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Relevance of 1,2,5,6,9,10-hexabromocyclododecane diastereomer structure on partitioning properties, column-retention and clean-up procedures

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ABSTRACT

To optimize clean-up procedures for the analysis of α-, β-, and γ-hexabromocyclododecanes (HBCD) in environmental and biological extracts, their retention behavior on silica gel and florisil was investigated using diverse mobile-phase solvents and accounting for matrix effects. The β-diastereomer, relative to the α- and γ-diastereomers, is substantially retained on both florisil and silica gel regardless of the solvent used. The β-diastereomer is therefore prone to undergo selective loss during clean-up. This sequence is counterintuitive to sequences based on reverse-phase chromatography with a C_{18}-column, in which the α- (and not the β-) isomer is eluted first when using a polar solvent. There has been some discrepancy regarding the structures of these diastereomers in the literature, with structures based on X-ray crystallography only becoming recently available. Based on these X-ray crystal structures, physical–chemical properties (the octanol–water partitioning constant, the Henry's law constant, subcooled liquid vapour pressures and subcooled liquid water solubilities) of the HBCD diastereomers were estimated using the quantum-chemistry based software COSMO*therm*, and were found to differ from previously calculated values using different structures (e.g. $\log K_{aw}$ for α-, β-, and γ-HBCD are here estimated to be −8.3, −9.3 and −8.2 respectively). Hypothesis relating differences in structure to physical–chemical properties and retention sequences are presented. The extra retention of the β-diastereomer on silica gel and florisil is likely because it can form both greater specific (i.e. polar) and non-specific (i.e. non-polar) interactions with surfaces than the other diastereomers. Non-specific interactions can also account for the counter-intuitive elution orders with C_{18}-reverse-phase chromatography. These results indicate that care should be taken when isolating HBCDs and other molecular diastereomers from environmental and biological samples, and that reported concentrations of β-HBCD in the literature may be negatively biased.

1. Introduction

1,2,5,6,9,10-Hexabromocyclododecane (HBCD) is one of the most frequently used brominated flame retardants (BFR) with an estimated annual demand of 16,700 metric tons in 2001 [1,2]. The industrial application of HBCD has increased during the last decade concomitantly with restrictions on the use of polybrominated diphenyl ethers (PBDEs) [3,4]. The European Union has recently implemented HBCD into its water framework directive, REACH, as a substance of very high concern (Press Release No. 69/2008). Concerns for HBCD in the environment have prompted international research efforts on developing good analytical protocols and understanding its environmental fate [5,6].

There are described 16 different possible HBCD diastereomers [7]. Technical mixtures of HBCD consist primarily of three environmentally relevant diastereomers, referred to as α-, β-, and γ-HBCD, each of which contain two enantiomeric pairs. The γ-diastereomer generally dominates in industrial mixtures, constituting more than 70% of the total mixture [8]. Analysis of HBCD has met with several challenges, in particular the diastereomer specific separation [5,6]. α-, β-, and γ-HBCD has been shown impossible to achieve with ordinary GC-columns. The compound is temperature labile and readily decomposed by the relatively harsh conditions in a GC-instrument [9,10]. Recent progress in LC-technology has, however, enabled both diastereomer and enantiomer specific separation of HBCD [11–13]. Further, commercially available ^{13}C- or deuterium (^{2}H)-labelled HBCD combined with the use of mass

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selective detectors has made the HBCD analysis more convenient and reliable [11]. These have led to several advances in elucidating the occurrence of the different diastereomers in the environment, such as α-HBCD dominating in monitored biological materials even though the γ-HBCD dominates in technical mixtures (e.g. [2,14,15]).

The 3D geometry of HBCD diastereomers has a substantial impact on their physical–chemical properties, and therefore their analytical separation and environmental behavior [16–18]. However, the relationship between structure and physical–chemical properties has been challenging to discern, due to differing experimental methods reporting several contradicting structures for individual HBCD diastereomers. For instance, structures, showing on which side of the cyclododecane plane the six bromines are substituted, recently determined using nuclear magnetic resonance (NMR) spectra [19], differ from those more recently obtained with X-ray crystallography [17]. As X-ray crystallography provides explicit information on which side of the plane the bromines are substituted, these structures are here considered to be definitive. Previously the NMR-based structures [19] were used to estimate dimensionless Henry's Law constants, K_{aw}, and octanol–water partition coefficients, K_{ow}, using the quantum-chemistry based software, COSMO*therm* [18]. In this manuscript, similar calculations are done using the substitution patterns isolated with X-ray crystallography. We note that COSMO*therm* is ideal for such calculations because they can account for liquid-state conformations in various solvents (e.g. [20]) and thus correct for the liquid state if solid state structures are used as input.

