



Solid lipid nanoparticles from amphiphilic calixpyrroles



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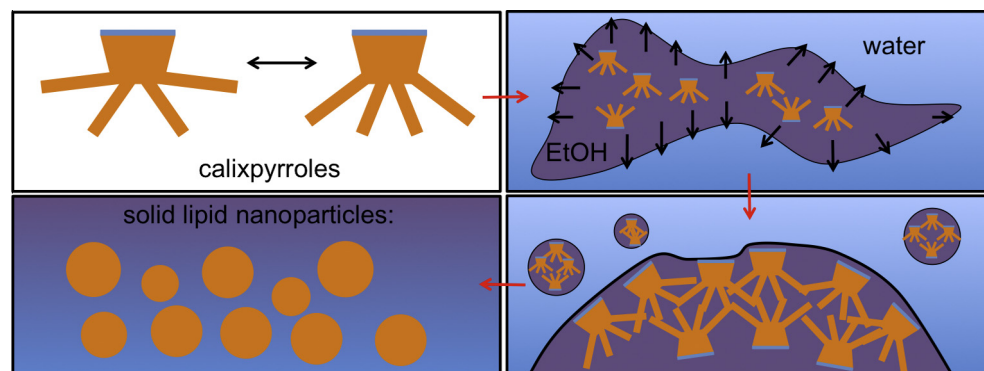
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GRAPHICAL ABSTRACT



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ABSTRACT

Hypothesis: Macrocyclic amphiphiles form interesting self-assembling structures, including solid lipid nanoparticles, which have potential applications in drug encapsulation. Aryl-extended calixpyrroles, which act as anion binding hosts, are expected to form solid lipid nanoparticles, even though the alkyl chains have unusual perpendicular geometry with respect to the hydrophilic head group. The preparation conditions and the alkyl chain length should affect the size and stability of the particles.

Experiments: Solid lipid nanoparticles of two aryl-extended calixpyrroles with resorcinol walls and either *meso*-dodecyl or *meso*-methyl alkyl chains were compared. Ethanolic solutions of the calixpyrroles were mixed with water and the resulting nanoparticle dispersions were studied with dynamic light scattering and nanoparticle tracking analysis. The effect of different calixpyrrole/ethanol/water ratios on particle size was tested. The surface charge of the particles at different pH and NaCl concentration was determined by zeta potential measurements.

Findings: The *meso*-dodecyl calixpyrrole produced small nanoparticles with mean hydrodynamic diameters between 40 and 70 nm in 0.86–4.28 M ethanol. The particles were stable in solution for several months. Particles prepared from *meso*-methyl calixpyrrole were larger and less stable. The smallest particles were obtained with low calixpyrrole concentration and calixpyrrole/ethanol ratio. Larger ethanol/water ratio induced broader particle size distributions. Increasing pH aided the stability of the particles due to increased negative surface charge.

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1. Introduction

Calixpyrroles are macrocyclic tetrapyrroles known for their binding affinity toward halide anions [1–3]. The four pyrrole rings are linked by *meso*-carbon bridges, which carry eight substituents, such as alkyl chains or aryl substituents in the aryl-extended calixpyrroles. The three dimensional structure of an aryl-extended calixpyrrole (Fig. 1) shows the cone shaped anion binding site formed by the pyrrole NH groups and the aromatic walls. The upper rim of the cavity is lined with hydroxyl groups, and the alkyl substituents attached to the *meso*-carbons extend to the sides of the molecule giving it unique amphiphilic properties.

Aryl-extended calixpyrroles have interesting applications as supramolecular capsules [4] and as ion transport agents [5]. The *meso*-methyl calixpyrrole **2** (Fig. 2) with resorcinol walls self-assemble in the solid state into a hexameric cage [6] reminiscent of the hexameric resorcinarene and pyrogallarene capsules [7]. An assembly into capsules was also observed in solution for amphiphilic *meso*-undecyl derivative **1b**, which formed a hexameric capsule in apolar solution [8]. In addition, the solid state structure of amphiphilic *meso*-dodecyl derivative **1** consists of alternating lipophilic and hydrophilic layers [9]. However, the aggregation properties of amphiphilic calixpyrroles in aqueous solutions have not been studied.

Nanoparticles composed of solid lipids, such as triglycerides or waxes, are called solid lipid nanoparticles (SLN) [10]. Solid lipid nanoparticles are typically between 150 and 300 nm in diameter and they have been developed as drug encapsulating structures for pharmaceutical and cosmetic products. SLNs can be prepared on a laboratory scale by a solvent replacement method, also known as a solvent diffusion method, where the amphiphile or lipid is first dissolved in an organic water-miscible solvent and then mixed with water [11]. The method has been applied for preparation of SLNs from macrocyclic amphiphiles, such as modified cyclodextrins, [12] calixarenes [13,14] and resorcinarenes [15,16]. Macrocyclic amphiphiles are interesting building blocks for nanoparticle preparation, since they have unique self-assembling properties [17] and they form inclusion complexes with lipophilic guest molecules within their cavities [18].

