Structural Diagrams and the Nomenclature of Hexabromocyclododecane Stereoisomer

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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[2-6].

HBCD technical mixtures consist mainly of the gamma (γ) diasteriomer and lower amounts of alpha (α) and beta (β) diasteriomers. Trace levels of two other HBCD isomers have been found in technical mixtures and have been named delta (d) and epsilon (d)[4].

HBCD structures have been represented in many different ways in the scientific literature and this has created some confusion. The difficulty in writing a three-dimensional representation of HBCD lies in the presence of six stereocenters in a large 12-membered ring. Several excellent reports[4,7] have recently been published in an attempt to clarify the stereochemistry of HBCD stereoisomers. However, there is still a lack of clarity about the rules that relates to the drawing of HBCD and the conversion between the various three-dimensional structures of the same HBCD isomer. This paper is aimed at addressing these two problems.

Discussions

The three major HBCD diasteriomers (alpha, beta and gamma) are produced by bromination of *cis,trans,trans*-1,5,9-cyclododecatriene. Technical grade *cis,trans,trans*-1,5,9-cyclododecatriene contains trace amounts of *trans,trans,trans*-1,5,9-cyclododecatriene which, upon bromination, leads to the formation of only two possible HBCD compounds, delta and epsilon.

It is perhaps not surprising that there has been some confusion about the best way to draw three-dimensional representations of the structures of the three major HBCD compounds. Two major difficulties arise. The task is complicated by the presence of six stereogenic atoms (asymmetric atoms/chirality centres) and the awkwardness of drawing an entirely convex dodecahedron (**1**). The latter difficulty has been avoided by drawing polygons with some re-entrant (non-convex) bond angles. The most commonly used alternatives (**2-5**) have two, or more, re-entrant positions (marked with asterisks). Although in Chemical Abstracts diagram **2** is used, most authors are now using the "cross" representation **5**, possibly because of ease of drawing. In addition, we have noted the utility of this form (**5**) in depicting the mode of formation of the three HBDC isomers (**6-8**)arising from trans addition of bromine to the three olefinic bonds in the precursor, *cis,trans,trans*-cyclododecatriene (CDT, see Scheme 1).

Unfortunately, with **5,** it is impossible to draw HBDC isomers without having stereogenic atoms at two re-entrant positions. According to IUPAC recommendations[8], one should avoid this type of representation if other options are available. It can be difficult to interpret what a "bold wedge" or a "hashed wedge"[9] is meant to imply at a re-entrant position. Indeed, interpretation can be particularly difficult if substituents are drawn to point outward from the re-entrant atom since normal bond angles would dictate that they should be directed toward the inside of the ring. Two different representations, **6** and **9**, have been used to represent alpha-HBDC. The former, with the substituents at the re-entrant positions oriented inwards, is preferable since one can imagine hydrogen atoms inserted into the drawing at the positions marked with an asterisk to give **10**, which then has clearly defined tetrahedral configurations for these carbon atoms**.** However, it is exceedingly difficult to envisage how one might draw hydrogen atoms at the corresponding positions in structure **9**, in a manner that would depict tetrahedral configurations.

Using alpha-HBCD as an example, drawings **11-13** would be more acceptable than **6** to IUPAC since they do not have substituents at re-entrant positions. (The interconversion between representations can easily be done in the following manner: when a re-entrant atom is redrawn in a normal convex position, a bold wedge becomes a hashed wedge and vice versa.) We find all three representations slightly more onerous to draw and, at first sight, planes and axes of symmetry are less obvious for **11** and **12**. For example, using representation **6** or **13** for alpha-HBDC, it is simpler to identify the presence of a two-fold axis of symmetry since an 180^{o} rotation around it regenerates the same drawing. Please note that with beta-HBDC (**7)**, which lacks a symmetry axis, a similar rotation simply generates an alternative way of drawing the same structure (**14**).

The bromination of *trans,trans,trans*-1,5,9-cyclododecatriene yields two possible products, **15** (or **16**) and **17** (or **18**). The first structure that elutes from a C18 HPLC column, which we will call delta-HBCD[10], has three planes of symmetry and a three fold axis of symmetry. This C_{3V} symmetry is easily seen with representation **16** but not with **15**. The second compound, epsilon-HBCD, has a plane of symmetry which is readily apparent in representation **18** but not in **17**. Therefore, if one is to discuss stereochemistry for delta and epsilon-HBCD, representation based on **4** is recommended.