Despite the large amount of information on many analytical procedures related to isolate HBCD diastereomers as well as enantiomers from various matrixes, detailed information on clean-up procedures is generally lacking. Typically, methodology used for other BFRs or organohalogenated compounds, such as polychlorinated biphenyls, is applied with only minor procedural changes for the clean-up of HBCD [6,8,21,22]. One common clean-up method used for persistent organic pollutants (POPs) as well as for HBCD is normal-phase clean-up with activated or deactivated florisil or silica gel, often followed by sulphuric acid treatment [11,13,15,22–28]. Few have emphasized that the different physical–chemical properties of the HBCD diastereomers may have implications on recovery and not all laboratories report use of labelled quantification standards, which covers all three diastereomers. The different physical and chemical properties of the HBCD diastereomers therefore, might imply a risk for diastereomer-selective loss during clean-up. In this study, we have assessed the retention properties of α-, β-, and γ-HBCD on silica and florisil columns with different types of regularly used solvents as eluents, and discussed their elution order. In addition the COSMO*therm* predicted parameters are used to account for the role of substitution patterns of the diastereomers on the physical–chemical properties and column-retention characteristics.

2. Experimental

2.1. Materials

The solvents *n*-hexane, isooctane and dichloromethane were of Suprasolv grade and purchased from Merck (Germany), whereas the diethyl ether (glass distilled grade) was from Rathburn (Scotland). The diethyl ether is filtered over a chromatography column (2 cm in diameter) with 20 cm activated aluminium oxide (pH 10, ICN Biomedicals GmbH, Germeny) before use. Acetonitrile and methanol used for liquid chromatography and mass spectrometry (LC/MS) were of high performance liquid chromatography (HPLC) grade (Merck). The column materials anhydrous sodium sulphate, silica gel (0.063–0.200 mm), and florisil (0.15–0.25 mm) were purchased from Merck and Supelco Inc. (USA), respectively, and were preheated/activated for 8 h at 550 °C prior to use. Individual HBCD diastereomer standards used for identification and quantification were purchased from Wellington Laboratories (Canada).

2.2. Solid phase chromatography

Glass columns with an inner diameter of 1 cm were prerinsed with hexane and packed at the tip with clean glass-wool (Apotekernes Felleskjøp, Norway) and mounted vertically. Activated adsorbent (4 g of either silica gel or florisil) was added into the column followed by approximately 1 g Na_2SO_4 on top. The solid phases were allowed to settle by applying an electrical vibrator (Mettler, USA) along the sides of the column. The columns were then preconditioned with 30 mL of either 25% dichloromethane in hexane or 10% diethyl ether in hexane by volume. Each column was spiked with a nominal concentration of 1 ng of each ^{13}C-labelled α-, β- and γ-HBCD diastereomer in approximately 0.5 mL hexane, followed by elution with the respective solvents. In order to test matrix effects, columns with activated silica as stationary phase were spiked with 50 μL cleaned cod liver oil mixed with the HBCD-solution. Fractions of 10 mL of a total eluting volume of 70 mL were collected. The resulting eluates were reduced in volume before solvent change to methanol and to each fraction 0.5 ng of d_{18}-labelled α-, β- and γ-HBCD were added as quantification standards.

2.3. Reverse-phase chromatography and analysis of HBCD diastereomers

The methanol extracts were analyzed for α-, β- and γ-HBCD using a Waters 2690 HPLC coupled to a single quadrupole Micromass z-spray mass detector (ZMD) in electro spray negative mode (ESI−) as previously described in detail [15]. The HBCD diastereomers were separated on a reversed-phase C_{18}-column from Atlantis (150 mm, 2.1 mm i.d., 3.0 μm particle size) employing a trinary gradient of methanol (A), acetonitril (B) and water (C) as eluent. The initial mobile-phase (time zero) composition of 30% A, 10% B and 60% C was changed to 83% A, 15% B and 2% C after 12 min. The HBCD diastereomers were monitored at mass-to-charge ratio (m/z) of the molecular ions $[M-H]^-$. m/z of the selected primary/secondary ions were 652.64/650.64 and 657.74/655.74 for the ^{13}C- and d_{18}-labelled standards, respectively. Sum of the primary and secondary ions were used in the quantification using the ratio between the two ions as verification. Limit of detection varied between 1 pg and 2 pg with a signal to noise ratio greater than 3 and an isotopic ratio within ±20% of the theoretical value.

