para-Acylcalix[*n*]arenes: from molecular to macroscopic assemblies

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The *para*-acylcalix[*n*]arenes possess a very rich capacity to self-assemble into a wide variety of structures and sizes ranging from molecular assemblies through dimeric capsules, molecular sheets to nanoparticles. All these assemblies are capable of taking guest molecules and in the process of this inclusion discrete nanoscopic reaction vessels may be formed for photochemistry. Interestingly this uptake of quite large organic molecules occurs in the bulk in non-porous crystals without loss of crystallinity. At the air–water interface either as Langmuir monolayers or as colloidal suspensions the *para*-acylcalix[*n*]arenes show interaction with ionic species. The extension from *para*-acylcalix[4]arenes to *para*-acylcalix[8]arenes is in its infancy but already there is much promise for novel assemblies to be found.

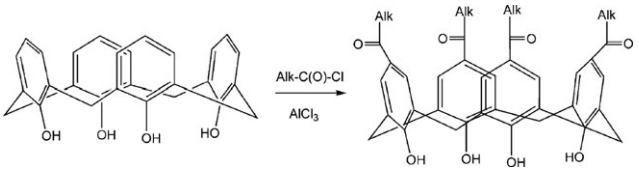
Introduction

The calix[*n*]arenes are perhaps the major class of organic receptor molecules in supramolecular chemistry.[1] They are simple to synthesize, with total selectivity for macrocyclic ring size, in multi- or even kilo-gram quantities from low cost starting materials.[2] Their use is facilitated by the two divergent chemistries, at the *para*-aromatic positions and at the phenolic hydroxylic groups not requiring protection–deprotection methodologies for selective chemical modification (Scheme 1).[3]

This ease of chemical modification has allowed the calix[*n*]arenes to serve as molecular platforms for the construction of receptors of gases,[4] both cations[5] and anions,[6] small organic molecules,[7] molecules of biological interest ranging from amino-acids[8] and peptides[9] through nucleotides,[10] steroids[11] to DNA[12] and proteins,[13,14] with such complexation being achieved in the gaseous,[15] solution[16] and solid-states.[17]

The calix[*n*]arenes have seen applications in material science, both for the construction of molecular edifices, and as sensors,[14] selective filters at interfaces,[18] non-linear optical materials,[19] thin films,[20] and for gas storage.[7] However they have also seen biological applications, as anti-thrombotic materials,[21] ion-channel blockers,[22] and as anti-body substitutes for the detection of the Prion protein.[23]

Suitable chemical modification allows the formation of nano-capsules by calix[*n*]arenes and their analogues, ranging from dimeric structures[24,25] through Russian Doll systems[26]



Scheme 1

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up to large Platonic and Archimedian geometric solids,[27] such structures use hydrogen bonding or metal coordination to ensure their structural integrity. In the solid-state the formation of nano-capsular materials is more common with either inclusion or van der Waals forces holding the structures together.[28] Such systems may absorb gases either as porous or even non-porous materials.[29,30]

In this article we will present the *para*-acylcalix[*n*]arenes, simple molecular derivatives of the base calix[*n*]arenes, but which present a rich capacity to self-assemble at levels ranging from dimeric van der Waals nanocapsules, through assemblies capable of absorbing *via* single crystal to single crystal transformations large organic guest molecules, to Langmuir monolayers and up to solid lipid nanoparticles which themselves may self-assemble into larger structures.

Synthesis

The synthetic route to the *para*-acylcalix[4]arenes was first described in 1988, and consisted in the esterification of the lower rim of the macrocycle, followed by a Fries rearrangement yielding the *para*-acylated derivatives with rather poor efficiency.[31] Shinkai in 1991 demonstrated that the direct acylation of calix[4]arenes could be achieved in better yields using a direct Friedel–Crafts acylation at the *para*-position of the calix[4]arene, as shown in Fig. 1.[32] In general, using nitrobenzene as solvent, no esterification is observed for acyl chains of ten carbon atoms or less. In case of such esterification a simple alcoholic potassium hydroxide hydrolysis may be used to yield quantitatively the *para*-acyl derivatives. One-pot *ipso*-acylation of the parent *para*-*tert*-butylcalix[4]arene into the *para*-acyl derivative has also been described.[33] Nevertheless, as this latter approach is believed to proceed *via* the formation of a carbocation from the corresponding acyl chloride, it is better adapted to the introduction of benzoyl groups for which the carbocation form is stabilized compared to aliphatic groups. We have recently developed a clean route to the analogous *para*-acylcalix[8]arenes,[34] however interestingly here esterification occurs much more readily for derivatives with shorter acyl chains. The situation for the synthesis of the *para*-acylcalix[6]-arenes appears much more complex and we have only in recent weeks been able to cleanly produce these molecules.

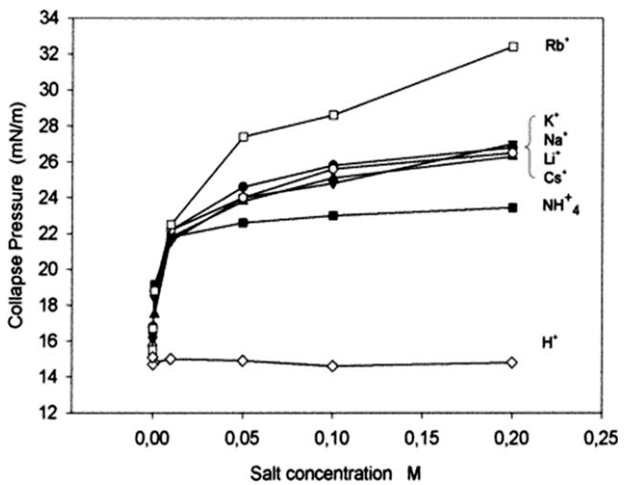


Fig. 1 Evolution of collapse pressure of Langmuir monolayers of *para*-dodecanoylcalix[4]arene with different concentrations of MCl Reproduced with permission from *Langmuir*, 2001, **17**, 6851. Copyright 2001, the American Chemical Society.

Langmuir monolayers

Langmuir monolayers are formed at the gas–liquid interface (commonly air–water) by the self-assembly of amphiphilic molecules, and are held by the interplay of a set of weak force interactions including van der Waals interactions between the lipophilic functions of the amphiphile in the plane of the monolayer and polar interactions (mainly electrostatic and hydrogen bonds) between the polar headgroups and the aqueous sub-phase.[35,36] Langmuir monolayers have been widely used for studying the self-assembling and molecular recognition properties of natural and synthetic amphiphiles.[37] They indubitably represent the simplest mimetic model of biological membranes.

The first communication reporting on the formation of Langmuir monolayers by amphiphilic calix[*n*]arenes was published by Regen in 1988.[38] It was demonstrated that alkylated and mercurated calix[6]arenes possess amphiphilic properties and are able to form stable Langmuir monolayers at the air–water interface. The possibility to transfer these monolayers onto solid substrates using the Langmuir–Blodgett approach was also demonstrated; these systems have been extensively used for their gas permeation properties.[18,39–41] Concerning the calix[4]arenes, Shinkai, in 1989, demonstrated that a *p*-*tert*-butylcalix[4]arene derivative, possessing ethoxyethyl ester functions at the lower rim, is able of self-assembly as Langmuir monolayers at the air–water interface; it was also demonstrated that this system possesses specific binding properties for alkali metal ions.[42] The same year, Boehmer and coworkers reported on the synthesis of a new amphiphilic calix[4]arene, the *para*-octadecanoylcalix[4]arene, produced by first esterifying the phenolic rim using stearoyl chloride in pyridine and consequently performing a Fries rearrangement using a large excess of aluminium chloride in nitrobenzene.[43] The tetra-acylated derivative was consequently reduced according the Wolff–Kishner reaction to produce *para*-octadecylcalix[4]arene; it was demonstrated that while this latter macrocycle could form stable Langmuir monolayers either on an alkaline subphase (10^{-3} M NaOH) or mixed with octadecylamine (molar ratio 1 : 1) on water, it could not form stable monolayers either as the pure compounds or on a pure water subphase. Surprisingly, the authors did not report on the self-assembling properties of the *para*-octadecanoyl derivative which does form stable Langmuir monolayers on water.

