HBCD ENANTIOMERS: ABSOLUTE CONFIGURATIONS AND THERMAL REARRANGEMENT

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Introduction

The cycloaliphatic 1,2,5,6,9,10-hexabromocyclododecane (HBCD) is worldwide the third most widely used brominated flame retardant (BFR). The main field of applications for this additive BFR are various plastic materials, upholstery textiles, adhesives, styrene-acrylonitrile resins and expanded polystyrene foams[1-3]. Due to the substitution of traditional BFRs, such as polybrominated diphenyl ethers, and stricter fire regulations, both the production of HBCD and its consumption is increasing[1]. As an additive BFR HBCD has the potential to migrate out of products into the environment, because it is not covalently bonded to the material but only mixed with or dissolved in the material.

Technical HBCD is derived by the addition of bromine to (1Z,5E,9E)-cyclododeca-1,5,9-triene and is a mixture of three diastereomeric pairs of enantiomers, termed (±) α-, β- and γ-HBCD (Fig. 1) with the γ-isomer as main component[4,5].

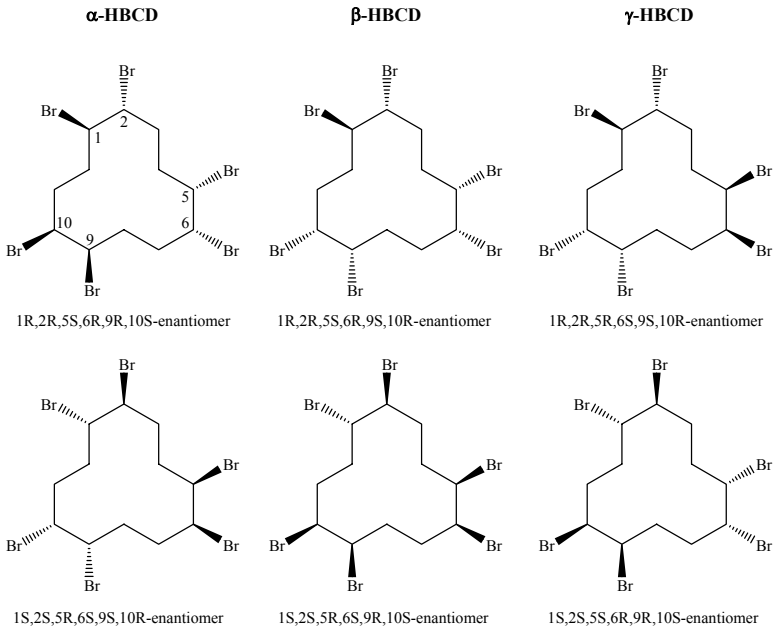

Figure 1. Structures of the HBCD enantiomers

First investigations have shown that HBCD decomposes at temperatures above 220 °C[6,7] and at temperatures between 160 and 200 °C thermal rearrangement of the HBCD isomers takes place[8,9]. During the processing of HBCD, dependent on the treatment of the polymer materials, the temperatures may rise up to more than 160 °C. This may lead to the thermal rearrangement of HBCD and so HBCD will migrate into the environment with a higher amount of α-diastereomer than in the original technical product.

HBCD is considered to be a ubiquitous contaminant, because of its widespread occurrence in the environment. In recent years investigations have shown increasing concentrations of HBCD in biota, with a dominance of the α- over the γ-diastereomer[9,10], which can be avowed (among other things) by biotransformation of HBCD[11]. Therefore, the diastereoselective analysis of the potential persistent and bioaccumulative HBCD in environmental samples becomes more important. However, so far only very limited information is available about environmental levels or toxic effects of individual HBCD diastereomers and enantiomers, respectively. In consideration of the fact that the different HBCD enantiomers can display different biological effects, an enantiospecific analysis and quantification of HBCD is needed. With the aspiration for enlightenment of fate and behaviour of HBCD in the environment, especially in biota, it is essential to obtain enantiomer-specific data on HBCD levels.

So far, the diastereomers were isolated[4,12] but pure enantiomers have not been characterised and their order of elution is unknown. Herein, the correlation of the order of elution with the absolute stereochemistry of HBCD enantiomers derived from x-ray crystallography is presented. Additionally, the thermal rearrangement of both γ-enantiomers isolated from technical HBCD by reversed-phase HPLC using a permethylated β-cyclodextrin-bonded stationary phase coupled to a diode array detector is described.

Materials and Methods

Chemicals. Native α-, β- and γ-HBCD as racemic solutions in toluene (chemical purity >98%) were provided by Wellington Laboratories Inc. (Ontario, Canada). Technical HBCD (CAS 3194-55-6) was purchased from Fluka (Buchs, Switzerland). High-performance liquid chromatography (HPLC)-grade acetonitrile and tetrahydrofurane were obtained from J.T. Baker (Deventer, Holland). Water was obtained from a demineralising system (DTS Wasser-Abwasser-Technik GmbH, Frankfurt/Main, Germany) consisting of a reverse osmosis plant (RO 1500) and three series-connected softening units (WSD60-800).