2.4. COSMOtherm

COSMO*therm* (Version C2.1 release 01.08, COSMO*logic* GmbH &Co. KG: Leverkusen, Germany, 2008) in combination with Turbomole 5.10 (University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, http://www.turbomole.com) [29] performs density functional quantum-chemical continuum solvation calculations with statistical thermodynamics to determine activity coefficients and vapour pressures, and has been shown to be successful at elucidating differences for different diasteromers for the case of hexachlorocyclohexanes [18]. Structures of individual enantiomers reported in [17] were used as input for the α-, β- and γ-HBCD diastereomers.

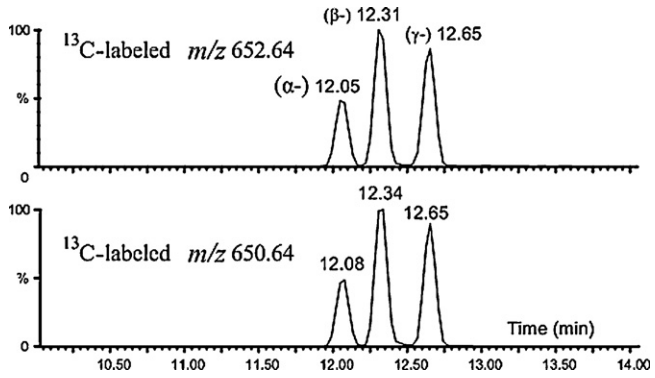

Fig. 1. HPLC chromatogram of ^{13}C-labelled α-, β- and γ-HBCD.

3. Results and discussion

3.1. Separation of HBCD diastereomers with the C_{18}-reversed-phase column

Diastereomer-selective separation of ^{13}C-labelled α-, β- and γ-HBCD on HPLC is shown in Fig. 1. It represents a typical chromatogram of the three major HBCD diastereomers on a C_{18}-reverse-phase column. The diastereomers elute in the order α, β and γ, respectively, as expected from similar methods (e.g. [11,12]). The deuterium labelled HBCD diastereomers have approximately 0.1 min longer retention time on the column (data not shown). It could be inferred from this that the α-diastereomer is the most polar and hydrophilic, and therefore most water soluble. However, as will be elaborated below, this may not necessarily be the case.

3.2. Separation of HBCD-diastereoemers with silica and florisil normal-phase chromatography

In order to reduce retention time and/or the selectivity of the fraction of which the chemicals are eluted from a chromatography column, it is common to mix mobile-phase solvents of different polarities. In the present study, hexane was mixed with the more polar solvents dichloromethane and diethyl ether, respectively. The retention experiment with activated silica showed that when using diethyl ether in hexane as eluent, 90% of the spiked α-, γ- and β-HBCD was recovered within 20 mL, 30 mL and 60 mL of solvent, respectively (Fig. 2). When eluting with DCM in hexane, on the other hand, 90% of the spiked α- and γ-HBCD were recovered within 70 mL solvent, whereas only ~10% of the β-diastereomer was recovered (Fig. 3). The β-HBCD was retained the strongest, independent of the solvent used. For both solvent mixtures, α-, and γ-HBCDs were also eluted within a much narrower band than the β-HBCD. The longer retention with DCM/hexane than with diethylether/hexane can be related to DCM having a weaker solvent strength than diethyl ether (ε° = 0.30 and 0.38, respectively) on silica [30]. Because DCM is a less polar solvent (solubility in water: 1.3 g/100 mL) than diethyl ether (solubility in water: 6.9 g/100 mL) [31], it does not as readily compete with and replace HBCD molecules sorbed to the silica surface.

In order to test if an introduction of a matrix affected the elution order or the elution volume of the respective diastereomers, HBCD mixed with 50 μL cod liver oil was added to the prepared columns with activated silica. No effect on the elution order or elution volume of the diastereomers was observed with the use of ether/hexane (data not shown), whereas a small reduction in elution volume was observed with use of DCM/hexane (Fig. 4).

