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A Novel Mode of Inclusion for Pyrene in *β*-Cyclodextrin Compounds: The Crystal Structures of *β*-Cyclodextrin with Cyclohexanol and Pyrene, and with *n*-Octanol and Pyrene[†]

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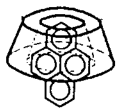
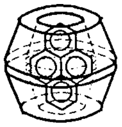
Much of the interest in cyclodextrin complexes hinges on the fact that the water-soluble, torus-shaped cyclodextrins have an apolar cavity that binds and solubilizes guests with low solubility in water.[1] A commonly accepted model for complex formation suggests that the complex forms when a suitable hydrophobic molecule displaces water from the cavity.[2] Such models for inclusion are supported by solution NMR studies,[3] also, many crystal structures have been reported that illustrate the interaction between the apolar cavity and the hydrophobic portion of guest molecules.[4] In this communication we show that the commonly accepted model for pyrene inclusion, with pyrene inserted well into the apolar cavity, is not supported by crystal structure data.

Guests that have been solubilized in aqueous solution as cyclodextrin complexes include many polynuclear aromatics.[5] Such solutions lend themselves well to analytical applications such as concentration determination for environmental assessment.[6] The archtypical complex of a polynuclear aromatic with *β*-cyclodextrin is that of pyrene. The favorable properties of pyrene as a fluorescent probe have made these complexes the subject of numerous studies.[7,8] Information has been obtained on the fundamental photochemistry as well as on the stoichiometry of the complex and the kinetics of complex formation. Many models have been presented for the geometry of the complex. Invariably, these involve insertion of pyrene into the apolar cavity, and construction of a model shows that about half of the pyrene protrudes (scheme 1).[9] A second cyclodextrin then can enclose the protruding portion, thus giving a 2:1 clamshell-like complex (scheme 2). The plausibility of such ideas has been confirmed by modeling calculations.[9]



Scheme 1



Scheme 2

From the effect of other molecules, especially alcohols, on pyrene solubility and the photochemical properties of aqueous cyclodextrin−pyrene solutions it has been postulated that co-inclusion takes place in the cyclodextrin cavity,[10] yielding very stable complexes. In view of the great interest in pyrene−cyclodextrin inclusions it was thought to be of considerable importance to obtain some structural data.

Crystals of cyclodextrin, pyrene, and the appropriate alcohol were prepared as described below.[11] The co-complex formation of pyrene and the alcohol was confirmed by solid-state ^{13}C NMR spectroscopy. Suitable crystals of 2*β*-cyclodextrin·1.5 octanol·pyrene·14.5H_2O (**1**) and of 2*β*-cyclodextrin·3 cyclohexanol·pyrene·10.5H_2O (**2**) were mounted and the structures were determined.[12] Each structure consists of stacks of tilted head-to-head cyclodextrin dimers extended along the *z* axis, a common motif for *β*-cyclodextrin compounds[4] (Figure 1). For **1**, one octanol molecule penetrates the cavities of adjacent cyclodextrin molecules on the primary hydroxyl side, thus linking dimers. For **2**, each cavity is occupied by one cyclohexanol molecule disordered over three sites. For both **1** and **2**, the pyrene molecule lies flat between two cyclodextrin molecules that form the head-to-head dimers, and lies at an angle of 81° to the *z* axis. *As such, there is no penetration of the deep cyclodextrin cavity by the pyrene molecule as proposed for many solution models and in modeling calculations.* Attempts to model the guest−host arrangement with the pyrene molecular plane along the *z* axis, thus penetrating two cavities as shown in scheme 2, showed that the cyclodextrins had to be moved apart by ∼2 Å to accommodate the pyrene. The 14.5 water molecules in **1** and 10.5 waters in **2** per unit cell are in the interstitial space between dimers and form a complete hydrogen-bonded network with the cyclodextrin hydroxyls. O−O distances lie between 2.75 and 2.90 Å for those oxygens connected by H bonds. For **1** a second octanol molecule is found in the interstitial space between the dimers with a site occupancy of ∼50%; similarly, for **2** there are two interstitial cyclohexanols.

