

The Chemistry and Stereochemistry of a less common Brominated Flame Retardant: 1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane

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Abstract

1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane, also known as tetrabromoethylcyclohexane (TBECH), is a commercial brominated flame retardant (BFR) which is apparently used as an additive in some polystyrene and polyurethane products. Nothing has been published about the identity of the stereoisomers present in the commercial mixture. ¹H-NMR spectroscopy and an x-ray structure determination have determined that the technical mixture consists largely of two (of the four possible) diastereomers, *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*S*)-1,2-dibromoethyl)cyclohexane and *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*R*)-1,2-dibromoethyl)cyclohexane, in a mole ratio of approximately 1:1.

1.0 Introduction

1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane, also known as tetrabromoethylcyclohexane (TBECH¹ or BCH²), is a commercial brominated flame retardant (BFR) which is apparently used as an additive BFR for polystyrene and polyurethane.³⁻⁵ TBECH can exist as four diastereomers, the stereochemistries of which are represented in Figure 1. However, nothing has been published about the identity and proportion of the stereoisomers present in commercial TBECH, also known as SAYTEK-BCL-462 (Albermarle).

It appears that there has been only one report of the detection of TBECH in the environment.⁶ Another study⁷ showed that TBECH can bioaccumulate in fish and, more importantly, two studies have been published indicating that TBECH may have negative health impacts on humans.^{2,8} These studies highlight the importance of learning more about the stereochemistry and fate of TBECH in the environment. The objective of the present work was to identify which isomers are present in commercial TBECH.

2.0 Experimental

2.1 Technical TBECH

Technical TBECH was obtained from Sigma-Aldrich. The technical material, which had a mp of 70-97°C, with sublimation starting at ~59°C, consisted very largely of isomers **1** (α 2) and **2** (α 1) in a mole ratio of 1:1, as determined by ¹H NMR. α 2-TBECH (**1**) was isolated from the technical sample by crystallization. It had mp 100.0-101.5°C, with sublimation starting at ~97°C; δ_{H} (22°C, CDCl₃) 4.75 (br m, ring CHBr, 1H), 4.66 (br m, ring CHBr, 1H), 4.23 (ddd, CHBr, 1H, ³J_{HH} = 3.8 Hz, ³J_{HH} = 5.0 Hz, ³J_{HH} = 10.2 Hz), 3.85 (dd, CH₂Br, 1H, ³J_{HH} = 10.2 Hz, ³J_{HH} = 10.7 Hz), 3.69 (dd, CH₂Br, 1H, ³J_{HH} = 5.0 Hz, ³J_{HH} = 10.7 Hz), 2.6 (m, 2H), 2.45 (ddd, 1H, ³J_{HH} = 3.0 Hz, ³J_{HH} = 11.7 Hz, ³J_{HH} = 14.6 Hz), 2.06 (m, 1H), 2.03 (m, 1H), 1.96 (br d, ³J_{HH} = 14 Hz, 1H), 1.56 (br d, ³J_{HH} = 12 Hz, 1H). In addition to these signals the commercial sample had resonances attributable to the CHBrCH₂Br moiety for **2** at 4.75 (br m, 1H), 4.66 (br m, 1H), 4.19 (ddd, 1H, ³J_{HH} = 5 Hz, ³J_{HH} = 8 Hz, ³J_{HH} = 10 Hz), 3.86 (dd, 1H, ³J_{HH} = 3.9 Hz, ³J_{HH} = 10.5 Hz), 3.76 (dd, 1H, ³J_{HH} = 10.5 Hz, ³J_{HH} = 10.5 Hz).

2.2 Synthesis of α - and β -TBECH

α - and β -TBECH were prepared by bromination of 4-vinylcyclohexene (Sigma-Aldrich) in dichloromethane at ambient temperature. The two pairs of diastereomers α 1/ α 2- and β 1/ β 2-TBECH were separated by chromatography.