High Performance Liquid Chromatography. Enantiospecific separations were performed using an Agilent 1100series HPLC sytem (Agilent Technologies, Waldbronn, Germany) equipped with a chiral NUCLEODEX β-PM preparative column (5 µm, 250 mm x 21 mm ID) from Macherey-Nagel GmbH & Co (Düren, Germany). The column outlet was coupled to a UV-detector with a fixed wavelength of 208 nm followed by a Foxy® Jr. fraction collector from Teledyne ISCO (Lincoln, USA). The column temperature was set to 30 °C and the flow rate was 5 mL min^{-1}. The injection volume was 100 µL (~ 100 mg HBCD g^{-1} tetrahydrofurane). Resolution of enantiomers was achieved using an acetonitrile/water gradient starting with an initial acetonitrile fraction of 100%, held for 0.1 min, followed by an acetonitrile fraction of 50%, held for 6.9 min and a linear gradient to 100% in 35 min held at 100% for 8 min. The collected fractions were concentrated under reduced pressure, freeze-dried and the enantiomers were crystallised from acetonitrile.

An Agilent 1100 series HPLC system (Agilent Technologies, Waldbronn, Germany), equipped with a vacuum degasser, binary pump, column thermostat, thermostated autosampler and DAD was used for diastereo- and enantioselective determinations of HBCD. Two analytical columns were used: (a) Zorbax XDB-C18 analytical column (5 µm particle size, 150 mm x 4.6 mm ID, Agilent Technologies, Waldbronn, Germany) and (b) NUCLEODEX β-PM chiral analytical column (5 µm particle size, 200 mm x 4.0 mm ID, Macherey-Nagel GmbH & Co, Düren, Germany). For both columns an acetonitrile/water mobile phase was used. Analysis on the Zorbax column was carried out with an isocratic flow of 80% acetonitrile with a flow rate of 1.0 mL min^{-1}. Resolution of enantiomers was achieved with the nucleodex column at a flow rate of 1 mL min^{-1} with an acetonitrile/water gradient (45% acetonitrile for 5 min, 45-100% in 25 min, 100% for 10 min). Samples were injected as solutions in tetrahydrofurane.

Thermal rearrangement. For the investigation of the thermal rearrangement of HBCD an chamber kiln N 11/H (Nabertherm GmbH, Bremen, Germany) equipped with the program controller B 150 was used. Technical HBCD and pure γ-enantiomers were kept at 160 °C and at different times samples were taken out, cooled and analysed by HPLC.

Results and Discussion

The isolation and characterisation of pure HBCD enantiomers has not been reported, to our knowledge, in the literature. Hence, the first step of our investigations was the isolation of the three diasteriomeric pairs of enantiomers from technical HBCD, by reversed-phase HPLC using a permethylated β-cyclodextrin-bonded stationary phase to assign their order of elution. HPLC is also the preferred analytical technique, because it gives the opportunity for diastereo- and enantioselective determination of HBCD in environmental compartments.