In 1995, we described the synthesis of a series of amphiphilic calix[4]arenes possessing one or four dodecanoyl chains at the upper rim and one or four methylene ethyl ester groups at the lower rim. Langmuir isotherm experiments revealed that the derivative possessing one acyl chain at the upper rim and one ester group at the phenolic rim exhibit a parallel molecular orientation with regard to the interface, while all the other derivatives were demonstrated to have an orthogonal orientation.[44] Using the procedure developed by Shinkai, we produced fully *para*-alkanoylated calix[4]arenes (with hexanoyl,

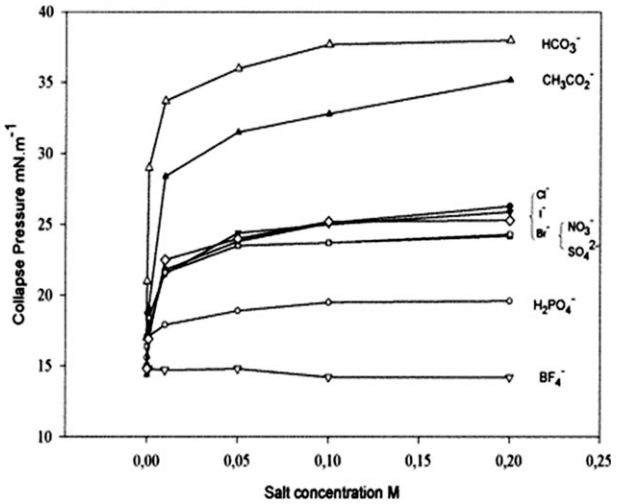


Fig. 2 Evolution of collapse pressure of Langmuir monolayers of *para*-dodecanoylcalix[4]arene with different concentrations of NaX). Reproduced with permission from *Langmuir*, 2001, **17**, 6851. Copyright 2001, the American Chemical Society.

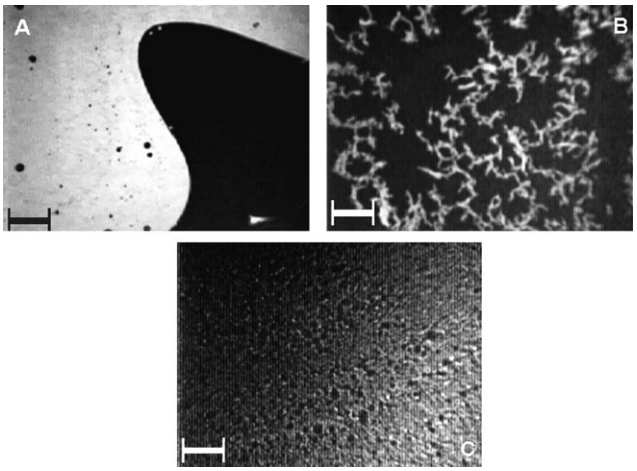


Fig. 3 BAM images of Langmuir film of a *para*-dodecanoylcalix[4]-arene (A); 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidic acid (B) and the 1 : 1 mixed film (C) before compression; scale bars indicate 800 μm.

octanoyl, decanoyl and dodecanoyl groups) and demonstrated that these four derivatives form stable Langmuir monolayers when spread on a pure water sub-phase. These amphiphiles were used to produce structural analogues of phospholipds *via* a regioselective 1,3-phosphorylation of the phenolic rim using diethylchlorophosphate in the presence of triethylamine. Trimethylsilyl bromide in methanol was used to hydrolyze the phosphoester groups in the corresponding phosphoric acids.

The interfacial molecular recognition of the *para*-dodecanoylcalix[4]arene, in the form of Langmuir monolayers, has been investigated. A systematic study of the evolution of surface pressure and apparent molecular area of films prepared in sub-phases containing group IA salts at varying concentrations showed that there is a selective stabilization of these monolayers with Rb^+ cations (Fig. 1).

In addition, it was also demonstrated that the stabilization of this monolayer is also governed by a counterion effect, with a selective stabilization in the presence of acetate and carbonate anions (Fig. 2).

The effect of the presence of monovalent and divalent cations (Na^+, K^+, Mg^{2+}, Ca^{2+}) in the sub-phase had also been studied for calix[4]arenes bearing alkyl chains (decyl or dodecyl) at the lower rim and dihydroxyphosphonyl groups on the upper rim. These monolayers revealed a selective stabilization and expansion with Na^+ ions while Mg^{2+} causes an increase in the collapse pressure accompanied by the creation of a novel phase and Ca^{2+} cations cause a decrease in the stability of the monolayer. Hyu and co-workers studied the interfacial behaviour of 1,3-*para* disubstituted calix[4]arene bearing octadecanoyl functions. They demonstrated that these systems exhibit significant molecular packing changes in response to pH changes, without drastic changes in the viscoelastic properties of the films; from this result the authors concluded that the rigidity of the monolayer is due to aromatic stacking and aliphatic chain interactions, rather than electrostatic interactions of head-groups with the aqueous subphase.[45] It was also demonstrated that these monolayers do not show relevant interactions with monovalent ions (Na^+, K^+, Cs^+) while organic polyionic species such as spermine, poly(ethylenimine), and poly(L-lysine) causes substantial changes in the interfacial behaviour of these monolayers.[46]

In order to use amphiphilic molecules in biological media in the form of self-assembled systems, it is of importance to investigate their behaviour in contact with biological membranes. Indeed, if these molecules cause a drastic perturbation of the fluid matrix structure of the membrane, it will cause, in most of the cases, the collapse of the membrane and consequently the death of the cell. Langmuir films, because of their monolayer structure, are considered as good mimetic systems of the plasma membrane, they represent a valuable tool to investigate the miscibility of a synthetic molecule with natural components of biological membranes. The miscibility of *p*-dodecanoylcalix[4]arene and its phosphorylated analogue 25,27-dihydroxyphosphoryloxytetradodecanoylcalix[4]arene, in mixed monolayers with four natural phospholipids, 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidic acid, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), and 1,2-dipalmitoyl-*sn*-glycero-3-phosphoserine, has been investigated by the Langmuir film method and Brewster angle microscopy,[47] images are presented in Fig. 3.[48] It was demonstrated that *para*-dodecanoylcalix[4]arene is miscible with DPPC only at high mole fractions of the phospholipid and immiscible in all proportions with DPPA, DPPE and DPPS. Nevertheless, the presence of the two polar phosphate groups at the lower rim of the macrocycle improves drastically the miscibility of these synthetic lipids with these four phospholipids.

The miscibility studies of these derivatives with cholesterol, a critical structural component of biological membranes, revealed that even if both repulsive and attractive interactions between the different components occur, they are fairly weak in nature; and no evidence for the formation of inclusion complexes were observed.[49] The BAM experiments revealed that there is little perturbation of the liquid states of the mixed films of *para*-dodecanoylcalix[4]arene and cholestereol during compression (Fig. 4).