β 1/ β 2-TBECH (**3/4**) is a colorless oil at 22°C; δ_{H} (22°C, CDCl_3 , signals for only the CHBrCH_2Br moiety) major isomer (54%): 4.01 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 4.6$ Hz, $^3J_{\text{HH}} = 10.7$ Hz), 3.83 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 4.8$ Hz, $^3J_{\text{HH}} = 10.7$ Hz), 3.65 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 10.7$ Hz, $^3J_{\text{HH}} = 10.7$ Hz); minor isomer (46%): 3.98 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 4.6$ Hz, $^3J_{\text{HH}} = 10.7$ Hz), 3.83 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 4.8$ Hz, $^3J_{\text{HH}} = 10.7$ Hz), 3.67 (dd, CH_2Br , 1H, $^3J_{\text{HH}} = 10.7$ Hz, $^3J_{\text{HH}} = 10.7$ Hz).

2.3 LCMS

LCMS experiments were conducted on a Waters Acquity Ultra Performance LC interfaced to a Micromass Quattro micro API (triple quad mass spectrometer). Separations were attempted on an Acquity UPLC BEH C_{18} column (1.7 μm , 2.1 x 100 mm). A typical LC method started at 64% (80:20 MeOH: ACN) and 36% water (both with 10 mM NH_4OAc) at a flow rate of 350 $\mu\text{L}/\text{minute}$ for 7 minutes. The program was then ramped to 80% (80:20 MeOH: ACN) over 5 minutes and held for 2 minutes before returning to initial conditions. Data were collected in SIM mode by monitoring the Br⁻ anion (m/z 79 and 81) under negative electrospray ionization conditions (capillary voltage 3kV, cone voltage 12V) and negative APCI conditions (corona current 1.5 μA , cone voltage 9V).

2.4 $^1\text{H-NMR}$ Experiments

$^1\text{H-NMR}$ analyses were performed on a 400 MHz Bruker instrument using deuteriochloroform (CDN Isotopes) as the solvent and TMS as an internal standard.

3.0 Results and Discussion

3.1 $^1\text{H-NMR}$ Analysis of Technical-TBECH

The $^1\text{H NMR}$ spectrum of technical TBECH clearly shows the presence of two compounds in a 1:1 ratio which we named α 1- and α 2-TBECH based on their order of elution during GC analysis.⁹ Further analysis of the spectrum reveals that:

- i) The chemical shift positions and coupling constants of the two ring CHBr protons indicate these protons are equatorial. Since the ring bromines are axial, the bulky side chain is almost certainly equatorial. This situation is expected as bromination of 4-*t*-butylcyclohexene results in an identical outcome.¹⁰
- ii) The two ring CHBr protons for both compounds have identical chemical shifts indicating very similar ring structures. With the observation noted in i) above, the stereochemistry for the ring can easily be deduced to be that present in *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*S*/*R*)-1,2-dibromoethyl)cyclohexane. The stereochemical difference between the two diastereomers results from the chirality at the CHBr moiety attached to the ring, where the carbon can have either the R or S configuration.
- iii) The dibromoethyl groups for the two isomers have easily distinguishable chemical shifts confirming that the stereochemical difference between them is at the CHBr group attached to the ring. Integration of the relevant signals shows that the isomers are present in a molar ratio of approximately 1:1.

These two isomers, α 1- and α 2-TBECH, can not be separated by the TLC or HPLC (C_{18} column) techniques that we investigated, further indicating the similarities of these two compounds.

