J Incl Phenom Macrocycl Chem (2010) 68:207–217
DOI 10.1007/s10847-010-9769-5

ORIGINAL ARTICLE

Para-acylcalix[6]arenes: their synthesis, per-O-functionalisation, solid-state structures and interfacial assembly properties

Said Jebors · Barbara Leśniewska · Oleksandr Shkurenko · Kinga Suwińska · Anthony W. Coleman

Received: 27 November 2009 / Accepted: 7 March 2010 / Published online: 25 April 2010

Abstract The *para*-acylcalix[6]arenes bearing butanoyl, hexanoyl and octanoyl chains have been synthesized by Friedel–Crafts acylation of the parent calixarene. Persubstitution at the phenolic face was achieved to yield the methoxy-diethoxy, ethoxycarbonylmethoxy, methoxycarboxylic acid and butoxysulphonate derivatives. In the case of the derivatives, 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexa-methoxy-diethoxy-calix[6]arene, 5,11,17,23,29,35-hexa-butanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene and 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene the solid state structures were determined and show inclusion of two ester groups in the cavity. While for the *para*-acylcalix[6]arenes no stable monolayers can be formed at the air–water interface, stable monolayers are formed with the methoxy-diethoxy, ethoxycarbonylmethoxy, methoxycarboxylato compounds which show apparent molecular areas in the range 150–200 $Å^2$ depending on the length of the acyl chains.

Keywords Calixarene · Amphiphilic · Structure · Langmuir · Synthesis

Electronic supplementary material The online version of this article (doi:10.1007/s10847-010-9769-5) contains supplementary material, which is available to authorized users.

S. Jebors · A. W. Coleman (✉)
Institut de Biologie et Chimie des Protéines, UMR 5086, CNRS, Université Lyon 1, 7 passage du Vercors, 69367 Lyon, France
e-mail: aw.coleman@ibcp.fr

B. Leśniewska · O. Shkurenko · K. Suwińska
Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka, 44/52, 01224 Warszawa, Poland
e-mail: kinga@ichf.edu.pl

Introduction

The calix[*n*]arenes are amongst the most highly studied classes of macrocyclic host molecules, this arises both from the facile selective synthesis and also from their ease of modification as they present two very different chemistries, at one face phenolic groups and at the other activated para-aromatic group [1]. Their complexation chemistry has been extensively studies [2], and more recently their biological activity has become of interest [3].

Of the calixarene derivatives we have been, for some time, studying the *para*-acylcalix[*n*]arenes [4], synthesised via Friedel–Crafts acylation at the *para*-aromatic position [5]. In the case of the *para*-acylcalix[4]arenes it has been demonstrated that they are capable of forming stable monolayers at the air–water interface, of forming Solid Lipid Nanoparticles [6], and that they possess extremely varied properties in the solid state. Particularly, in the solid-state they have been demonstrated to be non-porous materials, in the sense that there are no channels or voids in the packing [7] and yet that they are capable of undergoing guest exchange via single crystal to single crystal transformations [8], and also gas uptake [9]. The lack of porosity allows them to protect photosensitive materials [10] and allow stabilization of organic free radicals [11]. We have recently synthesized *para*-acylcalix[8]arenes [12], and have succeeded in fully and cleanly substituted them at the phenolic functions, interestingly these molecules do not form monolayers at the air–water interface and also do not form Solid Lipid Nanoparticles [13]. In recent work, the synthesis of the *para*-acylcalix[9]arenes has been achieved [14], and here the situation is analogous to that for the *para*-acylcalix[4]arenes with formation of monolayers, and also stable Solid Lipid Nanoparticles [6].

There, thus, remains the synthesis of the *para*-acylcalix[6]arenes and the study of their properties, for which it has taken several years to achieve clean and efficient *para*-acylation.

Previously, the synthesis of amphiphilic calix[6]arenes has been carried out either by introducing polar functions at the *para*-position for example quaternary amines [15], boronic acids or alcohols [16] along with coupling long alkyl chains at the phenolic face or by simple per-O-substitution at the phenolic face with, for example ethyleneglycol chains [17] or amide functions [18]. Selective di- and tri-substitution have been reported, and a selective di-demethylation using $TiCl_4$ was published some time ago [19]. Starting from the selective 1,3,5-O-methylation of *para-tert*-butylcalix[6]arene, a wide range of features can be introduced at the free hydroxyls positions [20, 21].

In the current paper we describe the synthesis of some *para*-acylcalix[6]arenes, and successful and unsuccessful work on the per-O-substitution of these molecules. The formation of stable monolayers at the air–water interface by the per-O-substituted derivatives is observed. The crystal structures of three compounds have been determined.

Experimental

General experimental details

NMR spectra were recorded on a Bruker 500 MHz for ^{1}H and 125 MHz for ^{13}C (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. **1** was synthesized as per the literature and all physical data concord with literature values [22].

Typical procedure for *para*-acylation of calix[6]arene

Under anhydrous nitrogen, aluminium trichloride (12 equiv.) and the relevant acid chloride (9 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** (5 g, 1 equiv.). The resultant solution was stirred at room temperature for 24 h. Pouring onto ice 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.

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–c** were precipitated by acidification with 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–c** were precipitated with methanol (500 mL).

5,11,17,23,29,35-Hexa-butanoylcalix[6]arene

2a: ^{1}H NMR (DMSO) δ 7.69 ppm (s, 12H, *H*mAr), 3.88 ppm (br s, 12H, Ar–C*H*$_2$–Ar), 2.92 ppm (s, 12H, C*H*$_2$CO), 1.45 ppm (s, 12H, –C*H*$_2$–CH$_2$–CO), 1.22 ppm (s, –C*H*$_2$–CH$_3$, 36H), 0.84 ppm (s, C*H*$_3$–CH$_2$, 18H). ^{13}C NMR ($CDCl_3$) δ 199.1 (C=O), 152.7 (C_{ipso}), 132.3 (C_{para}), 129.8 (C_{ortho}), 128.4 (C_{meta}), 40.2 (*C*H$_2$CO), 31.3 (CH$_2$), 17.8 (CH$_2$), 14.0 (CH$_3$). 1079.5 [+Na$^+$], m.p. >250 °C, Rf = 0.21 ($CHCl_3$), yield = 73%.

5,11,17,23,29,35-Hexa-hexanoylcalix[6]arene

2b: ^{1}H NMR (DMSO) δ 7.66 ppm (s, 12H, *H*mAr), 3.91 ppm (br s, 12H, Ar–C*H*$_2$–Ar), 2.75 ppm (s, 12H, C*H*$_2$CO), 1.46 ppm (s, 12H, –C*H*$_2$–CH$_2$–CO), 1.19 ppm (s, –(C*H*$_2$)$_2$–, 24H), 0.88 ppm (t, C*H*$_3$–CH$_2$, 18H). ^{13}C NMR ($CDCl_3$) δ 198.7 (C=O), 152.3 (C_{ipso}), 132.7 (C_{para}), 129.8 (C_{ortho}), 128.4 (C_{meta}), 38.8 (*C*H$_2$CO), 32.0–23.2 (4 × CH$_2$), 14.1 (CH$_3$). 1247.7 [+Na$^+$], m.p. >250 °C, Rf = 0.25 ($CHCl_3$), yield = 77%.

5,11,17,23,29,35-Hexa-octanylcalix[6]arene

2c: ^{1}H NMR (DMSO) δ 7.65 ppm (s, 12H, *H*mAr), 3.91 ppm (br s, 12H, Ar–C*H*$_2$–Ar), 2.71 ppm (br s, 12H, C*H*$_2$CO, 1.49 ppm (s, 12H, –C*H*$_2$–CH$_2$–CO), 1.22 ppm (s, –(C*H*$_2$)$_4$–, 48H), 0.81 ppm (s, C*H*$_3$–CH$_2$, 18H). ^{13}C NMR ($CDCl_3$) δ 198.9 (C=O), 152.6 (C_{ipso}), 132.6 (C_{para}), 129.8 (C_{ortho}), 128.3 (C_{meta}), 38.8 (*C*H$_2$CO), 32.2–23.0 (6 × CH$_2$), 14.5 (CH$_3$). MS (MALDI-TOF): 1415.9 [+Na$^+$], m.p. >250 °C, Rf = 0.28 ($CHCl_3$), yield = 83%.