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(11) Crystals of *β*-cyclodextrin with pyrene and the appropriate alcohol were prepared by suspending cyclodextrin powder in a hot, aqueous solution saturated with dissolved cyclodextrin. The alcohol was layered over the aqueous suspension, and powdered pyrene was added to the alcohol layer. Crystals developed over a period of time on storage of the reaction mixture in a closed container at a temperature of ∼ 70 °C.

(12) Diffractometer: Siemens Smart CCD. Radiation: Mo Kα. Wavelength: 0.71073 Å. Temperature of measurements: 293(2) K. Crystal structure of **1**: empirical formula $C_{104}H_{201}O_{86}$; formula weight 2827.65; space group *C*2; unit cell dimensions $a = 19.3267(10)$ Å, $b = 24.4409(12)$ Å, $c = 15.9220(6)$ Å, $\beta = 109.00(1)°$, volume = 7111.2(5) Å^3; $Z = 2$; GOF on F,^{2} 1.084; final *R* indices $[I > 2\sigma(I)]$: $R_1 = 0.070$, $wR_2 = 0.183$; *R* indices (all data): $R_1 = 0.094$, $wR_2 = 0.215$. Crystal structure of **2**: emprical formula $C_{118}H_{207}O_{83.5}$; formula weight 2961.84; space group *C*2; unit cell dimensions $a = 19.25440(10)$ Å, $b = 24.4673(12)$ Å, $c = 15.91360(10)$ Å, $\beta = 109.47(1)°$; volume = 7068.20(13) Å;^{3} $Z = 2$; GOF on F,^{2} 1.076; final *R* indices $[I > 2\sigma(I)]$; $R_1 = 0.061$, $wR_2 = 0.151$; *R* indices (all data): $R_1 = 0.082$, $wR_2 = 0.151$.

S0002-7863(97)02156-2 CCC: $15.00

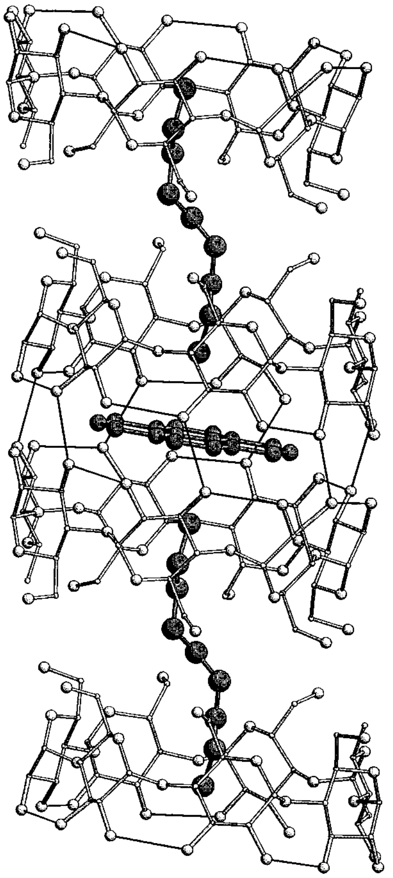

Figure 1. Channel structure of β-CD·1.5 octanol·pyrene·14.5H_2O; view is approximately along the *y* axis. The hydrogen bonds between the two CD's forming the head-to-head dimer are clearly visible, thus outlining the hydrophobic pyrene site.

