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Synthesis and properties of novel amphiphilic calix-[4]-arene derivatives

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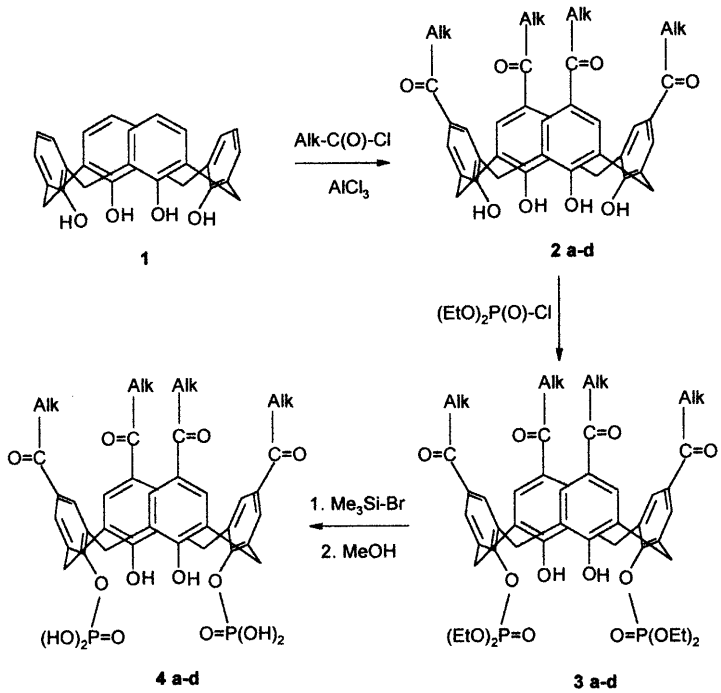
Abstract—A series of amphiphilic calix-[4]-arenes having four hydrophobic acyl chains (C6–C12) at the macrocyclic upper rim as well as two hydrophilic dihydroxyphosphoryloxy groups at the lower rim and analogous to the diacylphosphatidic acids lipids have been synthesised and characterised. The synthesis proceeds via regioselective 1,3 lower phosphorylation of the tetra-acyl calix-[4]-arene by diethylchlorophosphate in the presence of triethylamine. The ethyl groups are removed by consecutive treatment with trimethylbromosilane and methanol. All the new amphiphilic derivatives self-assemble at the air–water interface as stable Langmuir monolayers. © 2001 Published by Elsevier Science Ltd.

The calix-[*n*]-arenes[1] represent, along with the crown ethers[2] and the cyclodextrins,[3] one of the three major groups of synthetic macrocyclic host molecules in supramolecular chemistry.[4] They have been widely used for the complexation of small molecules and ions, and their solid state chemistry as novel materials is undergo-



Scheme 1. Synthetic route to 25,27-bis-dihydroxyphosphoryloxytetraacylcalix-[4]-arene. Alk = $CH_3(CH_2)_n$. $n = 4$ (**a**), 6 (**b**), 8 (**c**), 10 (**d**).

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ing high growth. In contrast, the application of the calix-arenes at the interface between biology and chemistry is much less well developed. Older reports showed activity against tuberculosis[5] and low toxicity.[6] More recently the development of hydrosoluble calix-[*n*]-arene derivatives has led to a resurgence in the study of their biological activities, with patents on their activity as anti-thrombotics,[7] chloride ion channel blockers[8] and enzyme inhibitors,[9] showing the biological potential of the molecules. In this paper we describe a second route to the exploitation of the calix-[*n*]-arenes in biological systems: their use as phospholipid analogues. We show that calix-[4]-analogues of the phosphatidic acids can be prepared in high yield, and that these compounds form well defined Langmuir monolayers at the air–water interface.

The phospholipids, the key components of biological membranes, are derivatives of glycerol, in which two hydrophobic acyl chains are attached in the 1 and 2 positions and a hydrophilic phosphatidyl head group is attached in the 3 position. The synthesis of the new amphiphilic derivatives was designed to retain an acyl chain to head group ratio of 2:1. The synthetic route is given below in Scheme 1.