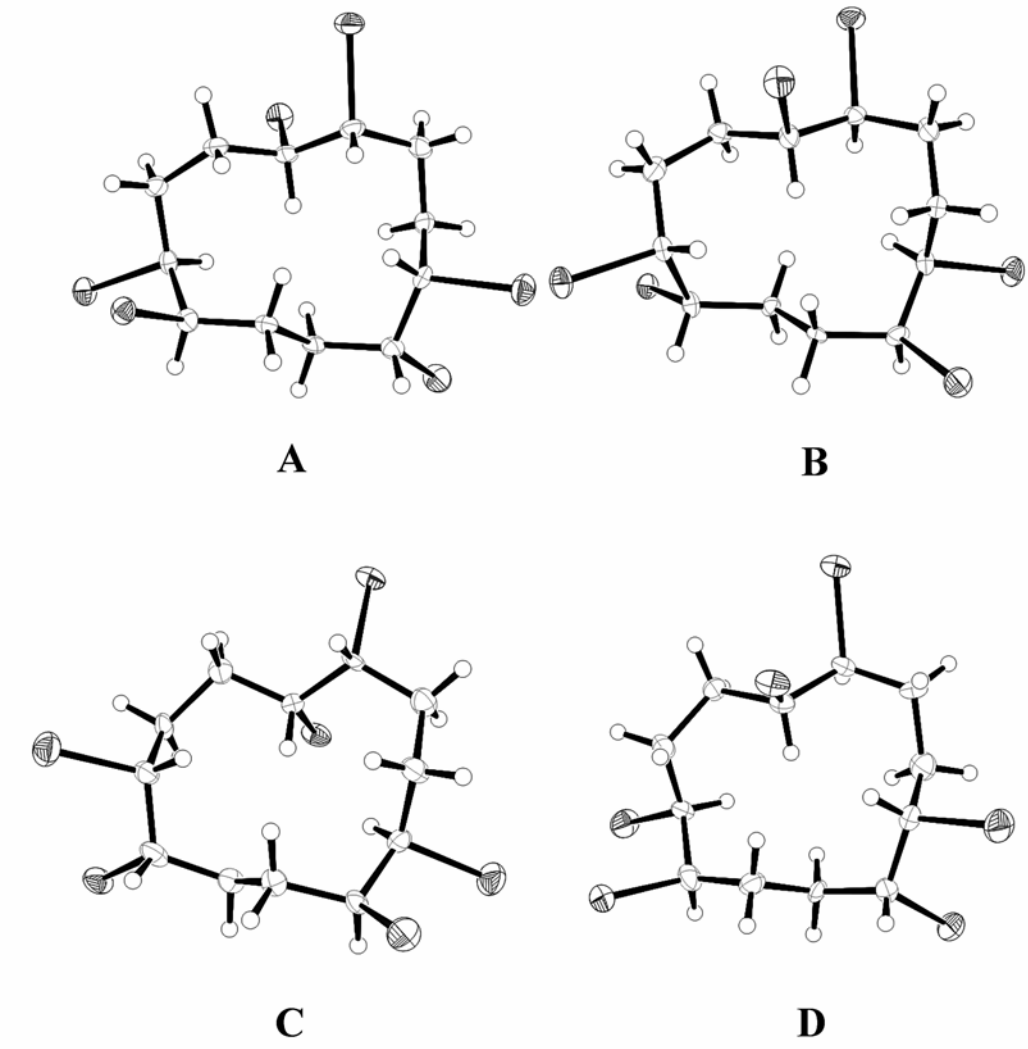

Figure 2. Crystal structures of the pure α- and γ-HBCD enantiomers with 50% vibration ellipsoids. **A:** 1R,2R,5S,6R,9R,10S-HBCD ((-) α-HBCD) $P2_12_12_1$ (No. 19), a = 7.1476(5) Å, b = 13.8284(9) Å, c = 17.5307(10) Å, V = 1732.73(19) Å^3, Z = 4; **B:** 1S,2S,5R,6S,9S,10R-HBCD ((+) α-HBCD) $P2_12_12_1$ (No. 19), a = 7.161(2) Å, b = 13.795(5) Å, c = 17.473(6) Å, V = 1726.3(10) Å^3, Z = 4; **C:** 1R,2R,5R,6S,9S,10R-HBCD ((+) γ-HBCD) $P2_12_12_1$ (No. 19), a = 24.269(3) Å, b = 10.0680(13) Å, c = 8.2295(10) Å, V = 2010.8(4) Å^3, Z = 4 and **D:** 1S,2S,5S,6R,9R,10S-HBCD ((-) γ-HBCD) $P2_12_12_1$ (No. 19), a = 24.3678(9) Å, b = 10.1248(4) Å, c = 8.2500(3) Å, V = 2035.43(13) Å^3, Z = 4.

Fig. 2 displays the crystal structures of the α- and γ-HBCD enantiomers, on which the main focus of our investigations was directed. The enantiomers were crystallised from acetonitrile and the absolute configurations

were determined by anomalous dispersion using single crystal X-ray crystallography. The preliminary assignment of optical rotation is done according to Heeb[12].

The α–HBCD enantiomers (A/B), corresponding to 1R,2R,5S,6R,9R,10S- and 1S,2S,5R,6S,9S,10R-configurations, as well as the γ-HBCD enantiomers (C/D), corresponding to 1R,2R,5R,6S,9S,10R- and 1S,2S,5S,6R,9R,10S-HBCD-configurations, crystallise in the orthorhombic space group $P2_12_12_1$. Crystallographic data for of all three diastereomeric pairs of enentiomers have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 604543 - 604548.

For the examination of the thermal rearrangement of HBCD samples 100 mg of the technical mixture were weighed into glass vials and stored in a chamber kiln at different temperatures. At 160 °C samples were taken for the diastereomeric analysis by HPLC in intervals of 5 minutes for a period of 100 minutes. First results of the modification of the HBCD diastereomeric composition in this time series display that after 55 minutes the thermal equilibrium of the three diastereomers is adjusted (80% α-HBCD, 13% β-HBCD and 7% γ-HBCD) corresponding to the values reported by Peled[8], with the α-diastereomer as predominant isomer.

As result of the investigations with the pure γ-enantiomers it was maintained that under thermal stress the 1S,2S,5R,6S,9S,10R-enantiomer ((+)α) mainly arises from the 1R,2R,5R,6S,9S,10R-enantiomer ((+)γ) and that the 1S,2S,5S,6R,9R,10S-enantiomer ((-)γ) gave predominantly the 1R,2R,5S,6R,9R,10S-enantiomer ((-)α). In both cases all of the six enantiomers were formed by thermal rearrangement. The pure and heated samples were analysed by reversed-phase HPLC using a permethylated β-cyclodextrin-bonded stationary phase for enantiomeric separation. This predominant pathway starting from one pure γ-enantiomer suggest that the inversion of the stereocenters in positions 1 and 2 proceeds faster than that in positions 5 and 6 or 9 and 10, respectively.

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