Diethyl ether in hexane was the only solvent tested on florisil. Florisil is a Mg-silicate with slightly different properties than pure silica and is used as a stationary phase to increase the selectivity of sample preparations. When using this mixture as an eluent, the separation of the β-HBCD from the other diastereomers was more complete. 90% of the α-, γ- and β-HBCD was recovered within 20 mL, 30 mL and 60 mL of solvent, respectively (Fig. 5). With florisil, a base line separation of β-HBCD from the γ- and α-HBCD was achieved. The use of florisil did not, however, result in reduced consumption of solvent compared to activated silica.

3.3. Physical–chemical properties of HBCD

In Table 1 physical–chemical properties of HBCD diastereomers estimated using COSMO*therm* or determined experimentally in the literature are reported. Reported properties include the COSMO*therm* predicted subcooled liquid vapour pressure, p_L^*, subcooled saturated water solubility, C_{wL}^{sat}, the log of the dimensionless Henry's law constants, $\log K_{aw}$, the log of the octanol–water partitioning constant, $\log K_{ow}$, as well as literature values for $\log K_{ow}$ and the non-subcooled water solubility, C_w^{sat}. The COSMO*therm* val-

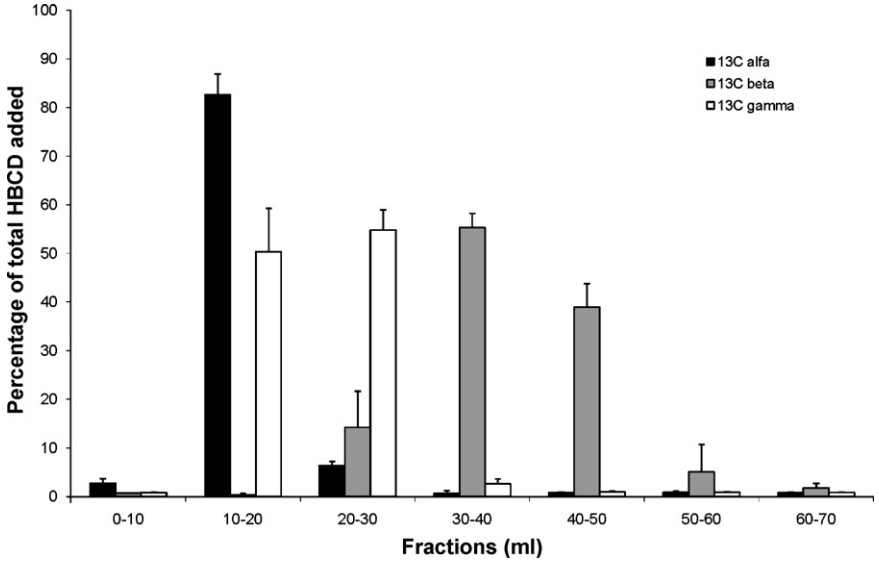

Fig. 2. Fractionation of HBCD diastereomers on a silica column with 10% diethylether in hexane as eluent. Each bar represents mean (±SD) from three separate experiments.

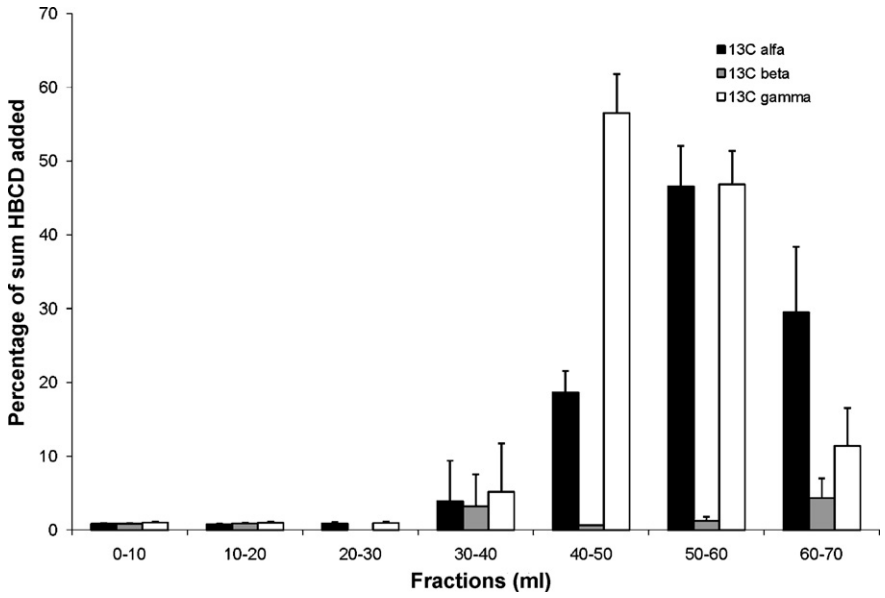

Fig. 3. Fractionation of HBCD diastereomers on a silica column with 25% DCM in hexane as eluent. Each bar represents mean (±SD) from three separate experiments.