Typical examples of non-ionic amphiphiles are *para*-acyl calix[4]arenes (**3**) and *C*-undecyl resorcinarene (**4**), which form 130 to 150 nm solid lipid nanoparticles in THF/water solution [13,15]. Both compounds consist of four aromatic rings connected by methylene carbons (Fig. 2). Calixarenes have four hydroxyl groups at the narrow rim of the aromatic cavity, whereas resorcinarenes have eight hydroxyl groups at the wider rim of the cavity providing larger cross-sectional area of the hydrophilic group. Interestingly,

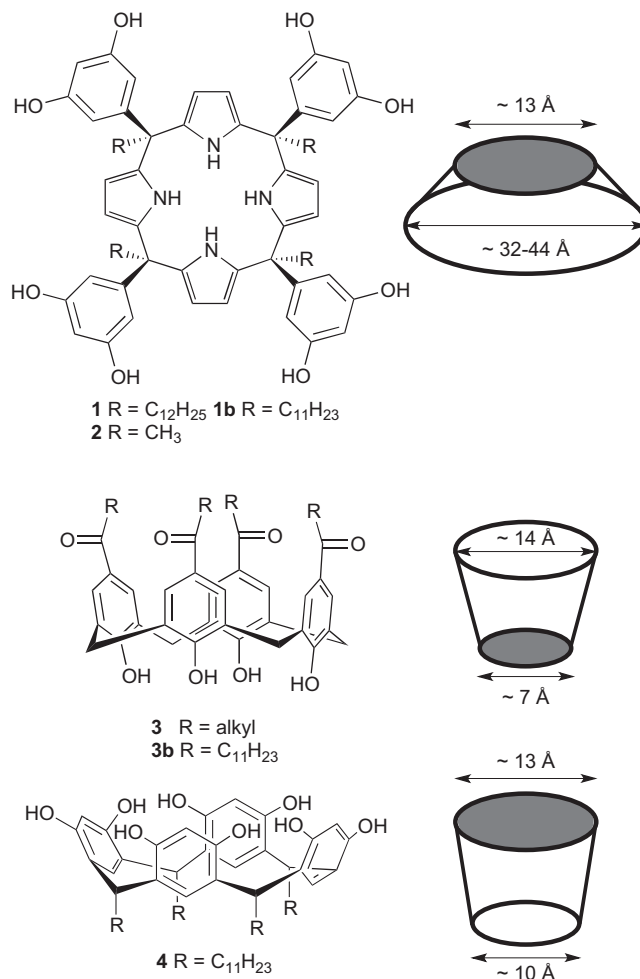


Fig. 2. Calixpyrroles (**1** and **2**), and structurally related macrocycles, *para*-acyl calixarene (**3**), and *C*-undecyl resorcinarene (**4**). The relative shape of each amphiphile is shown as a drawing with a gray circle representing the cross-sectional area of the hydrophilic head group.

the stirring speed did not affect the particle size, whereas, an increase in the concentration of the amphiphile in an organic solvent increased the particle size of calix[4]arene and resorcinarene SLNs. In case of *para*-dodecanoyl calix[4]arene (**3b**), preparation in ethanol and THF produced similar particle size while preparation in acetone or methanol increased the particle size by 30–40%. Small,

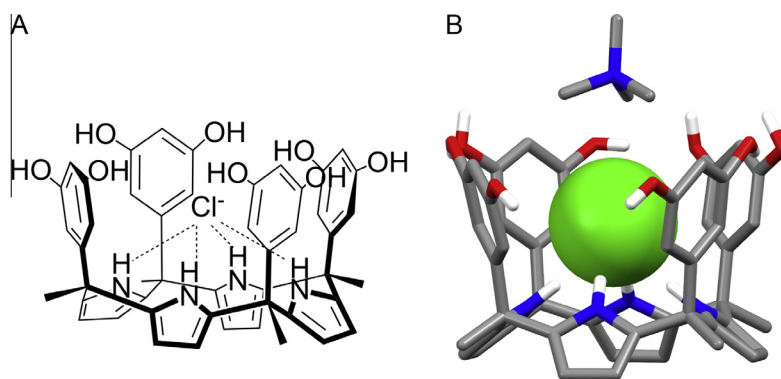


Fig. 1. A schematic drawing of *meso*-methyl calixpyrrole in a cone conformation, where all NH hydrogens point toward a complexed chloride anion (A), and a crystal structure of calixpyrrole tetramethylammonium chloride complex (B, CCDC code RIBBIO) [6]. The chloride anion is shown as a CPK model and only OH and NH hydrogens are shown for clarity.

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