Nomenclature

The naming for the three HBDC diastereomers is based on the approved IUPAC principle[8] of giving the *R* stereodescriptor precedence over the *S* designation. However, since these are equimolar mixtures of enantiomers (racemates), the chemical name should include an element that indicates this, for example, by using the prefix *rac*- (please see names in brackets).

Alpha-HBDC: (1*R*,2*R*,5*S*,6*R*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane

[*rac*-(1*R*,2*R*,5*S*,6*R*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane]

Beta-HBDC: (1*R*,2*R*,5*R*,6*S*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane

[*rac*-(1*R*,2*R*,5*R*,6*S*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane]

Gamma-HBDC: (1*R*,2*R*,5*R*,6*S*,9*S*,10*R*)-1,2,5,6,9,10-hexabromocyclododecane

[*rac*-(1*R*,2*R*,5*R*,6*S*,9*S*,10*R*)-1,2,5,6,9,10-hexabromocyclododecane]

An alternative name, (1*R*,2*R*,5*S*,6*R*,9*S*,10*R*)-1,2,5,6,9,10-hexabromocyclododecane (**7b**), has been suggested for beta-HBDC, as a result of numbering the carbon skeleton in an anticlockwise rather than a clockwise direction (**7b** rather than **7a**) . The naming of beta-HBCD should be derived from **7a** based on the IUPAC rules of giving *R* priority over *S*. Numbering the skeleton as in **7a** leads to the first 3 chiral carbons having the R configuration while in **7b** only the first two chiral carbons have the R configuration.

Delta and epsilon-HBCD are meso compounds because they are achiral even though they contain six asymmetric carbon atoms. The planes of symmetry present in both compounds makes each identical to its mirror image.

Delta-HBDC: (1*R*,2*S*,5*R*,6*S*,9*S*,10*R*)-1,2,5,6,9,10-hexabromocyclododecane

[*meso*-(1*R*,2*S*,5*R*,6*S*,9*S*,10*R*)-1,2,5,6,9,10-hexabromocyclododecane]

Epsilon-HBDC: (1*R*,2*S*,5*R*,6*S*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane

[*meso*-(1*R*,2*S*,5*R*,6*S*,9*R*,10*S*)-1,2,5,6,9,10-hexabromocyclododecane]

Conclusions

Representation **4** for HBCD is recommended if one wishes to conform strictly to the IUPAC rules or if a three-dimensional representation is required to clearly show the symmetry of all five HBCD isomers found in technical mixtures.

Representations **2** and **3** for HBCD are also acceptable to IUPAC rules. However, these are to be avoided as they do not clearly show the axis and planes of symmetry within the structure. The presence of stereochemistry is an important part in understanding the differences between HBCD isomers, and therefore, should be clearly observable from the three-dimensional representations.

Representation **5** does not conform to IUPAC rules but is by far the most commonly used three-dimensional representation of HBCD presumably due to the ease of drawing. If representation **5** is to be used, it is recommended that the substituents at the re-entrant positions be oriented inwards. Representation **5** is sufficient to clearly show the stereochemistry (axis of symmetry) when dealing with the three major HBCD diasteriomers; alpha, beta and gamma.

References

1. See for example; i) Alaee, M., Arias, P., Sjodin, A. and Bergman, A. (2003) Environ. Int., 29, 683-689 ii) 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.

4. Heeb, N.V., Schweizer, W.B., Kohler, M. and Gerecke, A.C. (2004) Third International Workshop on Brominated Flame Retardants, 337-340.

5. Lindberg,P., Sellstrom., Haggberg,L.,de Wit,C., (2004) Environ. Sci. Technol. 38, 93-96.

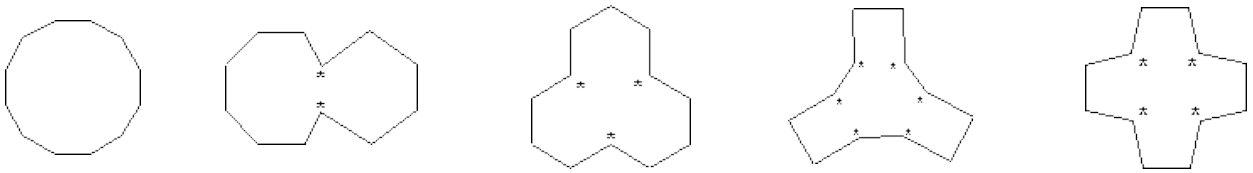
6. Remberger, M., Sternback,J., Palm,A., Kaj,L., Stromberg,K., Brorstrom-Lunden,E., (2004) Chemosphere 54, 9-21.