Total acylation at the *para* positions of calix-[4]-arene **1** via Friedel–Crafts reaction in accordance with the method of Shinkaï et al.[10] by treatment of **1** with the corresponding acyl chloride in nitrobenzene solution in the presence of aluminium trichloride as the Lewis acid yields **2a–d** as crystalline solids in good yield after crystallisation from acetone.[11] Regioselective 1,3-diphosphorylation[12] of tetra-acyl calix-[4]-arene tetrols **2a–d** by reaction with three equivalents of diethyl chlorophosphate and triethylamine in chloroform at reflux for 20 hours leads to 25,27-bis-diethoxyphosphorytetraacylcalix-[4]-arene **3a–d**.[13] Transformation of diethoxyphosphoryl groups into phosphoric acid moieties is achieved in good yields by the consecutive treatment of **3a–d** with bromotrimethylsilane in chloroform for 24 hours at room temperature, and then by desilylation of the intermediate silyl esters (omitted in Scheme 1) by refluxing with methanol for 24 hours.[14] The ^{31}P NMR spectra of calix-[4]-arene **3a–d** and **4a–d** show a single peak, confirming the existence of a single stereoisomer. The splitting of the signals of the axial and equatorial methylene links protons in the ^{1}H NMR spectra into an AB-spin system confirms the cone conformation in which all the benzene rings possess *syn* orientation.

All the compounds in series **2**, **3** and **4** form stable Langmuir monolayers. The observed apparent molecular area, 100 Å^2, is in agreement with previous work[15] on amphiphilic calix-[4]-arene and is determined by the area of the calix-arenes macrocycle. For the compounds of series 3, there is no effect of chain length on collapse pressure for all compounds of this series (22 mN m^{-1}). As expected, the collapse pressure for compounds **2a–d** and series **4a–d** increases with chain length, from 9 to 12 mN m^{-1} for compounds **3a–3d** and from 28 to 43 mN m^{-1} for compounds **4a–4d**. Work is currently underway to investigate the interactions of these new amphiphilic molecules with natural phospholipids.

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11. General: NMR spectra were recorded on a Varian 500 MHz for ^{1}H and Bruker 200 MHz (81.06 MHz) for ^{31}P, ($CDCl_3$, TMS as internal standard, chemical shifts in PPM). Mass spectra (electrospray) were recorded on a Perkin–Elmer Sciex API 165. Under anhydrous nitrogen, aluminium trichloride (23.5 g, 176 mmol) and the relevant acid chloride (138 mmol) were added to nitrobenzene (200 mL) and the mixture was stirred for 10 minutes. The solution became dark brown, to this was added **1** (9.7 g, 23 mmol). The resultant solution was stirred at room temperature for 4 hours. Pouring onto ice for 1 h stopped the reaction. The organic phase was extracted with chloroform (800 mL), washed with 1 M HCl (2×400 mL), 1 M NaCl (2×400 mL), water (4×400 mL) and dried under anhydrous $MgSO_4$. The chloroform was removed under reduced pressure, and the nitrobenzene distilled off under vacuum (10^{-2} T) to give a volume of 100 mL. Compounds **3a–d** were precipitated as white solids by the addition of methanol (300 mL). The products were recrystallised from acetone to yield the pure compounds. Compound **2a**: ^{1}H NMR: 10.18 ppm (s, 4H, ArO*H*), 7.76 ppm (s, 8H, H_mAr), 4.35 and 3.75 ppm (2d, 8H, Ar-CH_2-Ar), 2.83 ppm (t, 8H, CH_2CO), 1.65 ppm (m, 8H, -CH_2-CH$_2$-CO), 1.28 ppm (m, 16H, -(CH_2)$_2$-), 0.89 ppm (t, CH_3-CH$_2$, 12H), ES-MS (pos. mode): 817.3 [2a+H$^+$], 839.4 [2a+Na$^+$], mp = 190°C. Compound **2b**: ^{1}H NMR: 10.2 ppm (s, 4H, ArO*H*), 7.76 ppm (s, 8H, H_mAr), 4.35 and 3.75 ppm (2d, 8H, Ar-CH_2-Ar), 2.83 ppm (t, 8H, CH_2CO), 1.65 ppm (m, 8H, -CH_2-CH$_2$-CO), 1.28 ppm (m, -(CH_2)$_4$-, 32H), 0.87 ppm (t, CH_3-CH$_2$, 12H), ES-MS (pos. mode): 929.3 [2b+H$^+$], 951.5 [2b+Na$^+$], mp = 183°C. Compound **2c**: ^{1}H NMR: 10.14 ppm

