NMR Spectral Characterization and Semi-emperical Calculations for the Conformations of alpha- and gamma-1,2,5,6,9,10-Hexabromocyclododecane

Gilles Arsenault[1], Brock Chittim[1], Alan McAlees[1], Robert McCrindle[2]

[1]Wellington Laboratories Inc., Guelph
[2]University of Guelph, Guelph

Introduction

The hexabromocyclododecanes (HBCDs) constitute one of the most important groups of flame retardants[1]. Recently, there has been a growing interest among environmental laboratories in methods for determining the levels of the three HBCD isomers (alpha, beta and gamma) in the biota[2-8]. This has led to the interesting observation that the gamma (γ-) HBCD isomer is the predominant isomer in sediments and the alpha (α-) isomer is the predominant isomer in fish.

There are few literature references[9] reporting any NMR data on the individual HBCD isomers. This study reports the full ^{1}H- and ^{13}C-NMR spectral characterization of alpha (α-) and gamma (γ-) HBCD. 3-D models of the two structures are proposed based on the use of various NMR experimental techniques, an evaluation of coupling constant magnitudes and computer modeling of three dimensional structures. It is hoped that an understanding of the structural differences between isomers can shed some light into the different behavior of these isomers in the environment.

Materials and Methods

Chemicals. The α-, β- and γ-HBCD congeners were purified from a commercial technical mixture as described in the literature. The preparation of the deuterated ($^{2}H_{18}$) and carbon-13 ($^{13}C_{12}$) HBCD isomers is reported elsewhere[9].

NMR Experiments. The NMR experiments were performed either on a Bruker 400MHz or 600MHz instrument.

Results and Discussions

Alpha-Hexabromocyclododecane

The NMR spectra of α-HBCD are expected to be greatly simplified because the structure has a C_2 axis of symmetry. As illustrated in figure 1a, the cyclic structure has 6 unique carbons and 9 unique protons. The labeling schemes for the alpha isomer used in our work are shown in figure 1.

The full characterization of α-HBCD was achieved by performing the following NMR experiments on the compounds indicated in brackets: ^{1}H-NMR, 2D ^{1}H-NMR and 2D ^{1}H-^{13}C-NMR (on α-HBCD), 2D ^{13}C-^{13}C-NMR (on $^{13}C_{12}$-α-HBCD). The ^{1}H-NMR spectrum of α-HBCD and the ^{13}C-NMR spectrum of $^{13}C_{12}$-α-HBCD at ambient temperature are shown in figure 2. The presence of a minor conformer in equilibrium with the major conformer is evident.

Gamma-Hexabromocyclododecane

The NMR spectra of γ-HBCD are also expected to be greatly simplified because the structure has a C_2 axis of symmetry. As illustrated in figure 3, the cyclic structure has 6 unique carbons and 9 unique protons. The labeling schemes used in our work are shown in figure 3.

