

Para-acyl calix[4]arenes: amphiphilic self-assembly from the molecular to the mesoscopic level

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Studies of the properties of a series of amphiphilic calixarenes show that they can form stable monolayers, Langmuir–Blodgett layers and solid lipid nanoparticles, the mesostructures were investigated by atomic force microscopy and the crystal structure of one compound shows a partially interdigitated tilted bilayer structure.

Amphiphilic molecular self-assembly is an important topic in modern chemical and biological sciences.¹ Extensive literature exists on the synthesis of amphiphilic supramolecular systems.² These molecules have been widely studied for the complexation of small molecules and ions at the air–water interface,³ for membrane transport in liposomes,⁴ or for detection of small volatile organic molecules.⁵ In contrast to the cyclodextrins⁶ few reports are available on the ability of calixarenes to form three-dimensional mesoscopic self assemblies.⁷ Only three crystal structure of amphiphilic supramolecular compounds have been reported.⁸

In this paper we present studies on the *para*-acyl calix[4]arenes, (Scheme 1) their interfacial behavior at the air–water and air–solid interface as studied by Langmuir film techniques and by non-contact mode Atomic Force Microscopy (AFM). We also present the crystal structure of *para*-octanoyl calix[4]arene for which a partially interdigitated bilayer structure is observed, the structure is of particular utility in the interpretation of the interfacial behavior of the amphiphilic calixarenes.

A series of *para*-acyl calix[4]arenes have been synthesized in a one step synthesis from native calix[4]arene as previously described.⁹

At the air–water interface† the behaviour of the monolayer depends significantly on the hydrophobic chain length. The stability of the layers increases with increasing chain length, however the observed apparent molecular areas at collapse are almost invariant as a function of the chain length, this is in contrast to amphiphilic cyclodextrins which show molecular areas dependent on chain length.¹⁰

In order to characterize these films, a monolayer of *para*-dodecanoyl calix[4]arene was transferred onto a glass substrate by the Langmuir–Blodgett technique at two surface pressures (5 and 10 mN m⁻¹). Non-contact mode AFM observation‡ of these films showed a number of significant points. For the film deposited at 5 mN m⁻¹ ($C_s^{-1} = 120 \text{ mN m}^{-1}$) “crater-like” structures of variable diameter within the film are consistent with the presence of persistent expanded liquid domains in the

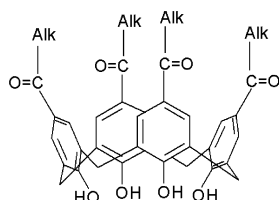
condensed liquid film. This interpretation is confirmed by the absence of such structures in films transferred at a higher pressure (10 mN m⁻¹) where $C_s^{-1} = 130 \text{ mN m}^{-1}$ for which the presence of only a liquid condensed phase can be postulated.

Solid lipid nano-spheres¹¹ of the acyl calixarenes were prepared by the interfacial solvent displacement method, as previously used for the preparation of analogous cyclodextrin based nano-spheres.¹² PCS (Photon Correlation Spectroscopy) reveals that amphiphilic molecules are self-assembled as sub-micronic particles of 130 nm diameter and a polydispersity index of 0.1. Such suspensions are stable as aqueous colloidal dispersions for more than 30 days at rt and at 40 °C. Non-contact mode AFM observation has been carried out on particles deposited on freshly cleaved mica and dried at 37 °C overnight (Fig. 1).

They show that the average size of the particles is 190 nm diameter and 50 nm height. In comparison to PCS measurements, the particles are non-spherical and slightly flattened when spread on mica. This result shows that the structure of these self-assemblies is very different from the calixresorcino-larene,^{7a} and cyclodextrin vesicles previously described,^{6a} which are double bilayer systems but similar to the cyclodextrin based nano-spheres.¹³ From the above, we believe these structures are solid lipid nanoparticles, the ¹H NMR data shows after 32K scans only broad features for the alkyl chains and a sharper peak at 0.85 ppm for the methyl head group which is consistent with previous ¹H NMR analysis of solid lipid nanoparticles.¹⁴

The crystal structure§ of the *para*-octanoyl calix[4]arene, has been obtained.

The synthetic macrocycle consists of phenolic residues in a cyclic array, containing a fourfold symmetry and is determined by the homo-planar arrangement of strong intramolecular hydrogen-bonds, involving the phenolic OH groups. The inclination of the phenyl rings with respect to the normal of the four phenolic oxygen atoms are respectively 122.7(1)°, 124.5(1)°, 121.0(1)° and 126.4(1)° and are in good agreement



Scheme 1 Schematic structure of *para*-acyl calix[*n*]arene where Alk = CH₃(CH₂)_{*n*}CO- and *n* = 4, 6, 8, 10.

