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Exploring 3D structural influences of aliphatic and aromatic chemicals on α-cyclodextrin binding

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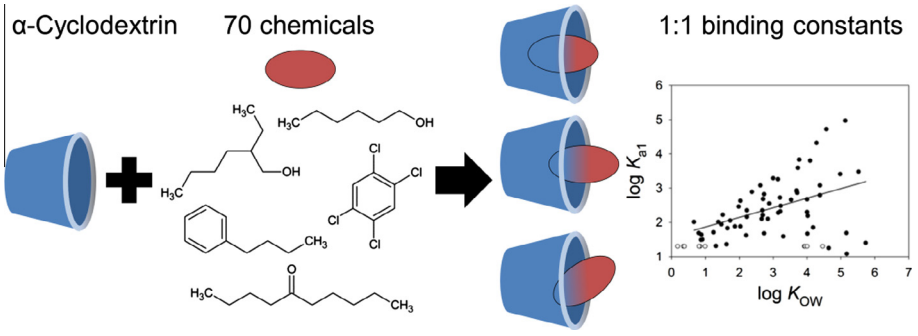
HIGHLIGHTS

- Determination of 70 primary α-cyclodextrin binding constants (K_{a1}).
- Interpretation of different steric effects depending on the 3D structure of the solutes.
- The position of the functional group identified as a critical factor for log K_{a1}.
- The correlation between log K_{a1} and log K_{ow} is weak.

GRAPHICAL ABSTRACT



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ABSTRACT

Binding of solutes to macromolecules is often influenced by steric effects caused by the 3D structures of both binding partners. In this study, the 1:1 α-cyclodextrin (αCD) binding constants (K_{a1}) for 70 organic chemicals were determined to explore the solute-structural effects on the αCD binding. K_{a1} was measured using a three-part partitioning system with either a headspace or a passive sampler serving as the reference phase. The K_{a1} values ranged from 1.08 to 4.97 log units. The results show that longer linear aliphatic chemicals form more stable complexes than shorter ones, and that the position of the functional group has a strong influence on K_{a1}, even stronger than the type of the functional group. Comparison of linear and variously branched aliphatic chemicals indicates that having a sterically unhindered alkyl chain is favorable for binding. These results suggest that only one alkyl chain can enter the binding cavity. Relatively small aromatic chemicals such as 1,3-dichlorobenzene bind to αCD well, while larger ones like tetrachlorobenzene and 3-ring aromatic chemicals show only a weak interaction with αCD, which can be explained by cavity exclusion. The findings of this study help interpret cyclodextrin binding data and facilitate the understanding of binding processes to macromolecules.

1. Introduction

The binding of small molecules to macromolecules is important in numerous processes such as enzymatic reactions, receptor binding, plasma protein binding, and drug formulation with excipients.

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While partitioning of small molecules between various homogenous phases such as solvents are well understood and quantified according to the contributions of specific molecular interactions [1], this is yet not the case for the binding to macromolecules. In contrast to homogeneous partitioning systems, the influence of the three-dimensional (3D) structure plays a decisive role in the sorption process to macromolecules. Generally, a good fit between the small molecule and the macromolecule is important for the efficiency of the binding process [2].

An example of macromolecules that are used to bind smaller chemicals are cyclodextrins (CDs). CDs are conic ring oligosaccharides and are also present naturally. CDs are usually made of 6, 7, and 8 glucopyranose units, which are named α-, β-, and γ-CD, respectively. The conic ring structure of CD generates a cavity. Its surface is mostly formed by the hydrophobic parts of the molecule [3]. The molecular structure of CDs can also be modified to increase their particular applicability, e.g., six modified CDs are widely used as excipients for clinical purposes [4]. Here, one advantage of CD as excipient is its low toxicity [4]; orally applied, CDs have shown low absorption to the blood circulation and therefore exerted no toxic effect [5].

In solution, CDs commonly form inclusion complexes (host–guest complexes) with many chemicals. Typically studied guests are drugs whose molecular mass ranges from 100 to 400 Da [6]. The specificity of CD binding appears to be relatively low, and the association constants (K [M^{-1}]) vary widely across different guest molecules: for example, protonated aniline has a log K of 0.36 for the association with α-CD [7] while decyltrimethylammonium bromide has a log K of 3.57 [8], and nucleotides can have log $K \geqslant 6$ for the association with aminocyclodextrins [7]. While CDs are sometimes considered like a normal, homogeneous phase [9], the 3D structure of the small molecules appears to play a critical role for the formation of the host–guest complex with CD [10] as for other macromolecular binding.

