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ORIGINAL ARTICLE

Calix[n]arenes as components for the construction of micellar systems: synthesis and self-assembly properties of 5,11, 17-Tris[(dimethylamino)methyl]-25-monoalkoxy-26,27, 28-trihydroxycalix[4]arene derivatives

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Abstract A series of mono-*O*-alkylated calix [4] arenes derivatives, with alkyl chain lengths of between 1 and 12 carbon atoms are reported. Monoalkylation is best achieved using potassium carbonate as the weak base and the respective alkyl iodide for chain lengths of one to three carbon atoms and using caesium fluoride as the base and the respective alkyl iodide for longer chain lengths. The mono-alkylated derivatives were converted into the tri-*para*-dimethylaminomethylene derivatives by the *para*-quinonemethide reaction in good yields. Surface tension measurements showed that at pH 2, 4, 6 and 8 all the tri-dimethylaminomethylene derivatives showed surfactant behaviour, and at pH 2 all show a Critical Micellar Concentration values. No correlation between Critical Micellar Concentration values and chain length is observed. Dynamic Light Scattering measurements showed that the CMC behaviour may be correlated with the observed aggregate sizes. The solid state structure of mono-*O*-ethoxy-calix[4]arene is described, in this structure a 1-D inclusion polymer is observed.

Keywords Calix[n]arenes · Surfactants · Mono-substitution · Self-assembly · Crystal structure

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Introduction

The calix[n]arenes are a class of macrocycle organic host compounds widely studied for their complexation properties [1], they have been shown to complex molecules at sizes varying from metallic cations [2], anions [3], small organic molecules [4] through peptides [5] to proteins [6] and DNA [7]. As they possess two different chemistries: at the *para*-aromatic position and at the phenolic hydroxyl position, their selective chemical modification may be achieved [8], and hence groups with divergent chemical and physical properties may be readily introduced at either face.

The parent *para-tert*-butyl-calix[n]arenes have been shown to possess surfactant properties and their behaviour has been studied with regard to ion adsorption [9]. A wide range of amphiphilic calix[n]arene derivatives have been developed by modification at one or two faces.

Work by Regen et al. [10] showed that monolayers of calix [6] arene derivatives showed useful gas permeation properties. More recently, we have studied the surfactant and assembly behaviour of *para*-acyl-calix [4] arenes [11] and their di-phosphonate derivates both at the air-water interface [12] and as solid lipid nanoparticles, both as colloidal suspensions [13] and in the solid-state [14].

Fluorinated calix[n]arenes derivatives have been synthesised by Martin et al. [15] and their interfacial properties studied. Recent work performed by Micali et al. [16] has demonstrated vesicle-to-micelle transitions for glyco- and glycosaminoacid-calix[8]arenes, depending on the solution pH.

Interestingly, even the apparently apolar derivative *para*-H-calix[4]arene-*O*-dodecylether has been demonstrated to form stable monolayers at the air–water interface [17].

A comprehensive study of the interactions of soluble proteins with Langmuir films of varying amphiphilic calix[4]arenes derivatives has been undertaken by Schrader, demonstrating the capacity of such systems to detect proteins in the nano-molar range [18]. In order to further probe calix[n]arene protein interactions and to extend our knowledge of the biochemical properties of these molecules [6a, b], the design of modified amphiphilic calix[n]arenes for interaction with membrane proteins in micelles or other colloidal aggregates is of interest.

The geometry of molecules apt to aggregate in micellar structures requires a cone shape with the polar head group occupying the upper rim. In order to produce such a geometry based on a calix[4]arene skeleton, mono-*O*-alkylated derivatives would appear to be good targets. The synthesis of such molecules has been studied by Casnati et al. [19] via the 1–3 dialkoxy or tetraalkoxycalix[4]arenes followed by hydrolysis with respectively 1 or 3 equivalents of trimethylsilyl iodide. We have previously demonstrated mono-substitution of calix[4]arene using potassium carbonate as a base, however yields are very low, ca 10%. Kalchenko [20] has used sodium hydroxide as a base with DMSO as a solvent for mono-substitution. Work by Groenen et al. [21] showed that caesium fluoride or potassium fluoride could be used as suitable mono-alkylating agents. An interesting article by Cunningham et al. [22] showed that certain organic bases such as diaminobicycloundecane (DBU) could be used, with total selectivity to mono-deprotonate all the calix[n]arenes.

In this paper, we describe the synthesis and assembly properties of a series of dimethylaminomethylene-calix[4]arene-*O*-monoalkylethers in multi-gram quantities. These molecules were specifically designed to present the correct geometry for the polar head groups and the hydrophobic tails to yield micellar aggregates.

The formation of aggregates at pH values of 2, 4, 6 and 8 has been shown by surface tension and dynamic light scattering measurements. At pH 2, for all the molecules studied, the surface tension measurements yield curves which are typical of those obtained for micelle formation. The observed aggregate sizes are consistent with micellar and large aggregates being present in suspension.

Experimental

Calix[4]arene, **1** was synthesised as per the literature [23]. Iodoalkanes, were purchased from Sigma-Aldrich, NaH 60% from Acros Organics, and used without further purification. All solvents were distilled, under a nitrogen atmosphere, over the appropriate drying agent immediately prior to use. All reactions were carried out under nitrogen.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXP 300 instrument operating at 500 MHz and 125 MHz respectively. The chemical shifts are reported from an internal tetramethylsilane standard. The melting point determinations were performed on a Beotius apparatus and are uncorrected.

Surface tension measurements were carried out on a Kibron μ-trough. Dynamic Light Scattering measurements were carried out on a Malvern Nanosizer.

Synthesis

General procedures for mono-alkylation of calix[4]arene

Synthesis via Potassium Carbonate as base

A suspension of calix[4]arene, **1** (20 g, 0.47 mol), and K_2CO_3 (4 g) in acetonitrile (500 mL) was stirred at reflux temperature for 0.5 h. The relevant iodoalkane (3.5 mmol) was added after cooling and the reaction mixture was then heated, with stirring, under reflux during 60 h. After cooling the solvent was removed under reduced pressure. The remaining solid was taken up in CH_2Cl_2 (250 mL) and washed with 1N HCl (2 × 150 mL) and water (150 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a crude product. This contained in most cases some syn-1,3-disubstituted calix[4]arene as well as unsubstituted calix[4]arene, **1**. The latter was for a large part removed by taking up the crude product in ethyl acetate and filtering off unsubstituted calix[4]arene, **1.** After evaporation of the solvent the product was purified by column chromatography (CH_2Cl_2/petroleum ether 3:1).

Synthesis via Cesium Fluoride as base

To a suspension of calix[4]arene **1** (20 g, 0.47 mol) in dry DMF (943 ml) were added a solution of CsF (8.49 g, 1.2 equiv) and the relevant iodoalkane (10 equiv). The reaction mixture was stirred at 40 °C for 96 h. The progress of the reaction was following by TLC and after completion the reaction was quenched with 1M Hydrochloric Acid (250 mL). The reaction mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with water (2 × 250 mL) and dried with $MgSO_4$. After evaporation of the solvent the remaining crude product was taken up in CH_2Cl_2/MeOH (1:1). The solution was filtered to remove unreacted calix[4]arene, the crude product is purified by column chromatography (CH_2Cl_2/hexane 1:1).

The calix[4]arenes **2a** and **2b** were synthesised using Potassium Carbonate as the base and the calix[4]arenes **2c–k** were synthesised using Cesium Fluoride as the base.

General procedures for the synthesis Tris-[(dimethylamino) methyl] monoalkyl tris-hydroxycalix[4]arene of **3a–k**

In a cooled round bottom flask, are placed 10 g of monoalkyl-tris hydroxycalix[4]arene in 230 mL of THF, to which were added 30 mL of acetic acid, 8 equivalents of 40% aqueous dimethylamine, and 8 equivalents of 35% aqueous formaldehyde. The reaction mixture was stirred for 72 h at room temperature; the progress of the reaction is followed by TLC (CH_2Cl_2 /Hexane 1:1). The THF was evaporated, and the residue was treated with 200 mL water. The aqueous solution was extracted two times with 150 mL of diethyl ether and neutralized with 10% K_2CO_3 solution. The product was collected by filtration and dried under vacuum and recrystallized from chloroform to give the compound.

*25-Methyloxycalix[4]arene (**2a**)*

White solid, yield = 67%, m.p. > 250 °C; ES mass spectrum (3MeOH:2$CHCl_3$: 1%HCOOH) *m/z*: 439.2 $[M + H]^+$, 460.0 $[M + Na]^+$, 477.1 $[M + K]^+$. NMR values conform to those in the literature [20].