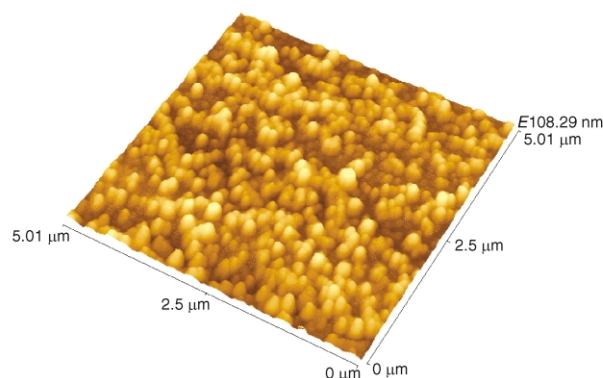


Fig. 1 AFM non-contact mode image of *para*-dodecanoyl calix[4]arene nanoparticles on a mica surface.

with values previously reported for calix[4]arene¹⁵ in the cone conformation, showing that the steric effects of the acyl substituents are negligible.

However the molecular geometry displays a novel arrangement, in spite of the cone conformation the fourfold symmetry is disrupted by the different arrangement of the hydrophobic chains. Two of them, *cis* to each other point outside the molecular cavity; whereas the other two are directed, by simple rotation of the acyl function, across the face of the cavity (Fig. 2). In this way the acyl chains are oriented in a close packed parallel arrangement tilted at 45° and with chain–chain distances of 4.3 Å, for phospholipids the chain tilt angle is typically around 28°.¹⁶

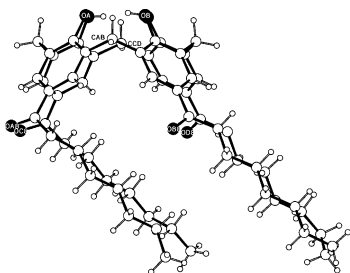


Fig. 2 Molecular structure of *para*-octanoyl calix[4]arene, distances between H-bond donors and acceptors in Å: OA–OC: 2.706, OB–OA: 2.716, OC–OD: 2.720, OD–OB: 2.671.

The system shows a partially interdigitated bilayer structure (Fig. 3), with alternate self-inclusion of the acyl chains. The width of the hydrophobic layer formed by the acyl chains is about 8.5 Å and the width of the calix bilayer is 6.2 Å. The shortest arene–arene distance is 3.5–3.8 Å. The molecular area is dominated by the size of the calix[4]arene cavity and the chain–chain distance across the molecule of 9 Å, as these distance will be expected to be invariant, it is not surprising that the observed molecular areas at the air–water interface are constant. Thus the amphiphilic supramolecular edifice can structurally be divided into two parts; the macrocyclic ring in the cone conformation and the acyl chains forming a cylindrical channel tilted with respect to the cone axis, the first is stabilized by strong intramolecular H-bonds and the second maintained by van der Waals contacts.

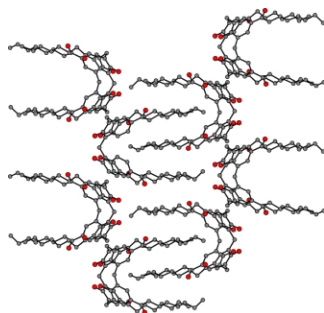


Fig. 3 Packing diagram of the crystal structure of *para*-octanoyl calix[4]arene.

Work is currently under way to assess the miscibility of these systems with natural phospholipids and to couple functional groups at the hydrophobic or hydrophilic faces.

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Notes and references

† Langmuir isotherm measurements were carried out in a Nima trough. 501 compressions were carried out continuously at a rate of 20 cm² min^{−1} at rt. Langmuir–Blodgett deposition was on untreated glass plates at a deposition speed of 0.5 cm² min^{−1}.

‡ AFM experiments were carried out in non-contact amplitude detection mode with a Thermomicroscope Explorer system using high resonance frequency silicon probes ($F_o = 320$ KHz) at a scanning speed of 1 Hz.

§ Crystal data for complex **1**: [C₆₀H₇₈O₈], $M = 927.22$, monoclinic, space group $P21/c$, $a = 11.588(5)$, $b = 15.685(7)$, $c = 29.496(11)$ Å, $\beta = 96.44(3)^\circ$, $V = 5327.2$ Å³, $Z = 4$, $T = 293$ °K, $\rho_{\text{calcd}} = 1.156$ g cm^{−3}, Enraf–Nonius Kappa-CCD diffractometer, Mo-K α radiation, 16357 collected reflections, 8428 independent reflections, 4140 observed $I > 2\sigma(I)$ theta range 1.39° to 24.23°. Data were analyzed with Kappa-CCD software. The structure was solved by direct methods with the program SHELXL86 and refined anisotropically on F^2 for all reflections by least-squares method using SHELXL93. The four hydrogen atoms of hydroxy groups were located from the $\Delta\rho$ and fixed during the subsequent calculations. The final conventional R factor is 0.089 for 4140 $F_o > 4\sigma(F_o)$ and 644 parameters and 0.188 for all data. The largest difference peak and hole are 0.32 and -0.26 e^{−3}, respectively. CCDC 166848. See <http://www.rsc.org/suppdata/cc/b1/b111367b/> for crystallographic files in .cif format.

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