7. Becher, G. (2005) Chemosphere 58, 989-991.

8.IUPAC, Basic Terminology of Stereochemistry, (prepared for publication by G.P.Moss), *Pure Appl. Chem*., **68**, 2193-2222 (1996) and references therein.

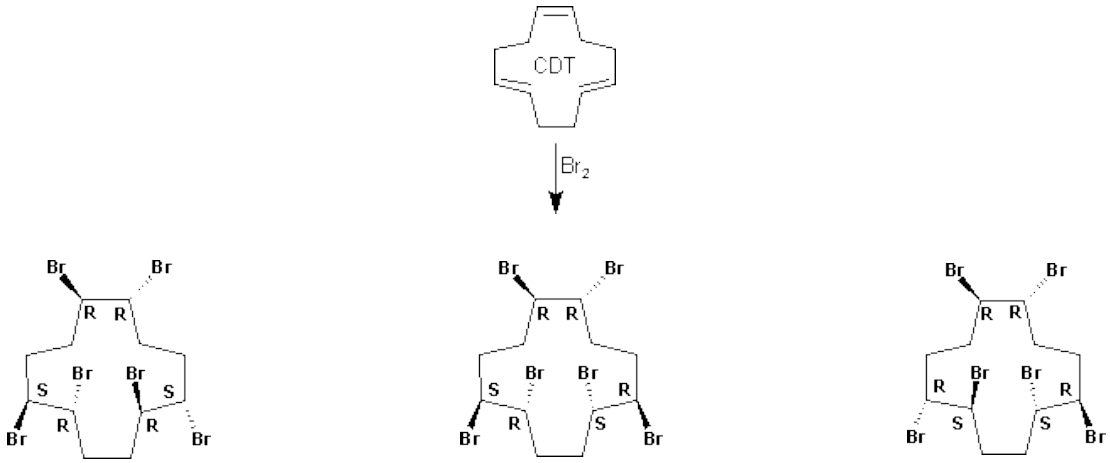
9. In the past (please see reference 8) there has been confusion about how to represent bonds to atoms below the plane. We have adopted, in this document, the format suggested in the recently published IUPAC Provisional Recommendations for Nomenclature of Organic Chemistry (Chapter 9, Specification of Configuration and Conformation, Draft 7, October 2004). “Bonds to atoms below the plane are shown with a hashed wedge which is used with the understanding that the narrow end of the wedge begins at the atom in the plane of the drawing.” Thus, a longer hashed line signifies an atom that is “further away” from the viewer.

10. The naming of alpha, beta and gamma-HBCD is apparently based on the order of elution observed for a HPLC. Using the same reasoning for these two new compounds, the first eluter should be called delta-HBCD followed by epsilon-HBCD.



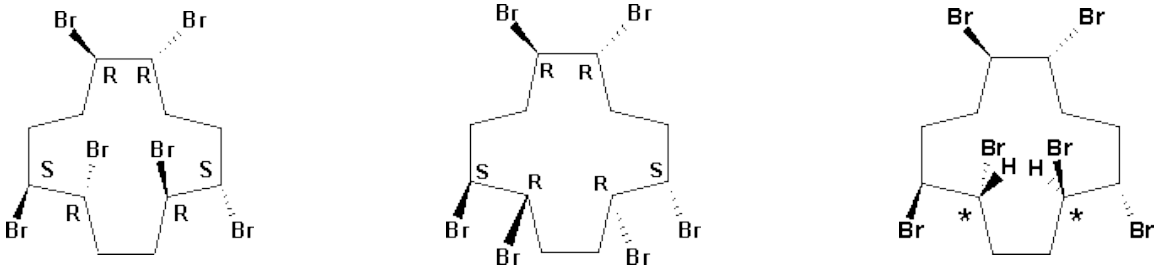
1 **2** **3** **4** **5**

* ≡ re-entrant positions

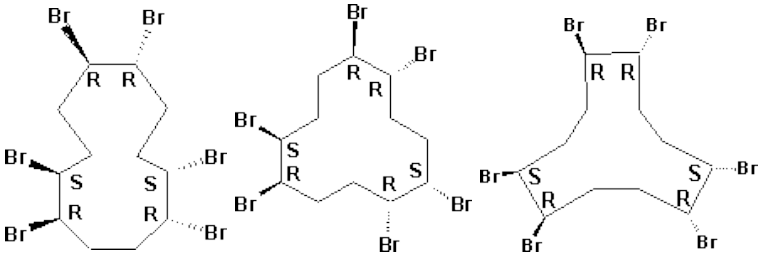


(**6**) (**7**) (**8**)