*25-Ethyloxycalix[4]arene (**2b**)*

White solid, was prepared in 70% yield by procedure described for (**2a**). m.p. > 250 °C; ES mass spectrum (3MeOH:2$CHCl_3$: 1%HCOOH) m/z: 453.2 $[M + H]^+$, 475.1 $[M + Na]^+$, 491.1 $[M + K]^+$. NMR values conform to those in the literature [21].

Crystal data and structure refinement details of **2b**

	2b
Empirical formula	$C_{30}H_{28}O_4 \cdot 0.5(C_7H_8)$
Formula weight	498.59
Temperature (K)	100(2)
Diffractometer	Bruker AXS KappaApexII
Wavelength (Å)	0.71073
Crystal	colourless
Crystal size (mm^3)	0.18 × 0.15 × 0.03
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimension	
a (Å)	6.6495(4)
b (Å)	19.6324(9)
c (Å)	19.7686(9)
α (°)	90
β (°)	89.963(3)
γ (°)	90
Volume ($Å^3$)	2580.7(2)
Z	4
Calculated density (g cm^{-3})	1.283
F(000)	1060
Absorption coefficient (mm^{-1})	0.083
θ Range for data collection (°)	2.92–23.53
hkl ranges	$-7 \le h \le 7$, $-22 \le k \le 22$, $-22 \le l \le 21$
Reflections collected/unique	14970/3799
Completeness (%) to θ	99.0/23.53
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3799/0/376
Goodness-of-fit on F^2	1.14
Final *R* indices [$I > 2\sigma(I)$]	$R = 0.057$, $wR = 0.102$
R indices (all data)	$R = 0.085$, $wR = 0.110$

*25-Propyloxycalix[4]arene (**2c**)*

White solid, yield 69%, m.p. > 250 °C; ES mass spectrum (3MeOH:2$CHCl_3$: 1%HCOOH) m/z: 467.3 $[M + H]^+$, 489.1 $[M + Na]^+$, 505.0 $[M + K]^+$. NMR values conform to those in the literature.

*25-Butyloxycalix[4]arene (**2d**)*

Yellow solid, was prepared in 68% yield by procedure (**2c**), m.p = 239 °C; ES mass spectrum (3MeOH:2$CHCl_3$: 1%HCOOH) m/z: 481.2 $[M + H]^+$, 503.3 $[M + Na]^+$, 519.2 $[M + K]^+$. NMR values conform to those in the literature [20].

*25-Pentyloxycalix[4]arene (**2e**)*

White solid, yield 62%, m.p = 239 °C; **^{1}H NMR** ($CDCl_3$) δ 1.15 (t, 3H, $^3J_{H-H}$ = 7.3 Hz, Ar–O$(CH_2)_4C\boldsymbol{H_3}$), 1.61 (m, 2H, Ar–O$(CH_2)_3C\boldsymbol{H_2}CH_3$), 1.71 (m, 2H, Ar–O$(CH_2)_2C\boldsymbol{H_2}CH_2CH_3$), 2.20 (m, 2H, Ar–O$CH_2C\boldsymbol{H_2}(CH_2)_2CH_3$), 3.50 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–C$\boldsymbol{H_2}$–Ar), 4.01 (t, 2H, $^3J_{H-H}$ = 7.0 Hz,

Ar–OC***H₂***$(CH_2)_3CH_3$), 4.16 (d, 2H, $^2J_{H–H} = 13.5$ Hz, Ar–C***H₂***–Ar), 4.36 (d, 2H, $^2J_{H–H} = 12.3$ Hz, Ar–C***H₂***–Ar), 6.68–7.08 (m, Ar–***H***), 9.45 (s, 2H, Ar–O***H***), 9.76 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.4 (Ar–$O(CH_2)_4$***C***H_3), 22.8 (Ar–$O(CH_2)_3$***C***H_2CH_3), 28.3 (Ar–$O(CH_2)_2$***C***$H_2CH_2CH_3$), 29.8 (Ar–OCH_2***C***$H_2(CH_2)_2CH_3$), 31.8 and 32.2 (Ar–***C***H_2–Ar), 77.7 (Ar–O***C***$H_2(CH_2)_3CH_3$), 121.2; 122.2; 122.5; 126.4; 128.7; 129.1; 129.2; 129.3; 129.6; 133.7; 134.5 (Ar), 151.1 and 151.8 (Ar***C***–OH), 153.6 (Ar***C***–$O(CH_2)_4CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 495.1 $[M + H]^+$, 517.1 $[M + Na]^+$, 533.0 $[M + K]^+$.

*25-Hexyloxycalix[4]arene (**2f**)*

White solid, yield 72%, m.p = 238 °C; **^{1}H NMR** ($CDCl_3$) δ 0.98 (t, 3H, $^3J_{H–H} = 7.0$ Hz, Ar–$O(CH_2)_5$C***H₃***), 1.48 (m, 4H, Ar–$O(CH_2)_3$C***H₂***C***H₂***CH_3), 1.62 (Ar–$O(CH_2)_2$C***H₂***$(CH_2)_2CH_3$), 2.15 (m, 2H, Ar–OCH_2C***H₂***$(CH_2)_3CH_3$), 3.45 (d, 4H, $^2J_{H–H} = 13.2$ Hz, Ar–C***H₂***–Ar), 4.14 (t, $^3J_{H–H} = 6.9$ Hz, Ar–OC***H₂***$(CH_2)_4CH_3$), 4.26 (d, 2H, $^2J_{H–H} = 13.1$ Hz, Ar–C***H₂***–Ar), 4.36 (d, 2H, $^2J_{H–H} = 13.3$ Hz, Ar–C***H₂***–Ar), 6.62–7.20 (m, 12H, Ar–***H***), 9.41 (s, 2H, Ar–O***H***), 9.80 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 Ar–$O(CH_2)_5$***C***H_3), 22.8 (Ar–$O(CH_2)_4$***C***H_2CH_3), 25.8 (Ar–$O(CH_2)_3$***C***$H_2CH_2CH_3$), 30.1 (Ar–$O(CH_2)_2$***C***$H_2(CH_2)_2CH_3$), 31.6 (Ar–OCH_2***C***H_2 $(CH_2)_3CH_3$), 31.8 and 32.0 (Ar–***C***H_2–Ar), 77.6 (Ar–O***C***H_2 $(CH_2)_4CH_3$), 121.0; 122.1; 122.4; 125.4; 128.3; 128.4; 128.6; 128.9; 129.1; 129.4; 133.6; 134.4 (Ar), 149.4 and 150.9 (Ar***C***–OH), 151.6 (Ar***C***–$O(CH_2)_5CH_3$). ES mass spectrum (3 MeOH:2 $CHCl_3$: 1%HCOOH) m/z: 509.1 $[M + H]^+$, 531.2 $[M + Na]^+$.

*25-Heptyloxycalix[4]arene (**2g**)*

White solid, yield 61%, m.p = 237 °C; **^{1}H NMR** ($CDCl_3$) δ 0.92 (t, 3H, $^3J_{H–H} = 7.1$ Hz, Ar–$O(CH_2)_6$C***H₃***), 1.37 (m, 4H, (Ar–$O(CH_2)_4$C***H₂***C***H₂***CH_3), 1.38 (m, 2H, Ar–$O(CH_2)_3$C***H₂*** $(CH_2)_2CH_3$), 1.61 (m, 2H, Ar–$O(CH_2)_2$C***H₂***$(CH_2)_3CH_3$), 2.15 (m, 2H, (Ar–OCH_2C***H₂***$(CH_2)_4CH_3$), 3.44 (d, 4H, $^2J_{H–H} =$ 13.2 Hz, Ar–C***H₂***–Ar), 4.11 (t, 2H, $^3J_{H–H} = 6.9$ Hz, Ar–OC***H₂***$(CH_2)_5CH_3$), 4.23 (d, 2H, $^2J_{H–H} = 13.2$ Hz, Ar–C***H₂***–Ar), 4.26 (d, 2H, $^2J_{H–H} = 12.9$ Hz, Ar–C***H₂***–Ar), 6.64–706 (m, 12H, Ar–***H***), 9.40 (s, 2H, Ar–O***H***), 9.70 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 (Ar–$O(CH_2)_6$***C***H_3), 22.8 (Ar–$O(CH_2)_5$***C***H_2CH_3), 26.0 (Ar–$O(CH_2)_4$***C***$H_2CH_2CH_3$), 29.3 (Ar–$O(CH_2)_3$***C***$H_2(CH_2)_2CH_3$), 30.0(Ar–$O(CH_2)_2$***C***H_2 $(CH_2)_3CH_3$), 331.6 (Ar– OCH_2***C***$H_2(CH_2)_4$***C***H_3), 31.9 and 32.1 (Ar–***C***H_2–Ar), 77.7 (Ar–O***C***$H_2(CH_2)_5CH_3$), 121.1; 122.1; 122.4; 126.2; 128.4; 128.6; 128.9; 129.1; 129.4; 134.4 (Ar), 149.4 and 150.9 (Ar***C***–OH), 151.6 (Ar***C***–$O(CH_2)_6CH_3$). ES mass spectrum (3MeOH:2$CHCl_3$: 1% HCOOH) m/z: 523.3 $[M + H]^+$, 545.2 $[M + Na]^+$, 561.0 $[M + K]^+$.

