

## Isomer specific synthesis of three nonabrominated diphenyl ethers and a chloro-nonabromodiphenyl ether

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### Introduction

Polybrominated diphenyl ethers (PBDEs) have been one of the most common brominated flame retardants (BFRs) in use over the last few decades<sup>1,2</sup>. PBDEs have been commercially manufactured as PentaBDE, OctaBDE and DecaBDE. The compositions of these products have been assessed and reported elsewhere<sup>3-7</sup>. Hence PentaBDE contain mainly diphenyl ethers with four to six bromine atoms but a total of ten PBDE congeners have been identified<sup>3</sup> and in OctaBDE seven congeners have been identified<sup>4</sup>. DecaBDE products contain mainly the perbrominated diphenyl ether (BDE-209) but also small amounts (up to 3%) of 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)<sup>5,7</sup>. Photochemical debromination of BDE-209 is another source of nonaBDEs as shown experimentally<sup>8,9</sup>. Microbially mediated reductive debromination of BDE-209 to nonaBDEs has been reported in sewage sludge<sup>10</sup> and in sediment<sup>11</sup>. BDE-209 has also been shown to be metabolized in rats to nonaBDEs<sup>12</sup> and most likely in rainbow trout (*Oncorhynchus mykiss*) and in humans exposed to DecaBDE<sup>7,13</sup>. NonaBDEs have been found in water<sup>14</sup>, sediment<sup>4</sup>, sewage sludge<sup>4,15</sup> and house dust<sup>16</sup>. In samples from biota, nonaBDEs have been reported to be present in e.g. various fish species<sup>17</sup> and in human blood<sup>7,18,19</sup>. The aim of the present work was to develop methods for the synthesis of the three nonaBDE congeners in order to provide authentic pure material for analytical standards, toxicological studies and for studies on physicochemical properties and reactivity. A chloro-nonabromodiphenyl ether, i.e. 4'-chloro-2,2',3,3',4,5,5',6,6'-nonabromodiphenyl ether (Cl-BDE-208), was also synthesized with the purpose to be a suitable internal standard for highly brominated compounds such as BDE-206, BDE-207, BDE-208 and BDE-209. Our strategy was to perform isomer specific synthesis of all three nonaBDEs via perbromination of diphenyl ethers protected by a functional group, which later was reduced.

### Materials and method

**Chemicals:** All solvents, acids and other chemicals used were of pro analysis quality. The starting materials, 2-phenoxyaniline, 3-phenoxyaniline and 4-phenoxyaniline were purchased from Sigma-Aldrich Chemie (Steinheim, Germany) and 4-chlorodiphenyl ether was from Acros Organics (New Jersey, USA). Decabromodiphenyl ether was bought from Fluka Chemie AG (Buchs, Switzerland).

**Instruments:** Gas chromatography-mass spectrometry (GC-MS) electron ionization (EI) mass spectra were recorded by an ion trap GCQFinnigan Mat instrument equipped with a fused silica capillary column, DB-5, 15 m x 0.25 mm i.d., 0.025-mm film thickness, J&W Scientific (Folsom, USA). The temperature program was set to: 80°C (2 min, then 15°C min<sup>-1</sup> to 300°C) and finally increased by 2°C min<sup>-1</sup> to 320°C. The injections were made in the splitless mode using an injection temperature of 260°C. Helium was used as carrier gas and mass spectra were recorded for *m/z* 150-1000 at an ion source temperature of 180°C and an electron energy of 70 eV. High-performance liquid chromatography (HPLC) was performed on a Knauer K-501 (Berlin, Germany) equipped with an UV detector UV100 from spectra-physics (Fremont, USA) and the column was a preparative C<sub>18</sub> reversed-phase column (Ace 5 C<sub>18</sub>, 250 x 21 mm, 5 µm particles) from Advanced Chromatography Technologies (Aberdeen, Scotland) using 8% water in acetonitrile as mobile phase with a flow rate of 10 mL min<sup>-1</sup> and with a UV detection at 310 nm.

**Synthesis:** 2,2',3,3',4,4',5,5',6-nonabromodiphenyl ether (BDE-206) was synthesized according to Scheme 1, starting from 2-phenoxyaniline **1**, whose acetyl derivative **4** was obtained using acetic acid anhydride. This acetamidodiphenyl ether (**4**) was perbrominated in an excess of bromine and AlBr<sub>3</sub><sup>20</sup>, which gave the nonabrominated acetamide **5**. Hydrolysis of the latter compound in concentrated sulfuric acid and THF yielded the nonabrominated phenoxyaniline **6**, which was diazotized using borontrifluoride and 3-methylbutyl nitrite<sup>21</sup> to obtain the

