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Molecular Organization in the 6-Bromo-6-deoxycyclodextrins, Formation of Molecular Layers, and the First Crystal Structure of a Selectivity Perfunctionalized β-Cyclodextrin

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We report here the first case, confirmed by solid-state structure analysis, of molecular layer formation from cyclodextrins (CD) rendered amphiphilic by remarkably short two-atom substituent chains. The native CD molecules have two hydrophilic hydroxyl faces surrounding a hydrophobic cavity. Recent developments of clean, efficient methods to selectively modify one face make these molecules attractive for preparing new self-organizing systems;[1] their molecular rigidity coupled with a large polar adhesion surface (150–250 Å^2) allows formation of self-organizing molecular monolayers with extremely short hydrophobic regions, in this case, a two-atom chain, CH_2Br.

The formation of Langmuir layers by amphiphilic molecules has been widely investigated;[2] while not written, it is a widely held tenet that an eight-carbon chain is normally necessary for constituting stable layers. For CD derivatives with hydrophobic esters grafted at the secondary face, molecular monolayers form from much shorter chains.[3]

In this communication we describe the formation of molecular monolayers at the air–water interface by the 6-bromo-6-deoxycyclodextrins, observed by Langmuir compression isotherms. In the case of the β-cyclodextrin derivative, the molecular structure has been determined by X-ray crystallography. The structure shows dimeric units associated by their secondary faces and held together by van der Waals interactions between substituent bromine atoms of their primary face. Comparison of the molecular area, as determined from the compression isotherm (220 Å^2) and the crystal structure (250 Å^2), suggest that there may exist a close analogy between layer arrangements in the solid state and in molecular monolayers.

Figure 1 shows schematically the hydroxyl–bromine substitution at the primary face. The title compounds **1**, **2**, and **3** were prepared with use of a modification of the method of Defaye[1] by action of PPh_3Br_2, formed in situ, on rigourously dry cyclodextrins in anhydrous dimethylformamide.[4]

The compression isotherms for **1**, **2**, and **3** were determined for spread monolayers using a Lauda film balance.[5] In all cases, molecular monolayers were observed with areas (A_0) close to those of the unsubstituted CDs: A_0 = 180, 220, and 260 Å^2 for **1**, **2**, and **3**, respectively. The stability of such layers, as determined by the first collapse pressures, varies as expected with the increasing number of hydroxyls adhering at the water surface: $6 < 16 < 19$ mN m^{-1}. Formation of a second aggregate species with areas A_1 half those of the monolayers is observed for **1** and **2**: A_1 = 70 and 100 Å^2, respectively. This should arise from the

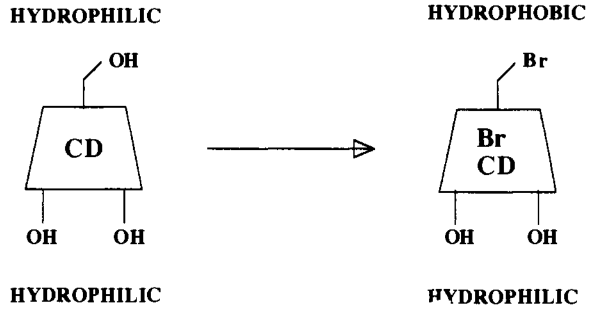

Figure 1. Hydrophobic modification of cyclodextrins yielding the amphiphilic bromo compounds: α-$CDBr_6$ (**1**), β-$CDBr_7$ (**2**), and γ-$CDBr_8$ (**3**).

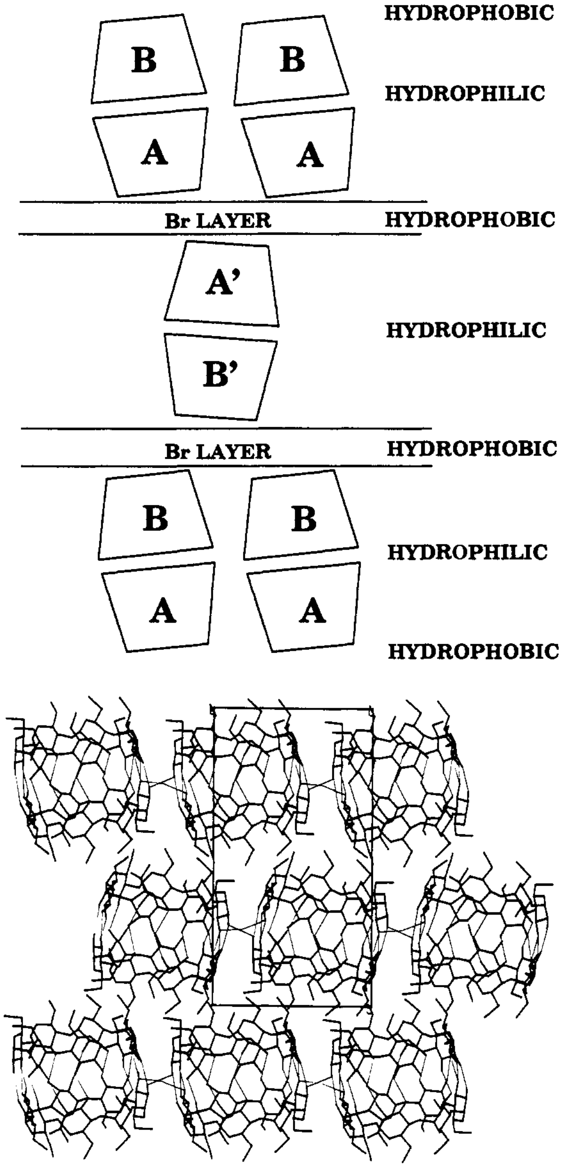

Figure 2. (Top) Schematic representation of the structure along the *a* axis; (Bottom) Projection of the structure along the *a* axis showing the packing of dimeric cyclodextrin layers.