5,11,17,23,29,35-Hexa-butanoyl-37,38,39,40,41,42-hexa-ethoxycarbonylmethoxycalix[6]arene

2a (1 g, 1 equiv.), ethyl bromoacetate (0.8 mL, 10 equiv.), potassium carbonate (1 g, 10 equiv.), were combined and refluxed in acetone during 48 h. The acetone was removed under reduced pressure and the resultant compound was solubilised in chloroform (30 mL) washed with 1 M HCl (2 × 30 mL), 1 M NaCl (2 × 30 mL), water (2 × 30 mL)

and dried under anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in methanol.

Compound **5a**: ^{1}H NMR ($CDCl_3$) δ 7.72 ppm (s, 12H, *H*mAr), 4.81–3.72 ppm (br s, 12H, Ar–O–C*H*$_2$–, 12H, O–C*H*$_2$–CH_3, 12H, Ar–C*H*$_2$–Ar), 2.79 ppm (s, 12H, C*H*$_2$CO), 1.66 ppm (s, 12H, –C*H*$_2$–CH_2–CO), 1.31 ppm (s, –$(CH_2)_4$–, 48H), 1.19 ppm (s, 18H, O–CH_2–C*H*$_3$), 0.95 ppm (s, C*H*$_3$–CH_2, 24H). ^{13}C NMR ($CDCl_3$) δ 199.1 (C=O), 168.2 (*C*OO), 158.8 (C_{ipso}), 133.4 (C_{para}), 133.2 (C_{ortho}), 129.7 (C_{meta}), 69.8 (Ar–O–*C*H_2), 61.1 (O–*C*H_2–CH_3), 40.2 (*C*H_2CO), 31.1 (CH_2), 17.8 (CH_2), 13.8 (2 × *C*H_3). MS (MALDI-TOF): 1595.8 [+Na^+], 1611.8 [+K^+], m.p. = 160 °C, Rf = 0.68 ($CHCl_3$), yield = 63%.

5,11,17,23,29,35-Hexa-butanoyl-37,38,39,40,41,42-hexa-2-carboxymethoxycalix[6]arene

5a (1 g, 1 equiv.) was added in 50 mL of a solution of KOH (10%) in ethanol/water (70/30) during 24 h. The ethanol was removed under reduced pressure. Compound was precipitated with a solution of HCl 2 M (60 mL) and filtered. The resultant compound was solubilised in chloroform (30 mL), washed with water (4 × 30 mL) and dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in hexane.

Compound **6a**: ^{1}H NMR ($CDCl_3$) δ 7.70 ppm (s, 12H, *H*mAr),4.38 ppm (s, 12H, Ar–O–C*H*$_2$–), 3.48 ppm (s, 12H, Ar–C*H*$_2$–Ar), 2.73 ppm (s, 12H, C*H*$_2$CO), 1.51 ppm (s, 12H, –C*H*$_2$–CH_2–CO), 1.20 ppm (s, –$(CH_2)_4$–, 48H), 0.79 ppm (s, C*H*$_3$–CH_2, 18H). ^{13}C NMR ($CDCl_3$) δ 199.4 (C=O), 169.5 (*C*OO), 158.5 (C_{ipso}), 133.6 (C_{para}), 133.2 (C_{ortho}), 129.4 (C_{meta}), 70.2 (Ar–O–*C*H_2), 39.9 (*C*H_2CO), 31.4 (CH_2), 17.7 (CH_2), 14.0 (*C*H_3). MS (MALDI-TOF): 1427.5 [+Na^+], 1443.5 [+K^+], m.p. = 175 °C, Rf = 0.2 ($CHCl_3$/MeOH/75/25), yield = 88%.

5,11,17,23,29,35-Hexa-hexanoyl-37,38,39,40,41,42-hexa-ethoxycarbonylmethoxycalix[6]arene

2b (1 g, 1 equiv.), ethyl bromoacetate (0.8 mL, 10 equiv) and potassium carbonate (1 g, 10 equiv.), were combined and refluxed in acetone during 48 h. The acetone was removed under reduced pressure and the resultant compound was solubilised in chloroform (30 mL) washed with HCl 1 M (2 × 30 mL), NaCl 1 M (2 × 30 mL), water (2 × 30 mL) and dried under anhydrous MgSO4. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in methanol.

Compound **5b**: ^{1}H NMR ($CDCl_3$) δ 7.72 ppm (s, 12H, *H*mAr),4.86–3.62 ppm (br s, 12H, Ar–O–C*H*$_2$–, 12H, O–C*H*$_2$–CH_3, 12H, Ar–C*H*$_2$–Ar), 2.81 ppm (s, 12H, C*H*$_2$CO), 1.64 ppm (s, 12H, –C*H*$_2$–CH_2–CO), 1.26 ppm (s, –$(CH_2)_4$–, 48H), 1.19 ppm (s, 18H, O–CH_2–C*H*$_3$), 0.91 ppm (s, C*H*$_3$–CH_2, 18H). ^{13}C NMR ($CDCl_3$) δ 199.2 (C=O), 168.2 (*C*OO), 159.2 (C_{ipso}), 133.3 (C_{para}), 129.9 (C_{ortho}), 129.3 (C_{meta}), 69.8 (Ar–O–*C*H_2), 61.1 (O–*C*H_2–CH_3), 38.3 (*C*H_2CO), 31.5–22.6 (4 × CH_2), 14.1 (2 × *C*H_3). MS (MALDI-TOF): 1765.3 [+Na^+], 1781.2 [+K^+], m.p. = 167 °C, Rf = 0.71 ($CHCl_3$), yield = 62%.

5,11,17,23,29,35-Hexa-hexanoyl-37,38,39,40,41,42-hexa-2-carboxymethoxy calix[6]arene

5b (1 g, 1 equiv.) was added to 50 mL of a solution of KOH (10%) in ethanol/water (70/30) during 24 h. The ethanol was removed under reduced pressure. Compound was precipitated with a solution of HCl 2 M (60 mL) and filtered. The resultant compound was solubilised in chloroform (30 mL), washed with water (4 × 30 mL) and dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in hexane.

Compound **6b**: ^{1}H NMR ($CDCl_3$) δ 7.70 ppm (s, 12H, *H*mAr),4.38 ppm (s, 12H, Ar–O–C*H*$_2$–), 3.48 ppm (s, 12H, Ar–C*H*$_2$–Ar), 2.73 ppm (s, 12H, C*H*$_2$CO), 1.51 ppm (s, 12H, –C*H*$_2$–CH_2–CO), 1.20 ppm (br s, –$(CH_2)_4$–, 48H), 0.79 ppm (s, C*H*$_3$–CH_2, 18H). ^{13}C NMR ($CDCl_3$) δ 199.6 (C=O), 169.3 (*C*OO), 159.5 (C_{ipso}), 133.3 (C_{para}), 129.8 (C_{ortho}), 129.6 (C_{meta}), 69.9 (Ar–O–*C*H_2), 38.4 (*C*H_2CO), 31.5–22.6 (4 × CH_2), 13.9 (*C*H_3). MS (MALDI-TOF): 1595.6 [+Na^+], 1609.6 [6a + K^+], m.p. = 220 °C, Rf = 0.23 ($CHCl_3$/MeOH/75/25), yield = 87%.

5,11,17,23,29,35-Hexa-octanoyl-37,38,39,40,41,42-hexa-ethoxycarbonylmethoxycalix[6]arene

2c (1 g, 1 equiv.), ethyl bromoacetate (0.8 mL, 10 equiv.) and potassium carbonate (1 g, 10 equiv.), were combined and refluxed in acetone during 48 h. The acetone was removed under reduced pressure and the resultant compound was solubilised in chloroform (30 mL) washed with HCl 1 M (2 × 30 mL), NaCl 1 M (2 × 30 mL), water (2 × 30 mL) and dried under anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in methanol.