*25-Octyloxycalix[4]arene (**2h**)*

White solid, yield 62%, m.p = 237 °C; **^{1}H NMR** ($CDCl_3$) δ 0.92 (t, 3H, $^3J_{H–H} = 7.0$ Hz, Ar–$O(CH_2)_7$C***H₃***), 1.36 (m, 4H, Ar–$O(CH_2)_5$C***H₂***C***H₂***CH_3), 1.37, (m, 2H, Ar–$O(CH_2)_4$C***H₂*** $(CH_2)_2CH_3$), 1.44 (m, 2H, Ar–$O(CH_2)_3$C***H₂***$(CH_2)_3CH_3$), 1.68 (m, 2H, Ar–$O(CH_2)_2$C***H₂***$(CH_2)_4CH_3$), 2.17 (m, 2H, Ar–OCH_2C***H₂***$(CH_2)_5CH_3$), 3.47 (d, 4H, $^2J_{H–H} = 13.1$ Hz, Ar–C***H₂***–Ar), 4.15 (t, 2H, $^3J_{H–H} = 7.1$ Hz, Ar–OC***H₂*** $(CH_2)_6CH_3$), 4.28 (d, 2H, $^2J_{H–H} = 13.2$ Hz, Ar–C***H₂***–Ar), 4.37 (d, 2H, $^2J_{H–H} = 13.2$ Hz, Ar–CH_2–Ar), 6.65–709 (m, 12H, Ar–***H***), 9.43 (s, 2H, Ar–O***H***), 9.74 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 (Ar–$O(CH_2)_7$***C***H_3), 22.9 (Ar–$O(CH_2)_6$***C***H_2CH_3), 26.1 (Ar–$O(CH_2)_5$***C***$H_2CH_2CH_3$), 29.4 (Ar–$O(CH_2)_4$***C***$H_2(CH_2)_2CH_3$), 29.6 (Ar–$O(CH_2)_3$***C***$H_2(CH_2)_3$ CH_3), 30.0 (Ar–$O(CH_2)_2$***C***$H_2(CH_2)_4CH_3$), 31.6 (Ar–OCH_2***C***$H_2(CH_2)_5CH_3$), 31.8 and 32.1 (Ar–***C***H_2–Ar), 77.7 (Ar–O***C***$H_2(CH_2)_6CH_3$), 121.1; 122.1; 122.4; 126.2; 128.4; 128.6; 128.9; 129.0; 129.1; 129.5; 134.4 (Ar), 149.4 and 150.9 (Ar***C***–OH), 151.6 (Ar***C***–$O(CH_2)_7CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 537.1 $[M + H]^+$, 559.1 $[M + Na]^+$, 575.1 $[M + K]^+$.

*25-Nonyloxycalix[4]arene (**2i**)*

White solid, yield 51%, m.p = 236 °C; **^{1}H NMR** ($CDCl_3$) δ 0.88 (t, 3H, $^3J_{H–H} = 6.9$ Hz, Ar–$O(CH_2)_8$C***H₃***), 1.34 (m, 4H, Ar–$O(CH_2)_6$C***H₂***C***H₂***CH_3), 1.36 (m, 2H, Ar–$O(CH_2)_5$C***H₂*** $(CH_2)_2CH_3$), 1.38 (m, 2H, Ar–$O(CH_2)_4$C***H₂***$(CH_2)_3CH_3$), 1.41 (m, 2H, Ar–$O(CH_2)_3$C***H₂***$(CH_2)_4CH_3$), 1.66 (m, 2H, Ar–$O(CH_2)_2$C***H₂***$(CH_2)_5CH_3$), 2.15 (m, 2H, Ar–OCH_2C***H₂*** $(CH_2)_6CH_3$), 3.43 (d, 4H, $^2J_{H–H} = 12.8$ Hz, Ar–C***H₂***–Ar), 4.13 (t, 2H, $^3J_{H–H} = 7.1$ Hz, Ar–OC***H₂***$(CH_2)_7CH_3$), 4.22 (d, 2H, $^2J_{H–H} = 12.9$ Hz, Ar–C***H₂***–Ar), 4.34 (d, 2H, $^2J_{H–H} =$ 12.9 Hz, Ar–C***H₂***–Ar), 6.63–7.07 (m, 12H, Ar–H), 9.41 (s, 2H, Ar–O***H***), 9.71 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 (Ar–$O(CH_2)_8$***C***H_3), 22.9 (Ar–$O(CH_2)_7$***C***H_2CH_3), 26.1 (Ar–$O(CH_2)_6$***C***$H_2CH_2CH_3$), 29.4 (Ar–$O(CH_2)_5$***C***$H_2(CH_2)_2$ CH_3), 29.6 (Ar–$O(CH_2)_4$***C***$H_2(CH_2)_3CH_3$), 29.7 (Ar–$O(CH_2)_3$***C***$H_2(CH_2)_4CH_3$), 30.1 (Ar–$O(CH_2)_2$***C***$H_2(CH_2)_5$ CH_3), 31.5 (Ar–OCH_2***C***$H_2(CH_2)_6CH_3$), 31.8 and 32.1 (Ar–***C***H_2–Ar), 77.7 (Ar–O***C***$H_2(CH_2)_7CH_3$), 121.1; 122.1; 122.4; 126.2; 128.4; 128.6; 128.9; 129.1; 129.5; 134.4 (Ar), 148.9 and 149.4 (Ar***C***–OH), 150.9 (Ar***C***–$O(CH_2)_8CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 551.3 $[M + H]^+$, 573.2 $[M + Na]^+$, 589.1 $[M + K]^+$.

*25-Decyloxycalix[4]arene (**2j**)*

White solid, yield 57%, m.p = 236 °C; **^{1}H NMR** ($CDCl_3$) δ 0.94 (t, 3H, $^3J_{H-H}$ = 6.8 Hz, Ar–O(CH_2)$_9$C***H*****$_3$**), 1.33 (m, 4H Ar–O(CH_2)$_7$C***H*****$_2$**C***H*****$_2$**CH_3), 1.36 (m, 2H, Ar–O(CH_2)$_6$C***H*****$_2$** (CH_2)$_2$$CH_3$), 1.39 (m, 2H, Ar–O($CH_2$)$_5$C***H*****$_2$**($CH_2$)$_3$$CH_3$), 1.46 (m, 2H, Ar–O($CH_2$)$_4$C***H*****$_2$**($CH_2$)$_4$$CH_3$), 1.54 (m, 2H, Ar–O($CH_2$)$_4$C***H*****$_2$**($CH_2$)$_4$$CH_3$), 1.74 (m, 2H, Ar–O($CH_2$)$_3$C***H*****$_2$** ($CH_2$)$_6$$CH_3$), 2.23 (m, Ar–OC$H_2$C***H*****$_2$**($CH_2$)$_7$$CH_3$), 3.53 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 4.20 (t, 2H, $^3J_{H-H}$ = 6.9 Hz, Ar–OC***H*****$_2$**(CH_2)$_8$$CH_3$), 4.32 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 4.41 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 6.71–7.14 (m, 12H, Ar–***H***), 9.49 and 9.81 (Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 (Ar–O(CH_2)$_9$***C***H_3), 22.9 (Ar–O(CH_2)$_8$***C***H_2CH_3), 26.1 Ar–O(CH_2)$_7$***C***$H_2CH_2CH_3$), 29.5 (Ar–O(CH_2)$_6$***C***H_2(CH_2)$_2$$CH_3$), 29.6 (Ar–O($CH_2$)$_5$***C*****H$_2$** ($CH_2$)$_3$$CH_3$), 29.7 (Ar–O($CH_2$)$_4$***C***$H_2$($CH_2$)$_4$$CH_3$), 30.0 (Ar–O($CH_2$)$_3$***C***$H_2$($CH_2$)$_5$$CH_3$), 31.6 (Ar–O($CH_2$)$_2$***C***$H_2$ (CH_2)$_6$$CH_3$), 31.8 (Ar–OC$H_2$***C***$H_2$($CH_2$)$_7$$CH_3$), 32.0 and 32.1 (Ar–***C***H_2–Ar), 77.6 (Ar–O***C***H_2(CH_2)$_9$$CH_3$), 121.0; 122.1; 122.4; 126.2; 128.4; 128.5; 128.6; 128.9; 129.1; 129.4; 134.4 (Ar), 149.4and 150.9 (Ar***C***–OH), 151.6 (Ar***C***–O (CH_2)$_9$$CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 564.1 $[M + H]^+$, 577.2 $[M + Na]^+$, 603.1 $[M + K]^+$.