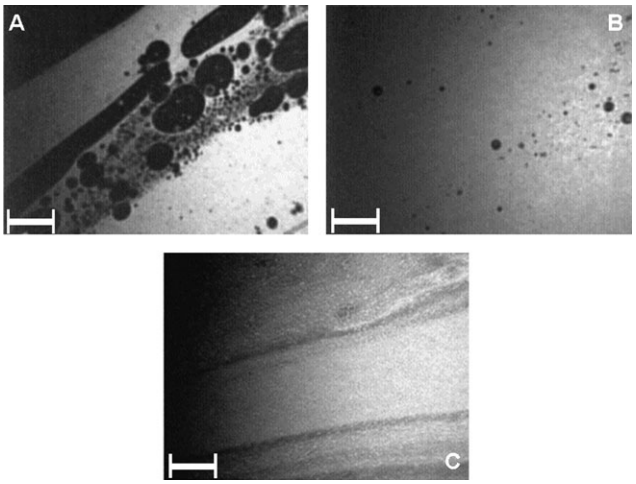


Fig. 4 BAM images of mixed film of a *para*-dodecanoylcalix[4]-arene –cholesterol mixed film (1 : 1) before compression (a), at a surface pressure of 0.5 mN m^{-1} (b), and at the collapse of the film (c); scale bars indicate 800 μm

Solid-state structures of the *para*-acylcalix[4]arenes

As for many calix[4]arenes unsubstituted at the lower rim,[1–3,7,29,50–60] the *para*-acylcalix[4]arene derivatives demonstrated a preferred cone conformation in the solid state and, hence, the cavity is potentially accessible to guest molecules.

The essential part of the molecule is the carbonyl group, which serves as an extension of the cavity due to the conjugation with phenyl ring. As the result, the four C=O groups fix the positions of two first carbon atoms of each chain in the plane with the corresponding phenyl rings and affects the space between the acyl arms. In comparison (Fig. 5), the cavity of *para*-hexylcalix[4]arene is less open and therefore it is expected to be less accessible to guests than the cavity of the *para*-hexanoyl counterpart. The ratio of flexible to rigid part of the calix[*n*]arene molecule[61] defines the types of inclusion, as well as the arrangements of molecules in the crystalline lattice in a similar manner to the approach developed for the systems with hydrophilic and hydrophobic parts.[62–66]

Depending on the size and polarity of guests, as well as on crystallization conditions, three general types of molecular arrangements can be distinguished.[67–72]

The first type can be termed a partially self-included or interdigitated complex (Fig. 6), where the role of the guest is played by another molecule of calix[*n*]arene, which provides chain fragments for entrapment by the first molecule and *vice versa*.[61,68,69,73] For the relatively short acyl chain lengths (C_4, C_6) some variety of interdigitation is possible,[61] which reflects the weakness of van der Waals interactions between short arms. Intercalation of solvent molecules between calix[*n*]arene arms or coordination to the lower rim phenolic OH groups *via* hydrogen bonding seems to be quite common for small molecules such as methanol,[68] ethanol[61] or *tert*-butylamine.[74] Interestingly, the intercalation of solvent does not always occur upon direct crystallization of *para*-acylcalix[*n*]arene from the corresponding media but sometimes needs the presence of another component, like nitroxyl radical 4-cyano-TEMPO,[61] which is not being included into the cavity of calix[*n*]arene during precipitation. Following the guest template phenomenon,[75] one can speculate about the possible influence of the nitroxide radical on the structure of the complex even if the former has not been included, but such speculation will require additional proof.

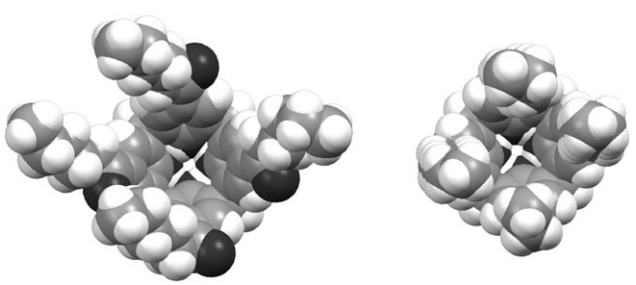


Fig. 5 Top view to the cavity of *para*-hexanoylcalix[4]arene (left) and *para*-hexylcalix[4]arene (right) (ref. 59).

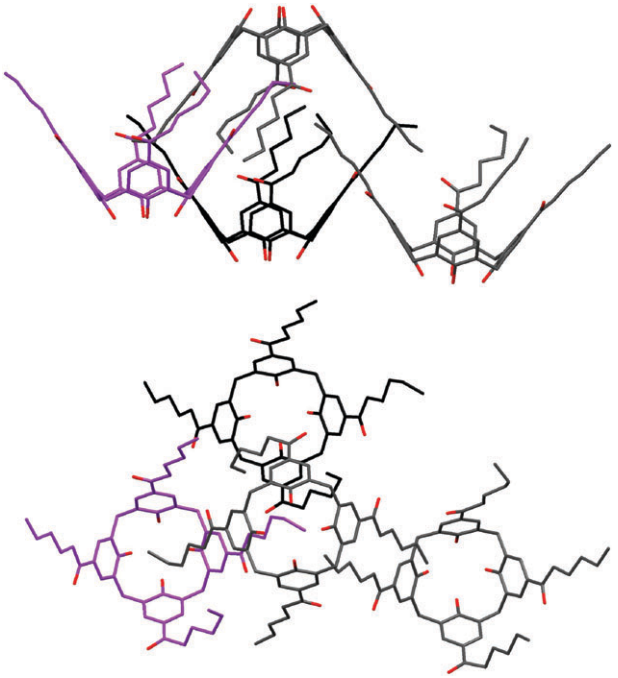


Fig. 6 Interdigitated structure of *para*-hexanoylcalix[4]arene. Hydrogen atoms are omitted for clarity (ref. 59).

In the second type of inclusion,[67,68,72] the calix[4]arene cavity, like a bowl, contains a foreign guest and is capped by a similar bowl above, usually providing a stabilization of the complex by hydrogen bonding of the OH-groups of the upper bowl with an appropriate group of the guest (Fig. 7). This structure can be called an open-container or head-to-tail complex and it is typical of *para*-butanoyl (C_4), *para*-hexanoyl (C_6) and *para*-octanoyl (C_8) calix[4]arenes with such guests as THF (in C_4[72] and C_8[71]), DMSO, DMF, nitrobenzene,[68] hydroxylamine TEMPO-H,[67] (in C_6), and acetone (in C_8),[76] as well as for some other calix[*n*]arenes.[1–3,7,29,50–60,77–86] In the case of the molecule with long alkanoyl arms (C_8) the cavity of the *para*-acylcalixarene becomes large enough to accommodate two molecules of the guest (THF,[71] acetone, or possibly others); however, these structures are not stable upon long storage at room temperature and easily transform to interdigitated guest-free form.

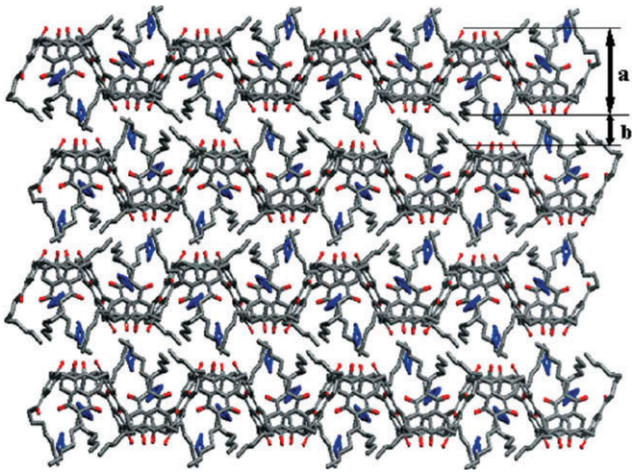


Fig. 7 Example of open-container type complex: *para*-octanoylcalix[4]arene with THF. Disorders and H-atoms are omitted for clarity (ref. 69).