(s, 4H, ArO*H*), 7.71 ppm (s, 8H, H_mAr), 4.23 and 3.67 ppm (2d, 8H, Ar-CH_2-Ar), 2.77 ppm (t, 8H, CH_2CO), 1.60 ppm (m, 8H, -CH_2-CH$_2$-CO), 1.21 ppm (m, -(CH_2)$_6$-, 48H), 0.82 ppm (t, CH_3-CH$_2$, 12H), ES-MS (pos. mode): 1041.4 [2c+H$^+$], 1063.5 [2c+Na$^+$], mp = 145°C. Compound **2d**: ^{1}H NMR: 10.14 ppm (s, 4H, ArO*H*), 7.71 ppm (s, 8H, H_mAr), 4.24 and 3.52 ppm (2d, 8H, Ar-CH_2-Ar), 2.78 ppm (t, 8H, CH_2CO), 1.60 ppm (m, 8H, -CH_2-CH$_2$-CO), 1.21 ppm (m, -(CH_2)$_8$-, 64H), 0.84 ppm (t, CH_3-CH$_2$, 12H), ES-MS (pos. mode): 1153.7 [2d+H$^+$], 1175.6 [2d+Na$^+$], mp = 134°C.

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13. Under a nitrogen atmosphere in anhydrous conditions, a mixture of **3** (8 mmol), diethyl chlorophosphate (3.4 mL, 24 mmol) and triethylamine (3.5 mL, 24 mmol) were refluxed in freshly distilled chloroform (20 mL) for 20 hours. After cooling, the solution was washed with water (2×200 mL) and the solvent removed on a rotatory evaporator. The viscous yellow oil obtained was dissolved in methanol (5 mL); cooling to −15°C for 1 hour yields the product as a light brown solid (75% yield). The compounds were purified by crystallisation from methanol at −15°C to yield yellow crystals. Compound **3a**: ^{1}H NMR: 7.84 ppm (s, 4H, H_mAr-OPO(OEt)$_2$), 7.42 ppm (s, 4H, H_m-Ar-OH) 4.50 and 3.58 ppm (2d, 8H, Ar-CH_2-Ar), 4.23 ppm (m, 8H, O-P(O)(O-CH_2-)), 2.95 ppm (t, 4H, -CH_2-CO-Ar-OPO(OEt)$_2$), 2.63 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.70 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OEt)$_2$), 1.45 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.35 (t, 12H, CH_3-CH$_2$-O-), 1.20 ppm (m, -(CH_2)$_2$-, 16H), 0.80 ppm (t, CH_3(CH$_2$)$_4$, 12H), ^{31}P NMR: −5.04 ppm (ref: H_3PO_4), ES-MS (pos. mode): 1089.2 [3a+H$^+$], 1111.3 [3a+Na$^+$], mp = 75°C. Compound **3b**: ^{1}H NMR: 7.84 ppm (s, 4H, H_mAr-PO(OEt)$_2$), 7.42 ppm (s, 4H, H_m-Ar-OH) 4.50 and 3.58 ppm (2d, 8H, Ar-CH_2-Ar), 4.23 ppm (m, 8H, O-P(O)(O-CH_2-)), 2.95 ppm (t, 4H, -CH_2-CO-Ar-OPO(OEt)$_2$), 2.63 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.70 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OEt)$_2$), 1.45 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.35 (t, 12H, CH_3-CH$_2$-O-), 1.20 ppm (m, -(CH_2)$_4$-, 32H), 0.84 ppm (t, CH_3(CH$_2$)$_6$, 12H), ^{31}P NMR: −5.12 ppm (ref: H_3PO_4), ES-MS (pos. mode): 1201.6 [3b+H$^+$], 1223.3 [3b+Na$^+$], mp = 112–5°C. Compound **3c**: ^{1}H NMR: 7.85 ppm (s, 4H, H_mAr-OPO(OEt)$_2$), 7.47 ppm (s, 4H, H_m-Ar-OH) 4.52 and 3.62 ppm (2d, 4H, Ar-CH_2-Ar), 4.27 ppm (m, 4H, O-PO(O-CH_2-)), 2.96 ppm (t, 4H, -CH_2-CO-Ar-OPO(OEt)$_2$), 2.69 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.75 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OEt)$_2$), 1.50 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.38 (t, 12H, CH_3-CH$_2$-O-), 1.24 ppm (m, -(CH_2)$_6$-, 48H), 0.87 ppm (t, CH_3-CH$_2$(CH$_2$)$_7$, 12H), ^{31}P NMR: −5.14 ppm (ref: H_3PO_4), ES-MS (pos. mode): 1313.6 [3c+H$^+$], 1335.5 [3c+Na$^+$], mp = 155°C. Compound **3d**: ^{1}H NMR: 7.82 