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COMMUNICATION

Direct evidence for symmetry control in cyclodextrin-water interactions

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The cyclodextrins, cyclic oligosaccharides possessing generally 6, 7, or 8 α, 1–4 linked glucopyranose units, are widely used for the solubilisation and transport of organic molecules in aqueous media.[3] Their solubilities 145 gL^{-1}, α-Cd; 20 gL^{-1}, β-CD; 220 gL^{-1}, γ-CD, are considerably lower than those of simple saccharides and in particular that of β-CD, the most widely available compound, is anomalously low. We have previously shown that the solubilities arise from symmetry determined interactions of the CDs with the dynamic hexagonal structure of water. In the case of the unmodified cyclodextrins all three compounds exist in solution as large aggregates, thus the solubility of these systems is controlled by the interactions between these hydrogen bonded aggregates and the hydrogen bonding networks present in water. In the case of α- or γ-CD there are favorable overlaps with the hexagonal water structure, however for the seven-fold symmetry of β-CD no such favorable interactions can occur between the odd symmetry element and the even symmetry elements of water. Hence the observed solubilities of α- and γ-CD are higher than that of β-CD.**[4]

In this communication we describe the measurement of surface potentials of two series of amphiphilic cyclodextrin derivatives: the first substituted at the primary face and the second, at the secondary face. Figure 1 represents the surface potential, ΔV, as a function of the surface density, for the two series of molecules: 2,3-bis-tetradecanoyl-cyclodextrins and 6-O-dimethyl-*tert*-butylsilyl-cyclodextrins, spread as monolayers on the aqueous sub-phase.[5]

The surface potential curves, for systems where the layer is deposited from chroloform-methanol (9/1), for the derivatives having 14 tetradecyl ester groups at the secondary face (C14-diesters) lead to collapse areas which correspond closely to those observed from the Langmuir compression isotherms.[6]

The knowledge of the surface potential (V) allows calculation of the effective dipole moments orthogonal to the air-water interface $\mu_\perp$ and may be calculated from[7]

$$\mu \text{ total} = A\Delta V/12\Pi$$

where A is the area of a molecule at the interface. The dipole moment arises from contributions from the apolar methyl groups of the alkyl chains in one direction and the polar hydroxyl groups of the cyclodextrin macrocycle in the other direction, plus the effects arising from the dipoles of water molecules hydrogen bonded to the hydroxyl groups.

In the case of the two series of compounds considered here, in the highly compressed state of monolayers close to the collapse pressure, the chain lengths, polar head group depth and molecular orientation are considered not to vary among the α-, β- and γ-CD derivatives from consideration of the molecular areas and the results of grazing angle X-ray diffraction on the diesters,[8] hence any variation may be supposed to arise from differences in the interaction of the head group with the aqueous sub-phase, and will be directly related to the symmetry determined nature of the water-CD interactions.

In Table 1 are given the apparent dipole moments for the compounds per-substituted with *tert*-butyldimethylsilyl groups at the primary face as well as for the C14 diesters.

Comparison of the observed dipole moments allows an assessment of the interaction of each face of the

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** It is useful at this point to consider the much advanced but totally fallacious argument that dimethylation of β-CD increases the hydrophilicity of the compound as a result of the observation that the solubility of the compound increases. In fact these are not comparable systems, as dimethyl β-CD exists as a dimer. More importantly, further methylation leads to a reduction in aqueous solubility, not the expected increase if the arguments concerning greater hydrophilicity as a result of changes in hydrogen bonding capacity on methylation are correct.

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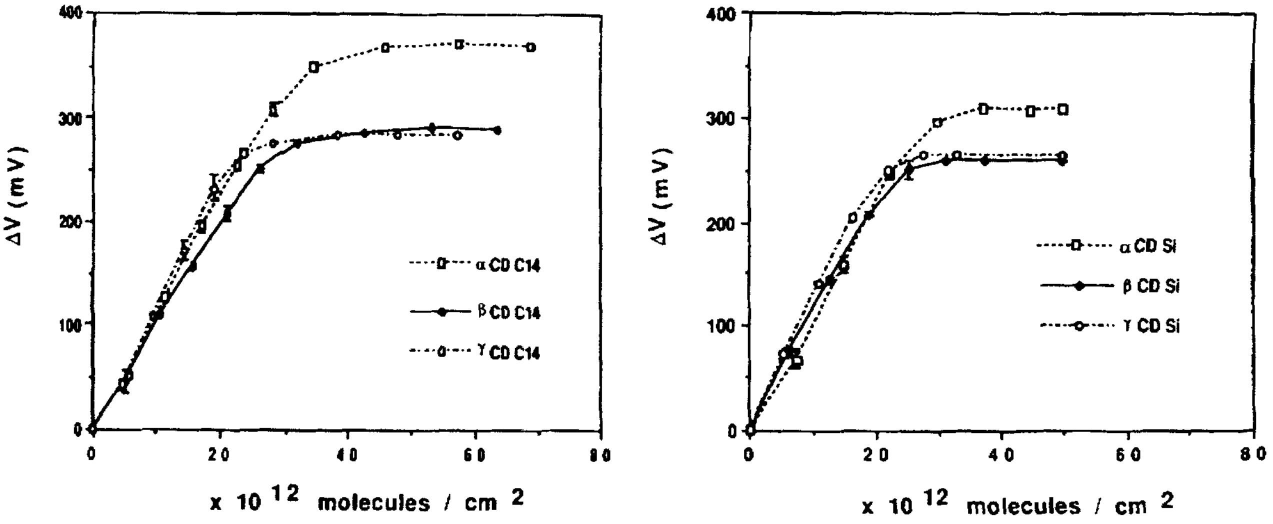

Figure 1 Surface potential as a function of surface density.