*25-Dodecyloxycalix[4]arene (**2k**)*

White solid, yield 48%, m.p = 234 °C; **^{1}H NMR** ($CDCl_3$) δ 1.01 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, Ar–O(CH_2)$_{11}$C***H*****$_3$**), 1.42 (m, 4H, Ar–O(CH_2)$_8$C***H*****$_2$**C***H*****$_2$**CH_3), 1.49 (m, 4H, Ar–O(CH_2)$_7$C***H*****$_2$** C***H*****$_2$**(CH_2)$_2$$CH_3$), 1.53 (m, 4H, Ar–O($CH_2$)$_5$C***H*****$_2$**C***H*****$_2$**($CH_2$)$_4$ CH_3), 1.62 (m, 4H, Ar–O(CH_2)$_3$C***H*****$_2$**C***H*****$_2$**(CH_2)$_6$$CH_3$), 1.80 (m, 2H, Ar–O($CH_2$)$_2$C***H*****$_2$**($CH_2$)$_8$$CH_3$), 2.29 (m, 2H, Ar–OC$H_2$C***H*****$_2$**($CH_2$)$_9$$CH_3$), 3.57 (d, 4H, $^2J_{H-H}$ = 13.3 Hz, Ar–C***H*****$_2$**–Ar), 4.26 (t, 2H, $^3J_{H-H}$ = 6.8 Hz, Ar–OC***H*****$_2$** (CH_2)$_{10}$$CH_3$), 4.39 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 4.48 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 6.77–7.18 (m, 12H, Ar–***H***), 9.57 (s, 2H, Ar–O***H***), 9.88 (s, 1H, Ar–O***H***). **^{13}C NMR** ($CDCl_3$) δ 14.3 (Ar–O(CH_2)$_{11}$***C***H_3), 22.9 (Ar–O(CH_2)$_{10}$***C***H_2CH_3), 26.1 (Ar–O(CH_2)$_9$***C***$H_2CH_2CH_3$), 29.6 (Ar–O(CH_2)$_8$***C***H_2(CH_2)$_2$$CH_3$), 29.7 (Ar–O($CH_2$)$_7$***C***$H_2$($CH_2$)$_3$ CH_3), 29.8 (Ar–O(CH_2)$_7$***C***H_2(CH_2)$_4$$CH_3$), 29.8 (Ar–O($CH_2$)$_5$ ***C***H_2(CH_2)$_5$$CH_3$), 29.9 (Ar– O($CH_2$)$_4$***C***$H_2$($CH_2$)$_6$$CH_3$), 30.1 (Ar–O($CH_2$)$_3$***C***$H_2$($CH_2$)$_7$$CH_3$), 31.6 (Ar–O($CH_2$)$_2$***C***$H_2$($CH_2$)$_8$ CH_3), 31.8 (Ar–OCH_2***C***H_2(CH_2)$_8$$CH_3$), 32.1 and 32.2 (Ar–***C***H_2–Ar), 77.7 (Ar–O***C***H_2(CH_2)$_{10}$$CH_3$) 121.1; 122.1; 122.4; 126.2; 128.4; 128.6; 128.9; 129.1; 129.5; 134.4 (Ar), 149.4 and 151.0 (Ar***C***–OH), 151.6 (Ar***C***–O(CH_2)$_{11}$$CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 593.2 $[M + H]^+$, 615.2 $[M + Na]^+$, 631.3 $[M + K]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monometyloxy 26,27,28 tris hydroxycalix[4]arene (**3a**)*

White solid, was prepared in 76%, m.p = 170 °C, **^{1}H NMR** (DMSO) δ 2.10 (sl, 18H, Ar–CH_2–N(C***H*****$_3$**)$_2$), 3.14 (d, 4H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H*****$_2$**–Ar), 3.18 (s, 6H, Ar–C***H*****$_2$**–N(CH_3)$_2$), 3.63 (s, 3H, Ar–OC***H*****$_3$**), 4.02 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H*****$_2$**–Ar), 4.41 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H*****$_2$**–Ar), 6.45 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***), 6.50 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.81 (s, 3H, Ar–***H***), 6.90 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 30.6 and 34.6 (Ar–***C***H_2–Ar), 45.1 (Ar–CH_2–N(***C***H_3)$_2$), 63.7 (Ar–***C***H_2N(CH_3)$_2$), 79.7 (Ar–O***C***H_3), 121.7; 123.0; 126.3; 128.3; 128.6; 129.0; 129.2; 129.7; 130.3; 133.9 (Ar), 155.2 and 157.3 (Ar***C***–OH), 160.6 (Ar***C***–OCH_3). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 610.4 $[M + H]^+$, 648.2 $[M + K]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monoethyloxy 26,27,28 tris hydroxycalix[4]arene (**3b**)*

White solid, yield 72%, m.p = 169 °C, **^{1}NMR** (DMSO) δ 1.30 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, Ar–OCH_2C***H*****$_3$**), 2.02 (s, 18H, Ar–CH_2–N(C***H*****$_3$**)$_2$), 3.10 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 3.14 (s, 6H, Ar–C***H*****$_2$**–N(CH_3)$_2$), 3.51 (q, 2H, ArOC***H*****$_2$**CH_3), 4.01 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 4.42 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 6.62 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***), 6.64 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.71 (s, 3H, Ar–***H***), 6.87 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 15.8 (Ar–OCH_2***C***H_3), 31.0 and 34.8 (Ar–***C***H_2–Ar), 45.5 (Ar–CH_2–N(***C***H_3)$_2$), 64.3 (Ar–***C***H_2–N(CH_3)$_2$), 71.5 (Ar–O***C***H_2CH_3), 123.0; 124.3; 127.0; 128.6; 130.8; 134.5; 136.9 (Ar), 154.6 and 156.0 (Ar***C***–OH), 160.0 (Ar***C***-OCH_2CH_3). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 624.1 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monopropyloxy 26,27,28 tris hydroxycalix[4]arene (**3c**)*

White solid, yield 75%, m.p = 170 °C; **^{1}H NMR** (DMSO) δ 1.07 (t, 3H, $^3J_{H-H}$ = 6.9 Hz, Ar–OCH_2CH_2C***H*****$_3$**), 1.72 (m, 2H, Ar–OCH_2C***H*****$_2$**CH_3), 2.04 (s, 18H, Ar–CH_2–N(C***H*****$_3$**)$_2$), 3.14 (d, 4H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H*****$_2$**–Ar), 3.17 (s, 6H, Ar–C***H*****$_2$**–N(CH_3)$_2$), 3.69 (t, 2H, $^3J_{H-H}$ = 7.1 Hz, Ar–OC***H*****$_2$**CH_2CH_3), 4.02 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 4,45 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H*****$_2$**–Ar), 6.59 (t, 1H, $^3J_{H-H}$ = 7.6 Hz, Ar–***H***), 6.63 (d, 2H, $^3J_{H-H}$ = 7.4 Hz, Ar–***H***), 6.72 (s, 3H, Ar–***H***), 6.88 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 14.8 (Ar–O(CH_2)$_2$***C***H_3), 24.0 (Ar–OCH_2***C***H_2CH_3), 30.4 and 34.1 (Ar–***C***H_2–Ar), 44.7 (Ar–CH_2–N(***C***H_3)$_2$), 63.4 (Ar–***C***H_2–N(CH_3)$_2$), 76.8 (Ar–O***C***$H_2CH_2CH_3$), 122.2, 126.0, 127.5, 128.3, 128.4, 128.6,

129.1, 129.9, 133.6 (Ar), 154.6 and 155.6 (Ar***C***–OH), 156.8 (Ar***C***–$O(CH_2)_2CH_3$). ES mass spectrum (3MeOH: $2CHCl_3$: 1% HCOOH) m/z: 638.1 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monobutyloxy 26,27,28 tris hydroxycalix[4]arene (**3d**)*