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(4) Extreme care should be taken to recrystallize the triphenylphosphine from EtOH and cyclodextrins from H_2O before use. For triphenylphosphine, drying is carried out in vacuo (10^{-2} T) at 40 °C during 24 h; for the cyclodextrins, drying is carried out in vacuo (10^{-2} T) at 110 °C during 48 h. Purity was determined by FABMS for **1**; no peaks were observed for undersubstituted derivatives. HPLC analysis of the 2,3-diacetylated derivatives showed the three compounds to be pure.

(5) Solutions of **1**, **2**, and **3** in DMSO/$CHCl_3$ (3:2) were spread on the surface of triply distilled water so as to give 2.65×10^{15}, 2.60×10^{15}, and 2.54×10^{15} molecules, respectively, at the air–water interface. A compression rate of 2.3 cm min^{-1} was used, and the experiment was repeated four times to ensure reproducibility.

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formation of bilayers at the interface. The almost vertical slopes of the compression isotherm of **2** for both the monolayer and the bilayer formations imply existence of a highly rigid (solid) system.

As little is known about the structure and physicochemical properties of these new assemblies, a first attempt to obtain more structural information about possible intermolecular interactions has been undertaken with use of X-ray crystal analysis. We report here the first crystallographic results on a CD having one face selectively persubstituted, perbromo-6-deoxy-β-cyclodextrin,[6] in view of attempting to correlate the formation of Langmuir layers with the solid-state structure.

The structure consists of a novel packing of β-CD dimers arranged in layers. The primary faces, constituted of Br atoms, play clearly an important role in the formation of such layers, with interlayer contacts involving uniquely van der Waals interactions between the Br atoms of adjacent layers.

The dimers, formed by a strong hydrogen-bonding association between the polar secondary faces of two (A and B) independent monomer units, are all stacked nearly parallel (13°) to the *c* axis (Figure 2a). The primary faces of these CDs present very different steric arrangements of their seven bromine atoms.

Several structural characteristics of this new dimer packing are surprising: β-CD dimers tied together by strong interdimer hydrogen bonds (2.77 and 2.82 Å) between secondary hydroxyl groups (four per dimer) are packed in layers with a nearly square arrangement due to crystallographic translations along the *a* and *b* axes, approximately perpendicular and equal (15.7 and 15.9 Å). Such an arrangement was previously unknown for dimeric β-cyclodextrins, which usually adopt a pseudo-C arrangement.[7] The molecular area obtained from this packing 250 Å^2, is close to the monolayer area of 220 Å^2. The dimeric interlayer distance (15 Å) is within the normal range,[7] although the CH_2Br groups are more sterically demanding than the CH_2OH groups. Successive layers related by symmetry are shifted about 11 Å in the diagonal **ab** direction: the approximate 7-fold axis of one dimer passes through the voids of layers below and above, leading to a close packing of dimeric layers.

The cohesion between adjacent dimeric layers is ensured only by direct van der Waals interactions between the Br atoms of primary substituted faces (Figure 2b). Each crystallographically independent interlayer (AA′ or BB′) is formed by the Br atoms of one molecule (A or B) and those of its symmetry-related one (A′ or B′). Short interdimer Br–Br contacts are observed for both interlayers: five between 3.5 and 4.0 Å for AA′ and two between 3.79 and 4.0 Å for BB′. The two Br interlayers form different intermeshing patterns: a zigzag pattern (AA′) with very small free spaces or an interlocking row pattern (BB′). Such van der Waals interactions seem to govern the stacking of the dimeric layers in a manner similar to the close (4 Å) Cl–Cl contacts that have been observed and used in the crystal engineering of planar chloroaromatics.[8]

The formation by these compounds of very stable Langmuir films may arise from the special characteristics of the crystal structure. In spite of the presence of such very short hydrophobic chains, the formation of quasiimpermeable hydrophobic layers of bromine atoms lying parallel to the air–water interface, as deduced from the crystallographic evidence, should lead to a stabilization of these bidimensional systems. The collapse and formation by **1** and **2** of a second layer, having a molecular area half that observed in the monolayer, may arise from dimeric structures as observed for **2**. We have also observed by Brewster angle microscopy the formation of rigid bidimensional structures at the 2-dimensional air–water interface.[9]

The effective structures at the air–water interface, monolayers, multilayers, and microcristalline forms, may be related to the structure observed in the solid 3-dimensional state.

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Supplementary Material Available: Compression isotherms for perbromocyclodextrin derivatives; tables of bond distances and angles, atomic coordinates, and thermal parameters for 6-bromo-6-deoxy-β-cyclodextrin (22 pages); tables of observed and calculated structure factors (20 pages). Ordering information is given on any current masthead page.

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(6) Crystal data: formula $(C_{42}H_{63}O_{28}Br_7)_2$; cell constants: $a = 15.714(3)$, $b = 15.917(6)$, and $c = 30.102(4)$ Å, $\beta = 90.55(2)°$, $V = 7529(6)$ Å^3; monoclinic $P2_1$, $Z = 2$. Least-squares refinement based on 3778 unique observed reflections (Mo Kα, $\lambda = 0.710\,73$ Å). Final $R = 0.098$, anisotropic thermal parameters for all Br atoms. Hydrogens atoms, except those of water molecules and hydroxyl groups, in ideal positions.

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