Close examination of the pyrene site shows that the guest lies in the broadest part of the dimer cavity with the positions of the host molecules unperturbed by the presence of the guest. The only interaction between guest and host appears to be the van der Waals contacts between pyrene H atoms and cyclodextrin hydroxyls. This illustrates that the space enclosed by a complete network of hydrogen-bonded water molecules and hydroxyl groups also can be considered as a hydrophobic site, a situation reminiscent of the cages formed by water molecules occupied by small hydrophobic molecules within in the clathrate hydrate lattices.[13]

For **1**, only one-half of the CD dimer sites are occupied by pyrene molecules. The octanol included in adjacent CD dimer cavities has one end of the molecule nearer to one pyrene site than the other. The diffraction experiment cannot distinguish the octanol OH from CH_3;[14] neither can it be stated with any certainty whether the chain end that penetrates more deeply is next to an occupied or vacant pyrene site.[15] For **2**, there is no close contact between the alcohol and the fully occupied pyrene sites, as cyclohexanol is inserted from the primary hydroxyl side with the alcohol hydroxyl group protruding so as to hydrogen bond with the alcohol extended from the neighboring dimer. For this structural arrangement that likely also exists in solution, pyrene would be remarkably well protected from the influence of external influences such as fluorescence quenchers when it is sandwiched between cyclodextrins with the open ends of the dimer stoppered by alcohol molecules. Certainly structural models of this kind should be taken into account when data for complex formation in solution are interpreted, especially when dealing with 1:2 pyrene−CD complexes. From our results, it is not clear how to deal with the geometry of complexes with higher pyrene concentrations.

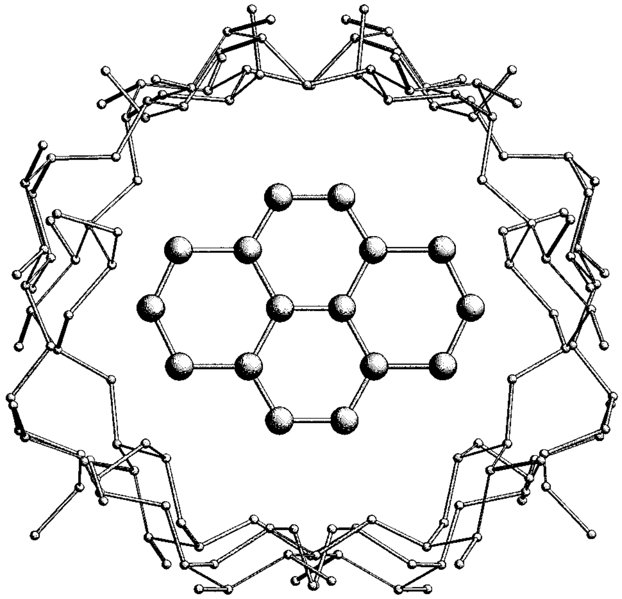

Figure 2. View of the pyrene molecular orientation with respect to that of the β-cyclodextrin molecule.

The common pattern for the two structures presented is that each guest, pyrene and the alcohol, interacts with the host in a noncompetitive way to fill space very effectively. This complementary space filling of the hydrophobic void space in the dimer must account for the enhanced stability of the ternary complex in solution.[5] Whether two guests interact in a competitive or complementary manner with CD should be reflected in different trends in the binding constant data,[16] and this may now also offer a clue as to the relative positioning of the guests in the cyclodextrin cavity. As a generalization, there seems to be no particular reason why other large polyaromatics should not occupy the same site as pyrene, or why the third component must be an alcohol.

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Supporting Information Available: Tables of crystal data, structure refinement data, atomic coordinates, bond lengths and angles, and anisotropic displacement parameters for **1** and **2** (32 pages). See any current masthead page for ordering and Internet access instructions.

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(14) The solid-state ^{13}C NMR spectrum taken with dipolar dephasing showed that large-amplitude motions for pyrene in the complex were absent. The spectrum for the alcohols showed that there was considerable motional averaging. The presence of single lines for each carbon of octanol is consistent with either an ordered situation (either CH_3 or OH next to pyrene) or dynamic averaging, where the groups can exchange rapidly on an NMR time scale.

(15) There are three close contacts between the terminal chain atom (O(H) or C(H_3)) and the two interior carbons and one peripheral quaternary carbon of pyrene at 2.6−2.7 Å if indeed the chain end is near an occupied pyrene site.

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