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Synthesis and self-assembly properties of *para*-acyl-calix[8]arenes

Saïd Jebors,[a] Gennady S. Ananchenko,[b,†] Anthony W. Coleman[a,*] and John A. Ripmeester[b,†]

[a]*Institut de Chimie et Biologie des Protéines, 7 Passage du Vecors, F-69367 Lyon Cedex 07, France*
[b]*NRC Steacie Institute for Molecular Science, 100 Sussex Dr., Ottawa, ON, Canada*

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Abstract—The synthesis of a series of novel *para*-acyl-calix[8]arenes is described, while for acyl chain lengths of greater than eight carbon atoms total substitution at the para position occurs, in contrast to the *para*-acyl-calix[4]arenes, some esterification at the phenolic face may also occur, particularly for shorter acyl chain lengths. Simple saponification with potassium hydroxide in ethanol allows the pure compounds to be obtained in good yields. All the derivatives show amphiphilic behaviour with formation of stable monolayers at the air–water interface and apparent molecular areas between 150 and 275 Å^2.

The calix[*n*]arenes are amongst the most studied organic macrocyclic host molecules.[1] Their complexation properties with a wide range of ionic and molecular ligands have been demonstrated.[2] Their use for the construction of novel systems in material science,[3] and more recently, in the biological and bio-medical fields shows great promise.[4]

Of their amphiphilic derivatives, the *para*-acyl-calix[4]-arenes[5] have proved to possess a wide range of novel self-assembly properties. Their formation of stable monolayers at the air–water interface,[6] and the study of interactions between such monolayers and cations and anions have been published.[7]

The formation of solid lipid nanoparticles has been demonstrated,[8] and numerous properties of the SLNs, including interaction with proteins such as bovine serum albumin have been described.[9]

Their solid-state properties have also proved to be interesting with the formation of van der Waals capsules.[10] We have studied the single crystal to single crystal incorporation of guest molecules,[11] and the photophysics of stilbene within the nanocapsules.[12]

In view of the above, extension of the work to the larger calix[*n*]arenes would seem logical. In this Letter we report the synthesis and self-assembly properties of a series of *para*-acyl-calix[8]arenes with acyl chain lengths ranging from 8 to 16 carbon atoms.

The synthetic route to the *para*-acyl-calix[8]arenes is shown in Scheme 1. Friedel–Crafts acylation of the *para*-H-calix[8]arene **1**, in nitrobenzene with 12 equiv of the corresponding acyl chloride in the presence of aluminium trichloride as the Lewis acid, yields the derivatives *para*-octanoyl-calix[8]arene **2a**, *para*-decanoyl-calix[8]arene **2b**, *para*-dodecanoyl-calix[8]arene **2c**, *para*-tetradecanoyl-calix[8]arene **2d** and *para*-hexadecanoyl-calix[8]arene **2e**, in 61–81% yields.[13]

For chain lengths of less than eight carbon atoms, there occurs both incomplete acylation at the *para* position coupled with esterification at the phenolic group, and as of now we have been unable to isolate the pure derivatives. While for the longer chain lengths acylation is total at the *para* position, some esterification at the phenolic face may occur. This parasite reaction is easily detected in the ESI-mass spectrum and simple hydrolysis of the ester by treatment with KOH in ethanol at room temperature during 24 h leads, cleanly, to the desired compound.[14]

The structure and full substitution of all derivatives is confirmed by the ^{1}H NMR, the phenolic OH protons appear as a singlet at 9.5 ppm,[15] typical of a calix-arene

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* Corresponding author. Tel.: +33 4 72 72 26 40; fax: +33 4 72 72 26 90; e-mail: aw.coleman@ibcp.fr
† Tel.: +1 613 993 2372; fax: +1 613 998 7833.