The third type is the nanocapsular complex,[7,27,29,51–55,70,72,87–99] which is also known for other "calix" type molecules, both in solution and in the solid state.[27,78–86,88–99] The complex is formed when calix[*n*]arene molecules are arranged in tail-to-tail pairs providing a hydrophobic cavity, which can entrap a variety of molecules of relatively low polarity and of appropriate size.[72] In this case the guest serves as a stabilizing factor, which prevents penetration of alkanoyl arms deep into the cavity and, hence, allows one to avoid the formation of the interdigitated guest-free form.

Solid-state nanocapsules of the *para*-acylcalix[4]arenes

The nanocapsular structure of *p*-acylcalix[*n*]arenes is a quite remarkable form of inclusion with many features, which can be potentially exploited for various applications. In terms of crystal structure, the capsular form has a layered motif, similar to the open container form,[68] but the layers are shifted on one calix[*n*]arene molecule (Fig. 8).[76] The capsular form has many similarities to that known for simple *para*-*tert*-butylcalix[4]arene (TBC).[7,29,54] However, in the latter, the *tert*-butyl groups provide some kind of sliding plane between the layers, so each inclusion complex is a result of adjustment of positions of each layer in dependence of the guests' size and shape.[54]

Generally, only two acylcalix[*n*]arenes: *para*-hexanoylcalix[4]arene[70,72,87] and *para*-octanoylcalix[4]arene[76] are found to form stable nanocapsular structures in the solid state. The ability to form capsular complexes, which preferably entrap an even number of guest molecules, seems to be solely the property of *para*-hexanoylcalix[4]arene. The first requirement[72] for capsule formation is the relatively low polarity of the guest and an inability to form strong hydrogen bonds with OH groups at the lower rim of the neighboring calix[*n*]arene, therefore preventing the formation of the open container complex. The second requirement is the size (and the molecular shape)[100] of the potential guest and the solvent.[101,102] Any molecule of a size smaller than the cavity dimensions

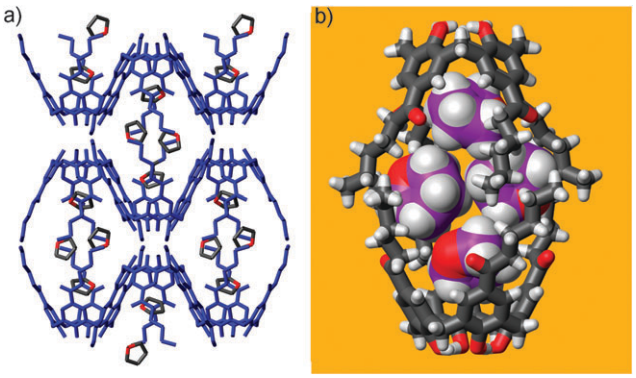


Fig. 8 Packing diagram of the complex of *para*-hexanoylcalix[4]arene with THF (a) and the capsule (b). Hydrogen atoms (in (a)) and disorders are omitted for simplicity (ref. 70).

potentially can be encapsulated, unless its size is too small to stabilize the capsule (such as methanol, ethanol).[61,68] The third requirement is an appropriate crystallization medium with alcohols appearing to be the best choice.[75]

There are two types of capsular complexes: those of $P4/nnc$ symmetry and those of $P2_1/n$ symmetry. Schematically, both types of complexes can be represented by square bipyramids (Fig. 9) where the components of the capsule are either twisted or shifted, respectively. Again, there is a parallel between hexanoyl and *para*-*tert*-butylcalix[*n*]arene,[54] when the latter forms the corresponding $P4/nnc$ and $P2_1/c$ (as well as $P2/n$ and $P4/n$) complexes.[7,29,51–55,78–86] In the $P4/nnc$ form of *para*-hexanoylcalix[4]arene, the structure represents a "pure" type of the capsule, the second type can be said to be a distorted or transient capsule, which resembles the "open capsule" reported for *para*-sulfonatothiacalix[4]arene complexes.[103] The

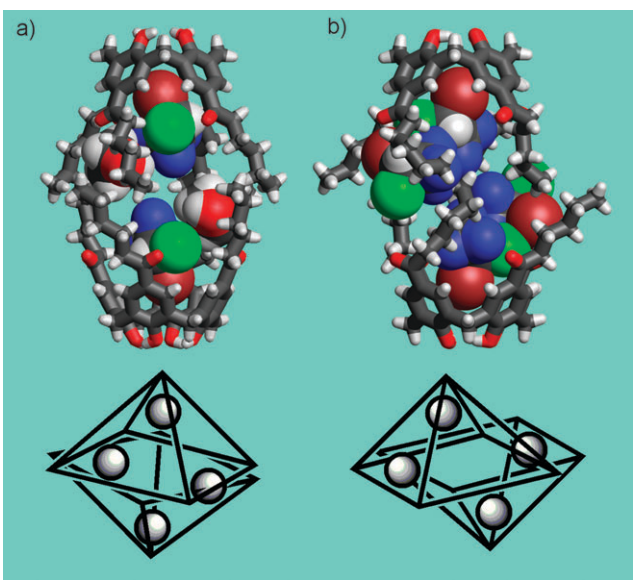


Fig. 9 X-Ray crystal structures of the complex of *para*-hexanoylcalix[4]arene with halothane: (a) $P4/nnc$ complex obtained from ethanol–halothane mixture, 2 : 1; (b) $P2_1/n$ complex obtained from halothane. Atom colours: Br – brown, Cl – green, F – blue, O – red. Bottom: square bipyramidal representation of the capsules (ref. 70, Fig. 6 and 8 combined).

$P2_1/n$ capsules of *para*-hexanoylcalix[4]arene are formed usually with large guest molecules, such as *trans*-stilbene,[87] *trans*-2-ethylhexyl-4-methoxycinnamate (*t*-EHMC)[104] or halothane.[72] In the latter case,[72] the formation of $P4/nnc$ or $P2_1/n$ pseudo-polymorphs depends on the crystallization media: crystallization from halothane provides the $P2_1/n$ capsule whereas crystallization from ethanol/halothane gives the $P4/nnc$ capsule with ethanol as co-guest (Fig. 9).

Among the forces responsible for stabilization of nanocapsules the main role belongs to van der Waals interactions host–host and host–guest. In addition, CH/π contacts[105] between guests' alkyl group and the π system of four benzene rings of the calix[*n*]arene provide stabilization of the guest in cavity. The absence of appropriate alkyl groups can change the overall stability of the nanocapsular complex or even prevent its formation. As example, a nanocapsular complex with tetrahydrofuran[72] is significantly more stable than that with chloroform.[70,72] In the latter case, halogen/π interaction[72,106] destabilizes the entire capsule. The same feature called "halophobocity" of the cavity has been mentioned for TBC.[54,82,83,85,86]

The capsular complexes of *para-hexanoyl*calix[4]arene cannot exist in the absence of guests and immediately collapse to an interdigitated structure when the last guest molecule leaves the capsule.[70,72] In contrast, guest-free *para-octanoyl*calix[4]arene based nanocapsular form (Fig. 10) is stable up to the melting point of the material.[76] The capsule is a good example of a self-included structure, where the role of guest is played by one of acyl arms of the same calix[*n*]arene molecule, and resembles therefore another "missing link"[73] in the family of self-included forms. The higher stability of the *para-octanoyl*calix[4]arene nanocapsular form over the self-included structure is explained by the fact that acyl arms of the calix[*n*]arene molecule are in constant motion, as revealed from X-ray structure and from ^{13}C CP-MAS NMR,[76] so there is a significant entropy component in the free energy of stabilisation of this form.