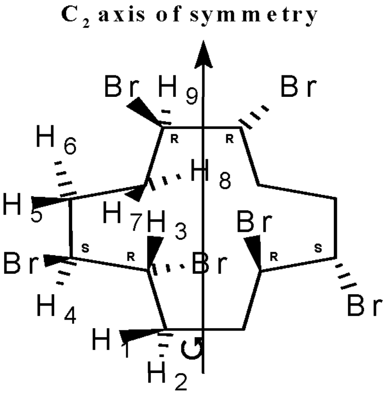

Figure 1a: Proton numbering scheme for α-HBCD

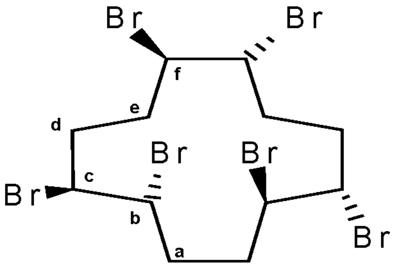

Figure 1b: Carbon numbering scheme for α-HBCD

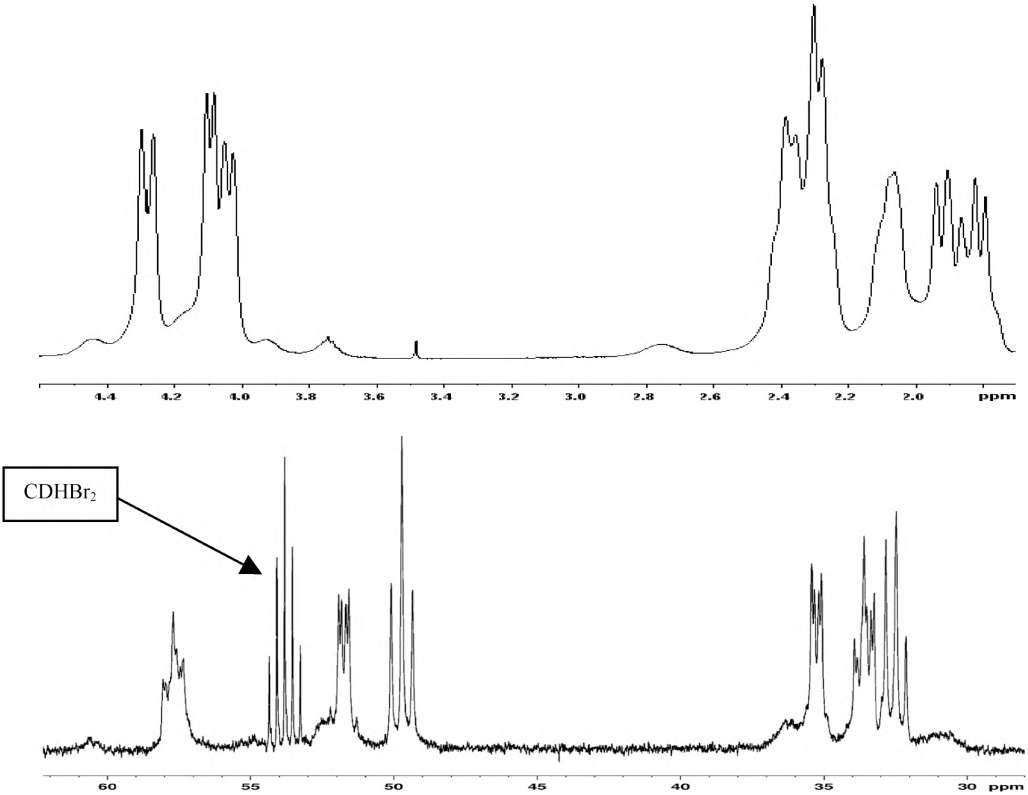

Figure 2. ^{1}H-NMR spectrum of α-HBCD (top) and ^{13}C-NMR spectrum of $^{13}C_{12}$-α-HBCD (bottom)

The full characterization of γ-HBCD was achieved by performing the following NMR experiments on the compounds indicated in brackets: ^{1}H-NMR, 2D ^{1}H-NMR, 2D ^{1}H-^{13}C-NMR and 1H-NMR gradient TOSCY (on γ-HBCD), ^{2}H-NMR (on $^2H_{18}$-γ-HBCD) , 2D ^{13}C-^{13}C-NMR (on $^{13}C_{12}$-γ-HBCD). The ^{1}H-NMR spectrum of γ-HBCD at ambient temperature is shown in figure 4.

