determinations are given in Table 5.1 below.

Table 5.1. Summary of crystal structure data for five of the octa-BDEs present in Paper IV.

Compound	I	II	III	IV	V
BDE-#	198	201	202	203	204
Br-substitution	2,2',3,3',4,5,5',6	2,2',3,3',4,5',6,6'	2,2',3,3',5,5',6,6'	2,2',3,4,4',5,5',6	2,2',3,4,4',5,6,6'
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	P bca (nr. 61)	P 2 ₁ /c (nr. 14)	C 2/c (nr. 15)	P -1 (nr. 2)	P -1 (nr. 2)
a / Å	11.6286(6)	8.6933(17)	26.706(3)	9.5297(12)	8.720(2)
b / Å	11.6040(6)	14.4833(14)	9.6054(5)	9.7074(13)	9.112(2)
c / Å	25.5419(14)	14.534(2)	16.5660(19)	9.9778(14)	12.710(3)
α / °	90	90	90	93.716(16)	72.58(2)
β / °	90	98.03(2)	121.772(11)	95.552(16)	75.78(3)
γ / °	90	90	90	104.323(15)	68.19(3)
V / Å ³	3446.6(3)	1812.0(5)	3612.7(6)	886.4(2)	884.3(4)
V per molecule / Å ³	430.8(1)	453.0(1)	451.6(1)	443.2(1)	442.2(2)
Z, Z'	8, 1	4, 1	8, 1	2, 1	2, 1
N _{ineas.}	29839	7497	16702	12658	7659
N _{unique} , R _{int}	3258, 0.0616	1883, 0.0834	4363, 0.0731	3356, 0.10	4183, 0.1282
N _{obs} , N _{par}	2370, 191	1062, 190	2500, 190	1842, 190	3060, 190
wR2(all data)	0.0985	0.1724	0.1046	0.1421	0.1485
R1 (obs data)	0.0413	0.0604	0.0430	0.0527	0.0611
S(all data)	1.107	0.923	0.976	0.925	1.025
Measurement device	Oxford Excalibur	STOE IPDS	STOE IPDS	Oxford Excalibur	STOE IPDS

Preliminary crystal data are available for another two crystal structures. These crystals structure models do have yet non-modeled absorption effects present in the reflection data. Further work is under way to process these data including measuring several crystals in order to reduce the importance of systematic errors due to absorption affects with the final goal to improve reflection data quality.

Table 5.2. Summary of crystal structure data for two of the octa-BDEs that needs improved reflection data quality before final publication.

Compound	X1	X2
BDE-#	194	196
Br-substitution	2,2',3,3',4,4',5,5'	2,2',3,3',4,4',5,6'
Crystal system	Triclinic	Triclinic
Space group	P -1 (nr. 2)	P -1 (nr. 2)
a / Å	5.089(3)	9.7457(4)
b / Å	12.746(9)	11.1716(3)
c / Å	14.022(9)	17.1956(7)
α / °	105.69(4)	81.9146(28)
β / °	90.67(5)	78.4892(36)
γ / °	94.46(5)	76.9474(31)
V / Å ³	872.5(10)	1778.14()
V per molecule / Å ³	436.2(5)	444.53
Z, Z'	2, 1	4, 2
N _{meas.}	4088	32783
N _{unique} , R _{int}	2495, 0.1704	10947, 0.0735
N _{obs} , N _{par}	1718, 192	3308, 331
R1 (obs data)	0.1593	0.0523
S(all data)	3.728	0.846
Measurement device	MARCCD; I911-5, Maxlab λ = 0.907Å	Oxford Excalibur
Temperature / K	100K	RT

ORTEP Figures of the octaBDE products are shown in the Appendix, Figure A1-A7.

The interplanar angle between the two rings planes of the two phenyl rings are in the range 80-90° angle for all seven structures. These dihedral angles of the least square planes fitted to the two phenyl rings are not strictly related to the torsion angles (e.g. C1-O-C1',C2' etc) of the different compounds due to the fact that the oxygen may be displaced from one or both of the ring-planes. Only a slight displacement of the oxygen atom in the order of 0.1Å, which is not uncommon among these compounds, is enough to make the comparison between torsion angles and interplanar angles difficult.