3.2 X-ray structure determination and $^1\text{H NMR}$ analysis of α 1-TBECH

One isomer, which we named α 2-TBECH was separated from the α 1/2-TBECH mixture, and purified, by crystallization. Its $^1\text{H NMR}$ spectrum clearly indicates that the second isomer (α 2-TBECH) is missing (see Figure 3). Crystals of this isomer were submitted for x-ray structure determination and the results (shown in Figure 4) demonstrated that it has structure **1** (*rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*S*)-1,2-dibromoethyl)cyclohexane). The crystal contained two independent molecules in the asymmetric unit but there are no significant differences in the magnitude of the bond lengths and angles within each molecule. Therefore, the other diastereomer (α 1-TBECH)

present in the technical TBECHE mixture has to be *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*R*)-1,2-dibromoethyl)cyclohexane (**2**, see Figure 1).

3.3 Preparation of β 1/2-TBECHE

The other two diastereomers for TBECHE are *rac*-(1*R*,2*R*)-1,2-dibromo-(4*R*)-4-((1*R*/*S*)-1,2-dibromoethyl)cyclohexane. Both isomers have the two ring bromines and the side chain in equatorial positions. We have named them β 1- and β 2-TBECHE (**3** and **4**, see Figure 1). The only stereochemical difference between the two diastereomers is at the CHBr moiety attached to the ring where the chiral carbon can have either the R or S configuration.

Bromination of 4-vinylcyclohexene in dichloromethane at ambient temperature gave a major product, α 1/ α 2-TBECHE (α -TBECHE), accompanied by a minor product, β 1/ β 2-TBECHE (β -TBECHE). α - and β -TBECHE were separated by TLC. The ¹H-NMR data (see Figure 5) for β -TBECHE confirm that two isomers are present in approximately a 1.16:1 mole ratio with structures corresponding to *rac*-(1*R*,2*R*)-1,2-dibromo-(4*R*)-4-((1*R*/*S*)-1,2-dibromoethyl)cyclohexane (**3** and **4**, see Figure 1). As with α -TBECHE, these two β -TBECHE compounds could not be separated by conventional TLC or HPLC techniques. Additional work is progressing in this area.

Reanalysis of technical TBECHE by TLC and ¹H-NMR did not show detectable amounts of β -TBECHE. We estimate that if β -TBECHE were present in the technical mixture, it must be at levels much less than 1%.

3.3 Analysis of α - and β -TBECHE by LCMS

The molecular ion for α -TBECHE can not be detected using LC/ESI-MS analysis. However, the compound can be detected when the bromide (Br⁻) ion is monitored in the SIM mode. Initial results using APCI conditions indicate that a very weak molecular ion adduct can be observed, but detection of the bromide (Br⁻) ion, monitored in the SIM mode, is still more practical due to its stronger signal.

LC-MS analysis of α - and β -TBECHE showed that all four diastereomers have essentially identical retention times using a C18 column with a methanol/acetonitrile/water solvent system. Further work is planned to study other columns and conditions. As mentioned above, the two pairs of diastereomers, α - and β -TBECHE, can be separated by TLC under normal phase conditions.

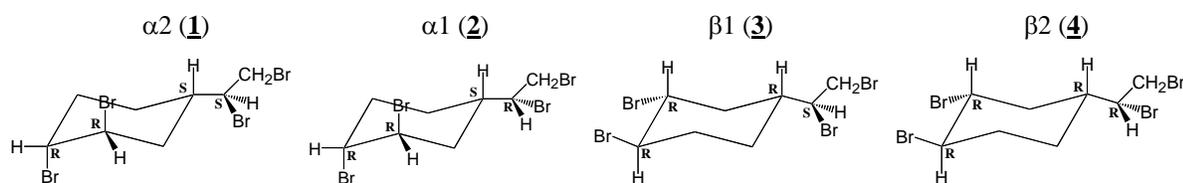
4. Conclusions

The stereochemistries of α 2- and α 1-TBECHE diastereomers, **1** and **2**, have been elucidated with the help of ¹H-NMR spectroscopy and x-ray structure determination to be *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*S*)-1,2-dibromoethyl)cyclohexane and *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*R*)-1,2-dibromoethyl)cyclohexane, respectively. The other two possible diastereomers for TBECHE have been synthesized and ¹H-NMR spectroscopy shows that they have structures **3** and **4**. Analysis of a technical TBECHE sample by analytical TLC and ¹H-NMR spectroscopy revealed only the presence of α 1- and α 2-TBECHE in a molar ratio of 1:1 with no indication (< 1%) of β -TBECHE being present.

