

Delta- and Epsilon-1,2,5,6,9,10-Hexabromocyclododecane

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1.0 Introduction

Hexabromocyclododecane (HBCD) stands third in production volume of brominated flame retardants (BFRs) after the decabromodiphenyl ether mixture and tetrabromobisphenol A (TBBPA).¹ HBCD is mainly used (85% of volume) as the principal flame retardant in polystyrene foams, while secondary applications include its use in residential, commercial and transportation upholstery, draperies, and wall coverings.^{2,3} In 2001, global production was approximately 16700 tons of which about 60% were consumed^{3,4} in Europe and 20% in North America (1999 numbers). With the implementation of mandatory (EU), or voluntary (Japan), restrictions on the production of some brominated flame retardants, the use of HBCD as a replacement product is expected to increase.^{3,4}

Industrial production of HBCD involves the bromination of *cis,trans,trans*-cyclododecatriene (ctt-CDT).¹¹ Since bromination of a carbon-carbon double bond mainly occurs in a 1,2-diaxial manner, a *cis*-double bond preferentially leads to *RR*- and *SS*-stereoisomers (*trans*-configuration), whereas the *RS*- and *SR*-stereoisomers (*cis*-configuration) are predominantly formed upon bromination of a *trans*-double bond.^{12,13} Therefore, three diastereomeric pairs of enantiomers are obtained via bromination of ctt-CDT [α -, β - and γ -HBCD]. Analysis of technical HBCD reveals the presence of two additional HBCD compounds in very low concentrations (<1%).¹² Chiral LC chromatography indicated that these two compounds exist as meso compounds, meaning that the structures of both compounds have no overall chirality. The stereochemistries of these two meso forms have not yet been assigned.^{12,14} Analysis of technical ctt-CDT in our lab revealed the presence of a small amount of ttt-CDT. Therefore, it is probable that the two meso compounds are formed by the bromination of the ttt-CDT isomer. These isomers have been referred to as delta(δ)- and epsilon(ϵ)-HBCD.^{5,12} In keeping with the naming of the α -, β - and γ -HBCD isomers, the designations δ and ϵ are given based on their order of elution from a C₁₈ LC column.

There have been additional reports⁴ involving the analysis of HBCD in which small additional peaks were detected but the identity of these peaks could not be confirmed due to a lack of standards.

The objective of this work was to synthesize the compounds presumed to be δ - and ϵ -HBCD, confirm their structures by NMR spectroscopy, and determine if these HBCD isomers are present in technical HBCD.

2.0 Experimental

2.1 Synthesis of δ - and ϵ -HBCD

δ - and ϵ -HBCD were prepared by bromination of ttt-CDT (Sigma-Aldrich) using published procedures.^{11,13} δ -HBCD (**1**): Mp 178-181°C; δ_{H} (80°C, C₆D₅Br) 4.12 (br s, 1H), 3.99 (t, 1H), 3.93 (br m, 1H), 2.10 (br s, 2H), 2.07 (m, 1H), 1.94 (br m, 1H), 1.83 (m, 1H), 1.67 (m, 1H); δ_{C} (80°C, C₆D₅Br) 57.7 (CHBr), 54.5 (CHBr), 52.4 (CHBr), 34.7 (CH₂), 33.0 (CH₂), 32.5 (CH₂). 2D ¹H-¹H and 2D ¹H-¹³C NMR

experiments showed the following geminal hydrogen pairings: δ 2.07 & 1.83; δ 1.94 & 1.83; both protons at δ 2.10. ϵ -HBCD (**2**): Mp 107-109°C; δ_{H} (22°C, CDCl_3) 4.33 (s, 1H), 2.40 (m, 1H), 2.24 (m, 1H). A 2D ^1H - ^1H NMR experiment showed the two signals at δ 2.40 & 2.24 are coupled; vicinal couplings were also observed for δ 4.33 & 2.40; δ 4.33 & 2.24.

2.2 High Resolution Gas Chromatography/Low Resolution Mass Spectrometry (HRGC/LRMS)

Experiments were conducted on a Shimadzu GC/MS-QP2010 using a J&W 30m DB-5 column (0.25 mm ID, 0.25 μm film). All injections were done in splitless mode. All experiments were done with the following GC conditions: helium carrier gas flow at 1.0 ml/minute, injector temperature at 200°C, temperature program set to the following parameters: initial oven temperature at 140°C, hold for 1 minute, ramp at 40°C/minute to 200°C, hold for 5.5 minutes, ramp at 10°C/minute to 325°C, hold for 20 minutes. A full scan range of 50 to 1000 amu was used in positive ion electron impact mode (EI+).

2.3 LC/MS

LC/MS experiments were conducted on a Waters Acquity Ultra Performance LC interfaced to a Micromass Quattro micro API (triple quad mass spectrometer). Separations were performed on an Acquity UPLC BEH C_{18} column (1.7 μm , 2.1 x 100 mm). A typical LC method started at 85% (80:20 MeOH: ACN) and 15% water (both with 10 mM NH_4OAc) at a flow rate of 300 μL /minute. The program was then ramped to 100% (80:20 MeOH: ACN) over 7 minutes and held for 3 minutes before returning to initial conditions.

2.4 ^1H -NMR Experiments

^1H -NMR analyses were performed on a 400 MHz Bruker instrument using either deuteriochloroform or deuterated bromobenzene (CDN Isotopes) as the solvent.