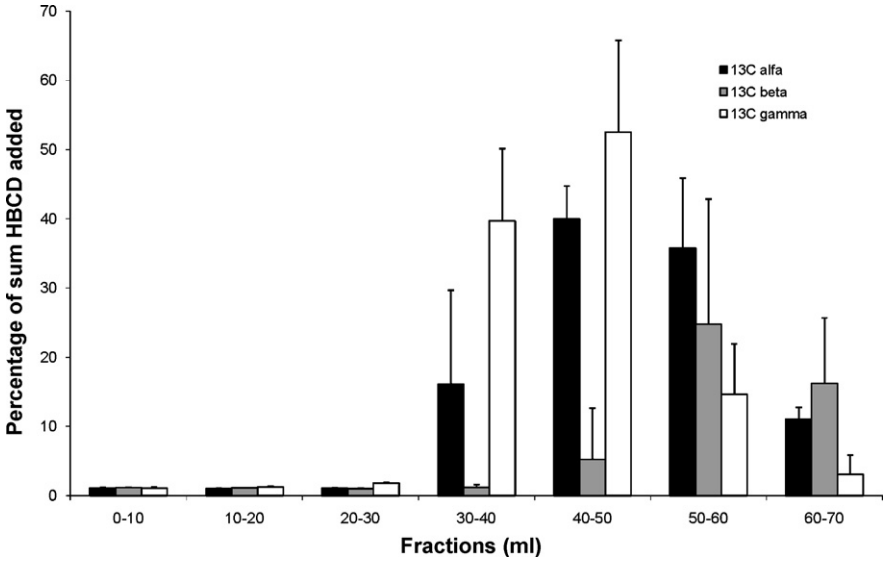

Fig. 4. Fractionation of HBCD diastereomers mixed with 50 μL fish-oil on a silica column with 25% DCM in hexane as eluent. Each bar represents mean (±SD) from three separate experiments.

ues for α-, β- and γ-diastereomers in Table 1, based on structures determined by X-ray crystallography [17] differ somewhat from those reported earlier [18] using the NMR-based structures [19]. Earlier reported COSMO*therm* estimated $\log K_{aw}$ values are −8.8, −9.2 and −8.6 for the α-, β- and γ-diastereomers, respectively; thus, the values here are 0.1–0.5 orders of magnitude lower, but the relative order remains the same with β-HBCD exhibiting the lowest $\log K_{aw}$ and γ-HBCD the highest. Earlier reported COSMO*therm* estimated $\log K_{ow}$ values for "dry" octanol are 5.59, 5.44 and 5.53 for the α-, β- and γ-diastereomers respectively [18], which are about an order of magnitude higher than estimates in Table 1 for "wet" octanol (i.e. water saturated octanol, to simulate K_{ow} values

Table 1
COSMO*therm* and literature physical–chemical properties for HBCD diasteromers.

Compound	COSMO*therm* predicted				Literature			
	p_L^* (Pa)	C_{wL}^{sat} (mg/L)	$\log K_{aw}$	$\log K_{ow}$[a]	C_w^{sat}[b] (mg/L)	$\log K_{aw}$[c]	$\log K_{ow}$[c]	$\log K_{ow}$[d]
α-HBCD	1.2E−08	0.60	−8.3	4.45	0.049	−8.8	5.59	4.11–5.07
β-HBCD	2.6E−09	1.31	−9.3	4.18	0.015	−9.2	5.44	4.17–5.12
γ-HBCD	1.1E−08	0.49	−8.2	4.40	0.002	−8.6	5.53	4.59–5.47

[a] Determined for "wet" octanol, not "dry" octanol [18].
[b] Values from [33], which are determined for the solid solubility, and are not C_{wL}^{sat}.
[c] Values from [18].
[d] A range of $\log K_{ow}$ values based on experimental evidence is presented, as a definitive value could not be isolated in [32].