6 PBDEs synthesis and the future

Today more than 170 individual PBDE congeners are available as authentic reference standards from commercial sources and academia, together. This is an impressive number of standards and far more than the number of individual PBDE congeners hitherto identified in the environment. Several different methods have been developed or applied to make it possible to prepare this vast number of PBDEs. The methods used for synthesis of PBDEs have been discussed in Chapter 4, above. The present methods allow us to prepare a few more PBDEs but in case all 209 PBDE congeners should be synthesized we likely need some more developmental work. On the other hand, probably only a small number of additional PBDEs might be discovered, potentially originating from reductive debromination of known PBDEs, which might call for new synthesis and potentially for methodological development for their preparation. I feel that there is no further urgent need to prepare additional PBDEs at this moment. It is now more interesting to search for new challenges in synthesis and for development of future environmental exposure assessments.

However there is a lack of standards regarding PBDE metabolites and abiotically formed transformation products such as hydroxylated polybrominated diphenyl ethers (OH-PBDEs). PBDEs are metabolized to OH-PBDEs as reported for numerous individual PBDE congeners (159,161,175,176). Some OH-PBDEs have been identified in e.g. human blood but there are still others to be identified (19). Also, OH-PBDEs were very recently identified in air and water samples indicating abiotic pathways for their formation (177). A few methods for the preparation of single OH-PBDE congeners and the corresponding methoxylated PBDE (MeO-PBDE) have been reported but these methods have primarily been devoted to producing standards with the hydroxyl (methoxyl) group in an *ortho*-position to the diphenyl ether bond (178-181). Additional MeO-PBDEs and OH-PBDEs are required. The polybrominated phenoxyanisols are easily demethylated to form OH-PBDEs.

Also, some metabolites of BDE-209 i.e. PBDEs substituted with five to seven bromine atoms and interpreted to have a hydroxy group as well as a methoxy group (159,182), need to be synthesized. Thus, future works on PBDEs will probably focus on their phenolic metabolites.

To better cover the environmental problems that other BFRs may cause I can see a need for synthesis of some other brominated compounds, e.g. individual polybrominated trimethyl phenyls, indanes and decabromodiphenyl ethane

transformation products. Further, to understand and distinguish between anthropogenic and endogenous brominated compounds there will be a need for synthesis also of some standards for natural products. Potentially there will be a need for PBDF and PBDD standards in the future as well.

Without individual authentic reference standards it will be difficult to make progress in relation to both exposure assessments and to in depth toxicological understanding. The PBDE congeners synthesized within the frame of this thesis have been of great value for determination of congener reactivity for development of the persistency concept (183), a work that will require continuation with other pure individual compounds.

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Appendix

ORTEP figures of seven OctaBDE products are shown.

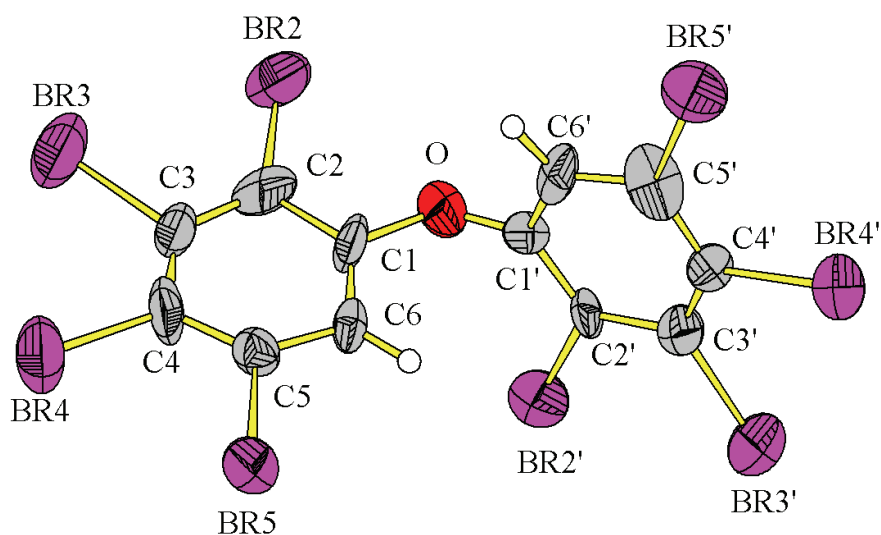


Figure A1. The structure of 2,2',3,3',4,4',5,5'-octabromodiphenyl ether (BDE-194).