5c: ^{1}H NMR ($CDCl_3$) δ 7.71 ppm (s, 12H, *H*mAr), 4.26 ppm (s, 12H, Ar–O–C*H*$_2$–), 4.13 ppm (s, 12H, O–C*H*$_2$–CH_3), 4.01 ppm (s, 12H, Ar–C*H*$_2$–Ar), 2.79 ppm (s, 12H, C*H*$_2$CO), 1.61 ppm (s, 12H, –C*H*$_2$–CH_2–CO), 1.27 ppm (s, –$(CH_2)_4$–, 48H), 1.17 ppm (s, 18H, O–CH_2–C*H*$_3$), 0.88 ppm (s, C*H*$_3$–CH_2, 18H). ^{13}C NMR ($CDCl_3$) δ 199.1 (C=O), 168.1 (*C*OO), 159.3 (C_{ipso}), 133.6 (C_{para}), 133.2 (C_{ortho}), 129.8 (C_{meta}), 69.7 (Ar–O–*C*H_2), 61.3 (O–*C*H_2–CH_3), 38.7

(CH_2CO), 31.6–22.7 (6 × CH_2), 14.3 (CH_3), 14.1 (CH_3). MS (MALDI-TOF): 1933.2 [$+Na^+$], 1949.1 [$+K^+$], mp = 120 °C, Rf = 0.74 ($CHCl_3$), Yield = 66%.

5,11,17,23,29,35-Hexa-octanoyl-37,38,39,40,41,42-hexa-2-carboxymethoxy calix[6]arene

5c (1 g, 1 equiv.) was added in 50 mL of a solution of KOH (10%) in ethanol/water (70/30) during 24 h. The ethanol was removed under reduced pressure. Compound was precipitated with HCl 2 M (60 mL) and filtered. The resultant compound was solubilised in chloroform (30 mL), washed with water (4 × 30 mL) and dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in hexane**.**

Compound **6c**: ^{1}H NMR ($CDCl_3$) δ 7.78 ppm (s, 12H, *H*mAr),4.37 ppm (s, 12H, Ar–O–C*H*$_2$–), 3.46 ppm (s, 12H, Ar–C*H*$_2$–Ar), 2.90 ppm (s, 12H, C*H*$_2$CO), 1.61 ppm (s, 12H, –C*H*$_2$–CH$_2$–CO), 1.19 ppm (s, –(CH$_2$)$_4$–, 48H), 0.79 ppm (s, C*H*$_3$–CH$_2$, 18H). ^{13}C NMR ($CDCl_3$) δ 199.3 (C=O), 169.6 (*C*OO), 159.5 (C_{ipso}), 133.7 (C_{para}), 133.2 (C_{ortho}), 129.9 (C_{meta}), 69.9 (Ar–O–*C*H$_2$), 38.8 (*C*H$_2$CO), 31.6–22.7 (6 × CH_2), 14.2 (*C*H$_3$). MS (MALDI-TOF): 1764.0 [$+Na^+$], 1781.0 [$+K^+$], m.p. = 245 °C, Rf = 0.25 ($CHCl_3$/MeOH/75/25), yield = 90%.

5,11,17,23,29,35-Hexa-octanoyl-37,38,39,40,41,42-hexa-methoxy-diethoxycalix[6]arene

2c (1 g, 1 equiv.), 1-bromo-2-(2-methoxyethoxy)ethane (0.97 mL, 10 equiv.), potassium carbonate (1 g, 10 equiv.), were combined and refluxed in acetone. The introduction of potassium carbonate and 1-bromo-2-(2-methoxyethoxy)ethane was repeated 1 time. The acetone was removed under reduced pressure and the resultant compound was solubilised in chloroform (30 mL) washed with water (4 × 30 mL) and dried under anhydrous $MgSO_4$. The chloroform was removed under reduced pressure to give a volume of 5 mL and the product was precipitated in methanol.

Compound **3c**: ^{1}H NMR (CDCl3) δ 7.62 ppm (s, 12H, *H*mAr), 4.11 ppm(s, 12H, Ar–O–C*H*$_2$), 3.83 ppm (br s, 12H, Ar–C*H*$_2$–Ar), 3.60 ppm (s, 12H, –CH$_2$–C*H*$_2$–O–), 3.51 ppm (s, 24H, O–C*H*$_2$–C*H*$_2$–O), 3.29 ppm (s, 18H, O–C*H*$_3$), 2.77 ppm (s, 12H, –C*H*$_2$–CH$_2$–CO), 1.59 ppm (s, 12H, CH$_2$–CH$_2$–CO), 1.21 ppm (s, –(CH$_2$)$_4$–, 48H), 0.86 ppm (s, CH$_3$–CH$_2$, 18H). 14.5. 13C NMR ($CDCl_3$) δ 199.1 (C=O), 159.1 (C_{ipso}), 134.2 (C_{para}), 133.4 (C_{ortho}), 129.3 (C_{meta}), 72.8 ($ArOCH_2$), 71.5 ($ArOCH_2CH_2$), 71.1–705 (OCH_2CH_2O), 58.2 (OCH_3), 38.3 (CH_2CO), 31.8–22.3 (6 × CH_2), 14.5 (CH_3). MS (MALDI-TOF): 2045.1 [+K+], m.p. = 115 °C, Rf = 0.65 (CHCl3/MeOH 95/05), yield = 62%.

5,11,17,23,29,35-Hexa-octanoyl-37,38,39,40,41,42-hexa-sulphonatobutoxycalix[6]arene

Under nitrogen atmosphere **2c** (1 g, 1 equiv.) was dissolved in 50 mL of freshly distilled THF and was added an excess of NaH (0.35 g, 12 equiv.). The mixture was stirred and refluxed and after 20 min, 1,4-butanesultone (0.88 mL, 12 equiv) was added. The introduction of NaH and 1,4-butanesultone was repeated 1 time for 2 days allowing total substitution of the hydroxyl groups. MeOH was added to the solution for neutralise the excess of NaH. The precipitate was filtered and washed with THF and MeOH, dissolved in water, passed on an exchange resin, and lyophilised.

Compound **4c**: ^{1}H NMR ($CDCl_3$) δ 7.66 ppm (broad s, 12H, *H*mAr), 4.09 ppm (br s, 12H, Ar–O–C*H*$_2$), 3.67 ppm (br s, 12H, Ar–C*H*$_2$–Ar), 2,94 (br s, 12H, S–C*H*$_2$), 2.79 ppm (br s, 12H, –C*H*$_2$–CO), 1.69–1.52 ppm (br s, 36H, C*H*$_2$–CH$_2$–CO, C*H*$_2$–C*H*$_2$–CH$_2$–S), 1.24 ppm (s, –(CH$_2$)$_4$–, 48H), 0.86 ppm (s, C*H*$_3$–CH$_2$, 18H). ^{13}C NMR ($CDCl_3$) δ 199.8 (C=O), 157.6 (C_{ipso}), 133.1 (C_{para}), 132.9 (C_{ortho}), 129.9(C_{meta}), 73.7 ($ArOCH_2$), 51.4 (S–CH_2), 39.8 (CH_2CO), 31.7–21.9 (7 × CH_2), 14.2 (CH_3). (MALDI-TOF): 2208.9 [$-H^+$] m.p. = 160 °C, yield = 51%.

Crystallographic data

Crystals were obtained by slow evaporation of 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexa-methoxy-diethoxy-calix[6]arene, 5,11,17,23,29,35-hexa-butanoyl-37,38,39,40,41,42-hexaethoxycarbonyl-methoxy-calix[6]arene and 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexaethoxycarbonylmethoxy-calix[6]arene directly from the reaction medium.

Intensity data were collected at 100(2) K on a Nonius KappaCCD diffractometer using Mo$K\alpha$ radiation (λ = 0.71073 Å). Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by direct methods and Fourier techniques (SHELXS-86) and refined, on $|F|^2$ (SHELX-97). H-atoms were included in geometric positions and refined as 'riding' atoms with isotropic thermal parameters based upon the corresponding bonding carbon atom [$U_{iso} = 1.5U_{eq}$ for CH_3 and $U_{iso} = 1.2U_{eq}$ for the rest].

Crystal data for **3c**: $C_{120}H_{180}O_{24}$, M_r = 2006.64, colourless prism, 0.45 × 0.24 × 0.20 mm, triclinic, $P\bar{1}$, a = 13.1862(3), b = 13.3901(4), c = 18.6719(7) Å, α = 84.965(2), β = 77.480(2), γ = 63.165(1)°, V = 2871.6(2) Å^3, Z = 1, ρ_{calc} = 1.160 Mg/m^3, θ_{max} = 26.7°, μ(Mo$K\alpha$) = 0.079 mm^{-1}, 42104 reflections collected, 12109 independent reflections, 7403 [$I > 2\sigma$ (I)]. R = 0.057, wR = 0.136 (R = 0.100, wR = 0.1518 for all data), GOF = 0.97.