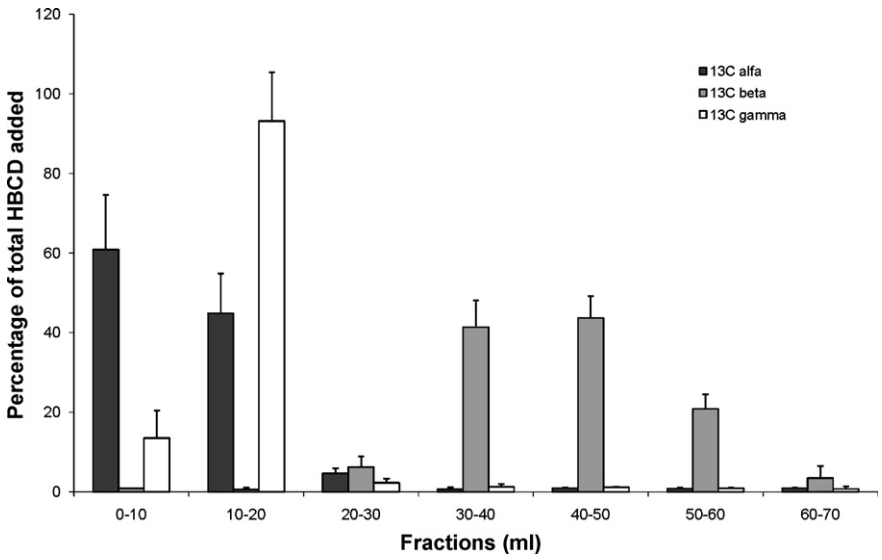

Fig. 5. Fractionation of HBCD diastereomers on a florisil column with 10% diethyl ether in hexane as eluent. Each bar represents mean (±SD) from three separate experiments.

determined in the laboratory by octanol–water batch flasks). Differences in log K_{ow} due to diastereomer structure are expected to be minor compared to the difference between "wet" and "dry" octanol. Indeed, as before, the K_{ow} is similar for the different diastereomers (within 0.3 units). Also the respective order remains the same (with β-HBCD exhibiting the lowest K_{ow}). The estimated log K_{ow} values for both structures are within or close to the lower range of experimentally derived values reported previously [32] (Table 1). Because COSMO*therm* values reported in Table 1 are based on X-ray crystal structures, they are recommended over predictions we reported earlier [18].

The predicted C_{wL}^{sat} are all higher than experimental C_{w}^{sat} values reported previously [33], and their order is different. For instance, COSMO*therm* predicts β-HBCD to have the highest C_{wL}^{sat} value (of 1.31 mg/L) followed by α-HBCD (0.60 mg/L); whereas, experimental C_{w}^{sat} values indicate α-HBCD as the most soluble, though by an order of magnitude less than COSMO*therm* predictions (0.059 mg/L). The experimental values being lower can be accounted for them being determined for the solid, and not sub-cooled liquid state, as extra-energy is required to overcome the free-energy of crystallization [34]. We note that C_{wL}^{sat} values are more appropriate for relating to solid/water partitioning processes of dissolved solids in both analytical systems and the environment, as crystallization of solid particles does not occur in water or other phases at low concentrations [34]. Accounting for the liquid state is especially important for HBCD, which are expected to have large enthalpies of crystallization, thus showing markedly different solubilities in the solid and liquid state, not only for water but other samples as well. This may account for the apparent low solubility in acetonitrile [24]. Color coded pictures of the molecular surface charge densities of the various diastereomers, as predicted by the quantum-chemical software Turbomole, can be found in the Supporting Information. We note finally that the enantiomeric pairs of the individual diastereomers are expected to exhibit similar physico-chemical properties shown in Table 1, based on COSMO*therm* predictions and the fact that to our knowledge there is no example of enantiomeric pairs exhibiting such differences.

3.4. Influence of partitioning properties on column-retention

The results of the reversed-phase and normal-phase column experiments may appear contradictory. For the reverse-phase columns the α-HBCD exhibited the highest affinity for the polar-mobile phase and from this may appear to be the most polar; whereas for the normal-phase columns the β-HBCD exhibited the most affinity for the polar stationary phase, and from this may be considered the most polar. However, partitioning between the stationary and mobile phases is dependent on both specific (i.e. polar) and non-specific (i.e. non-polar) interactions. To account for these observations collectively, both types of interactions need to be considered.