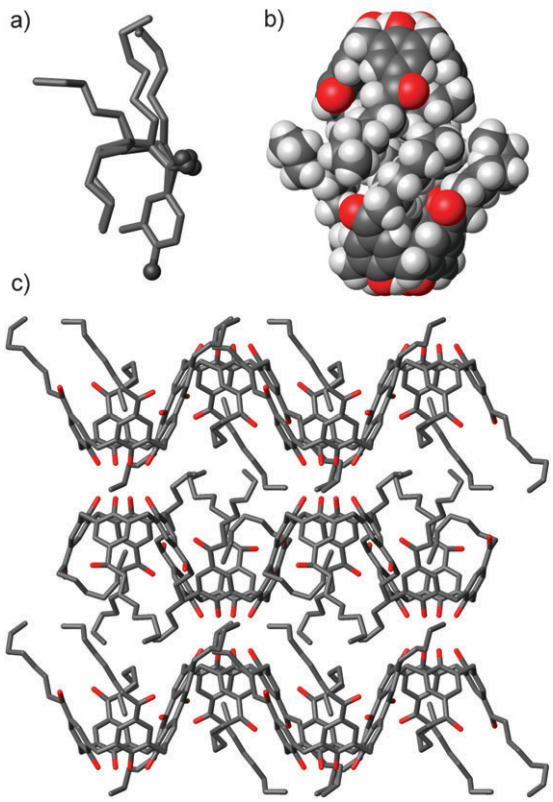


Fig. 10 Asymmetric unit (a), capsular structure (b), and crystal packing (c) of the capsular form of *para*-octanoylcalix[4]arene. H atoms are omitted in parts (a) and (c) for clarity (ref. 65).

Nanocapsules of the *para*-hexanoylcalix[4]arenes as nanoreactors

The rational design of host–guest structures enables one to achieve not only controlled capture and release of guest materials, but also the controlled chemical transformations of captured guest molecules within the host.[27,88,92,107–110] To carry out chemical reactions in such environments, the construction of large capsules that can accommodate two or more substrates in the cavity is particularly important. The frameworks constructed using covalent, metal–ligand[27,88,92,107–114] or hydrogen bonds[114–118] have been successfully exploited to probe selectivity of reactions occurring in restricted environment with particular focus on photochemical transformations. In this contest, the ability of the *para*-hexanoylcalix[4]arene nanocapsule to accommodate various guests seems to be particularly interesting since the weak van der Waals interactions collectively can potentially create relatively stable structures, which can control selectivity of reactions occurring between encapsulated entities.[119–122]

We paid particular attention to [2 + 2]-photocycloaddition reactions using stilbene to illustrate the principle.[87] Single-crystal X-ray diffraction (Fig. 11) revealed that the nanocapsule can accommodate two molecules of the guests. The molecules of *cis*-stilbene are located in the centre of the capsule and are beautifully intermeshed in attempt to achieve π–π interaction of the benzene rings. The alignment of *trans*-stilbene molecules in the capsule is such that the smallest distance between two molecules is *ca.* 3.7 Å between the benzene rings and *ca.* 4.4 Å between the olefinic carbons, *i.e.* near to the necessary 4.2 Å.[123] Only a small slippage of the molecules is needed to give overlapping orbitals and, hence, to yield photodimerization products upon excitation. Indeed, the

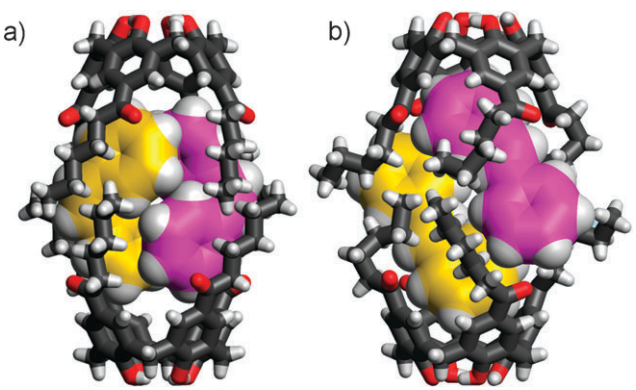
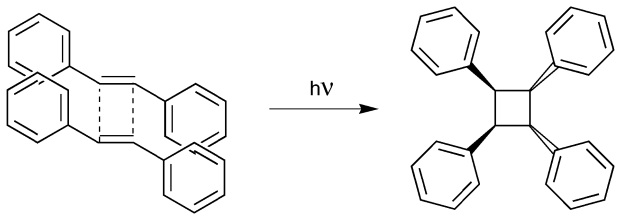


Fig. 11 *para*-Hexanoylcalix[4]arene capsules containing two molecules of (a) *cis*- and (b) *trans*-stilbene (ref. 68, redrawn).

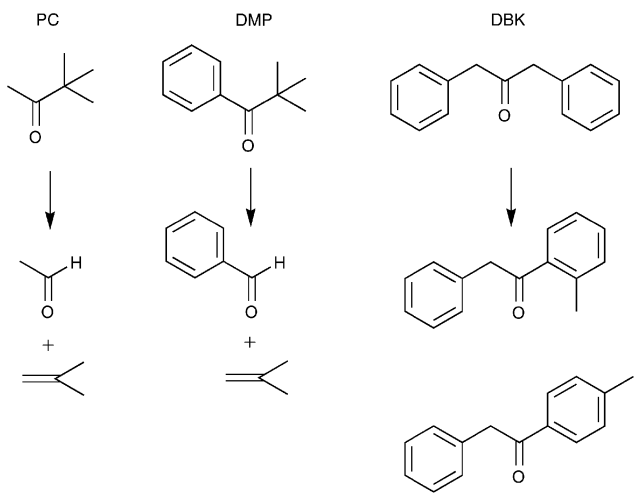


Scheme 2

corresponding products—tetraphenylcyclobutanes—have been found in the mixture after the photolysis. Significant stereoselectivity of the dimerization, where mainly *syn*-dimer (Scheme 2) is present in the mixture, is in agreement with the preferable orientation of both stilbene molecules.

If the molecule is too large to provide a double occupation of the cavity, the capsule serves as a dilution media to isolate guests and therefore suppress undesired reactions. It has been shown that encapsulation eliminates the photodimerization of *t*-EHMC and, hence, prolongs the lifetime of that common sunblocker.[104]

To probe these mechanisms of photoprotection of guests, we prepared crystalline capsular complexes of the calix[*n*]arene with three different ketones (Scheme 3): pinacolone (PC), 2,2-dimethylpropiophenone (DMP) and dibenzyl ketone DBK). The photochemistry of the ketones in solution[124] is well known: after excitation in the n–π* absorption region at *ca.* 300 nm and intersystem crossing, they undergo α-cleavage from the triplet state to yield geminate acyl–alkyl radical pairs. These pairs recombine to the starting compound and disproportionate to an aldehyde and an alkene. If one considers the calix[4]arene nanocapsule as a solvent cage, the presence of disproportionation (for the case of PC and DMP) or rearrangements products (DBK, head-to-tail reaction between phenylacetyl and benzyl radicals) would indicate that the photocleavage really occurs. Irradiation of the solid complexes using the procedure previously described[87] for 3 h yielded only *ca.* 10% (estimated from NMR) of disproportionation products and only for the complex with DMP. From these experiments one can conclude that both size restrictions (for DBK) and UV-filtering by calix[*n*]arene (four acylphenol units per molecule) play the main role in the photoprotection properties of the nanocapsule.



Scheme 3

These properties of the *para*-hexanoylcalix[4]arene nanocapsules can be utilized in cosmetology (sunscreen gels *etc.*) and medicine (protection of photosensitive drugs) if the pertinent formulations (such as solid lipid nanoparticles, *vide infra*) are developed.