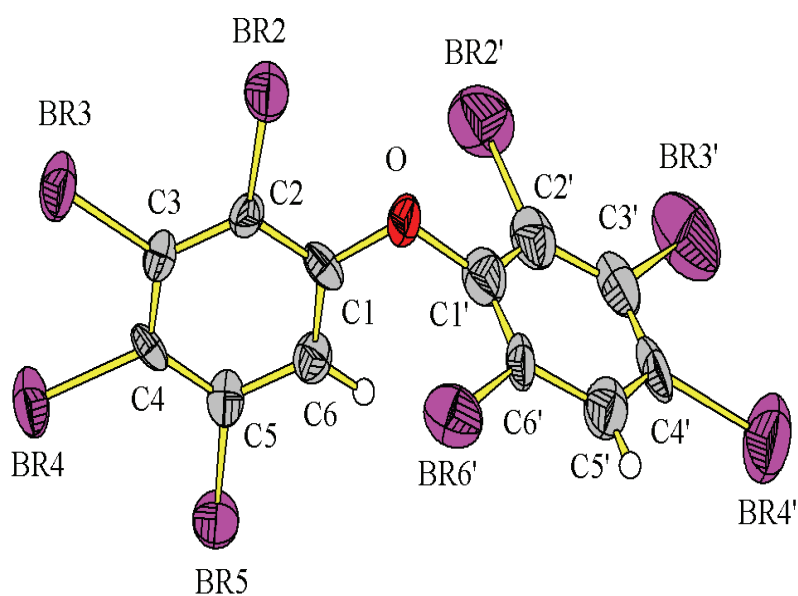


Figure A2. The structure of 2,2',3,3',4,4',5,6'-octabromodiphenyl ether (BDE-196).

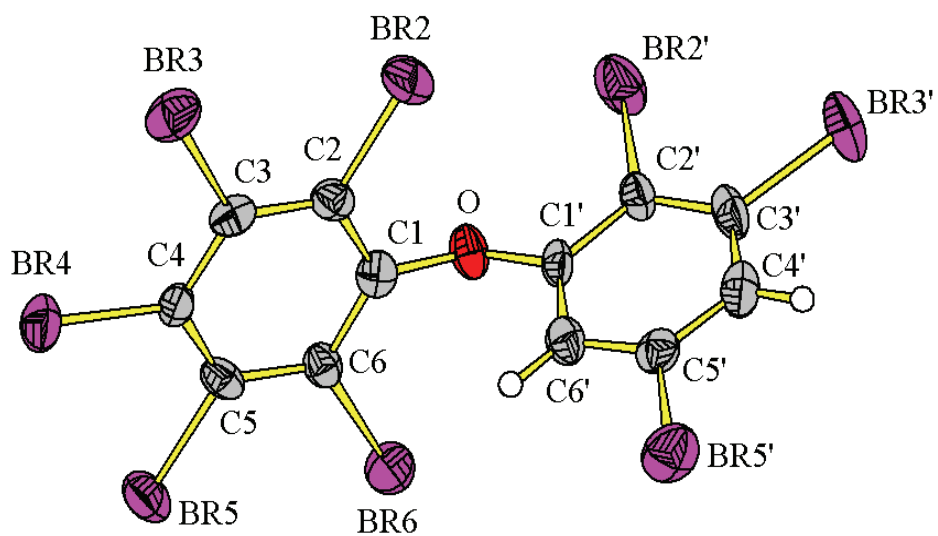


Figure A3. The structure of 2,2',3,3',4,5,5',6-octabromodiphenyl ether (BDE-198).