Contrary to reversed-phase chromatography results, COSMO*therm* predicts β-HBCD to be the most water soluble and to have the lowest K_{ow}, and thus to exhibit the highest affinity for polar mobile-phases. These predictions may not be readily evident from the images of surface charges (Fig. S1), as the polar (electron accepting) areas of the β-diastereomer (indicated in dark blue) are slightly less prevalent than on the α-diastereomer. However, further examination shows that this polar area is on a planar-part of the electron surface for β-diastereomer rather than buried within a "valley" of the electron topography, as in the case of the α-isomer. This could indicate the polar area is less shielded on the β-diastereomer, and thus more readily undergoes specific (i.e. polar) interactions, particularly with polar surfaces, and possibly be more accessible to water and other polar solvents. Though, whether this alone explain the increased predicted C_{wL}^{sat} (and subsequently lower K_{aw} and K_{ow}) is only speculation, as it could be influenced by both the polar interactions of small water molecules having more access to polar areas of the β-diastereomer, or by the non-specific interactions in terms of the structure of the water cavity surrounding this diasteromer. Nevertheless, for the case of adsorption, the planar-polar surface alone could account for higher retention of β-HBCD on silica and florisil, but not for its sorption behavior to the C_{18}-column.

An additional hypothetical explanation to account for the β-HBCD isomer being retained the longest for silica gel and florisil is additional non-specific, van der Waal interactions with the stationary phase surface compared to the of α- and γ-HBCD. One strong indication for this is evident from the structures previously reported [17], where 5 of the 6 Br-atoms are on one side of the cyclododecane plane for the β-HBCD, whereas only 3 Br-atoms are on each of side in the case of α- and γ-HBCD. As the β-diastereomer can bring 5 of 6 Br-atoms into the adsorption plane in close contact with the surface, this is favorable for adsorption because the bromines have a higher polarizability than the car-

bon backbone of the HBCD, thus allowing stronger van der Waal interactions with the surface. The structure of β-HBCD is therefore unique from the other two diastereomers, as one side of the cyclododecane plane is capable of making stronger specific interactions than the other isomers, whereas the other side is capable of making stronger non-specific interactions. However, the additional non-specific interactions of Br-rich side of the β-HBCD is likely more substantial than the additional specific interactions of the opposite side, and thus non-specific interactions most likely account for the enhanced retention of β-HBCD on silica gel and florisil.

Why the α-HBCD elutes faster than the β-HBCD isomer for the reverse-phase C_{18}-column can, therefore, also be related to increased van der Waals interactions of β-HBCD to the apolar C_{18} surface compared to α-HBCD, as this could overcompensate for β-HBCD being more soluble in the mobile phase. Previously it was reported [12] that when using a C_{30}-column β-HBCD was more retained than both α- and γ-HBCD isomers when methanol is used as a mobile phase. This is in agreement with this hypothesis here, as C_{30} surface can form more van der Waal interactions than C_{18} (due to an increased amount of methylene groups), and thus exhibit stronger non-specific adsorptive interactions with β-HBCD. More subtle differences between elution order of α- and γ-HBCD reported are likely also related to structural-related differences in their ability to make specific and non-specific interactions with stationary and mobile phases.

4. Conclusions

The HBCD diastereomers exert substantial different retention characteristics on silica gel and florsil and it is recommended to use α-, β- and γ-HBCD internal standards to see if quantitative yield is obtained. Not doing so may have contributed to previously reported β-HBCD concentrations in the literature to be underestimated. These results also indicate that other artifacts relevant to environmental and biological sample analysis may result, such as stability and solubility of HBCD in the solvents used. There is reported loss of HBCD stored in hexane/isooctane extracts that were not sufficiently purified [35] and diastereomer-selective loss of the γ-HBCD when using acetonitrile as injection solvent [24]. Selective loss due to glass adsorption during clean-up is less likely because the amount of surface area in the silica/florisil packing is orders of magnitude larger than the glass surface and usually vials are rinsed and deactivated with solvent before transfer. The new COSMO*therm* predictions of physical–chemical properties for the revised structures are recommended over those shown earlier for the HBCD diastereomers [18]. The β-HBCD is considered more polar than α- or γ-HBCD, and is likely also capable of greater non-specific interactions with surfaces. The different physical–chemical properties for the diastereomers are considered significant enough to lead to different environmental fate pathways and thus are part of the explanation as to why ratios of diastereomers in environmental samples and industrial mixtures differ.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2009.12.076.

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