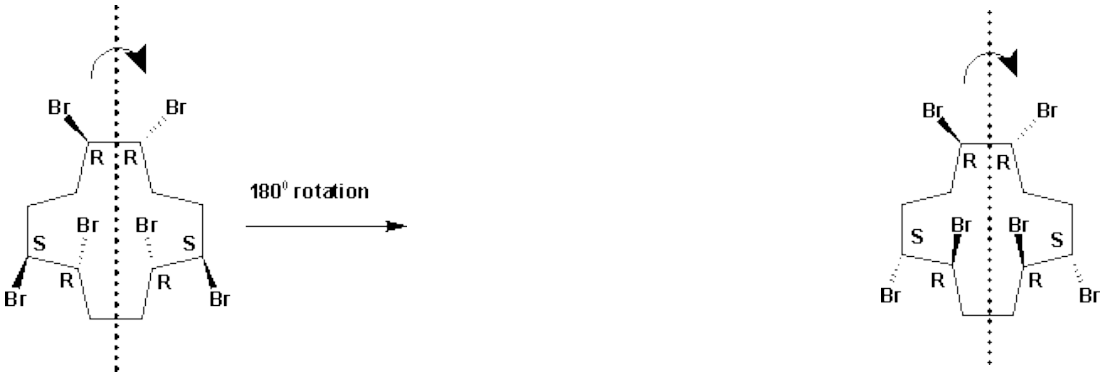
Scheme 1. Bromination of *cis,trans,trans*-cyclododecatriene (CDT) to give alpha-, beta- and gamma-HBCD



6 **9 (≡ 6)** **10 (≡ 6)**



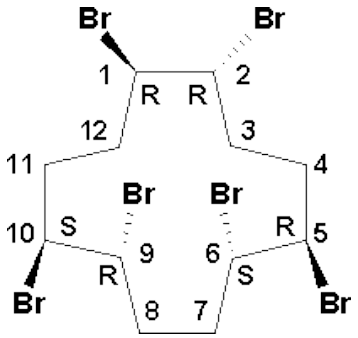
11 **12** **13**



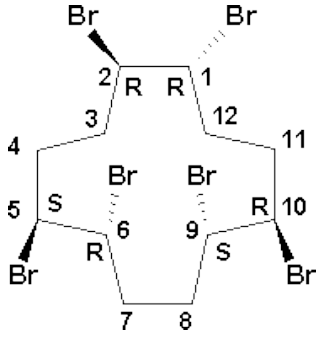
Axis of rotation

14 (≡ **7**)

7



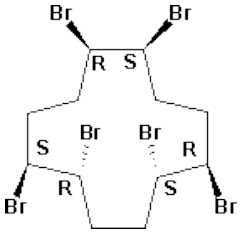
7a



7b

1R,2R,5R,6S,9R,10S

1R,2R,5S,6R,9S,10R



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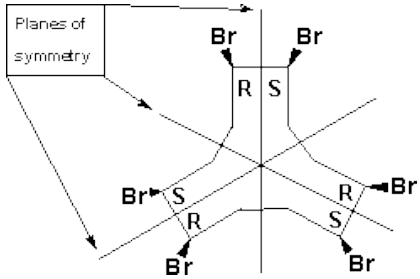
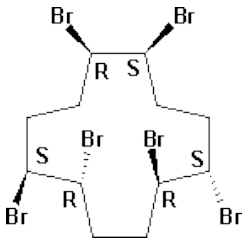


16

Delta-HBCD



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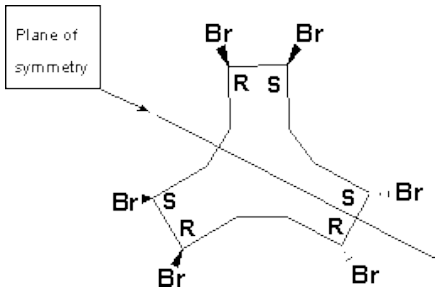

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Epsilon-HBCD