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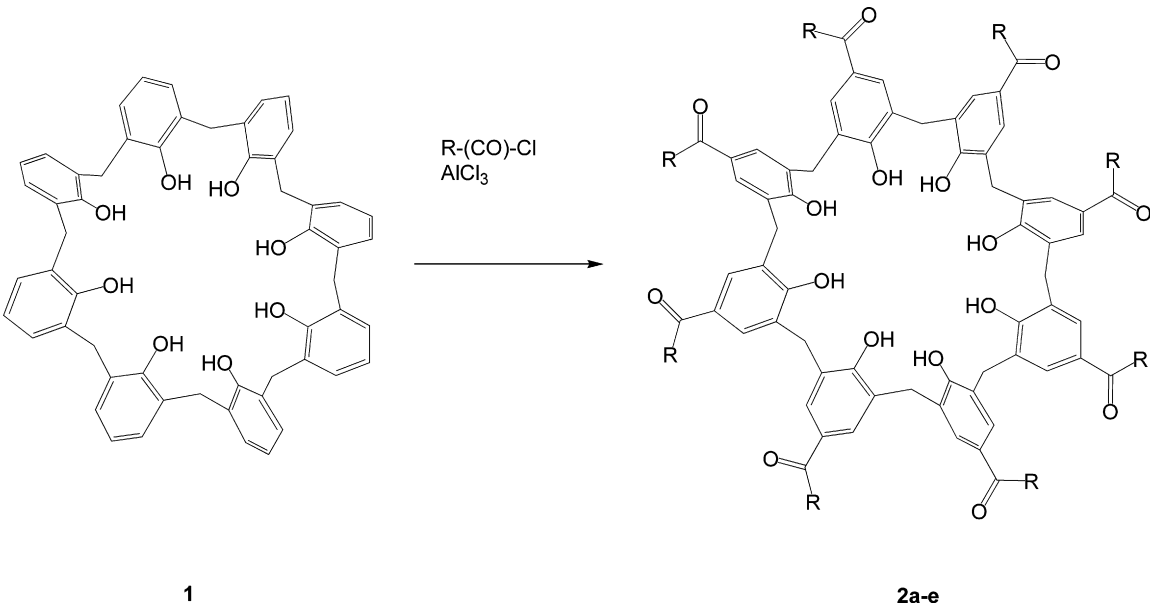

1 2a-e

Scheme 1. Synthetic route to the amphiphilic *para*-acyl-calix[8]arenes, **2a**–**e**; **a** R = C_7H_{15}; **b**, R = C_9H_{19}; **c** R = $C_{11}H_{23}$; **d**, R = $C_{13}H_{27}$; **e** R = $C_{15}H_{31}$.

fully hydrogen-bonded at the phenolic face.[15] Interestingly the methylenic CH_2 protons appear as a resolved AB pattern at 3.7 and 4.4 ppm, the $\Delta\delta$, 0.7 ppm, observed here is close to that observed for the cone conformation in calix[4]arenes and it is possible that the *para*-acyl-calix[8]arenes are present in a cone conformation. Similarly in the ^{13}C NMR spectra the methylenic carbon is observed at 23 ppm.

The calorimetric behaviour was measured using DSC/TGA, as shown below for **2c**, all compounds show an endothermic peak in the region 70–80 °C, and a second endothermic peak at around 300 °C. The high temperature peak is associated with melting–decomposition of the compounds, however it is unclear with what phase change the low temperature peak is associated. In the case of **2b**, the TGA curve shows a small but significant weight increase is associated with the low temperature DSC transition (Fig. 1).

The Langmuir isotherms for compounds **2a**–**e** are shown in Figure 2 and the isotherm data is summarised in Table 1.

It can be seen clearly that all the *para*-acyl-calix[8]arenes form stable monolayers at the air–water interface, however in contrast to the *para*-acyl-calix[4]arenes,[5–7] there are very considerable differences in the behaviour of these compounds at the air–water interface both with regard to apparent molecular areas and also collapse pressures. In a key paper by Baglioni,[16] the authors analysed the possible molecular areas for various conformations of the native *para-tert*-butylcalix[8]arene. They found areas of 322 Å^2 for the pleated loop, 244 Å^2 for the *anti*-cone/cone, 273 Å^2 for the *syn* cone/cone and 183 Å^2 for the 1,3,5,7 alternate conformations, respectively. The limiting area values (A_{lim}) observed for the compounds, unexpectedly, decrease with chain length,

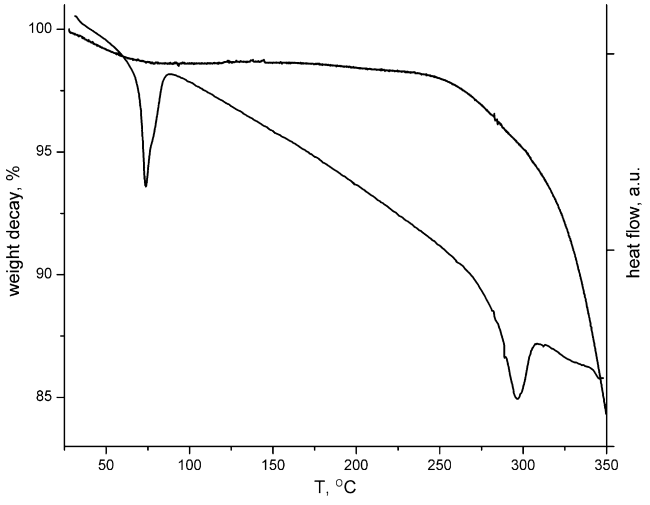

Figure 1. DSC and TGA curves for compound **2b**.