References

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$\alpha 2$ -TBECH \equiv *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*S*)-1,2-dibromoethyl)cyclohexane
 $\alpha 1$ -TBECH \equiv *rac*-(1*R*,2*R*)-1,2-dibromo-(4*S*)-4-((1*R*)-1,2-dibromoethyl)cyclohexane
 $\beta 1$ -TBECH \equiv *rac*-(1*R*,2*R*)-1,2-dibromo-(4*R*)-4-((1*S*)-1,2-dibromoethyl)cyclohexane
 $\beta 2$ -TBECH \equiv *rac*-(1*R*,2*R*)-1,2-dibromo-(4*R*)-4-((1*R*)-1,2-dibromoethyl)cyclohexane

Figure 1. Structures and nomenclature of the four possible TBECH diastereomers

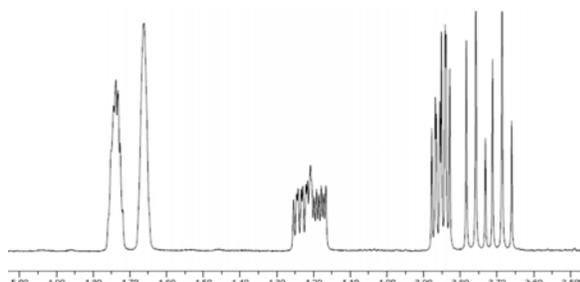


Figure 2. ^1H NMR of $\alpha 1/\alpha 2$ -TBECH (3.5 to 5.0 ppm region only)

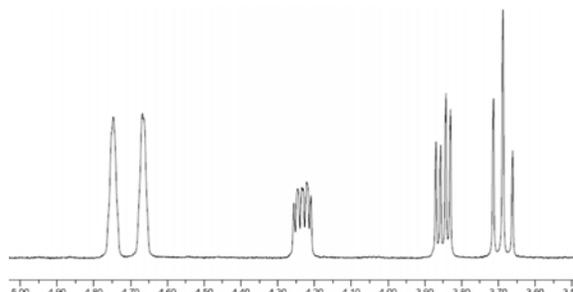


Figure 3. ^1H NMR of $\alpha 2$ -TBECH (3.5 to 5.0 ppm region only)

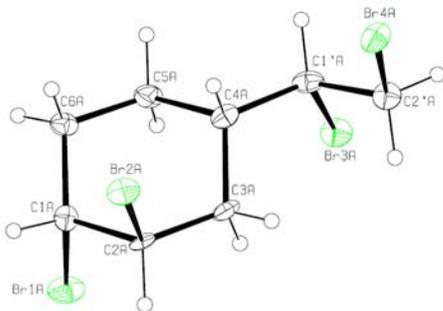


Figure 4. Ortep diagram for $\alpha 2$ -TBECH

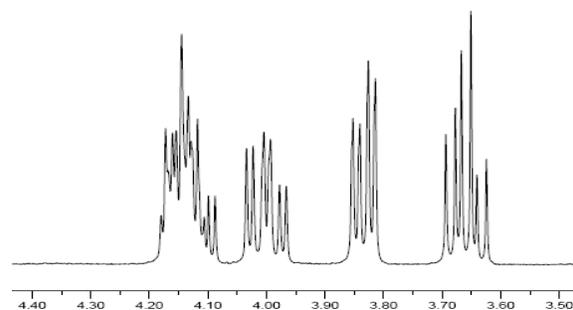


Figure 5. ^1H NMR of $\beta 1/2$ -TBECH (3.5 to 5.0 ppm region only)