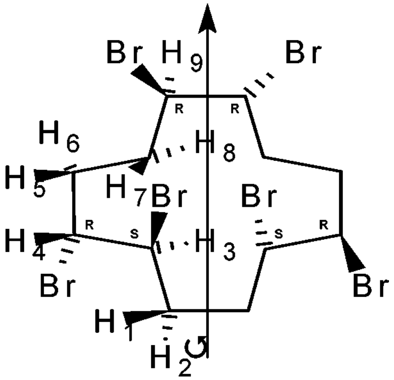

Figure 3a: Proton numbering scheme on γ-HBCD

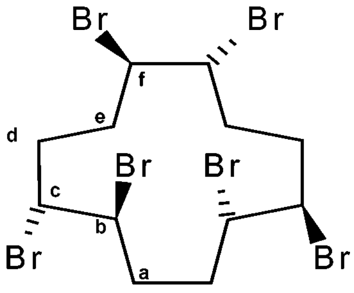

Figure 3b: Carbon numbering scheme on γ-HBCD

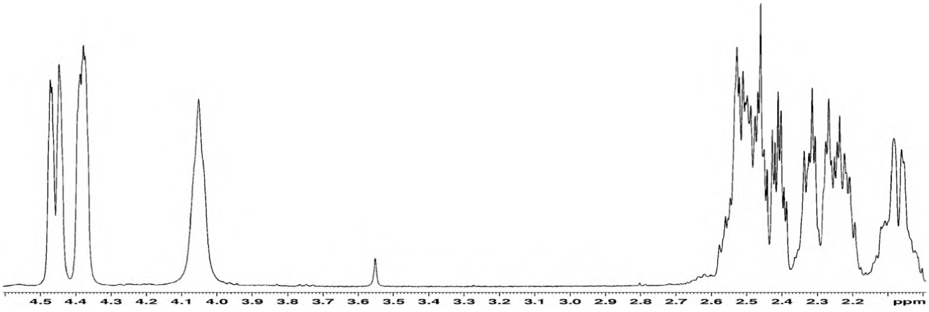

Figure 4. ^{1}H-NMR of γ-HBCD

Structure Assignment

The carbon connectivities for both α- and γ-HBCD were easily assignable from the ^{13}C-NMR experiments. It was not possible to assign all non-equivalent protons for either diastereomers using only the data generated by the NMR experiments. To help in the full assignment of the ^{1}H-NMR signals, 3D structure for both α- and γ-HBCD were calculated for the equilibrium conformers using the semi-empirical method available in the Spartan program[10] (Spartan'02 Windows version). The generated 3D structures are shown in figure 5. These calculations would be expected to provide a good first approximation of the lowest energy conformer for the HBCD. Indeed, the 3D structure generated in this study for α-HBCD resembles closely the solid state structure obtained from an X-ray crystallographic study[11]. However, the published[11] crystal structure for γ-HBCD differs from the 3D structure generated in this study. The differences may be due to γ-HBCD adopting a different conformer in the solid state as a result of crystal packing forces. The dihedral angle between vicinal protons taken from the calculated structure and the measurable J_3 (^{1}H-^{1}H) coupling constants from the NMR experiments are reported in Table 3. The Karplus equation predicts large coupling constants for dihedral angles close to 0° or 180°, and the smallest couplings when the angles are at 90°. From these calculated dihedral angles and measure coupling constants, all nine protons could be individually assigned (see Table 1 for α-HBCD and Table 2 for γ-HBCD).

Due to the complexity of the spectra and the fluxional behavior of the molecule, we did not attempt to elucidate the three dimensional structure of β-HBCD using NMR data.

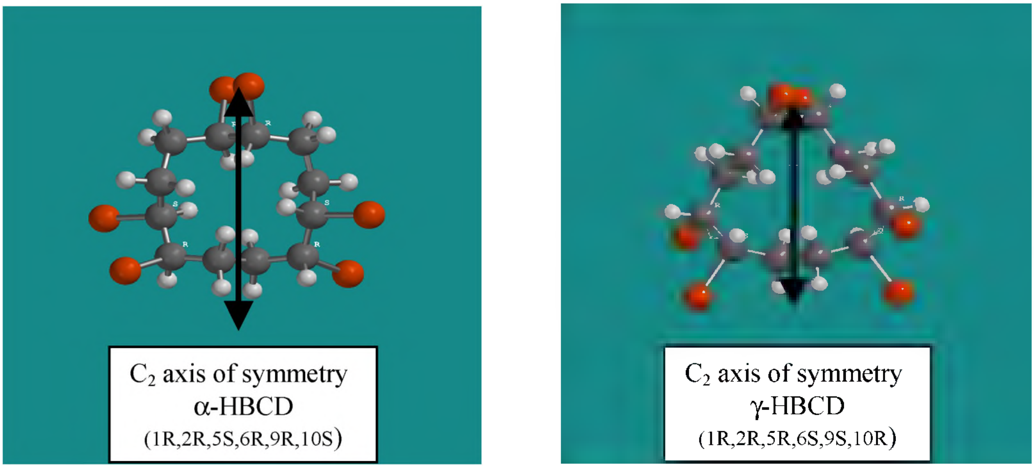

Figure 5: 3-D structure of α- and γ-HBCD

Structure Differences

It is clearly seen from figure 5 that the structures of α- and γ-HBCD are visually quite different. These distinctions in structure will almost certainly lead to differences in properties such as polarity, dipole moment, solubility and rates of biological uptake or metabolism. Calculated dipole moments from the semi-empirical calculations gave values of 1.29 and 2.23 Debye, respectively. Not surprisingly, we have observed significant differences in solubility in various organic solvents among the three diastereomers (α, β and γ) in our laboratory. It is thus a mistake to assume that these compounds would behave in a similar fashion in the environment. This information should provide useful insight for other researchers into the possible different behavior of the alpha and gamma-HBCD diastereomers in the environment. These results also show that more work needs to be done with the individual diastereomers in determining their physico-chemical properties and how this relates to the differences observed so far in their analysis in sediments and fish samples. Indeed, differing water solubilities for the three isomers may be one of the key factors in these differences

Summary

The full ^{1}H- and ^{13}C- NMR spectral characterization of α- and γ-1,2,5,6,9,10- HBCD is reported in this paper. The use of various NMR experiments, an analysis of the magnitude of the NMR chemical shifts and coupling constants, and computer modeling has enabled the visualization of the 3-dimensional structures for both the α- and γ-diastereomers. This information may provide useful insight into the different behavior of the α- and γ-HBCD diastereomers in the environment.