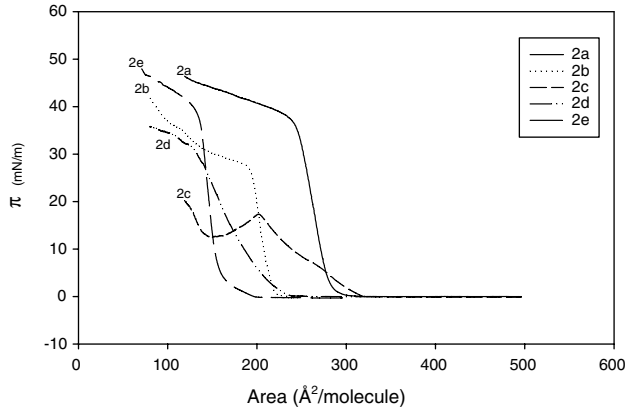

Figure 2. Surface pressure–molecular area isotherms of *para*-acyl-calix[8]arenes **2a**–**e** at air–water interface at 20 °C.

Table 1. Isotherm data for the *para*-acyl-calix[8]arene derivatives

	Π coll (mN/m)	A coll (Å^2)	A_{lim} (Å^2)	A_0 (Å^2)	A_1 (Å^2)	Cs^{-1}
2a	36.4	236	242	330	290	254
2b	27.3	188	201	234	220	385
2c	17.1	193.5	275	323	305	30
2d	31.6	129	207	232	221	58
2e	38.0	134	152	196	184	211

Area in Å^2/molecule, Π collapse and Cs^{-1} in mN/m at 20 °C.
Π_{coll} is the collapse pressure, A_{coll} is the area at collapse, A_{lim} is the extrapoled molecular area, A_0 is the apparent molecular area at $\pi = 0$, A_1 is the apparent molecular area at $\pi = 1$, Cs^{-1} is the compressibility modulus.

but are in the above range, except for **2e** where the value, 152 Å^2, is smaller than expected. In the case where the rings and the acyl chains are oriented perpendicular to the air–water interface, the limiting area for the acyl chains is approximately 20 Å^2 per acyl chain and so if the chains were playing a determinant role in the apparent molecular area a value of 160 Å^2 would be expected. Thus in the case of **2e** possibly one or more of the acyl chains are bent over and insert into the macrocyclic cavity, as has been observed in the crystal structures of *para*-acyl-calix[4]arenes.[17] However, if the molecules are not oriented perpendicular to the surface and the chains are spread out the calculated limiting molecular area could approach 600 Å^2, as all of the A_0 values are much less than this. It can be proposed that the aromatic rings are oriented more or less vertically with respect to the air–water interface.

For compounds **2a**, **2b** and **2e** the isotherms show normal behaviour, with compressibility indices in the range typical for condensed liquid phases.[18] For the derivatives with intermediate chain lengths, **2c** and **2d**, the behaviour is very different and in particular for **2c**, the isotherm shows a very low collapse area with an apparent rearrangement of the film after the initial collapse. Also here the compressibility modulus values, according to the literature, correspond to a liquid expanded phase.[18]

The Langmuir isotherms observed are highly reproducible even between different syntheses for each derivative, which rules out small differences in the substitution patterns below detection limits for mass spectrometry or NMR. The unexpectedly large differences in the observed apparent molecular areas, which are calculated on the basis of the concentration of molecules deposited at the air–water interface, may arise, in part, from the presence, even after the products have been dried in vacuo of residual included solvent.[13,14]

In conclusion, a novel series of *para*-acyl-calix[8]arenes has been synthesised and the self-assembly properties at the air–water interface have been studied, the compounds are obtained cleanly in good yields which will allow the study of a second functionalisation at the phenolic rim. Work is currently underway to study the complexation properties of these molecules at the air–water interface and also to obtain crystals suitable for X-ray diffraction.

