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Structure elucidation of hexabromocyclododecanes—a class of compounds with a complex stereochemistry

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Abstract

Hexabromocyclododecanes (HBCDs) are high production volume chemicals (16700 t worldwide in 2001) used as flame-retardants for plastics and textiles. HBCDs exhibit typical properties of persistent organic pollutants (POPs). They are highly lipophilic and accumulate in biota. Increasing environmental concentrations of HBCDs, mostly reported as sum values, have been observed. As such, HBCDs have to be considered as potential emerging POPs, but their occurrence and environmental fate have not yet been addressed at the level of individual HBCD stereoisomers. Considering the six stereogenic centers of HBCDs, 16 stereoisomers, six diastereomeric pairs of enantiomers as well as four meso forms, can be deduced. Herein, we report spectroscopic and chromatographic data for eight out of 16 possible HBCD stereoisomers, which were isolated from a technical product. Six stereoisomers were identified as three pairs of enantiomers ((±) α-, β-, and γ-HBCDs), differing in optical rotation and chromatographic retention on a chiral phase. The crystal structures of these pairs of enantiomers were determined. Another two of these eight HBCD stereoisomers, not yet described in the literature, showed no optical rotation and are tentatively assigned as meso forms (δ- and ε-HBCD). The given spectroscopic and chromatographic information allows the unambiguous identification of eight HBCD stereoisomers and the occurrence, fate, and toxicology of these individual stereoisomers can now be studied.

Keywords: HBCDs; Crystal structure; Stereoisomers; Diastereomers; Resolution of enantiomers

1. Introduction

Brominated flame-retardants (BFRs) are high production volume chemicals that have become the second most important polymer additive next to plasticizers. Hexabromocyclododecanes (HBCDs) are the third most used BFR following tetrabromobisphenol A (TBBPA) and the polybrominated diphenylethers (DecaBDE, OctaBDE, and PentaBDE). The estimated annual production figure for HBCDs was 16700 t worldwide in 2001 (BSEF, 2003).

Currently, concentrations of BFRs, including HBCDs, are increasing for many environmental

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compartments (De Wit, 2002; Alaee et al., 2003). A comprehensive study of the occurrence of HBCDs in Sweden by Remberger et al. (2004) revealed that increased HBCD concentrations were not only found near point sources (e.g., textile or polymer industry, landfills of construction and demolition waste), but also in rural areas, indicating diffuse sources of HBCDs. More recently, HBCDs have been detected in remote areas of the arctic, where background air concentrations of 2–5 pg m^{-3} and atmospheric deposition rates of 0.02 up to 13 ng m^{-2} d^{-1} were reported, indicating that HBCDs are subject to long-range transport (Remberger et al., 2004).

HBCDs have been found in sediments of rivers, lakes, and sea, demonstrating that HBCDs enter the aquatic environment (Sellström et al., 1998; Remberger et al., 2004). In these systems, HBCDs have been shown to accumulate in several aquatic organisms. HBCD concentrations of 4000–8000 ng g^{-1} (lipid weight) were detected in pike (*Esox lucius*) downstream of a suspected point source in the Swedish river Viskan (Sellström et al., 1998). We determined HBCD concentrations of 25–210 ng g^{-1} (lipid weight) in whitefish (*Coregonus* sp.) from six Swiss lakes (Gerecke et al., 2003). In UK, HBCD levels of 20–82 ng g^{-1} (wet weight) have been reported for trout (*Salmo trutta*) upstream of the river Tees and even higher levels were found downstream in the river Skerne below a known point source for both, trout (*Salmo trutta*) and eel (*Anguilla anguilla*) at levels of 120–2340 and 400–3220 ng g^{-1} wet weight, respectively (Allchin and Morris, 2003). Other biotic samples, such as eggs from guillemot (*Uria algae*) and falcon (*Falco peregrinus*), have also been found to contain HBCDs (Sellström et al., 2003; Lindberg et al., 2004).

Currently, the EU is undertaking a risk assessment considering, among other properties, persistence, and bioaccumulation of HBCDs in the environment (OECD, 2003). Tomy et al. (2003a) reported for several aquatic organisms in Lake Ontario biomagnification factors of 2–12 along the food chain. In addition, they found significant variations of the isomer distribution. Enrichment of the first-eluting HBCD isomer relative to the later eluting ones was observed on a reverse phase C18 column when comparing the isomer patterns of top predators (e.g., trout) with those of lower organisms of the Lake Ontario food chain (e.g., mysis).

At similar reverse phase conditions (C18 column), comparable distributions of HBCD isomers with higher levels of fast-eluting, but lower levels of late-eluting, HBCD isomers were found for whitefish from six Swiss lakes (Gerecke et al., 2003). The investigated fish samples of all lakes showed similar patterns with proportions of 60–90% for the fast-eluting HBCD isomers. These patterns are clearly distinguishable from that of a low-melting technical HBCD mixture with increased proportions of late-eluting HBCD isomers, as discussed here.

The toxicology of HBCDs has been reviewed recently (De Wit, 2002; OECD, 2003; Birnbaum and Staskal, 2004). So far, only a few effect studies were carried out and none of them addressed effects at the level of individual HBCD stereoisomers. Neurotoxic effects of technical HBCD mixtures have been reported in vitro, indicating that HBCDs have an inhibiting effect on the uptake of neurotransmitters into synaptosomes and synaptic vesicles (Mariussen and Fonnum, 2003). Recently, it was shown that HBCDs stimulate the thyroid responsive element in an in vitro assay, indicating that HBCDs might interfere with the thyroid hormone system (Sakai et al., 2003).

Considering the increasing global use of HBCDs, their now ubiquitous occurrence even in remote areas and their increasing concentrations in biota, very limited information is available about environmental levels or toxic effects of individual HBCD stereoisomers. At first glance, the stereochemistry of 1,2,5,6,9,10-HBCDs seems to be similar to that of 1,2,3,4,5,6-hexachlorocyclohexanes (HCHs). In both cases, six stereogenic centers are formed upon complete halogenation of the corresponding precursor molecules. For HCHs, nine stereoisomers, seven meso forms and one pair of enantiomers, are known. Occurrence and long-range transport of HCHs have been studied at a resolution of diastereomers (Kallenborn et al., 1998) and of enantiomers as well (Oehme et al., 1997; Wiberg et al., 1998). Buser and Müller (1995) reported diastereo- and enantioselective biodegradation of HCHs in sewage sludge. Bromination of 1,5,9-cyclododecatrienes (CDTs), for which there are four known isomers, is also expected to result in a mixture of different stereoisomers. So far, only three HBCD isomers, named as α, β-, and γ-HBCD have been distinguished, but their absolute stereochemistry is not yet solved. Several groups have published contradicting structures. Some of the reported HBCD data relied on analysis by gas chromatography mass spectrometry (Sellström et al., 1998; Sellström et al., 2003; Lindberg et al., 2004; Remberger et al., 2004). However, under the reported conditions, no separation of individual stereoisomers could be achieved. We have shown that reverse-phase liquid chromatography with negative ion atmospheric pressure chemical ionization mass spectrometry (RP-LC-NI–APCI-MS) is a suitable method for separation of α, β-, and γ-HBCD diastereomers (Heeb, 1997). Within the ongoing EU-risk assessment for HBCDs, this method has been widely used for separation and quantification of HBCD isomers at the μg/l level in effluents from production and wastewater treatment plants. Separation of HBCD isomers on reverse-phase columns has also been reported by others (Budakowski and Tomy, 2003; Gerecke et al., 2003; Morris et al., 2003; Tomy et al., 2003b).