Crystal data **5a**: $C_{90}H_{108}O_{24}$, M_r = 1573.76, colorless, 0.18 × 0.18 × 0.15 mm, triclinic, $P\bar{1}$, a = 15.6156(6),

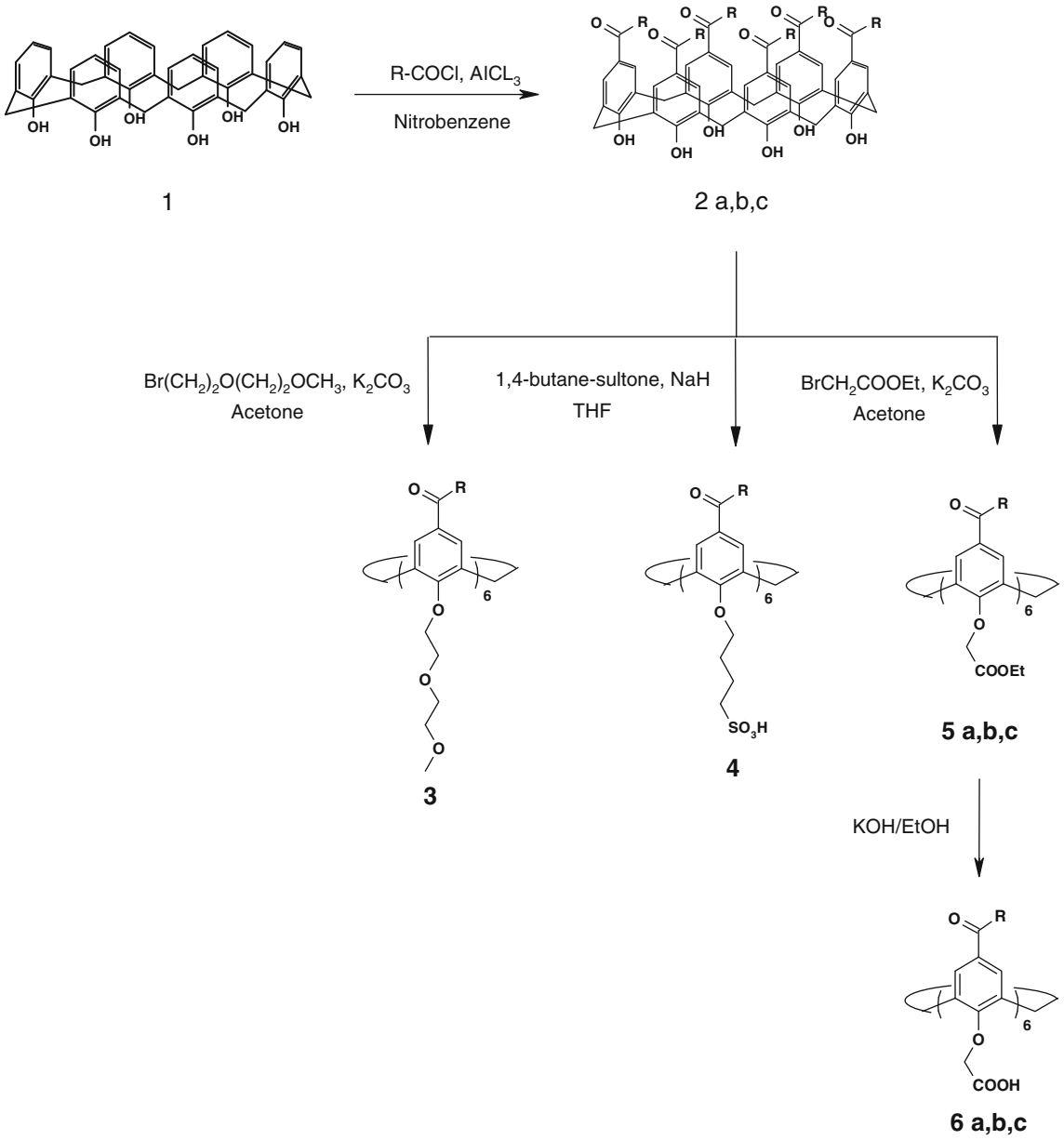
$b = 16.1077(6)$, $c = 18.6192(5)$ Å, $= 73.445(2)$, $\beta = 80.540(2)$, $\gamma = 70.099(1)°$, $V = 4209.3(3)$ Å^3, $Z = 2$, $\rho_{calc} = 1.283$ Mg/m^3, $\theta_{max} = 20.81°$, μ(Mo$K\alpha$) = 0.093 mm^{-1}, 17546 reflections collected, 8996 independent reflections, 6045 [$I > 2\sigma$ (I)]. $R = 0.087$, $wR = 0.213$ ($R = 0.129$, $wR = 0.235$ for all data), $GOF = 1.03$.

Crystal data for **5c**: $C_{122}H_{170}O_{29}$, $M_r = 2100.58$, colourless prism, 0.60 × 0.50 × 0.20 mm, triclinic, $P\bar{1}$, $a =$! 13.6346(10), $b = 17.8962(13)$, $c = 26.0386(18)$ Å, $\alpha = 70.839(3)$, $\beta = 78.043(3)$, $\gamma = 77.150(4)°$, $V = 5788.9(7)$ Å^3, $Z = 2$, $\rho_{calc} = 1.205$ Mg/m^3, $\theta_{max} = 24.7°$, μ(Mo$K\alpha$) = 0.085 mm^{-1} 136610 reflections collected, 19043 unique, 13008 [$I > 2\sigma$ (I)]. $R = 0.079$, $wR = 0.207$ ($R = 0.118$, $wR = 0.248$ for all data), $GOF = 1.02$.

Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 752129, 752130, 752131.

Results and discussion

The synthetic route to the *para*-acylcalix[6]arenes along with the routes to clean per-O-substitution are given in Scheme 1.



Scheme 1 Synthetic route to the *para*(acylcalix[6]arene derivatives, 3 and 3 are the octanoyl derivatives, **3c** and **4c**

The *para*-acyl compounds **2a–c**, a = butanoyl, b = hexanoyl and C = octanoyl, were prepared in good final yields, 73, 77 and 83%, respectively, by reacting the parent compound **1** with 9 equivalents of the corresponding acid chloride in nitrobenzene in the presence of 12 equivalents of aluminium trichloride at room temperature for 24 h. When esterification at the phenolic face also occurred, de-esterification was achieved in 100% yield by treatment of the ester with ethanolic-potassium hydroxide for 24 h.

The MALDI mass spectra show only a single peak, Fig. 1, corresponding to the fully acylated products. This is similar to the previously reported *para*-acylcalix[8]arene analogues, and confirms the utility of MALDI for the analysis of substitution reactions on the larger calix[*n*] arenes [23].

The ^{1}H NMR spectra show the Ar–CH_2–Ar methylenic protons as a broad peak in the region 3.9 ppm consistent with a conformationally flexible structure in solution. In the ^{13}C NMR the corresponding carbon atoms give rise to signals at 31 ppm and the C=O carbon atoms give a single peak at 199 ppm.

Treatment of **2a** with 10 equivalents of 1-bromo-2-(2-methoxyethoxy)ethane and 10 equivalents of K_2CO_3 in acetone under reflux yields the polar ethylene glycol derivative **3c,** denominated Long PEG in 62% yield. In the MALDI-TOF Mass Spectrum a single peak at 1247.7 mass units is observed confirming complete substitution at the phenolic face. In the ^{1}H NMR spectrum the terminal methyl group appears as a sharp triplet at 3.29 ppm, here the Ar–CH_2–Ar bridging methyelene protons are present as a broad peak at 3.88 ppm. In the ^{13}C NMR the carbonyl groups are present as a singlet at 199 ppm.

Treatment of **2a-c** with ethylbromoacetate, 10 equivalents and K_2CO_3, 10 equivalents under reflux in acetone for 48 h yields **5a-c** in yields of 62, 83 and 63%, respectively. All the compounds show a single peak in the MALDI-TOF Mass Spectrum corresponding to the fully O-substituted derivatives. In the ^{1}H NMR spectra the methyl groups are present at 1.19 and 0.95 ppm. Again there is a single peak for the C=O function at 199 ppm.