White solid, yield 72%, m.p = 168 °C; **^{1}H NMR** (DMSO) δ 0.97 (t, 3H, $^3J_{H-H}$ = 6.8 Hz, Ar–$OCH_2CH_2CH_2CH_3$), 1.75 (m, 4H, Ar–$OCH_2CH_2CH_2CH_3$), 2.06 (s, 18H, Ar–CH_2–$N(CH_3)_2$), 3.09 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 3.16 (s, 6H, Ar–CH_2–$N(CH_3)_2$), 3.71 (t, 2H, $^3J_{H-H}$ = 6.9 Hz, Ar–$OCH_2(CH_2)_2CH_3$), 4.02 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 4.44 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 6.42 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***), 6.45 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.75 (s, 3H, Ar–***H***), 6.88 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 14.6 (Ar–$O(CH_2)_3CH_3$), 19.6 (Ar–$O(CH_2)_2CH_2CH_3$), 19.8 (Ar–$OCH_2CH_2CH_2CH_3$), 30.9 and 34.7 Ar–CH_2–Ar), 45.4 (Ar–CH_2–$N(CH_3)_2$), 64.1 (Ar–CH_2–$N(CH_3)_2$), 75.5 (Ar–$OCH_2(CH_2)_2CH_3$), 126.6; 128.1; 128.5; 128.8; 128.9; 129.2; 129.6; 130.4; 130.5; 134.1 (Ar), 155.1 and 156.4 (Ar***C***–OH), 160.3 (Ar***C***–$O(CH_2)_3CH_3$) ES mass spectrum (3MeOH: $2CHCl_3$: 1% HCOOH) m/z: 652.4 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monopentyloxy 26,27,28 tris hydroxycalix[4]arene (**3e**)*

White solid, yield 76%, m.p = 169 °C; **^{1}H NMR** (DMSO) δ 0.91 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, Ar–$O(CH_2)_4CH_3$), 1.51 (m, 4H, Ar–$O(CH_2)_2CH_2CH_2CH_3$), 1.72 (m, 2H, Ar–$OCH_2CH_2(CH_2)_2CH_3$), 2.04 (s, 12H, Ar–CH_2–$N(CH_3)_2$), 3.06 (d, 4H, $^2J_{H-H}$ = 13.2, Ar–CH_2–Ar), 3.12 (s, 6H, Ar–CH_2–$N(CH_3)_2$), 3.70 (t, 2H, $^3J_{H-H}$ = 6.9 Hz, Ar–$OCH_2(CH_2)_3CH_3$), 4.01 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar–CH_2–Ar), 4.41 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar–CH_2–Ar), 6.37 (t, 1H, $^3J_{H-H}$ = 7.6 Hz, Ar–***H***), 6.40 (d, 2H, $^3J_{H-H}$ = 7.4 Hz, Ar–***H***), 6.76 (s, 3H, Ar–***H***), 6.81 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 14.6 (Ar–$O(CH_2)_4CH_3$), 19.6 (Ar–$O(CH_2)_3CH_2CH_3$), 24.7 (Ar–$O(CH_2)_2CH_2CH_2CH_3$), 26.8 (Ar–$OCH_2CH_2(CH_2)_2CH_3$), 30.9 and 32.3 (Ar–CH_2–Ar), 45.4 (Ar–CH_2–$N(CH_3)_2$), 63.9 (Ar–CH_2–$N(CH_3)_2$), 75.8 (Ar–$OCH_2(CH_2)_3CH_3$), 122.3; 126.6; 128.1; 128.5; 128.8; 129.2; 129.6; 130.4; 130.5; 134.1 (Ar), 155.1 and 156.5 (ArC–OH), 160.5 (Ar***C***–$O(CH_2)_4CH_3$). ES mass spectrum (3MeOH: $2CHCl_3$: 1% HCOOH) m/z: 666.2 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monohexyloxy 26,27,28 tris hydroxycalix[4]arene (**3f**)*

White solid, yield 77%, m.p = 166 °C; **^{1}H NMR** (DMSO) δ 0.90 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, Ar–$O(CH_2)_5CH_3$), 1.49 (m, 4H, Ar–$O(CH_2)_3CH_2CH_2CH_3$), 1.55 (m, 2H, Ar–$O(CH_2)_2CH_2(CH_2)_2CH_3$) 1.79 (m, 2H, Ar–$OCH_2CH_2(CH_2)_3CH_3$), 2.08 (s, 18H, Ar–$CH_2$–$N(CH_3)_2$), 3.12 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 3.19 (s, 6H, Ar–CH_2–$N(CH_3)_2$), 3.75 (t, 2H, $^3J_{H-H}$ = 7.0 Hz, Ar–$OCH_2(CH_2)_4CH_3$), 4.05 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 4.45 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–CH_2–Ar), 6.15 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***) 6.20 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.73 (s, 3H, Ar–***H***), 6.89 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 15.2 (Ar–$O(CH_2)_5CH_3$), 23.4 (Ar–$O(CH_2)_4CH_2CH_3$), 24.5 (Ar–$O(CH_2)_3CH_2CH_2CH_3$), 24.6 (Ar–$O(CH_2)_2CH_2(CH_2)_2CH_3$), 26.6 (Ar–$OCH_2CH_2(CH_2)_3CH_3$), 30.6 and 32.5 (Ar–$CH_2$–Ar), 45.5 (Ar–$CH_2$–$N(CH_3)_2$), 64.1 (Ar–$CH_2$–$N(CH_3)_2$), 75.6 ((Ar–$OCH_2(CH_2)_4CH_3$), 121.2; 122.4; 126.5; 127.9; 129.5; 129.8; 130.0; 130.4; 131.1; 131.3; 134.7 (Ar), 155.1 and 155.8 (Ar***C***–OH), 156.8 (Ar***C***–$O(CH_2)_5CH_3$). ES mass spectrum (3MeOH: $2CHCl_3$: 1% HCOOH) m/z: 680.4 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monoheptyloxy 26,27,28 tris hydroxycalix[4]arene (**3g**)*

White solid, yield 79%, m.p = 169 °C; **^{1}H NMR** (DMSO) δ 0.91 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, Ar–$O(CH_2)_6CH_3$), 1.19 (m, 4H, Ar–$O(CH_2)_4CH_2CH_2CH_3$), 1.21 (m, 2H, Ar–$O(CH_2)_3CH_2(CH_2)_2CH_3$), 1.23 (m 2H, Ar–$O(CH_2)_3CH_2(CH_2)_2CH_3$), (1.41 (m, 2H, Ar–$OCH_2CH_2(CH_2)_4CH_3$), 2.09 (s, 18H, Ar–$CH_2$–$N(CH_3)_2$), 3.11 (d, 4H, $^2J_{H-H}$ = 12.9 Hz, Ar–CH_2–Ar), 3.17 ((s, 6H, Ar–CH_2–$N(CH_3)_2$), 3.77 (t, 2H, $^3J_{H-H}$ = 6.8 Hz, Ar–$OCH_2(CH_2)_5CH_3$), 4.31 (d, 2H, $^2J_{H-H}$ = 12.9 Hz, Ar–CH_2–Ar), 4.41 (d, 2H, $^2J_{H-H}$ = 12.9 Hz, Ar–CH_2–Ar), 6.17 (t, 1H, $^3J_{H-H}$ = 7.6 Hz, Ar–***H***), 6.21 (d, 2H, $^3J_{H-H}$ = 7.4 Hz, Ar–***H***), 6.71 (s, 3H, Ar–***H***), 6.92 (s, 3H, Ar–***H***). ^{13}C NMR (DMSO) δ 13.8 (Ar–$O(CH_2)_6CH_3$), 22.2 (Ar–$O(CH_2)_5CH_2CH_3$), 23.2 (Ar–$O(CH_2)_4CH_2CH_2CH_3$), 25.2 (Ar–$O(CH_2)_3CH_2(CH_2)_2CH_3$), 28.4 (Ar–$O(CH_2)_2CH_2(CH_2)_3CH_3$), 29.9 (Ar–$OCH_2CH_2(CH_2)_4CH_3$), 30.9 and 33.8 (Ar–$CH_2$–Ar), 44.2 (Ar–$CH_2$–$N(CH_3)_2$), 62.7 (Ar–$CH_2$–$N(CH_3)_2$), 75.0 (Ar–$OCH_2(CH_2)_5CH_3$), 121.9; 122.3; 122.6; 125.5; 127.1; 128.4; 128.7; 129.7; 131.2; 133.1 (Ar), 155.2 and 157.6 (Ar***C***–OH), 159.4 (Ar***C***–$O(CH_2)_6CH_3$). ES mass spectrum (3MeOH: $2CHCl_3$: 1% HCOOH) m/z: 694.2 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monooctyloxy 26,27,28 tris hydroxycalix[4]arene (**3h**)*