Xenon NMR of the *para*-acyl[4]arenes and gas adsorption

Hyperpolarized ^{129}Xe NMR (HP-Xe) is a highly useful *in situ* probe of the temperature-dependent access to the guest sites in porous materials.[125–130] In many cases, quantitative information about the adsorption sites, such as heat of adsorption and space geometry can be derived[30,126,131–133] and the corresponding theoretical approach have been developed in a number of publications.[30,131–140]

The capsules of *para*-hexanoyl and *para*-octanoyl[4]arenes were studied by means of HP-Xe NMR with the objective of monitoring the transformations of the nanoenvironment upon guest release. For example, the confirmation that two different guests—DBK and chloroform—can occupy the same capsule of *para*-hexanoylcalix[4]arene has been derived by monitoring changes in ^{129}Xe NMR spectra during chloroform release.[70]

The phase change during the release of guests from open-container type *para*-octanoylcalix[4]arene complex with tetrahydrofuran (Fig. 8) is shown in Fig. 12. The DSC trace reveals a broad endothermic peak commencing at *ca.* 80 °C. This very likely reflects the elimination of the THF molecule that is responsible for the H-bond stabilization of layers in crystalline lattice (Fig. 7). The appearance of some emptiness after removal of this THF molecule can be easily seen on HP-Xe NMR spectrum (Fig. 12), where a broad signal appears at *ca.* 120 ppm. When all the THF has been removed from the complex (*ca.* 130 °C and higher), the latter transforms to the nanocapsular structure (Fig. 11) and this corresponds to the transformation of symmetrical broad signal of HP-Xe to another signal at *ca.* 110 ppm (Fig. 12(c)), that possesses chemical shift anisotropy (CSA), this CSA is retained upon cooling the material (Fig. 12(d)). The appearance of CSA reflects the non-spherical environment for Xe in the nanocapsule.

Once capsules come to "steady-state" conditions, *i.e.* when no guests can be released at a broad interval of temperatures, the dynamics of the xenon adsorption can be monitored. The typical picture of transformations in ^{129}Xe-NMR spectra with the temperature change for the capsular complex of *para*-hexanoylcalix[4]arene with THF is shown in Fig. 13.

It is easy to distinguish three main regions in the spectra. The first region around 80 to 40 °C is the high temperature zone and the signal of encapsulated Xe slowly moves downfield with increasing temperature and shows direct proportionality $\delta_{Xe} \sim T$. This behaviour is quite similar to that found in some dipeptides[141] and other systems,[142,143] and can be attributed to a high mobility of acyl chains that results in effectively less void space for Xe with the increase of temperature. In the intermediate temperatures region (*ca.* +20 to −40 °C) the signal becomes broader and tends to split, and in the low

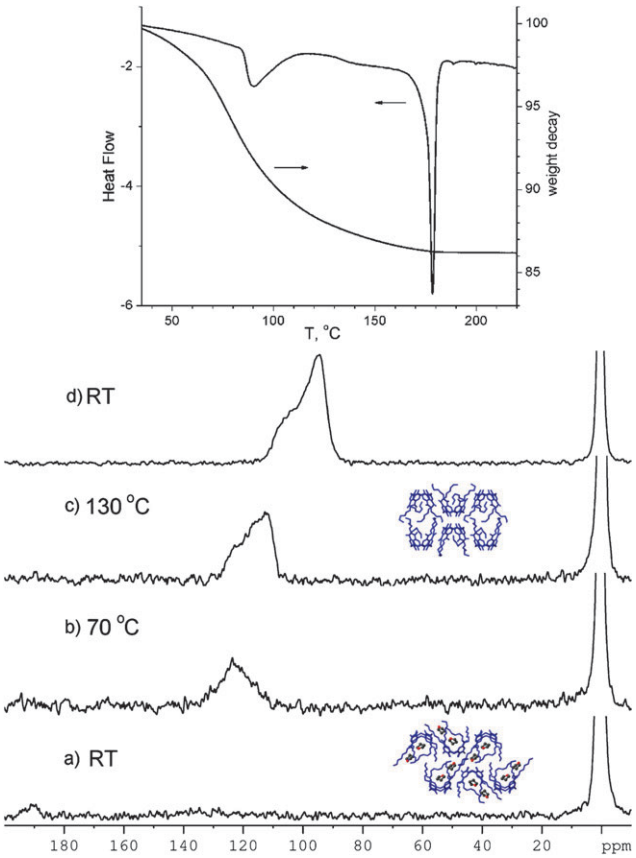


Fig. 12 HP-^{129}Xe NMR monitoring of the transformation of *para*-octanoylcalix[4]arene complex with THF into nanocapsular one. Top: the pertinent TGA and DSC traces.

temperature region (below −40 °C) the signal gradually disappears. In addition, a peak attributed to the interstitial[53] Xe splits off from the free gas signal (0 ppm). Such behaviour suggests restricted access to the capsular cavity at low temperature, so the exchange between gas inside and outside the capsule stops and xenon becomes invisible at the typical conditions of the NMR experiment. This does suggest that molecules trapped at room temperature at high pressure may well be held at low pressure and at low temperature; therefore, there is the possibility of temperature-programmed storage and release.

The chemical shift of xenon, especially in the high T region, where the signals are relatively sharp, depends on the guest encapsulated in *para*-hexanoylcalix[4]arene. Fig. 14 (upper) demonstrates that the slope of the dependence $\delta_{Xe} \sim T$ at high T decreases with the decreasing size of the guest (*i.e.* with increasing void space in the capsule).[144] Due to the large uncertainty in the estimation of free volume it is hard to say whether the chemical shift of Xe is proportional to the effective radius or effective volume of the space available—this problem has been discussed for microporous solids.[145–147] The corresponding linear dependences can be well extrapolated to low temperatures and will intersect at *ca.* 30 ppm and *ca.* −140 °C. Interestingly, the chemical shift of Xe adsorbed in *para-tert*-butylcalix[4]arene nanocapsule shows a similar trend.[53,148] These results well suggest that this approximate intersection

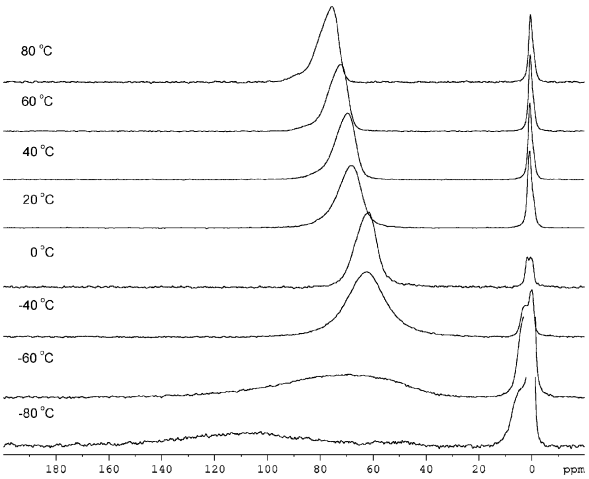


Fig. 13 Temperature dependence of HP-^{129}Xe NMR spectra for the capsular complex of *para*-hexanoylcalix[4]arene with THF.

point is the chemical shift of ^{129}Xe in the calix[*n*]arene deep cavity in the absence of exchange with outer gas. This shift does not strongly depend on the type of substituent in the upper rim of calix[*n*]arene providing the deep cavity is