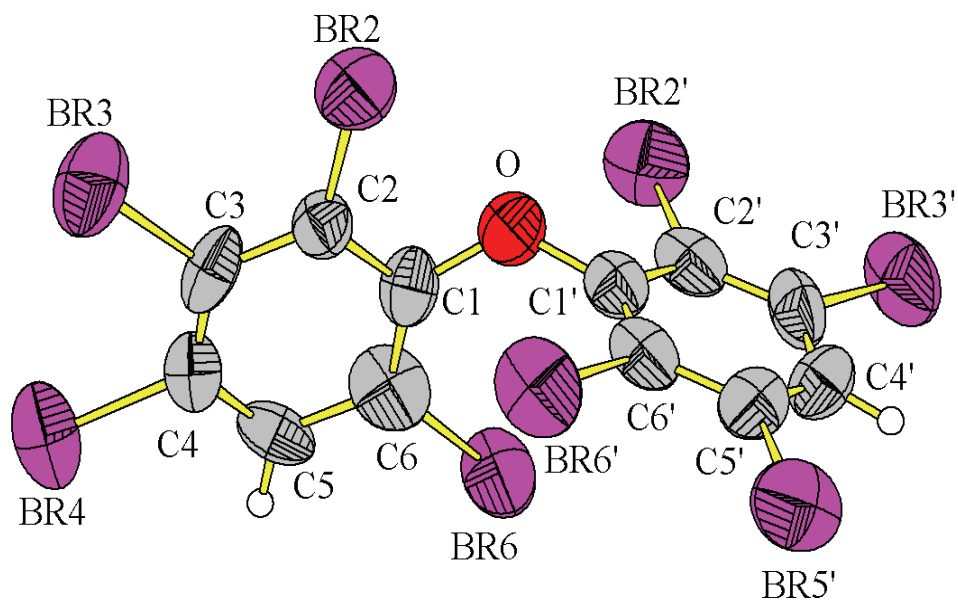


Figure A4. The structure of 2,2',3,3',4,5',6,6'-octabromodiphenyl ether (BDE-201).

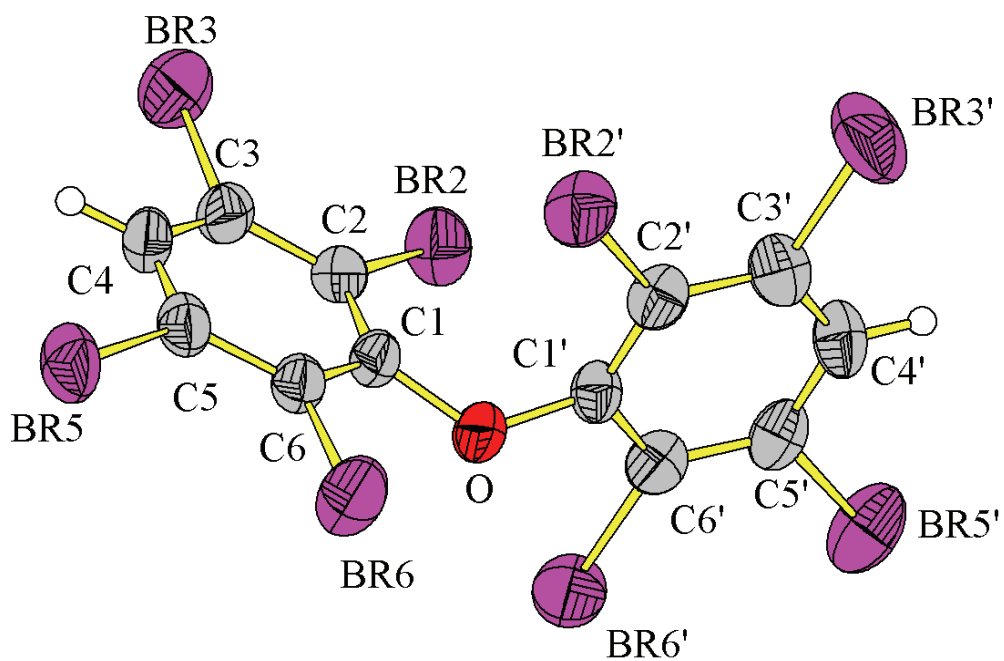


Figure A5. The structure of 2,2',3,3',5,5',6,6'-octabromodiphenyl ether (BDE-202).