White solid, yield 81%, m.p = 169 °C; **^{1}H NMR** (DMSO) δ 0.91 (t, 3H, $^3J_{H-H}$ = 6.9 Hz, Ar–$O(CH_2)_7CH_3$), 1.31 (m, 4H, Ar–$O(CH_2)_5CH_2CH_2CH_3$), 1.37 (m, 2H, Ar–$O(CH_2)_4CH_2(CH_2)_2CH_3$), 1.39 (m, 2H, Ar–$O(CH_2)_3CH_2(CH_2)_3CH_3$),

1.42 (m, 2H, Ar–O(CH_2)$_2$C***H***$_2$(CH_2)$_4$$CH_3$), 1.51 (m, 2H, Ar–OC$H_2$C***H***$_2$($CH_2$)$_5$$CH_3$), 2.10 (s, 18H, Ar–$CH_2$–N(C***H***$_3$)$_2$), 3.09 (d, 4H, $^2J_{H-H}$ = 13.0 Hz, Ar–C***H***$_2$–Ar), 3.15 (s, 6H, Ar–C***H***$_2$–N(CH_3)$_2$), (3.71 (t, 2H, $^3J_{H-H}$ = 7.0 Hz, Ar–OC***H***$_2$(CH_2)$_6$$CH_3$), 4.14 (d, 2H, $^2J_{H-H}$ = 12.9 Hz, Ar–C***H***$_2$–Ar), 4.49 (d, 2H, $^2J_{H-H}$ = 12.9 Hz, Ar–C***H***$_2$–Ar), 6.20 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***), 6.47 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.68 (s, 3H, Ar–***H***), 6.92 (s, 3H, Ar–***H***). ^{13}C NMR (DMSO) δ 14.0 Ar–O(CH_2)$_7$***C***H_3), 21.8 (Ar–O(CH_2)$_5$***C***$H_2$$CH_3$), 24.2 (Ar–O($CH_2$)$_5$***C***$H_2$$CH_2$$CH_3$), 25.5 (Ar–O($CH_2$)$_4$***C***$H_2$($CH_2$)$_2$$CH_3$), 28.4 (O($CH_2$)$_3$***C***$H_2$($CH_2$)$_3$$CH_3$), 28.6 (Ar–O($CH_2$)$_2$***C***$H_2$($CH_2$)$_4$$CH_3$), 29.9 (Ar–OC$H_2$***C***$H_2$($CH_2$)$_5$$CH_3$), 31.2 and 34.1 (Ar–$CH_2$–Ar), 44.5 (Ar–$CH_2$–N(***C***$H_3$)$_2$), 63.5 (Ar–***C***$H_2$–N($CH_3$)$_2$), 74.7 (ArO***C***$H_2$($CH_2$)$_6$$CH_3$), 121.7; 122.1; 122.4; 123.1; 123.4; 125.9; 126.0; 127.3; 128.9; 129.9; 133.6 (Ar), 154.7 and 155.7 (Ar***C***–OH), 160.2 (Ar***C***–O(CH_2)$_7$$CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 708.4 $[M + H]^+$, 746.4 $[M + K]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monononyloxy 26,27,28 tris hydroxycalix[4]arene (**3i**)*

White solid, yield 75%, m.p = 168 °C; **^{1}H NMR** (DMSO) δ 0.92 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, Ar–O(CH_2)$_8$C***H***$_3$), 1.33 (m, 4H, Ar–O(CH_2)$_6$C***H***$_2$C***H***$_2$$CH_3$), 1.36 (m, 4H, Ar–O($CH_2$)$_4$C***H***$_2$C***H***$_2$($CH_2$)$_2$$CH_3$), 1.38 (m, 2H, Ar–O($CH_2$)$_3$C***H***$_2$($CH_2$)$_3$$CH_3$), 1.42 (m, 2H, Ar–O($CH_2$)$_3$C***H***$_2$($CH_2$)$_4$$CH_3$), 1.56 (m, 2H, Ar–O($CH_2$)$_2$C***H***$_2$($CH_2$)$_5$$CH_3$), 1.69 (m, 2H, Ar–OC$H_2$C***H***$_2$($CH_2$)$_6$$CH_3$), 2.09 (s, 18H, Ar–$CH_2$–N(C***H***$_3$)$_2$), 3.08 (d, 4H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H***$_2$–Ar), 3.14 (s, 6H, Ar–C***H***$_2$–N(CH_3)$_2$), 3.40 (t, 2H, $^3J_{H-H}$ = 6.9 Hz, Ar–Ar–OC***H***$_2$(CH_2)$_7$$CH_3$), 3.72 (d, 2H, $^2J_{H-H}$ = 13.2 Hz, Ar–C***H***$_2$–Ar), 4.51 (d, 2H, $^3J_{H-H}$ = 13.2 Hz, ArC***H***$_2$–Ar), 6.21 (t, 1H, $^3J_{H-H}$ = 7.6 Hz, Ar–***H***), 6.49 (d, 2H, $^2J_{H-H}$ = 7.4 Hz, Ar–***H***), 6.68 (s, 3H, Ar–***H***), 6.83 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 13.8 (Ar–O(CH_2)$_8$***C***H_3), 22.0 (Ar–O(CH_2)$_7$***C***$H_2$$CH_3$), 24.4 (Ar–O($CH_2$)$_6$***C***$H_2$$CH_2$$CH_3$), 24.5 (Ar–O($CH_2$)$_5$***C***$H_2$($CH_2$)$_2$$CH_3$), 25.5 (Ar–O($CH_2$)$_4$***C***$H_2$($CH_2$)$_3$$CH_3$), 28.6 (Ar–O($CH_2$)$_3$***C***$H_2$($CH_2$)$_4$$CH_3$), 28.9 (Ar– O($CH_2$)$_2$***C***$H_2$($CH_2$)$_5$$CH_3$), 29.4 (Ar–OC$H_2$***C***$H_2$($CH_2$)$_6$$CH_3$), 31.2 and 34.0 (Ar–$CH_2$–Ar), 44.7 (Ar–$CH_2$–N(***C***$H_3$)$_2$), 63.0 (Ar–***C***$H_2$–N($CH_3$)$_2$), 75.6 (Ar–O***C***$H_2$($CH_2$)$_7$$CH_3$), 121.3; 122.6; 123.1; 123.4; 124.5; 126.1; 126.5; 127.3; 128.6; 129.7; 133.3 (Ar), 154.4 and 155.7 (Ar***C***–OH), 159.1 (Ar***C***–O(CH_2)$_8$$CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 722.4 $[M + H]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monodecyloxy 26,27,28 tris hydroxycalix[4]arene (**3j**)*

White solid, yield 78%, m.p = 168 °C; **^{1}H NMR** (DMSO) δ 0.91 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, Ar–O(CH_2)$_9$C***H***$_3$), 1.15 (m, 4H, Ar–O(CH_2)$_7$C***H***$_2$C**H**$_2$$CH_3$), 1.21 (m, 2H, Ar–O($CH_2$)$_5$C***H***$_2$C***H***$_2$($CH_2$)$_2$$CH_3$), 1.23 (m, 2H, Ar–O($CH_2$)$_4$C***H***$_2$($CH_2$)$_3$$CH_3$), 1.39 (m, 2H, Ar–O($CH_2$)$_4$C***H***$_2$($CH_2$)$_4$$CH_3$), 1.47 (m, 2H, Ar–O($CH_2$)$_3$C***H***$_2$($CH_2$)$_5$$CH_3$), 1.71 (m, 2H, Ar–O($CH_2$)$_2$C***H***$_2$($CH_2$)$_6$$CH_3$), 1.87 (m, 2H, Ar–OC$H_2$C***H***$_2$($CH_2$)$_7$$CH_3$), 2.11 (s, 18H, Ar–$CH_2$–N(C***H***$_3$)$_2$), 3.09 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 3.14 (s, 6H, Ar–C***H***$_2$–N(CH_3)$_2$), 3.71 (t, 2H, $^3J_{H-H}$ = 7.1 Hz, Ar–OC***H***$_2$(CH_2)$_8$$CH_3$), 4.12 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 4.51 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 6.21 (t, 1H, $^3J_{H-H}$ = 7.6 Hz, Ar–***H***), 6.48 (d, 2H, $^3J_{H-H}$ = 7.4 Hz, Ar–***H***), 6.69 (s, 3H, Ar–***H***), 6.97 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 13.8 (Ar–O(CH_2)$_9$***C***H_3), 22.1 (Ar–O(CH_2)$_8$***C***$H_2$$CH_3$), 24.3 (Ar–O($CH_2$)$_7$***C***$H_2$$CH_2$$CH_3$), 25.5 (Ar–O($CH_2$)$_6$***C***$H_2$($CH_2$)$_2$$CH_3$), 28.6 (Ar–O($CH_2$)$_5$***C***$H_2$($CH_2$)$_3$$CH_3$), 28.9 (Ar–O($CH_2$)$_4$***C***$H_2$($CH_2$)$_4$$CH_3$), 29.4 (Ar–O($CH_2$)$_3$***C***$H_2$($CH_2$)$_5$$CH_3$), 30.2 (Ar–O($CH_2$)$_2$***C***$H_2$($CH_2$)$_6$$CH_3$), 30.6 (OC$H_2$***C***$H_2$($CH_2$)$_7$$CH_3$), 31.1 and 34.1 (Ar–$CH_2$–Ar), 44.5 (Ar–$CH_2$–N(***C***$H_3$)$_2$), 63.3 (Ar–***C***$H_2$–N($CH_3$)$_2$), 75.2 (Ar–O***C***$H_2$($CH_2$)$_8$$CH_3$), 121.3; 122.4; 126.1; 126.6; 127.6; 128.5; 128.9; 130.2; 133.6 (Ar), 154.7 and 155.7 (Ar***C***–OH), 159.4 (Ar***C***–O(CH_2)$_9$$CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 736.5 $[M + H]^+$, 758.5 $[M + Na]^+$.