Alcoholysis of **5a-c** was achieved using KOH in ethanol/water(70/30) during 24 h to yield **6a-c**, the peak at 1.19 ppm has totally disappeared in the ^{1}H NMR spectra and here the terminal methyl groups of the cay chains are observed at 0.79 ppm. Again the MALDI-TOF Mass Spectra show single peaks corresponding to the per-carboxylic acid.

Compound **4c** containing an *O*-butyl-sulphonato function requires much more forcing conditions in the synthesis, **2c** is treated with sodium hydride (12 equivalents) in tetrahydrofuran under reflux for 20 min and then 1,4-butanesultone (12 equivalents) is added and the mixture refluxed for 48 h. After this period NaH (12 equivalents) and 1,4-butanesultone (12 equivalents) are again added to the reaction mixture which was heated under reflux during a further 48 h. After workup and freeze drying **4c** was obtained in 51% yield. The MALDI-TOF Mass Spectrum, is given in Fig. 2.

However, in a large number of cases substitution at the phenolic face does not occur, is incomplete with intractable mixtures of varying degree of substitution or is incomplete with clean disubstitution. In the case of the bromomethyl, bromoethyl or bromoproyl pthalamides no reaction occurs, this is also the case with all the activated compounds with three carbon atoms: for example ethylbromopropriate. For

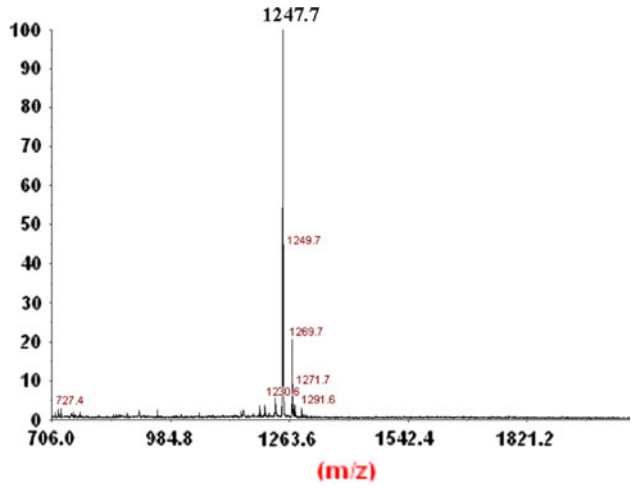


Fig. 1 MALDI-TOF Mass Spectrum for **2b**, the peak at 1247.7 correspond to M + Na^+

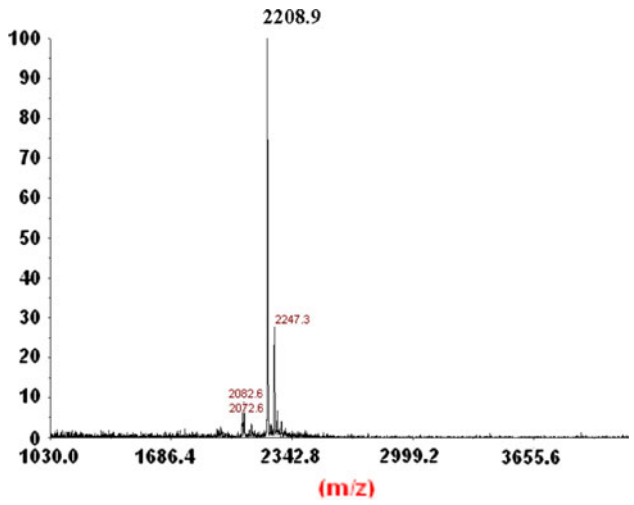


Fig. 2 MALDI-TOF Mass Spectrum of **4c** the peak at 2208.9 corresponds to M − H^+

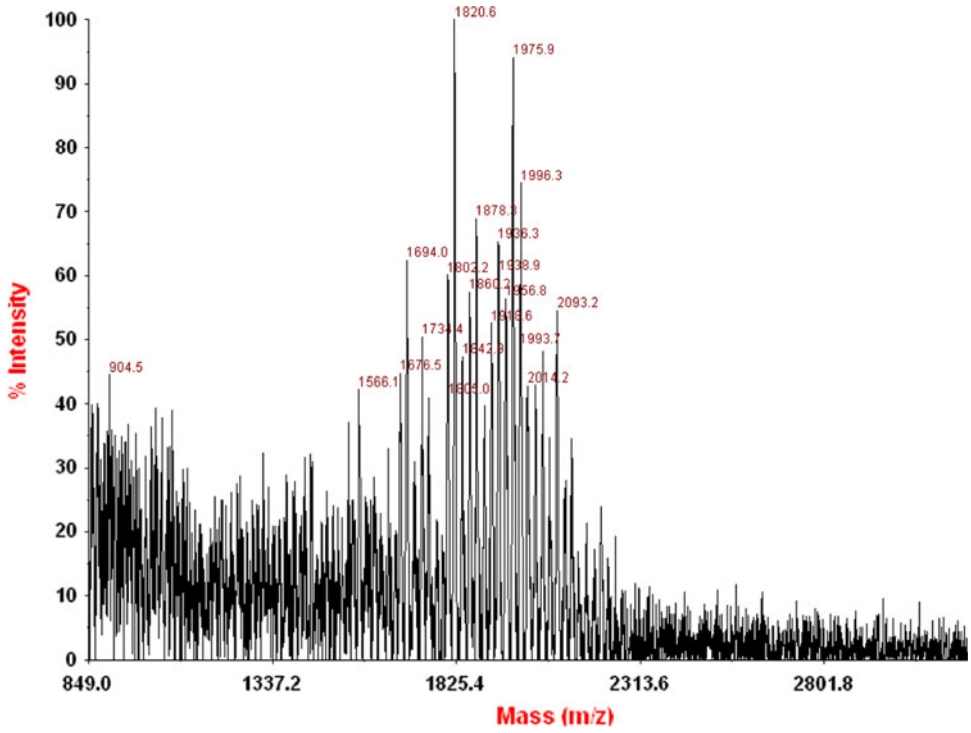


Fig. 3 MALDI-TOF Mass Spectrum for the reaction between *para*-octanoyl-calix[6]arene and bromoacetonitrile using K_2CO_3 as base

bromoacetonitrile or bromobutorynitrile only mixtures are obtained, Fig. 3. However for ethylbromobutyrate or 1,4-butanesultone using a weak base clean 1,4 disubstitution occurs.

Thus a somewhat chemically constrained route is available for clean substitution of the *para*-acylcalix[6]arenes, and this should open up the possibility by further substitution of introducing more complete moieties at the phenolic face of these compounds.

Solid state structures

The solid-state structures of **3c**, **5a**, and **5c** have been determined. All molecules are in the alternate cone conformation with two symmetry related sets of three aromatic rings pointing up and down, this corresponds to the conformation ***uo***, ***u***, ***d***, ***do***, ***d***, ***u*** as defined by Gutsche and coworkers [24] (see Fig. 7a). In the case of **3c** the conformation is stabilized by a number of C–H···O hydrogen bonds (2.48–2.72 Å), where the oxygen atoms belong to methoxydiethoxy (methyldiethylene glycol) groups (Fig. 4). In hexaethoxycarbonyl methoxy-calix[6]arenes **5a** and **5c** two of the ester groups are deeply included on the molecular cavity and two opposing aromatic groups lie parallel to each other. However, while the two aromatic rings are parallel they are not in close contact with a centroid to centroid distance of 10.77 and 10.50 Å in **5a**, 10.77 and 10.83 Å in **5c**. In contrast the two ester functions interact strongly (through the center of calixarene macrocycle!) with two C–H···O=C< hydrogen bonds of 3.25 and 3.24 Å C···O distance and >C=O···O=C< contacts of 3.63 and 3.55 Å in the structure of **5a**. The corresponding distances in **5c** equals to 3.15 and 3.03 Å for C–H···O=C< hydrogen bonds and 3.29 and 3.37 Å for carbonyl–carbonyl contacts (Figs. 5, 6).