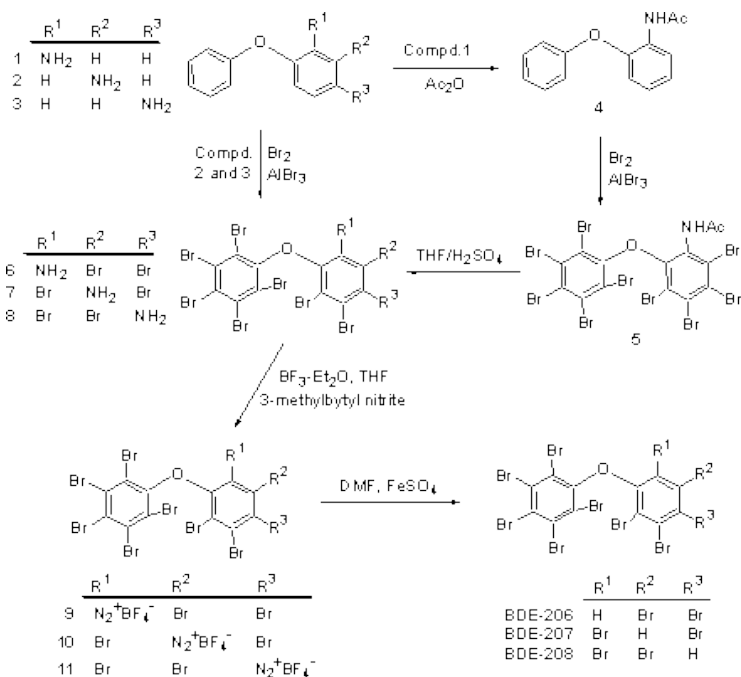
diazonium salt **9**. This salt was reduced in DMF with iron sulfate heptahydrate as a catalyst<sup>22</sup> giving BDE-206 in an overall yield of 6%.

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) were both synthesized without protection of the amino group via perbromination of phenoxyanilines **2** and **3**, respectively. This was done using bromine and aluminium tribromide similarly as for the preparation of the acetamidodiphenyl ether **5**. The perbrominated phenoxyanilines **7** and **8** were similarly diazotized as compound **6** giving diazonium salts **10** and **11**, which gave BDE-207 and BDE-208 after reduction with iron sulfate heptahydrate in DMF. The overall yields of BDE-207 and BDE-208 were 12% and 35% respectively.

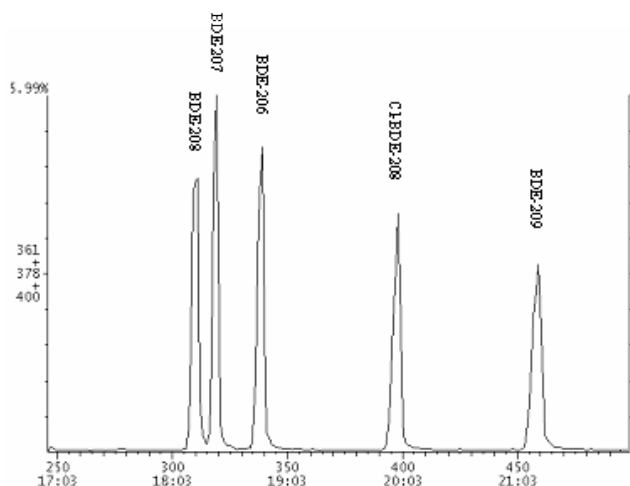
4-chloro-nonabromodiphenyl ether (Cl-BDE-208) was synthesized via perbromination of 4-chlorodiphenylether using an excess of bromine and  $\text{AlBr}_3$ <sup>20</sup>. The product was isolated in 62 % yield.

## Results and discussion

Reductive debromination of BDE-209 with sodium borohydride<sup>23</sup> and sodium thiolate<sup>24</sup> has given BDE-206 as the major product<sup>23</sup>. BDE-207 and BDE-208 were obtained in rather small amounts via reductive bromination with sodium borohydride<sup>23</sup> and the three nonaBDEs were isolated using preparative HPLC. With the pathway used here the crude products of the three nonaBDEs were all obtained as the pure individual isomers, which facilitated their purification. However, BDE-207 required purification by preparative HPLC whereas BDE-206 and BDE-208 did not. Efforts were made to prepare BDE-206 without protection of the amino group. However, perbromination of 2-phenoxyaniline **1** failed and the desired product **6** was not formed according to GC-MS. On the other hand, BDE-207 and BDE-208 were both synthesized without protection of the amino group via perbromination of phenoxyanilines **2** and **3**, respectively. Cl-BDE-208 was prepared with the purpose to be useful as an internal standard for highly brominated PBDEs. Cl-BDE-208 is well separated from the three nonaBDEs and BDE-209 on a 15 m non-polar GC column as shown in Figure 1. Thus, Cl-BDE-208 may be used as an internal standard, measuring highly brominated diphenyl ethers.



Scheme 1



**Figure 1.** GC-MS chromatogram recorded in the EI mode, showing the elution order of BDE-206, BDE-207, BDE-208, BDE-209 and Cl-BDE-208, on a non-polar GC column (DB-5, 15 m x 0.25 mm i.d. and 0.025-mm film thickness).

### Acknowledgements

Financial support has been gained through the European Community within the 5<sup>th</sup> framework programme for research, technological development and demonstration activities "FIRE".

Financial support was also gained from the Swedish foundation for strategic environmental research (MISTRA) through the frame of the NewS programme. The support from Ioannis Athanassidis with GC-MS is very much appreciated.

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