*5,11,17 Tris-[(dimethylamino)methyl] 25-monododecyloxy 26,27,28 tris hydroxycalix[4]arene (**3k**)*

White solid, yield 82%, m.p = 168 °C; **^{1}H NMR** (DMSO) δ 0.93 (t, 3H, $^3J_{H-H}$ = 6.9 Hz, Ar–O(CH_2)$_{11}$C***H***$_3$), 1.15 (m, 4H, Ar–O(CH_2)$_9$C***H***$_2$C***H***$_2$$CH_3$), 1.24 (m, 2H, Ar–O($CH_2$)$_8$C***H***$_2$($CH_2$)$_2$$CH_3$), 1.25 (m, 2H, Ar–O($CH_2$)$_7$C***H***$_2$($CH_2$)$_2$$CH_3$), 1.34 (m, 2H, Ar–O($CH_2$)$_6$C***H***$_2$($CH_2$)$_4$$CH_3$), 1.46 (m, 2H, Ar–O($CH_2$)$_5$C***H***$_2$($CH_2$)$_5$$CH_3$), 1.53 (m, 2H, Ar–O($CH_2$)$_4$$CH_2$($CH_2$)$_4$$CH_3$), 1.67 (m, 2H, Ar–O($CH_2$)$_3$C***H***$_2$($CH_2$)$_7$$CH_3$), 1.73 (m, 2H, Ar–O($CH_2$)$_2$C***H***$_2$($CH_2$)$_8$$CH_3$), 1.89 (m, 2H, Ar–OC$H_2$C***H***$_2$($CH_2$)$_9$$CH_3$), 2.11 (s, 18H, Ar–$CH_2$–N(C***H***$_3$)$_2$), 3.14 (d, 4H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 3.14 (s, 6H, Ar–C***H***$_2$–N(CH_3)$_2$), 3.73 (t, 2H, $^2J_{H-H}$ = 7.1 Hz, Ar–OC***H***$_2$(CH_2)$_{10}$$CH_3$), 4.10 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 4.67 (d, 2H, $^2J_{H-H}$ = 13.1 Hz, Ar–C***H***$_2$–Ar), 619 (t, 1H, $^3J_{H-H}$ = 7.7 Hz, Ar–***H***), 6.47 (d, 2H, $^3J_{H-H}$ = 7.5 Hz, Ar–***H***), 6.67 (s, 3H, Ar–***H***), 6.89 (s, 3H, Ar–***H***). **^{13}C NMR** (DMSO) δ 13.8 (Ar–O(CH_2)$_{11}$***C***H_3), 22.0 (Ar–O(CH_2)$_{10}$***C***$H_2$$CH_3$), 22.4 (Ar–O($CH_2$)$_9$***C***$H_2$$CH_2$$CH_3$), 23.7 (Ar–O($CH_2$)$_8$***C***$H_2$($CH_2$)$_2$$CH_3$), 25.5 (Ar–O($CH_2$)$_7$***C***$H_2$($CH_2$)$_3$$CH_3$), 28.6 (Ar–O($CH_2$)$_6$***C***$H_2$($CH_2$)$_4$$CH_3$), 28.9 (Ar–O($CH_2$)$_5$***C***$H_2$($CH_2$)$_5$$CH_3$), 29.1 (Ar–O($CH_2$)$_4$***C***$H_2$($CH_2$)$_6$$CH_3$), 29.3 (Ar–O($CH_2$)$_3$***C***$H_2$($CH_2$)$_7$$CH_3$), 30.2 (Ar–O($CH_2$)$_2$***C***$H_2$($CH_2$)$_8$$CH_3$), 31.2 (Ar–OC$H_2$***C***$H_2$($CH_2$)$_9$$CH_3$), 31.7 and 33.9 (Ar–***C***H_2–Ar), 44.2 (Ar–CH_2–N(***C***H_3)$_2$), 63.0 (Ar–***C***H_2–N(CH_3)$_2$), 75.2 (Ar–O***C***H_2(CH_2)$_{11}$$CH_3$), 121.6; 122.6; 125.8; 128.6; 129.5; 129.9; 133.4 (Ar), 154.7 and

155.7 (Ar***C***–OH), 159.7 (Ar***C***–O$(CH_2)_{11}CH_3$). ES mass spectrum (3MeOH: 2$CHCl_3$: 1% HCOOH) m/z: 764.4 $[M + H]^+$.

Results and discussion

Monoalkylation of calix[4]arene

The phenolic hydroxyl functions of calix[4]arene, **1**, are known to possess quite different pKa values, with the first deprotonation occurring in the region pH 8, thus a wide range of weak bases are available for mono-alkylation of calix[4]arene via the Williamson reaction. However, the yields of the mono-substituted products isolated vary considerably, depending on the base, the solvent, and the nature of alkyl halide used in the coupling reaction.

The synthetic route to the various derivatives is given below in Fig. 1.

In order to obtain a reaction pathway that allow synthesis of the mono-alkylated derivatives of **1** in multigram quantities, a number of synthetic routes were studied and the experimental condition and yields are summarized in Table 1.

It can be seen that the use of caesium fluoride or potassium carbonate as weak bases, under suitable conditions, allow isolation of the mono-alkylated species in good to high yields, with relatively facile work up procedures.

The obtained yields for chain lengths up to five carbon atoms are given below in Table 2.

With the use of K_2CO_3 as the deprotonating agent, yields of the desired compound rapidly decline for chain lengths greater than two carbon atoms, while those for CsF as base rest unchanged, thus the synthetic route using, the more expensive, CsF has been used for mono-alkylation with chain lengths equal to or greater than three carbon atoms.

All compounds show the expected molecular mass by Electrospray Mass Spectrometry. ^{1}H NMR shows for the methylenic protons a doublet in the region 3.5 ppm and two doublets in the region 4.2 and 4.4 ppm, corresponding to the equatorial and axial protons of the bridge, thus as previously noted by Ungaro [19], the mono-substituted derivatives are present in the cone conformation. All compounds show singlet peaks at 9.5 ppm (2H) and 9.8 ppm (1H), corresponding to the phenolic hydroxyl protons.

The use of the *para*-quinonemethide reaction via treatment of the monoalkyl-*tris* hydroxycalix[4]arene **2a**–**k** in tetrahydrofuran in the presence of acetic acid, 40% aqueous dimethylamine, and excess of 35% aqueous formaldehyde, yields the desired compounds **3a**–**k**, in good (>70%) yields after recrystallization from chloroform [24].