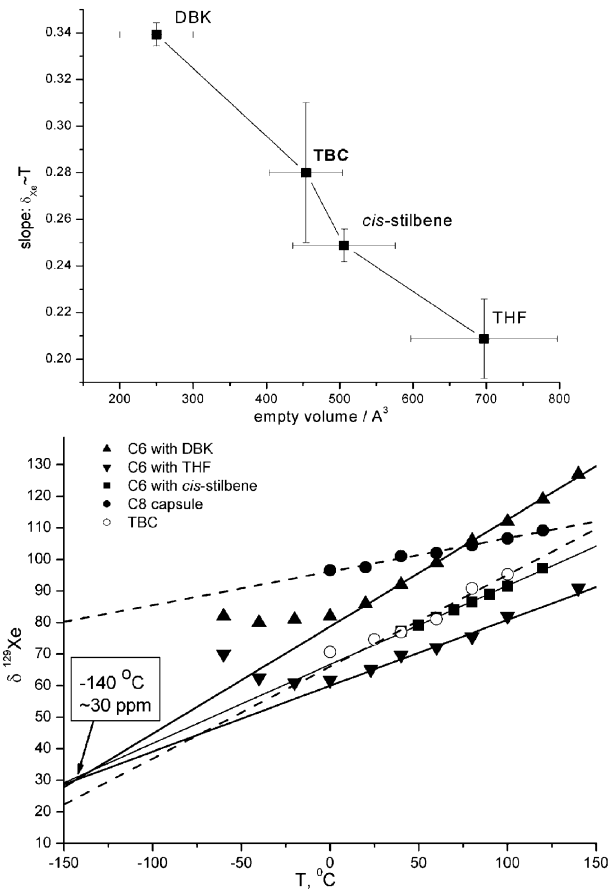


Fig. 14 Bottom: δ(Xe) $\sim$ T dependences for *para*-hexanoylcalix[4]-arene capsules with different guests, *para*-octanoylcalix[4]arene capsule, and *para-tert*-butylcalix[4]arene[53] (mixture of $P4/n$ and $P2_1/c$ forms). Top: correlation between slope in high T region and empty volume in the capsule.[149] Spectral data[148] were kindly provided by Dr I. L. Moudrakovski.

accessible for the gas. One can see from the Fig. 13 that xenon in the *para*-octanoylcalix[4]arene nanocapsule does not follow the same trend because the access to cavity in this capsule is locked by one of acyl arms of the host calix[*n*]arene.

HP-^{129}Xe NMR experiments with *para*-hexanoylcalix[4]arene and *para*-octanoylcalix[4]arene nanocapsules lead to the conclusion that both materials can be potentially exploited for gas adsorption and separation. However, the main problem of the *para*-hexanoylcalix[4]arene nanocapsule is that it must always contain a guest. Xenon (or other gas) can only be a co-guest, so that upon release the gas may be contaminated by the original guest of the capsule. The *para*-octanoylcalix[4]arene nanocapsule does not have foreign guest molecules and its application for the prospective gas storage is more optimistic.

Solid lipid nanoparticles from the *para*-acylcalix[4]arenes

Colloidal transporters[150,151] based on the self-assembling properties of amphiphilic molecules are of major interest in medicine because they offer new possibilities and therapeutic approaches for the use of cytotoxic drug such as antineoplastic agents.[152] Indeed, as these pharmaceutically active molecules are toxic against cell lines exhibiting a high mitotic activity, they are toxic not only against neoplastic (tumor) cells but also against healthy tissues and cause disagreeable side effects including nausea, hair loss, suppression of bone narrow functions, *etc*. In order to increase the efficiency of action of these drugs and to diminish their side effects, one approach consists in using transport systems bringing the anticancer drug specifically to the tumor and avoiding its dispersal in the whole body. These transport systems include micelles, liposomes and nanoparticles. Among the nanoparticulate systems developed, solid lipid nanoparticles (SLNs) represent a promising approach because of their improved physico-chemical properties.[153,154] They are usually prepared using natural lipids but macrocyclic amphiphilic molecules may represent a valuable alternative. Even if the possibility to assemble calix[*n*]arenes as vesicular systems was demonstrated in 1989[155] and has been developed since then,[156–161] their use as building blocs for preparing nanoparticles was reported only in 2002.[69] It was demonstrated that *para*-acylcalix[4]arenes based solid lipid nanoparticles could be prepared by the interfacial solvent displacement method; photon correlation spectroscopy revealed that these particles are monodisperse in size and present a hydrodynamic diameter of 130 nm, *cf*. Fig. 15. The slight flattening of the particles when dried on a solid surface and imaged by atomic force microscopy (AFM) demonstrated their nanosphere structure implying a solid matrix.

The physical properties of these systems were consequently studied carrying out systematic investigation of a broad range of parameters. In terms of preparation parameters, the nature and the volume of the organic solvent used, the concentration of the amphiphile and the presence of a stabilizing co-surfactant were shown to influence significantly the size of the produced particles, while the effects of the stirring speed, viscosity and acidity of the aqueous phase and the amphiphile lipophilic chain length have no significant effect. Storage and post-preparation parameters the SLNs might be subjected

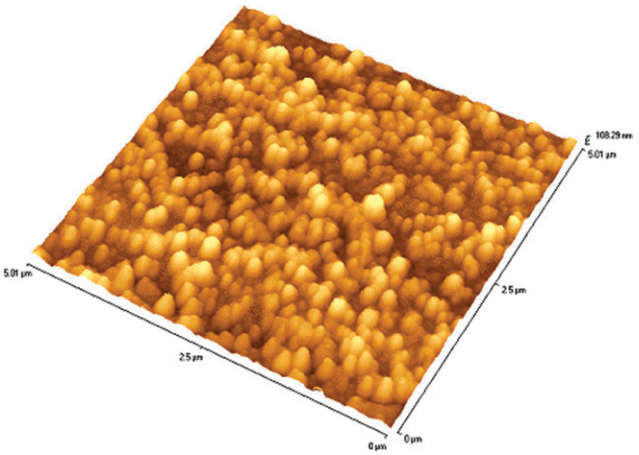


Fig. 15 Non-contact mode AFM image of solid lipid nanoparticles of *para*-dodecanoylcalix[4]arene spread on a mica surface (image size 5 µm × 5µm.

have been tested, they include: ionic strength, pH, UV irradiation, ultrasonic treatment, temperature effects, microwave irradiation, centrifugation, freeze-drying and freezing–defreezing cycles. It was shown that these systems are stable in solution at rather high salt concentration (0.1 M) with NaCl, NaI, NaH_2PO_4, $NACH_3CO_2$, $NaHCO_3$, KCl, KNO_3 and KH_2PO_4, but precipitate with Na_2SO_4. The nanoparticles are stable from pH 2 to 8 and show no destabilization when boiled, submitted to UV irradiation, microwave and ultrasonic treatments. In summary, this study revealed that these systems are remarkably robust and stable; the only drawback encountered was the difficulty of re-dispersion after freeze-drying.[162] This disadvantage was circumvented using cryoprotectant carbohydrates (glucose, fructose, mannose and maltose) which are believed to improve the mechanical stability of the SLNs because of the presence of a protective layer of carbohydrate on the surface of the SLNs.[163] In order to foresee the use of this family of SLNs for parenteral drug delivery purposes, it is essential to know their behaviour in contact with circulatory proteins found at high concentrations in the blood.

