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Methods for synthesis of nonabromodiphenyl ethers and a chloro-nonabromodiphenyl ether

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Abstract

Polybrominated diphenyl ethers (PBDEs) have been used extensively as brominated flame retardants (BFRs) in textiles, upholstery and electronics. They are ubiquitous contaminants in wildlife and humans. A low concentration of nonabrominated diphenyl ethers (nonaBDEs) is present in commercial DecaBDE and they are also abiotic and biotic debromination products of decabromodiphenyl ether (BDE-209). The objective of the present work was to develop methods for synthesis of the three nonaBDEs, 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), with the intention of making them available as authentic standards for analytical, toxicological and stability studies, as well as studies regarding physical–chemical properties. Two methods were developed, one based on perbromination of phenoxyanilines and the other via reductive debromination of BDE-209 by sodium borohydride followed by chromatographic separation of the three nonaBDE isomers formed. An additional nonabrominated compound, 4′-chloro-2,2′,3,3′,4,5,5′,6,6′-nonabromodiphenyl ether (Cl-BDE-208), was also synthesized in the present work. Cl-BDE-208, prepared by the perbromination of 4-chlorodiphenyl ether, may be used as an internal standard in analysis of highly brominated diphenyl ethers. BDE-206, BDE-207, BDE-208 and Cl-BDE-208 were characterized by ^{1}H NMR, ^{13}C NMR, electron ionization mass spectra and by their melting points. The structures of all three nonaBDEs have been characterized previously by X-ray crystallography.

Keywords: Polybrominated diphenyl ethers (PBDEs); Nonabrominated diphenyl ethers (nonaBDEs); Perbromination; Diazotation; Phenoxyaniline; Reductive debromination

1. Introduction

In the last few decades, polybrominated diphenyl ethers (PBDEs), commercially manufactured as PentaBDE, OctaBDE and DecaBDE, have been among the dominating types of brominated flame retardants (BFRs) (Alaee et al., 2003; BSEF, 2004a). The compositions of these products have been assessed and reported elsewhere (Sjödin et al., 1998; Björklund et al., 2003; Thuresson et al., 2005). PBDEs are present in the abiotic environment, in many forms of wildlife, and humans worldwide (de Wit, 2002; Law et al., 2003; Hites, 2004). However, due to the ban of PentaBDE and

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OctaBDE by the European Union (EU) (Cox and Efthymiou, 2003) and a voluntary halt in production by the sole US producer (BSEF, 2004b; Great Lakes Flame Retardants, 2005), no PentaBDE or OctaBDE have been manufactured after 2004. The world production of DecaBDE reached 56 000 tons in 2001 (BSEF, 2004a) and no changes in its production has, to our knowledge, occurred.

DecaBDE products contain low concentrations (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) (WHO, 1994; Thuresson et al., 2005). Debromination of BDE-209 is another source of nonaBDEs and lower brominated diphenyl ethers, for example formation via photochemical debromination (Eriksson et al., 2004; Söderström et al., 2004). Further, microbially mediated reductive debromination of BDE-209 to nonaBDEs has been reported to occur in sewage sludge (Gerecke et al., 2005) and in sediment (Parsons et al., 2004). BDE-209 has also been shown to be metabolized to nonaBDEs in rats (Mörck et al., 2003), most likely in rainbow trout (*Oncorhynchus mykiss*) (Kierkegaard et al., 1999) and in humans (Thuresson et al., 2005) exposed to DecaBDE.

NonaBDEs have been reported in water (Oros et al., 2005), sediment (Kierkegaard et al., 2004), sewage sludge (Kierkegaard et al., 2004; North, 2004) and house dust (Stapleton et al., 2004). In samples from biota, nonaBDEs have been reported to be present in various fish species (Burreau et al., 2004) and in human blood (Sjödin et al., 2001; Jakobsson et al., 2002; Thuresson et al., 2005). In fish, the three nonaBDEs and BDE-209, were found to be bioavailable but they did not biomagnify (Burreau et al., 2004). However, BDE-209 is absorbed effectively from the diet by grey seals (*Halichoerus grypus*) and can be stored in the blubber after exposure (Thomas et al., 2005). Concentrations ranging between 20 and 430 ng/g lipid weight of BDE-209 was determined in eggs from Peregrine Falcons (*Falco peregrinus*) (Lindberg et al., 2004) indicating a high uptake of highly brominated diphenyl ethers.

The aim of the present work was to develop methods for synthesis of the three nonaBDE congeners in order to provide authentic pure material for analytical standards, toxicological studies and for studies on physical–chemical properties and stability. A monochlorononabromodiphenyl ether, i.e. 4′-chloro-2,2′,3,3′,4,5,5′,6,6′-nonabromodiphenyl ether (Cl-BDE-208), was also synthesized as a suitable internal standard for highly brominated compounds such as PBDEs.

Several methods for the synthesis of PBDEs containing 1–7 bromine atoms have been described previously including (i) the coupling of symmetrical or unsymmetrical iodonium salts with bromophenols (Marsh et al., 1999; Chen et al., 2001), (ii) aromatic nucleophilic substitution reactions (S_NAr) by the coupling of a bromofluoronitrobenzene with bromophenols followed by diazotization and the treatment with copper bromide (Chen et al., 2001) and (iii) bromination of diphenyl ether or a PBDE (Norström et al., 1976; Örn et al., 1996; Marsh et al., 1999). The fully brominated diphenyl ether, BDE-209 has been synthesized by perbromination of diphenyl ether using bromine and aluminium tribromide (Golounin et al., 1994). However, we considered these method, to be too difficult for successful synthesis of the three nonaBDEs. Therefore, our strategy was to synthesize all three nonaBDEs via perbromination of diphenyl ethers protected by a functional group, which could be subsequently reduced to a hydrogen. An alternative strategy was to investigate the possibility to perform reductive debromination of BDE-209.

2. Results and discussion

BDE-206, BDE-207 and BDE-208 can, as shown in this study, be synthesized and isolated in pure form, either by applying a route of reactions leading to each one of the three individual compounds or using a method leading to the formation of a mixture of the three nonaBDEs. In the latter case, chromatographic separations are required to allow the three nonaBDE isomers to be isolated individually. This study describes the first report of the synthesis and characterization of all three nonaBDEs.

A route starting from amino-substituted diphenyl ethers is shown in Scheme 1. BDE-206 was synthesized from 2-phenoxyaniline **1**, whose acetyl derivative **4** was obtained using acetic acid anhydride. The acetamidodiphenyl ether **4** was perbrominated in an excess of bromine and aluminum tribromide (Golounin et al., 1994) giving the nonabrominated acetamide **5**. Hydrolysis of the latter compound (**5**) in concentrated sulfuric acid and THF yielded the nonabrominated phenoxyaniline **6**, which was diazotized using boron trifluoride diethyl etherate and 3-methylbutyl nitrite (Doyle and Bryker, 1979) to obtain the diazonium salt **9**. This salt was reduced with iron(II) sulfate heptahydrate in DMF (Wassmundt and Kiesman, 1995) giving BDE-206 in an overall yield of 6%. Efforts were made to prepare BDE-206 without protection on the amino group. However, perbromination of 2-phenoxyaniline **1** failed and the desired product **6** was not formed according to GC–MS.

BDE-207 and BDE-208 were both synthesized without protection of the amino group via perbromination of the phenoxyanilines **2** and **3**, respectively. This was achieved using bromine and aluminium tribromide as in the preparation of the acetamidodiphenyl ether **5**. The reaction time for **5** was 16.5 h while the bromination of the corresponding amino compounds only required a