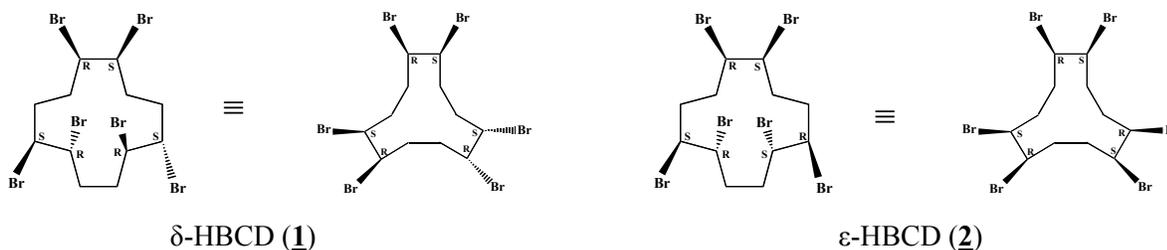


Figure 1. Structures for δ - and ϵ -HBCD

3.0 Results and Discussion

3.1 Analysis of technical cis-trans-trans-1,5,9-cyclododecatriene (ctt-CDT)

GC-MS analysis of a technical sample of ctt-CDT (Aldrich) indicates the presence of approximately 3% of a second CDT isomer. ^1H -NMR spectra of this technical sample confirm the presence of ttt-CDT in ctt-

CDT. This is not surprising as the synthesis of ctt-CDT typically results in the formation of ttt-CDT as an impurity.^{15,16} Bromination of ttt-CDT should only produce two possible isomers, **1** and **2**. Therefore, bromination of technical ctt-CDT containing small amounts of ttt-CDT will produce HBCD containing **1** and **2** as minor components.

3.2 Bromination of ttt-CDT and product characterization

Technical ttt-CDT was brominated using published methods. The products, δ - and ϵ -HBCD, were isolated by a combination of crystallization and HPLC separation techniques and characterized by NMR spectroscopy, GC/MS and LC/MS analyses. The assignment δ and ϵ were based on their order of elution from a C18 LC column, δ eluting before ϵ . Their NMR spectra confirm that δ - and ϵ -HBCD have structures **1** and **2**, respectively. ϵ -HBCD (**2**) has a very simple NMR spectrum due to the three planes of symmetry present in the structure. All CHBr and CH₂ moieties within the structure are equivalent. However, the geminal protons in CH₂ are non-equivalent due to different magnetic environments above and below the ring. δ -HBCD (**1**) also shows a simplified NMR spectrum due to the single plane of symmetry present in the structure. This creates six non-equivalent carbons within the ring structure.

3.3 Analysis of δ - and ϵ -HBCD by GC/MS and LC/MS

α -, β - and γ -HBCD can not be separated when analyzed by gas chromatography (GC) because the isomers tautomerize at temperatures $> 160^\circ\text{C}$ ⁷ and give a single broad peak. The same issue arises when one attempts to analyze δ - and ϵ -HBCD by GC. Significantly, the signal seen for δ/ϵ -HBCD has a different retention time than that for $\alpha/\beta/\gamma$ -HBCD (see Figure 2) indicating that there is no interconversion between these two groups. Integration of the signals in Figure 2 indicates that the response factors are one-to-one even though the γ -HBCD signal is broader.

The interconversion of isomers is not a problem during LC analysis of HBCD. Under careful LC conditions, all five isomers (α -, β -, γ -, δ - and ϵ -HBCD) can be cleanly separated on a C₁₈ column (see Figure 3). The response factors vary significantly among the five isomers (see peak areas in parentheses in Figure 3).

It should be noted that the LC elution order of δ - and ϵ -HBCD relative to $\alpha/\beta/\gamma$ -HBCD is very similar to that of the unknown HBCD signals observed in previous studies.^{4,12}

3.4 Analysis of technical grade HBCD

LC/MS analysis of a technical grade HBCD shows the presence of five signals corresponding to the five HBCD isomers. Therefore, this supports the presence of δ - and ϵ -HBCD in the technical mixture as having structures **1** and **2**. This, in turn, would indicate that the minor HBCD contaminants observed in the environment⁴ are the same isomers.

4. Conclusions

The two minor HBCD components (δ - and ϵ -isomers) found in technical grade HBCD have been identified as having the structures **1** and **2**. These components originate from the bromination of residual amounts of ttt-CDT present in technical ctt-CDT.

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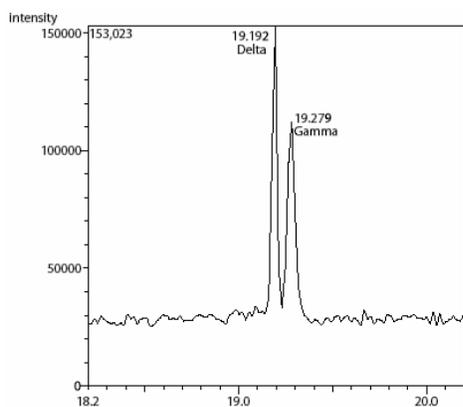


Figure 2. GC chromatogram of δ - and γ -HBCD

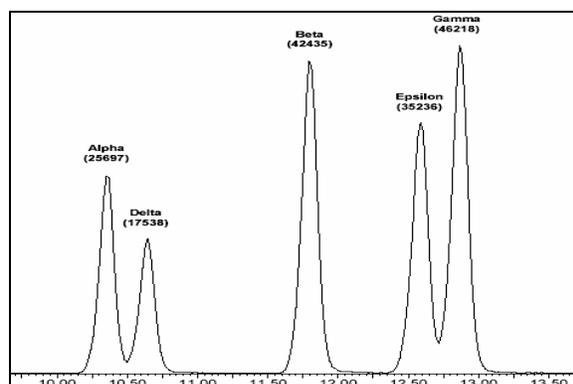


Figure 3. LC chromatogram of the 5 HBCD isomers