Table 1: Assignment of the protons and carbons, and correlation between proton and carbon for the α-HBCD structure

Proton Assignment[a]	**Proton NMR signal (ppm)**	**Carbon NMR signal (ppm)**	**Carbon Assignment**[a]	**C13 Coupling Constants measured from $^{13}C_{12}$-α-HBCD**
H1	1.8	35.5	a	J_2 (Ca-Cb)=35Hz J_3 (Ca-Cb′)=10Hz
H2	2.3			
H5	1.9	32.5	d	J_2 (Cd-Cc)=35Hz J_2 (Cd-Ce)=35Hz J_3 (Cd-Cf)=10Hz
H6	2.07			
H7	2.3	33.5	e	J_2 (Ce-Cd)=35Hz J_2 (Ce-Cf)=35Hz
H8	2.38			
H3	4.25	57	b	J_2 (Cb-Ca)=35Hz J_3 (Cb-Ca′)=10Hz J_2 (Cb-Cc)=35Hz
H4	4.05	50	c	J_2 (Cc-Cb)=35Hz J_2 (Cc-Cd)=35Hz
H9	4.0	52	f	J_2 (Cf-Ce)=35Hz J_3 (Cf-Cd)=10Hz

[a] See figure 1a for the proton assignments and figure 1b for the carbon assignments

Table 2: Assignment of the protons and carbons, and correlation between proton and carbon for the γ-HBCD structure

Proton Assignment[a]	**Proton NMR signal (ppm)**	**Carbon NMR signal (ppm)**	**Carbon Assignment**[a]	**C13 Coupling Constants measured from $^{13}C_{12}$-γ-HBCD**
H1	2.0	35.2	a	These could not be measured as the signals were still broad due to fluxional behaviour between major and minor conformer
H2	2.5			
H5	2.25	35.5	d	
H6	2.35			
H7	2.17	35.0	e	
H8	2.5			
H3	4.45	57	b	
H4	4.38	50	c	
H9	4.05	52	f	

[a] See figure 3a for the proton assignments and figure 3b for the carbon assignments

Table 3: Dihedral angles between vicinal protons from the calculated structures of α-HBCD and γ-HBCD, and the measurable J_3 (^{1}H-^{1}H) coupling constants from the ^{1}H-NMR spectra done at 22°C. (empty cell signifies that the coupling constant was not measurable)

	α-HBCD		γ-HBCD	
Protons[a]	**Dihedral angle (°)**	**Measured coupling (Hz)**	**Dihedral angle (°)**	**Measured coupling (Hz)**
H1-H3	173	12	131.3	9.5
H2-H3	70	<1	112.3	1.8
H3-H4	64	<1	58.05	<1
H4-H5	89	<1	48.4	<1
H4-H6	155	9.2	163.2	5.6
H5-H7	175		59.2	
H5-H8	69		173.4	
H6-H7	70		174.1	
H6-H8	46		71.7	
H7-H9	68	3.2[b]	57.3	
H8-H9	175	11.2	171.7	
H9-H9′	79		78.5	
H1-H2′	167		154	
H1-H1′	77		40	
H2-H2′	50		91	

[a] The location of the assigned protons can be found either in figure 1a or figure 3a .

[b] Coupling observed at -10°C.

References

1. See for example; i) Hyotylainen, T., Hartonen, K., (2002) Trends in Anal. Chem. 21, 13-27. ii) Bergman, A., (2000) Organohal. Comp. 47, 36- 40. iii) De Wit, C.A., (2002) Chemosphere 46, 583-624.
2. Allchin, C.R., Morris, S., (2003) Organolhal. Comp. 61, 41-44.
3. Tomy, G., Budakowski, W., Halldorson, T., Whittle, M., Keir, M., Alaee, M., (2003) Organohal. Comp. 61, 111-114.
6. Gerecke, A.C., Kohler, M., Zennegg, M., Schmid, P., Heeb, N.V., (2003) Organohal. Comp. 61, 155-158.
7. Lindberg,P., Sellstrom., Haggberg,L.,de Wit,C., (2004) Environ. Sci. Technol. 38, 93-96.
8. Remberger, M., Sternback,J., Palm,A., Kaj,L., Stromberg,K., Brorstrom-Lunden,E., (2004) Chemosphere 54, 9-21.
9. Arsenault, G., Chittim, B., Halldorson, T., Konstantinov, A., McAleees, A. McCrindle, R., Tomy, G., Yeo, B., 2003. Organolhal. Comp. 61. 267-270, and references therein.
10. W.J.Hehre, A Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction Inc., Irvine, California. 2003.
11. Groweiss, A., Hermolin, J., Goldberg, I., 1991. Advances in Organobromine Chemistry, 61-67. Desmurs, J.R., Gerard. B. (Eds.), Elsevier, Amsterdam.