Table 1 Calculated dipole moments for amphiphilic cyclodextrins, deposition at the air-water interface from chloroform-methanol (9/1)

	per molecule	*per glucopyranose unit**
Bu^{t}Me$_2$Si-α-CD	2922	487
Bu^{t}Me$_2$Si-β-CD	2781	397
Bu^{t}Me$_2$Si-γ-CD	3291	411
C14-α-CD	2877	479
C14-β-CD	2657	379
C14-γ-CD	3162	395

* Dipole moments per glucopyranose unit are obtained by dividing the value obtained for the molecule by the number of glucopyranose units present in the cyclodextrin.

cyclodextrins with water. The results clearly show that these interactions vary γ-CD > α-CD ≫ β-CD, in complete agreement with the relative solubilities. In terms of interaction per-glucopyranose unit the order is α ≫ γ > β, a situation expected from consideration of the symmetry-derived interactions of the macrocycles with the dynamic hexagonal structure of water. These values are also in agreement with molecular dynamics-derived calculations on water-CD interactions.[9]

The above results and their comparison with the theoretical calculations clearly demonstrate that at the air-water interface the interactions between the cyclodextrins and water are controlled by symmetry considerations and that these interactions correlate with the observed solubility of the native cyclodextrins, γ > α ≫ β.

The contributions of each glucopyranose cycle is expected to represent the fit between the macrocycle and the structure of the sub-phase. Given the dynamic hexagonal structure of water, from purely geometrical considerations, a relation α ≫ γ > β is expected and indeed observed in both deries of amphiphiles. In the case of the α-CD compounds the dipole moments are closely similar ($\delta\Delta V = 45\,mV$), even though for the silyl derivatives two hydroxyl functions are available for hydrogen-bonding to water, whilst for the diester only one group is available. The presence of an extremely strong network of intramolecular OH2... OH3 hydrogen bonds,[9] coupled with a best fit of only one hydroxyl with the water structure may explain this result. For both the β- and γ-CD derivatives there is a much larger increase in the dipole for the silyl derivatives, consistent with both secondary hydroxyl groups participating in interactions with water as compared to the presence of only one type of hydroxyl for the diesters, hence more water molecules may hydrogen bond in the case of silyl derivatives. A second explanation of this difference between the silyl (primary substituted) and diester (secondary substituted) systems may arise from a difference in packing of the molecules. The α-CD derivatives would be expected to pack more closely, whereas there may be a more open packing for the β- and γ-CD silyl derivatives, thus allowing some water to be included in the intermolecular voids. As yet we cannot differentiate between the two possibilities.

In conclusion, the use of surface potential measurements permits a decoupling of aggregation and large scale solvation effects from the basal water-hydroxyl group interactions, and a better understanding of these effects on such macroscopic properties as solubility.

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5 Experimenta: **Surface potential measurements** Amphiphilic cyclodextrins were spread from a solution of pure chloroform by means of a micropipette (Microman Gilson 25 μL) at the aqueous sub-phase surface. Aliquots of cyclodextrin were thus successively deposited for the surface potential measurements at constant area (11.7 cm^2). The measurements were performed at 23 ± 0.5 °C in thermostated enclosed chambers to reduce airborne contamination. Prior to the surface potential measurements of deposited monolayers, the water interface was cleaned by suction through a narrow pipette.

The surface potential of spread cyclodextrin monolayers was measured as previously described.[10] The Keithley Instruments Electrometer (model 610C) was connected to two identical 241 Am air ionising α-emitting electrodes suspended at about 2–3 mm above the reference (left cell) and the measuring cell (right cell) as previously described.[9] The two cells are connected by a liquid bridge for electrical continuity. The measured difference in surface potential (ΔV) is that between the surface potential of the measuring cell (VM) and the monolayer free reference cell (VR). In the presence of a monolayer, the surface potential of the system is given by the following equation:

$$\Delta V = V(M) - V(R)$$

The potential jump at the water-air interface, ΔV, induced by formation of a monolayer, is defined by the Helmholz equation as:

$$\Delta V = \varepsilon_0^{-1} n \mu_{\perp}$$

where $n = 1/A$ is the number of molecules, A the mean area per molecule and ε_0 the permittivity in the vacuum. The quantity $\mu_{\perp}$ is the effective dipole moment in direction perpendicular to the surface.

The sensitivities of measurements were 1 mV in the 0–100 mV range and 10 mV in the 100–400 mV range. It was considered that equilibrium was established when the value of ΔV did not change after 30 min. All reported surface potential values are mean values of at least three measurements. The standard deviation of the mean never exceeded ±5 mV.

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