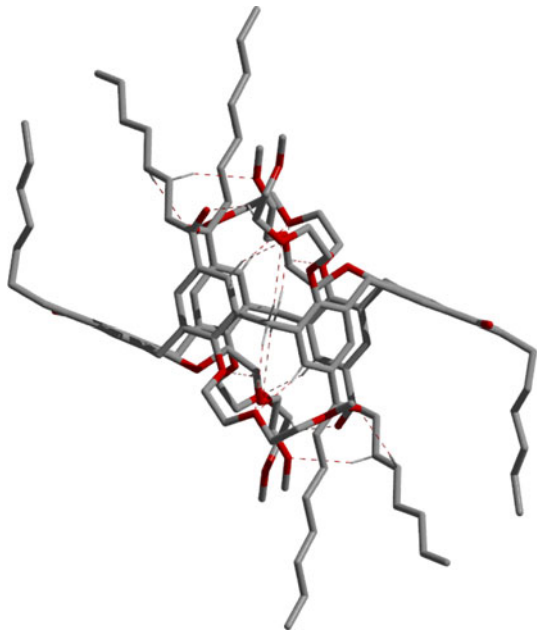


Fig. 4 Molecular structure of **3c** 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexa-methoxy-diethoxy -calix[6]arene. Intramolecular C–H···O hydrogen bonds are shown. The hydrogen atoms which do not participate in the hydrogen bonds are omitted

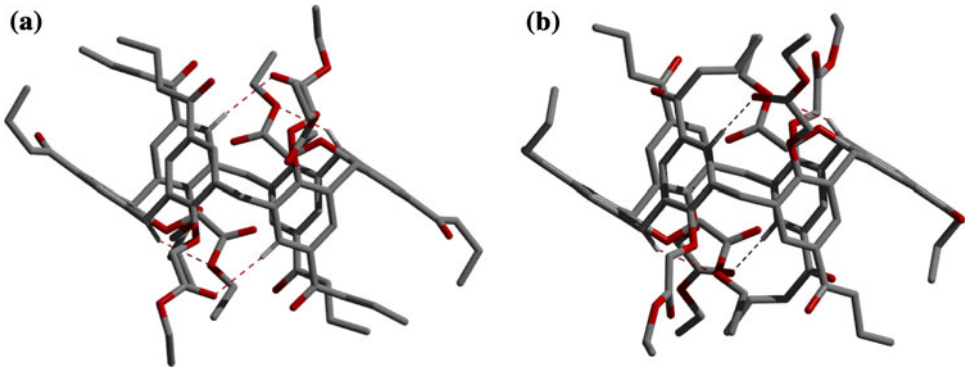


Fig. 5 The two independent molecules of **5a**; 5,11,17,23,29,35-hexa-butanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene

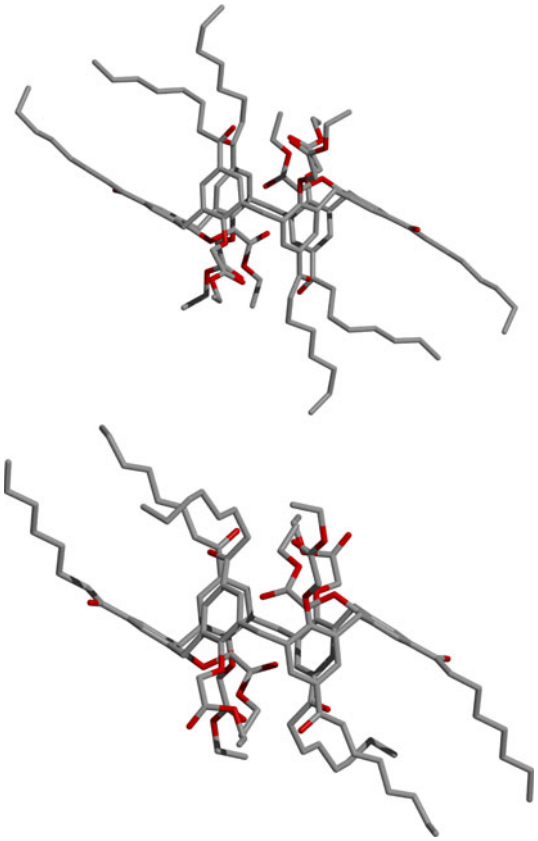


Fig. 6 The two independent molecules of **5c**; 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene

It is necessary to note that if calix[6]arene macrocycle conformations in all described structures are the same (***uo***, ***u***, ***d***, ***do***, ***d***, ***u***) [24], in the case of a crystallographically independent molecule of **5a** the ethoxycarbonylmethoxy groups are tilted in the opposite direction to that seen in all the other structures (Fig. 7 blue).

Intramolecular C–H···O interactions stabilize the calix[6]arene conformation while intermolecular interactions one strong and seven weaker (2.53 Å and other of about 2.70–2.72 Å, are responsible for layer formation as a 2D network in the *ab* plane, where layers have hydrophobic surfaces covered with alkyl chains which are combined into a 3D structure by hydrophobic chain interdigitation. The interpenetrating of neighbouring layers is shown in Fig. 8.

The packing of **5a** is shown in Fig. 9, and consists of two sets of columns arranged perpendicular to each other along the ***a*** and ***b*** axes, respectively. The intra column molecular spacings are 15.62 and 16.7 Å. Coherence in the columns is via short aromatic–aromatic contacts, 4.3 Å (Fig. 10).

As in the structure of **3c**, the molecules in **5c** aggregate into a layer structure. A molecule of $EtO_2CCH_2OCH_2$-CO_2Et is present in the crystal structure of the host and plays different roles. Firstly, it forms quite strong C–H···O hydrogen bonds about 2.41–2.66 Å with one of crystallographically independent molecules. Secondly, it loosens

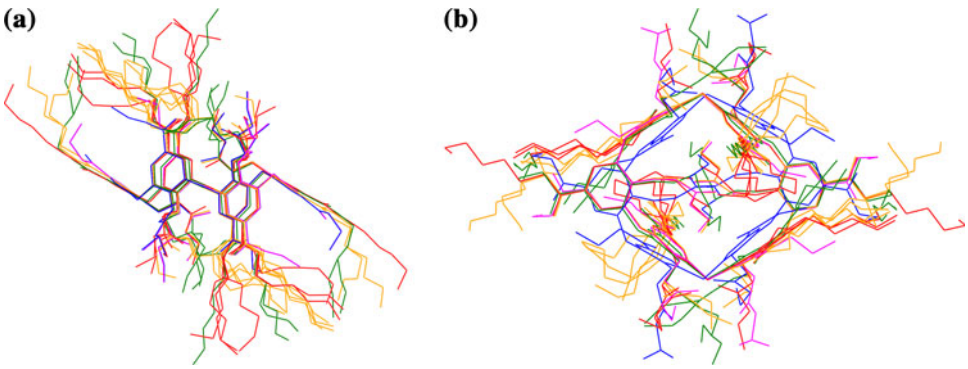


Fig. 7 Overlaid molecular structures of **3c**—*green*, **5a**—*magenta and blue*, and **5c**—*red and orange*. (Color figure online)

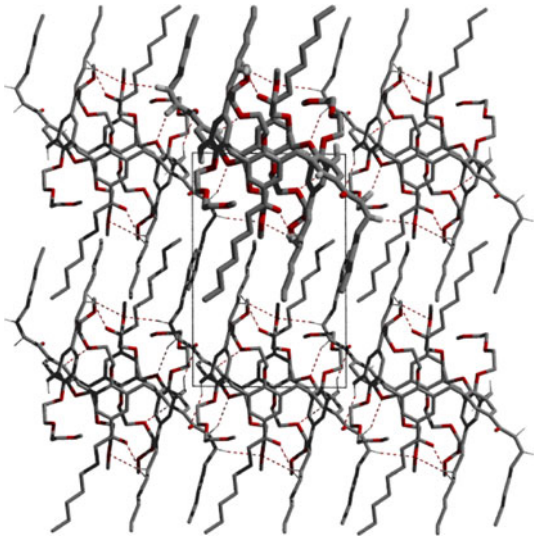


Fig. 8 Packing diagram for **3c**, 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexa-methoxy-diethoxy-calix[6]arene, view along *a* axis. Only intermolecular C–H···O hydrogen bonds are shown