The main circulatory proteins are the serum albumins with concentrations up to 46 g l^{-1} in the blood, they are known to attach at both hydrophilic and hydrophobic surfaces; a high absorption of albumin on transport systems could cause their aggregation and the formation of a blood clot which could be fatal for the patient. The interaction of SLNs formed with three different amphiphilic calix[*n*]arenes (*para*-dodecanoylcalix[4]arene, *para*-dodecanoyl-25-(ethoxycarbonylmethyloxy)-calix[4]arene, and *para*-dodecanoyl-25-(2-carboxymethyloxy)-calix[4]arene) were investigated by photon correlation spectroscopy and AFM.[164] It was demonstrated that even if an albumin protecting capping layer is formed at the surface of the SLNs; no aggregation is observed even at high concentrations of albumin (40 g L^{-1}). In addition, the preliminary studies of *para*-acylcalix[*n*]arene based SLNs in contact with cellular systems revealed no evident toxicity at all the concentrations tested (50–150 mg L^{-1}).[165]

Because of their excellent stability, the use of these systems for topical application could also be foreseen. In order to test the behaviour of *para*-dodecanoylcalix[4]arene in gel matrices,

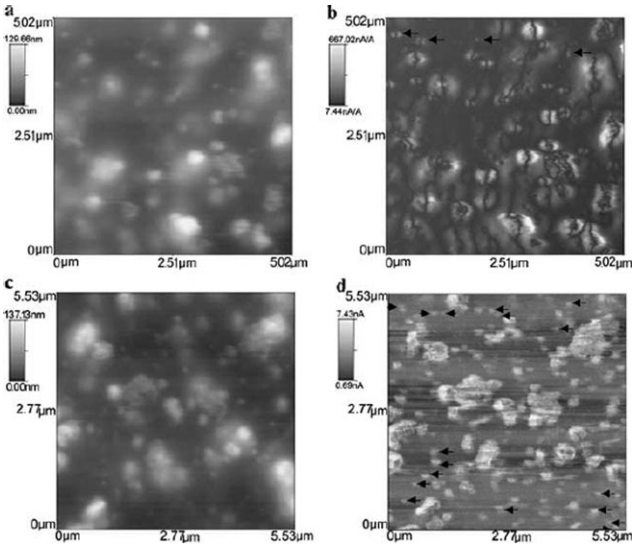


Fig. 16 AFM image of solid lipid nanoparticles of *para*-dodecanoylcalix[4]arene embedded in carbopol 980 gel at a 5 µm scan range, in[67] topographic mode, (b) force modulation mode and (d) lateral force mode.

it was integrated in four different formulations used for cosmetic applications. The AFM study of these systems revealed that the particles remain stable as non aggregated objects, *cf*. Fig. 16. In addition to these results, it was recently demonstrated that SLNs of *para*-hexanoylcalix[4]arene could act as a controlling agent in the photochemistry of one of the most used UV absorbers, *trans*-2-ethylhexyl-4-methoxycinnamate (*t*-EHMC); this opens new perspectives for the use of these systems as additive in cosmetic formulations.[104]

Concerning the structural characterization of calix[*n*]arene-based SLNs, they were mainly achieved using atomic force microscopy and dynamic light scattering. Additional insights were gained with hyperpolarized ^{129}Xe solid-state NMR spectroscopy. Freeze–dried SLNs prepared with *para*-acylcalix[4]-arenes with a chain length ranging from 6 to 16 carbons exhibit a greater spectral intensity than corresponding crystal-

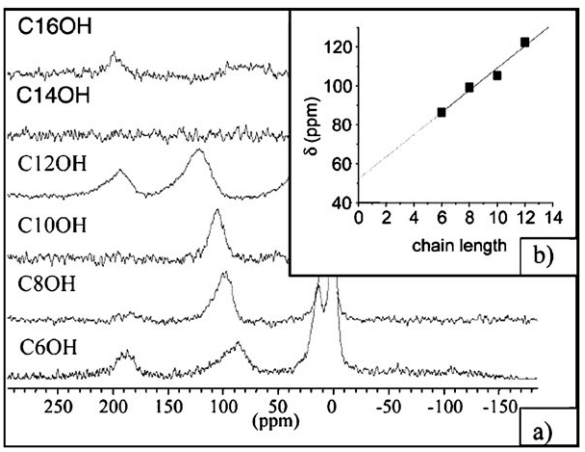


Fig. 17 (a) Static ^{129}Xe NMR spectra recorded on freeze-dried powders of *para*-acylcalix[4]arene SLNs under continuous flow of hyperpolarized xenon; (b) Plot of the chemical shift of Xe in the host cavity *vs*. the chain length of the amphiphilic calix[*n*]arenes.

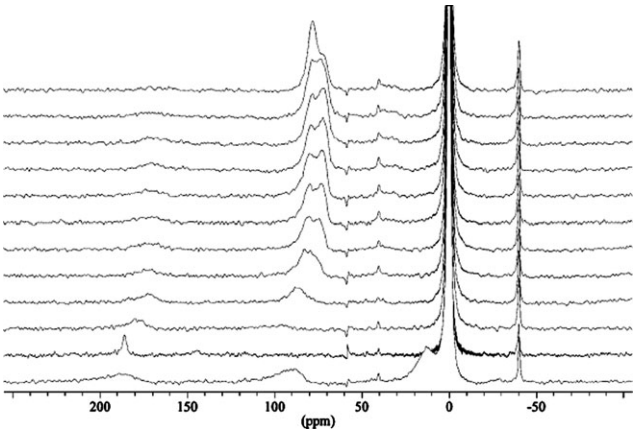


Fig. 18 *In situ* transformation of *para*-hexanoylcalix[4]arene SLNs (bottom) after a pulse of methylene chloride (next to bottom) as monitored by continuous flow hyperpolarized ^{129}Xe MAS NMR. Consecutive spectra were recorded every 4.5 min at room temperature.

line powders because of the increased surface area of this material, from the NMR experiments it was demonstrated that (1) host cavities present at the surface of the particles are still accessible to small atoms or molecules; (2) host cavities are loaded with the hydrophobic chains of adjacent calix[*n*]arenes, thus hindering complexation of guest molecules, and (3) flowing vapor of guest molecule can displace these included chains in the case of *para*-hexanoyl[4]arene, therefore increasing the number of sorption sites (Fig. 17 and 18).[166]

Higher *para*-acylcalix[*n*]arenes

We have recently reported on the synthesis and interfacial properties of *para*-acylated calix[8]arenes bearing chains of 8, 12, 14 and 16 carbon atoms.[167] It was demonstrated that all these derivatives possess the ability to self-assemble as stable Langmuir monolayers on water subphases. In contrast to the *para*-acylcalix[4]arenes, the interfacial behaviour of these derivatives vary insignificantly with the hydrophobic chain length, showing relevant changes in collapse pressures and apparent molecular areas. These differences have been attributed to conformational changes of the macrocycle at the interface.

Interestingly these molecules undergo relatively easy eight-fold substitution at the phenolic face to yield the pure fully substituted derivatives. These novel amphiphiles present quite different properties than the *para*-acylcalix[4]arenes. They show a strong tendency to assemble in non-two-dimensional layer. For the *para*-octanoyl[8]arene derivative with an O-butyl sulfonate function at the phenolic face, there is reasonable aqueous solubility and it was possible to determine that the molecule while having interesting anti-coagulant properties presents no haemolytic toxicity.[167]

Conclusions

The *para*-acylcalix[4]arenes show a truly remarkable capacity to self assemble, generating structures ranging from van der Waals nanocapsules, to solid lipid nanoparticles to stable monomolecular films at the air–water interface. The nano-

capsules show abilities for inclusion of molecules ranging in size from small gaseous guest up to quite large organic polycyclics. The possibility to use nanocapsules as isolated photochemical reactors is of strong interest.

From a biomedical point of view the *para*-acylcalix[4]arenes present new transport properties which combined with a lack of toxicity makes them useful candidates for drug vectorisation.

While the field of the *para*-acylcalix[8]arenes is just opening it would seem that they will present a unique set of properties and that numerous applications will be found.

Acknowledgements

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