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13. Under anhydrous nitrogen, aluminium trichloride (10.04 g, 16 equiv) and the relevant acid chloride (9.68 mL, 12 equiv) were added to nitrobenzene (75 mL) and the mixture was stirred for 10 min. The solution became dark brown, to this was added **1** (4 g, 1 equiv). The resultant solution was stirred at room temperature for 24 h. Pouring onto ice for 1 h stopped the reaction. The organic phase was extracted with chloroform (400 mL), washed with 1 M HCl (2×400 mL), 1 M NaCl (2×400 mL), water (4×400 mL) and dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure, and the nitrobenzene distilled off under vacuum (10^{-2} T) to give a clear brown paste.
14. A saponification reaction was realised on the relevant product with 150 mL of a solution of KOH (10%) in ethanol/water (70:30) during 24 h. The ethanol was removed under reduced pressure. Compounds **2a**–**e** were precipitated with a solution of HCl 1 M (500 mL) and filtered. The resultant compounds were solubilised in chloroform (400 mL), washed with water (4×400 mL) and dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 60 mL and compounds **2a**–**e** were precipitated with methanol (500 mL). Compound **2a**: ^{1}H NMR ($CDCl_3$) δ 9.57 ppm (s, 8H, ArO*H*), 7.82 ppm (s, 16H, *H*mAr), 4.38 and 3.70 ppm (2d, 16H, Ar–CH_2–Ar), 2.89 ppm (t, 16H, CH_2CO), 1.69 ppm (m, 16H, –CH_2–CH_2–CO), 1.30 ppm (m, –$(CH_2)_4$–, 64H), 0.89 ppm (t, CH_3–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 198.9, 152.6, 132.6, 129.8, 128.3, 38.8, 32.2, 30.1, 29.9, 29.7, 24.7, 23.0, 14.5. MS (MALDI-TOF): 1881.1 [2a+Na^+], 1897.1, [2a+K^+], mp > 250 °C. Yield = 72%. Compound **2b**: ^{1}H NMR ($CDCl_3$) δ 9.58 ppm (s, 8H, ArO*H*), 7.84 ppm (s, 16H, *H*mAr), 4.36 and 3.70 ppm (2d, 16H, Ar–CH_2–Ar), 2.89 ppm (t, 16H,

CH_2CO), 1.70 ppm (m, 16H, –CH_2–CH_2–CO), 1.26 ppm (m, –$(CH_2)_6$–, 96H), 0.89 ppm (t, CH_3–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 199.0, 152.1, 132.7, 129.9, 128.5, 38.9, 32.3, 32.2, 29.9, 29.8, 29.7, 29.6, 24.1, 23.1, 14.5. MS (MALDI-TOF): 2105.1 [2b+Na^+], [2b+K^+], mp > 250 °C. Yield = 69%. Compound **2c**: ^1H NMR ($CDCl_3$) δ 9.58 ppm (s, 8H, ArO*H*), 7.85 ppm (s, 16H, *H*mAr), 4.37 and 3.68 ppm (2d, 16H, Ar–CH_2–Ar), 2.90 ppm (t, 16H, CH_2CO), 1.70 ppm (m, 16H, –CH_2–CH_2–CO), 1.27 ppm (m, –$(CH_2)_8$–, 128H), 0.89 ppm (t, CH_3–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 199.0, 152.7, 132.7, 129.9, 128.8, 38.9, 32.3, 31.7, 31.3, 30.1, 30.0, 29.9, 29.8, 29.7, 24.8, 23.1, 14.5. MS (MALDI-TOF): 2329.7 [2c+Na^+], 2345.7 [2c+K^+], mp > 250 °C. Yield = 79%. Compound **2d**: ^1H NMR ($CDCl_3$) δ 9.57 ppm (s, 8H, ArO*H*), 7.83 ppm (s, 16H, *H*mAr), 4.37 and 3.71 ppm (2d, 16H, Ar–CH_2–Ar), 2.89 ppm (t, 16H, CH_2CO), 1.69 ppm (m, 16H, –CH_2–CH_2–CO), 1.26 ppm (m, –$(CH_2)_{10}$–, 160H), 0.89 ppm (t, CH_3–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 199.0, 152.6, 132.6, 129.9, 128.7, 38.8, 32.3, 31.8, 30.3, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 24.8, 23.2, 14.5. MS (MALDI-TOF): 2554.7 [2d+Na^+], 2569.7 [2d+K^+], mp > 250 °C. Yield = 61%. Compound **2e**: ^1H NMR ($CDCl_3$) δ 9.57 ppm (s, 8H, ArO*H*), 7.82 ppm (s, 16H, *H*mAr), 4.39 and 3.67 ppm (2d, 16H, Ar–CH_2–Ar), 2.89 ppm (t, 16H, CH_2CO), 1.69 ppm (m, 16H, –CH_2–CH_2–CO), 1.28 ppm (m, –$(CH_2)_{12}$–, 192H), 0.89 ppm (t, CH_3–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 199.0, 152.8, 132.6, 129.9, 128.5, 38.9 32.3, 31.8, 30.4, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 24.8, 23.1, 14.5. MS (MALDI-TOF): 2778.0 [2e+Na^+], 2794.0 [2e+K^+], mp > 250 °C. Yield = 81%. NMR spectra were recorded on a Varian 500 MHz for ^1H and Brucker 300 MHz for ^{13}C ($CDCl_3$, TMS as internal standard, chemical shifts in ppm). Mass spectra (MALDI-TOF) were recorded on a Voyager DE-PRO instrument (Applied Biosystems). Langmuir isotherms were recorded on a NIMA 6010 film balance on pure water (>18 MΩ) at 20 °C, all isotherms were repeated at least three times, variability was less than 3% in all cases. DSC and ATG were recorded on a TA Instrument with a temperature ramp of 3 °C/min.

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