Energetics associated with the formation of the host–guest complex with CD are discussed in the literature based on two concepts: (a) Direct intermolecular interactions between host and guest via van der Waals forces and hydrogen bonding which are influenced by the fit between the guest and the CD cavity, and (b) additional positive energy gains through the formation of the host–guest complex. The latter includes mechanisms such as: the release of bound water from the cavity to bulk water, and the relief of conformational stress of the cyclodextrin [11]. The relative importance of the different factors on the partition process should depend on the guest molecule.

In addition to the beneficial use for clinical and other industrial purposes, CD is often considered a model macromolecule to study host–guest complexation. An advantage of using CD for studying molecular steric effects on binding behavior is its well-investigated 3D structure. The binding is flexible to some degree but restricted in the conic main structure [12]. The angles between the glucopyranose units vary depending on the solvation medium, the host–guest complex, and the aggregate state. Binding coefficients of CD give direct indications of the strength of binding, but experimental data found in the literature (e.g., [10,13]) are derived from many sources that use different methods. Thus, the data are not always comparable and the composition of the data set might not be designed to answer specific questions regarding the influence of the 3D structure.

In this study we experimentally determined a large, consistent dataset of binding constants for αCD with 70 aliphatic and aromatic chemicals such as alcohols, ethers and chlorobenzenes. The aim of this study was to identify the 3D-structural features of guest molecules that influence the binding affinity to αCD. Particularly, we sought for explanations for substantially different binding constants that we found for apparently similar chemicals.

2. Materials and methods

2.1. Materials

The chemicals were purchased from various providers- and their purity was at least 94% and mostly >98%, as listed in the supporting information (SI). There were some chiral chemicals, the chirality of which was not specified. All test chemicals used for binding experiments were first dissolved in methanol to make stock solutions. Three to five chemicals of one compound class were mixed into one stock solution. Only those chemicals that were distinctly separated through the gas-chromatographic (GC) system (see below) were mixed together. The concentration of each chemical in methanol stock solution did not exceed 10% of the water solubility so that the final concentration after dilution in water was well below the solubility limit. For all experiments pure water produced by a MilliQ Gradient A10 system (Millipore) was used. Polyacrylate (PA, coating thickness 36 μm, volume of the coating 16.5 μL/m)- and poly(dimethylsiloxane) (PDMS, coating thickness 30 μm, volume of the coating 13.2 μL/m)-coated glass fibers produced by Polymicro Technologies Inc. (Phoenix, AZ) were purchased from Optronics GmbH (Kehl, Germany). αCD was obtained from Wacker Chemie AG with a purity of at least 98.0% and a maximum residual complexant (1-decanol) of 20 ppm. αCD (0.5–2 g) was weighed into a 100 mL volumetric flask and dissolved with MilliQ water to prepare CD stock solution, which was diluted further before the binding experiment.

2.2. Instruments

The following equipment was used for the quantitative analysis: Hewlett Packard GC System HP 6890 series gas-chromatographs with a flame ionization detector (FID) or an electron capture detector (ECD), both systems connected to an HP 7694 Headspace Sampler; an Agilent 7890A GC System equipped with a 5975C inert MSD Triple Axis Detector and a Gerstel Multi Purpose Sampler (MPS 2XL). The chemicals were analyzed on either of the following two columns from Agilent Technologies: HP-1 (30 m × 0.32 mm i.d., 4 μm film thickness), or HP-5MS (30 m × 0.25 mm i.d., 0.25 μm film thickness).

2.3. Binding experiments

Binding constants for 70 chemicals were measured in batch systems. The used methods have been described in detail previously [14] and are briefly explained below. In both methods, the unbound, freely dissolved concentration of the chemical was determined via the measurement of a third phase, either air (headspace approach) or a PA or PDMS fiber (passive sampling approach). All binding experiments were performed at 30 °C, which was the lowest possible temperature that the sample tray of the GC autosampler was able to control.

2.3.1. Headspace approach

Air was the common third phase (reference phase) for this approach [15]. Two groups of weighed 20 mL vials were prepared with four vials per group. One group was filled with 5 mL water and the other was filled with 5 mL αCD solution (2–15 g/L). The vials were spiked with 10 or 25 μL of methanolic stock solution of the selected chemicals and were immediately closed with a PTFE- or aluminum-lined silicone septum to prevent loss of the chemicals. From the experience of preliminary experiments, the equilibrium time was set to a minimum of four hours: first three hours on a horizontal shaker at 30 °C with 300 rpm and then at least one hour on the GC-sample tray at 30 °C with low shaking