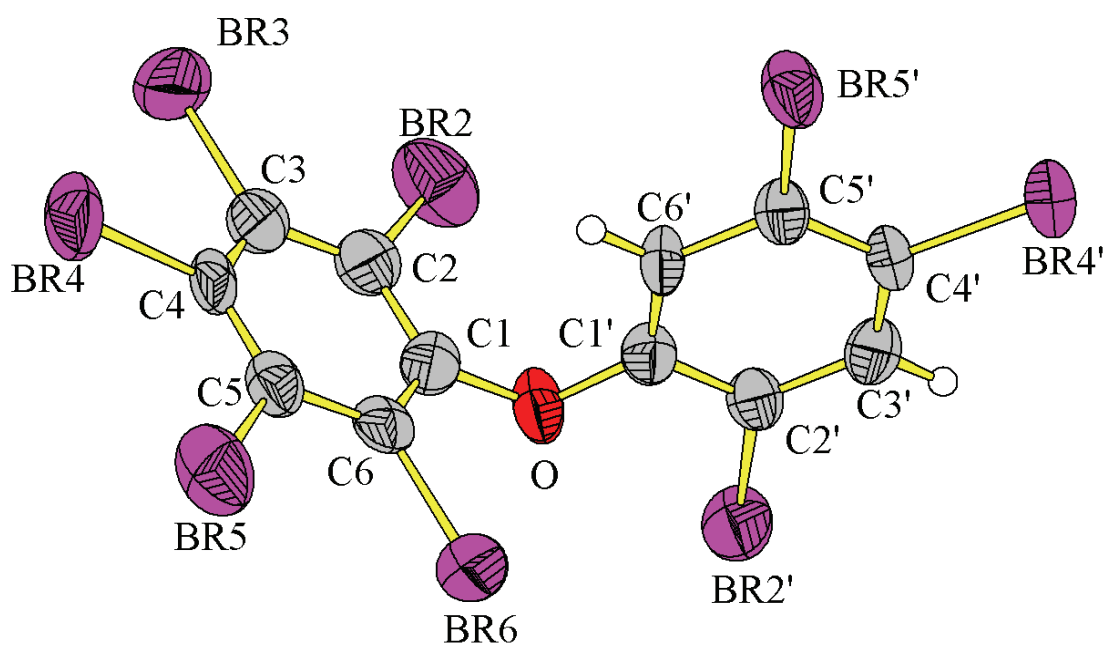


Figure A6. The structure of 2,2',3,4,4',5,5',6-octabromodiphenyl ether (BDE-203).

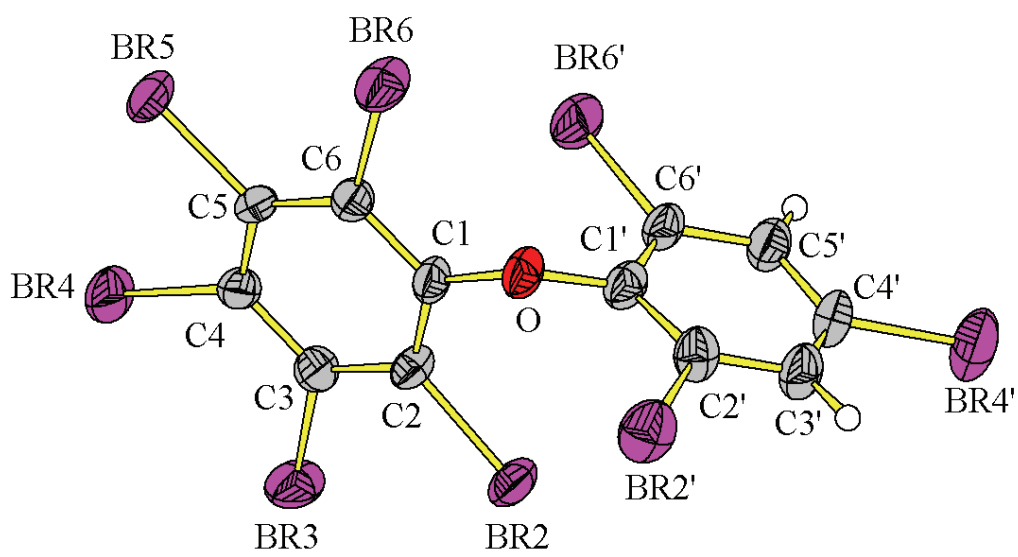


Figure A7. The structure of 2,2',3,4,4',5,6,6'-octabromodiphenyl ether (BDE-204).