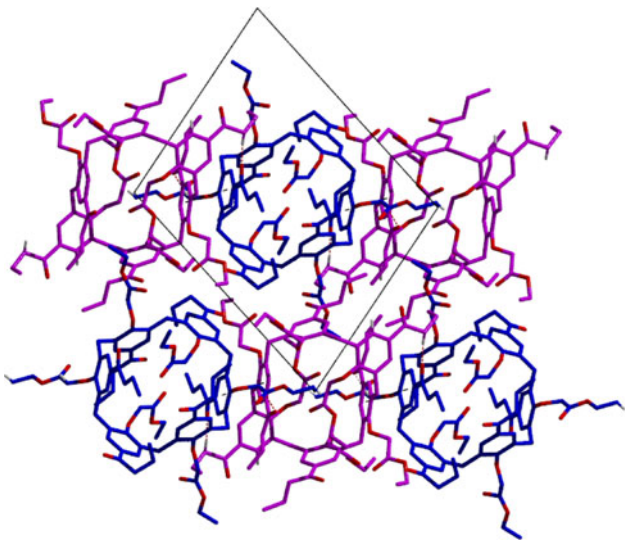


Fig. 9 Packing diagram for **5a**, 5,11,17,23,29,35-hexa-butanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene

the layers of the host molecules, so hydrogen atoms of long alkyl chains and ester groups can take part in strong and weak C–H···O hydrogen bonds not only in the *ac* plane (layer formation, 2.37–2.77 Å), but also in *b* axis direction (2.30–2.71 Å), as a result, a 3D network of hydrogen bonds is formed. The molecule of $EtO_2CCH_2OCH_2CO_2Et$ is undoubtedly formed by a hydrolysis of bromoethylacetate to hydroxyethylacetate followed by a Williamson coupling to a second molecule of bromoethylacetate, its presence is explained by the fact that the crystals grew directly from the reaction medium.

Interfacial assembly

The use of Langmuir compression isotherms provides information on the molecular areas, mechanical properties, phase changes and stabilities of monolayers of insoluble amphiphilic molecules at the air–water interface. In the experiment a known quantity of the amphiphilic molecule is spread as a solution in an immiscible solvent onto a water surface of a known area. The surface pressure is measured using a Wilhemy plate balance. The available area for the amphiphilic molecules is reduced by compressing with a movable Teflon barrier and the apparent molecular is measured as a function of the observed surface pressure.

The formation of monolayers was studied for the hexa-ester compounds **5a**, **5b** and **5c** and the hexa-acids **6a**, **6b** and **6c** and for comparison the *para*-octanoyl compounds **3c**, **5c** and **6c**. Compound **4c** does not yield a stable monolayer.

The surface pressure, π, versus apparent molecular area isotherms for **5a**, **5b** and **5c** are given in Fig. 11 and the plot of the compression modulus, Cs against π in Fig. S1 (see Supplementary Data) [25], Fig. 12 and Fig. S2 (see Supplementary Data), present the same information for the per-acid derivatives **6a**, **6b** and **6c**, for comparison in Fig. 13 and Fig. S3 (see Supplementary Data), are given the isotherms and Cs versus π data for **3a**, **5a** and **6a**. The isotherm data are summarized in Table 1. The values for A_{limit}, calculated by taking a tangent from the steepest part of the isotherm to a value of zero for π, are in the region 150 $Å^2$ which is in agreement with previously reported values [16–18], however the apparent A_{limit} observed for **6a** at 100 $Å^2$ is much lower than expected and may imply molecular folding due to intramolecular hydrogen bonding. For the series **6a–6c** there is an increase in the observed molecular area of about 30 $Å^2$ for the addition of two carbon atoms in the acyl chain length, the derived molecular radii are 5.44, 6.72 and 7.35 Å the difference of approximately 1 Å is not in agreement with the increase of about 2 Å expected for the increase in the chain length implying some tilt in the molecular orientation. There is no real difference in the collapse pressure π_c at around 37 mN/m for all the compounds this behaviour is the inverse of that observed for the *para*-acylcalix[4]arenes where the observed molecular area remains constant while the collapse pressure increases as a function of chain length. The use of Cs against π plots allows the identification of a phase change for **6b** at around 17 mN/m (see Supplementary Data).

For **5a**, **5b** and **5c** both observed molecular areas and collapse pressures increase with increasing chain length, the Cs against π plots allows confirmation that for **5a** and **5b** there exists a phase change at 22 mN/m for each

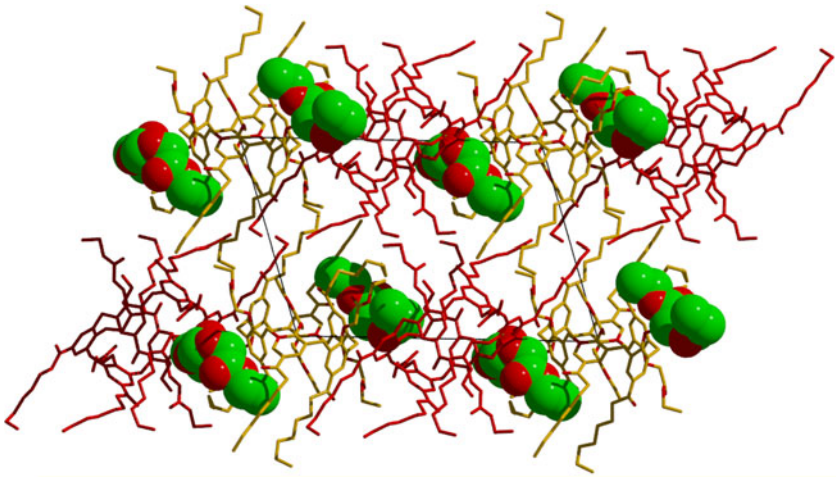


Fig. 10 Packing diagram for **5c**, 5,11,17,23,29,35-hexa-octanoyl-37,38,39,40,41,42-hexaethoxycarbonyl methoxy-calix[6]arene, view along *a* axis

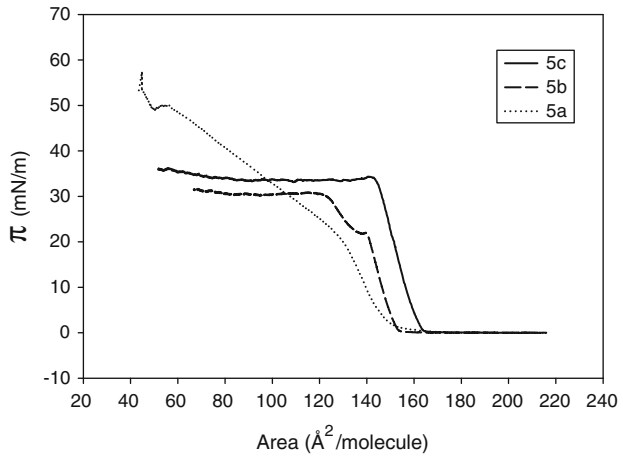


Fig. 11 Compression isotherms for the per-ester derivatives, **5a**, **5b** and **5c**

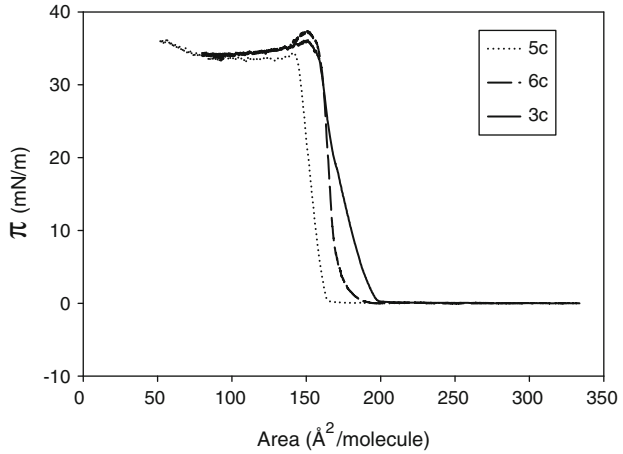


Fig. 12 Compression isotherms for the *para*-octanoyl derivatives **3c**, **5c** and **6c**