ppm (s, 4H, H_mAr-OPO(OEt)$_2$), 7.42 ppm (s, 4H, H_m-Ar-OH) 4.50 and 3.60 ppm (2d, 8H, Ar-CH_2-Ar), 4.25 ppm (m, 8H, O-PO(O-CH_2-)), 2.90 ppm (t, 4H, -CH_2-CO-Ar-OPO(OEt)$_2$), 2.65 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.70 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OEt)$_2$), 1.45 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.35 (t, 12H, CH_3-CH$_2$-O-), 1.21 ppm (m, -(CH_2)$_8$-, 64H), 0.82 ppm (t, CH_3-CH$_2$(CH2)$_9$, 12H), ^{31}P NMR: −5.16 ppm (ref: H_3PO_4), ES-MS (pos. mode): 1425.9 [3c+H$^+$], 1448.6 [3c+Na$^+$], mp = 112°C.
14. In freshly distilled chloroform (20 mL) under a nitrogen atmosphere, a solution of **3** (5 mmol) was treated with bromotrimethylsilane (10.5 mL, 80 mmol). The resultant solution was stirred at room temperature for 48 hours. The solvent and excess of bromotrimethylsilane were removed under reduced pressure. The white solid obtained was treated, under reflux, in methanol (300 ml) for 24 hours. The methanol was removed to yield **4** as an off white solid (98% yield). Compound **4a**: 8.92 ppm (s, 4H, H_mAr-OPO(OH)$_2$), 7.35 ppm (s, 4H, H_m-Ar-OH) 5.12 and 3.94 ppm (2d, 8H, Ar-CH_2-Ar), 3.21 ppm (t, 4H, -CH_2-CO-Ar-OPO(OH)$_2$), 2.79 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.88 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-PO(OH)$_2$), 1.69 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.30 ppm (m, -(CH_2)$_3$-, 24H), 0.91 ppm (t, CH_3-CH$_2$(CH$_2$)$_5$, 12H), ^{31}P NMR: 4.75 ppm (ref: H_3PO_4), ES-MS (neg. mode): 975.2 [4a-H$^+$], mp = 144–6°C. Compound **4b**: 8.88 ppm (s, 4H, H_mAr-OPO(OH)$_2$), 7.42 ppm (s, 4H, H_m-Ar-OH) 5.05 and 3.90 ppm (2d, 8H, Ar-CH_2-Ar), 3.18 ppm (t, 8H, -CH_2-CO-Ar-OPO(OH)$_2$), 2.75 ppm (t, 8H, -CH_2-CO-Ar-OH), 1.85 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OH)$_2$), 1.74 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.24 ppm (m, -(CH_2)$_4$-, 32H), 0.90 ppm (t, CH_3-CH$_2$(CH$_2$)$_5$, 12H), ^{31}P NMR: 4.75 ppm (ref: H_3PO_4), ES-MS (neg. mode): 1087.6 [4b-H$^+$], mp = 143–6. Compound **4c**: 8.90 ppm (s, 4H, H_mAr-OPO(OH)$_2$), 7.38 ppm (s, 4H, H_m-Ar-OH) 5.00 and 3.87 ppm (2d, 8H, Ar-CH_2-Ar), 3.20 ppm (t, 4H, -CH_2-CO-Ar-PO(OH)$_2$), 2.75 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.87 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-PO(OH)$_2$), 1.74 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.21 ppm (m, -(CH_2)$_6$-, 48H), 0.88 ppm (t, CH_3-CH$_2$(CH$_2$)$_7$, 12H), ^{31}P NMR: 4.75 ppm (ref: H_3PO_4), ES-MS (neg. mode): 1199.7 [4c-H$^+$], mp = 146–8°C. Compound **4d**: 8.93 ppm (s, 4H, H_mAr-OPO(OH)$_2$), 7.42 ppm (s, 4H, H_m-Ar-OH) 5.05 and 3.85 ppm (2d, 8H, Ar-CH_2-Ar), 3.05 ppm (t, 4H, -CH_2-CO-Ar-PO(OH)$_2$), 2.70 ppm (t, 4H, -CH_2-CO-Ar-OH), 1.90 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OPO(OH)$_2$), 1.70 ppm (m, 4H, -CH_2-CH$_2$-CO-Ar-OH), 1.21 ppm (m, -(CH_2)$_8$-, 64H), 0.90 ppm (t, CH_3-CH$_2$(CH$_2$)$_9$, 12H), ^{31}P NMR: 4.75 ppm (ref: H_3PO_4), ES-MS (neg. mode): 1311.8 [4d-H$^+$].
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