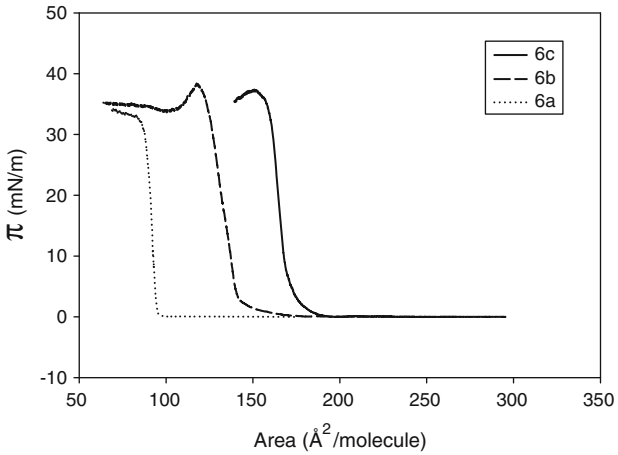


Fig. 13 Compression isotherms for the acid derivatives **6a**, **6b** and **6c**

Table 1 Monolayer data, π_c is the collapse pressure, A_{coll} collapse area, A_{lim} the limiting area defined from extrapolation of the isotherm, A_1 is the molecular area at 1 mN/m and A_0 is the molecular area at the point of non-zero pressure for compounds **3c**, **5a**, **5b**, **5c**, **6a**, **6b** and **6c**

	π_c (mN/m)	A_{coll} (Å^2)	A_{lim} (Å^2)	A_1 (Å^2)	A_0 (Å^2)
3c	35.7	149	191	195	209
5a	49.9	53	148	155	172
5b	30.4	121	151	153	160
5c	34.18	139.98	161	163	189
6a	33.3	82	93	95	105
6b	37.8	117	142	155	183
6c	37.3	152	170	182	195

derivative. The very small increase in the molecular areas as compared to those observed in the per-acid series **6a–c** suggest that the molecules **5a–c** of the per-ester series are arranged in a more perpendicular conformation with respect to the water surface.

For the series **3a**, **5a** and **6a** the chain length, at 4 carbon atoms is kept constant and the effect of changing the polar function studied, the least polar headgroup the ester

function in **5a** yields the lowest collapse pressure, while those of **3a**, with a di-ethylene glycol chain and **6a** with a carboxylic acid function are essentially the same.

Conclusion

A reasonable synthetic route to the *para*-acylcalix[6]arenes has been established, the per-O-derivatisation with certain activated halo-alkyl substituents has been demonstrated. The synthesis of the carboxylato derivatives opens up the possibility to use peptide coupling to generate a wider range of compounds. The compounds form stable monolayers at the air–water interface and may be useful for prodrug transport. Work is currently underway to investigate the interactions of the *para*-acylcalix[6]arene derivatives with phospholipids and other membrane constituents including membrane proteins.

Acknowledgements This research was partially supported by the Polish Ministry of Science and Higher Education (Grant 401/ERA-NET/2009), and the DGA and CNRS.

References

1. Steed, J.W., Atwood, J.L.: Supramolecular Chemistry, 2nd edn. Wiley, West Sussex (2009)
2. Gutsche, C.D.: Calixarenes: An Introduction. Royal Society of Chemistry, Cambridge (2008)
3. Perret, F., Lazar, A.N., Coleman, A.W.: Biochemistry of the *para*-sulfonato-calix[*n*]arenes. Chem. Commun. 2425–2438 (2006)
4. Coleman, A.W., Jebors, S., Shahgaldian, P., Ananchenko, G.S., Ripmeester, J.A.: *Para*-acyl calix[*n*]arenes: from molecular to macroscopic assemblies. Chem. Commun. 2291–2303 (2008)
5. Shinkai, S.N., Takeshi, I., Koji, I., Atsushi, H., He, G.X., Matsuda, T., Iwamoto, M.: Bull. Chem. Soc. Jpn. **64**, 381–386 (1991)
6. Shahgaldian, P., Cesario, M., Goreloff, P., Coleman, A.W.: *Para*-acyl calix[4]arenes: amphiphilic self-assembly from the molecular to the mesoscopic level. Chem. Commun. 326–327 (2002)
7. Ramon, G., Coleman, A.W., Nassimbeni, L.R.: Inclusion of terpenes by *para*-acyl calix[4]arenes. Cryst. Growth Des. **6**(1), 132–136 (2006)
8. Ananchenko, G.S., Udachin, K.A., Ripmeester, J.A., Perrier, T., Coleman, A.W.: Phototransformation of stilbene in van der Waals nanocapsules. Chem. Eur. J. **12**, 2441–2447 (2006)
9. Ananchenko, G.S., Moudrakovski, I.L., Coleman, A.W., Ripmeester, J.A.: A channel-free soft-walled capsular calixarene solid for gas adsorption. Angew. Chem. Int. Ed. **47**, 5616–5618 (2008)
10. Pojarova, M.A., Gennady, S., Udachin, K.A., Daroszewska, M., Perret, F., Coleman, A.W., Ripmeester, J.A.: Solid lipid nanoparticles of p-hexanoyl calix[4]arene as a controlling agent in the photochemistry of a sunscreen blocker. Chem. Mater. **18**, 5817–5819 (2006)
11. Bagryanskaya, E.G., Polovyanenko, D.N., Fedin, M.V., Kulik, L., Schnegg, A., Savitsky, A., Mobius, K., Coleman, A.W., Ananchenko, G.S., Ripmeester, J.A.: Multifrequency EPR study of the mobility of nitroxides in solid-state calixarene nanocapsules. Phys. Chem. Chem. Phys. **11**, 6700–6707 (2009)
12. Jebors, S.A., Gennady, S., Coleman, A.W., Ripmeester, J.A.: Synthesis and self-assembly properties of *para*-acyl-calix[8]arenes. Tetrahedron Lett. **48**, 5503–5506 (2007)
13. Jebors, S., Fache, F., Balme, S., Devoge, F., Monachino, M., Cecillon, S., Coleman, A.W.: Designer amphiphiles based on *para*-acyl-calix[8]arenes. Org. Biomol. Chem. **6**, 319–329 (2008)
14. Ghera, B.B., Qiongzhi, X., Leydier, A., Coleman, A.W.: *Para*-acyl calix[9]arenes: synthesis and interfacial assembly. J. Incl. Phenom. Macrocycl. Chem. **64**, 367–371 (2009)
15. Li, J.J., Janout, V., Regen, S.L.: Gluing Langmuir-Blodgett monolayers onto hydrocarbon surfaces. J. Am. Chem. Soc. **128**, 682–683 (2006)
16. Hendel, R.A.J., Janout, V., Lee, W., Regen, S.L.: Extraordinary cohesiveness of a boronic acid-based calix[6]arene monolayer at the air–water interface. Langmuir **12**, 5745–5746 (1996)
17. Conner, M.K., Ivo, K., Regen, S.L.: Octopus molecules at the air–water interface. Mechanical control over tentacle orientation. Langmuir **7**, 982–987 (1991)
18. Lo Nostro, P.C., Casnati, A., Bossoletti, L., Dei, L., Baglioni, P.: Complexation properties of calixarenes in Langmuir films at the water–air interface. Colloids Surf. B **116**, 203–209 (1996)
19. Bott, S.G., Coleman, A.W., Atwood, J.L.: Preparation and structure of the first complex of an early transition metal and a calixarene, calix[6]arene[TiCl2(μ-O)TiCl3]2. Chem. Commun. 610–611 (1986)
20. Chawla, H.M., Rahul, S.: Synthesis of novel cone-configurated hexa-tert-butyl-trimethoxy-calix[6]arenes bearing tris(bipyridyl) pendants and their use in recognition and ionic speciation. J. Incl. Phenom. Macrocycl. Chem. **64**, 255–263 (2009)
21. Over, D., de la Lande, A., Zeng, X., Parisel, O., Reinaud, O.: Replacement of a nitrogen by a phosphorus donor in biomimetic copper complexes: a surprising and informative case study with calix[6]arene-based cryptands. Inorg. Chem. **48**, 4317–4330 (2009)
22. Parker, D.: Macrocycle Synthesis: A Practical Approach. Oxford University Press, Oxford (1996)
23. Loiseau, F.A., Hill, A.M., Hii, K.K.M.: Replacement of a nitrogen by a phosphorus donor in biomimetic copper complexes: a surprising and informative case study with calix[6]arene-based cryptands. Tetrahedron **63**, 9947–9959 (2007)
24. Kanamathareddy, S., Gutsche, C.D.: Synthesis and conformational properties of calix[6]arenes bridged on the lower rim—self-anchored rotaxanes. J. Am. Chem. Soc. **115**, 6572–6579 (1993)
25. Hac-Wydro, K., Wydro, P., Jagoda, A., Kapusta, J.: The study on the interaction between phytosterols and phospholipids in model membranes. Chem. Phys. Lipids **150**, 22–34 (2007)