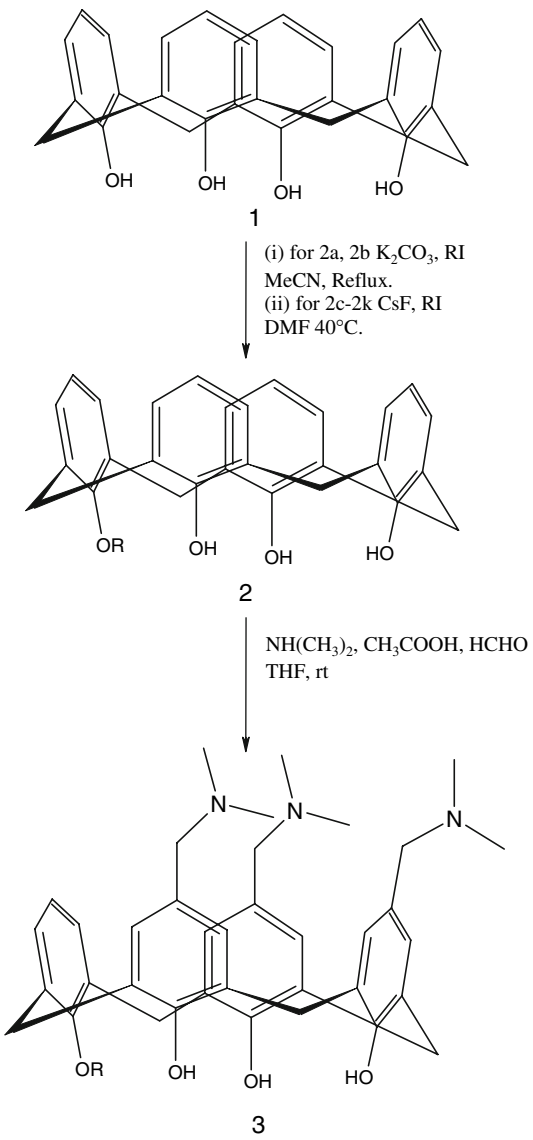

Fig. 1 The two step synthetic route to derivatives **3a–k**

Table 1 Yields of compound **2d**, as a function of solvent, base, equivalents of alkylating agent and temperature

Solvents	Reagents		Temp. (°C)	Yield (%)
DMSO	1.2 eq. NaOH	1.2 eq. C_4H_9–I	60	23
DMSO	1.2 eq. NaOH	2.5 eq. C_4H_9–I	60	25
CH_3CN	1.2 eq. DBU	1.2 eq. C_4H_9–I	r.t.	17
CH_3CN	1.2 eq. DBU	2.5 eq. C_4H_9–I	r.t.	25
CH_3CN	0.6 eq. K_2CO_3	1.2 eq. C_4H_9–I	reflux	5
CH_3CN	0.6 eq. K_2CO_3	10 eq. C_4H_9–I	reflux	39
DMF	1.2 eq. KF	10 eq. C_4H_9–I	40	21
DMF	1.2 eq. CsF	10 eq. C_4H_9–I	40	68

Table 2 Yields obtained for the synthesis of **2a–e** as a function of the base

Reagents		Molecule				
		2a (%)	**2b** (%)	**2c** (%)	**2d** (%)	**2e** (%)
0.6 eq. K_2CO_3	10 eq. RI	67	70	33	39	10
1.2 eq. CsF	10 eq. RI	60	54	69	68	62

The ^{1}H NMR spectrum of **3a** shows a doublet (4H) at 3.14 ppm (J = 13.2 Hz) for the equatorial protons and two 2H doublets at 4.02 and 4.41 ppm (J = 13.2 Hz) for axial protons of the bridging methylene groups. The ^{13}C NMR spectrum of **3a** show two peaks at 30.6 and 34.6 ppm for the bridge methylene carbon atoms, one peak at 45.1 ppm for the N-methyl carbons, one peak at 63.7 ppm for the Ar–CH_2–N carbon, one peak at 79.7 ppm for the methoxy carbon. The NMR data for the other compounds of series **3** is similar.

Electrospray Mass Spectrometry showed clean complete tri-substitution at the *para*-position. Loss of dimethylamine can be detected at high orifice energies, >20V.

Thus the desired compounds are readily available in multigram quantities in two stages from **1**.

Solid-state structural studies

The molecular structure of **2b** is given in Fig. 2a, b. As expected from the solution NMR results **2b** is present in the cone conformation with cone angles of 73.01(5) and 50.76(5)°, and hydrogen bonding between the three phenolic hydroxyl groups of 2.737(3), 2.688(3) and 2.716(3) Å.

Calixarene molecule **2b** stacks into one-dimensional inclusion polymer which are arranged in an alternating anti-parallel packing (Fig. 2a), similar to that observed for 25-Mono-(ethoxycarbonylmethoxy)-calix-[4]arene [25]. The methyl group of the alkyl chain is situated almost perfectly at the centroid of the *para*-carbon atoms of the aromatic rings of the adjacent molecule (C–H···π contacts 3.529(4), 3.576(4) and 3.708(4) Å).

The toluene molecules play a considerable role in stabilization of crystal structure 2**b**. They are included in the framework of C–H···π interactions; as given in Fig. 2b and show methyl group C–H···π (3.30(1) Å) contacts , *ortho*-carbon atom C–H···π contacts to the same phenyl ring of adjacent (−1 + x, y, z) calix[4]arene (3.71(2) Å), and the π-electrons of toluene also take part in weak C–H···π interactions with other adjacent (x, ½−y, ½+z; −1−x, −½+y, ½−z) calix[4]arene rings (3.831(8) Å). 1D inclusion polymer chains are combined into a 3D structure due to a bridging function of solvent molecules, strong *meta*-C–H···π binding to adjacent (x, ½−y, ½+z) calix[4]arene (3.532(4) Å), and C–H···π contacts between methylene group of calix[4]arene macrocycle (3.684(4) Å) and adjacent (−x, −½+y, ½−z) calix[4]arene (Fig. 2b).

Self-assembly of compounds 3a–k

In order to study the self-assembly properties of **3a–k**, the Critical Micellar Concentrations were determined at pH 2, 4, 6 and 8 by use static surface tension versus concentration

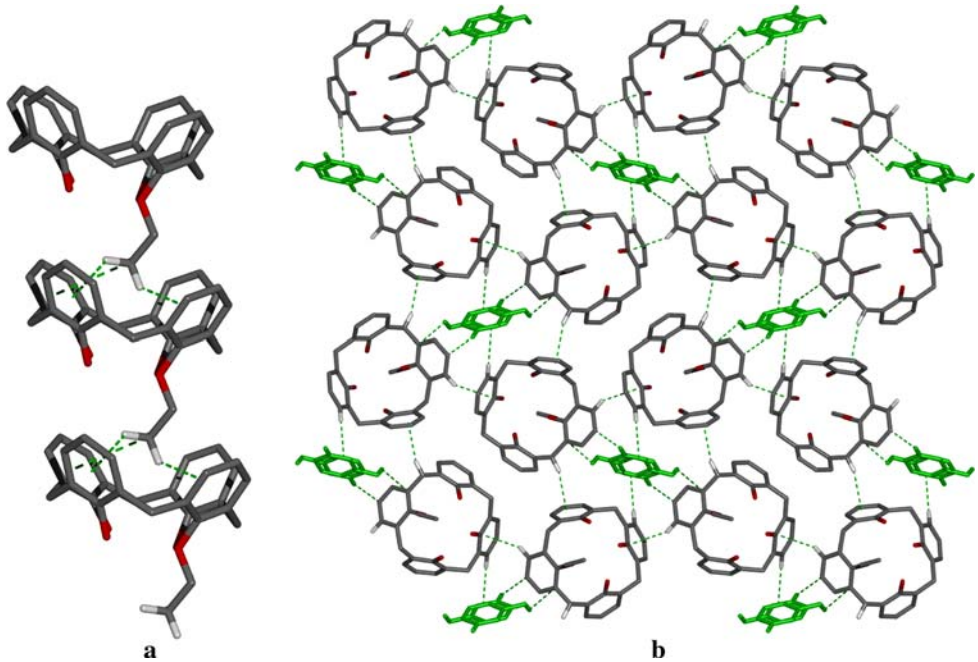

Fig. 2 (**a**) 1D inclusion polymer chain formed by **2b**. (**b**) Intermolecular interactions between solvent (toluene) and calix[4]arene **2b**, and between adjacent 1D polymeric chains. Structure projected down the *a* axis

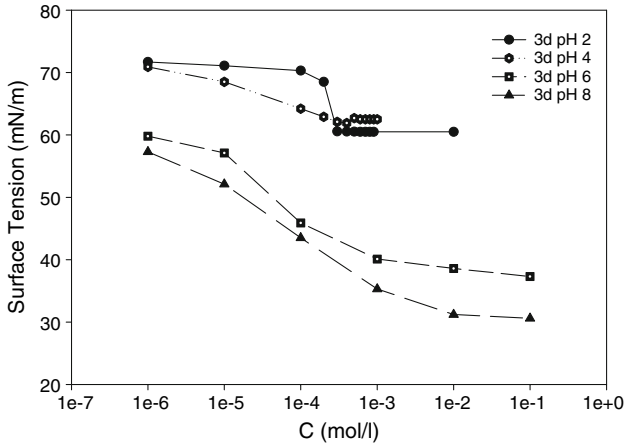

Fig. 3 Surface pressure-concentration isotherms for **3d** at pH 2, 4, 6 and 8

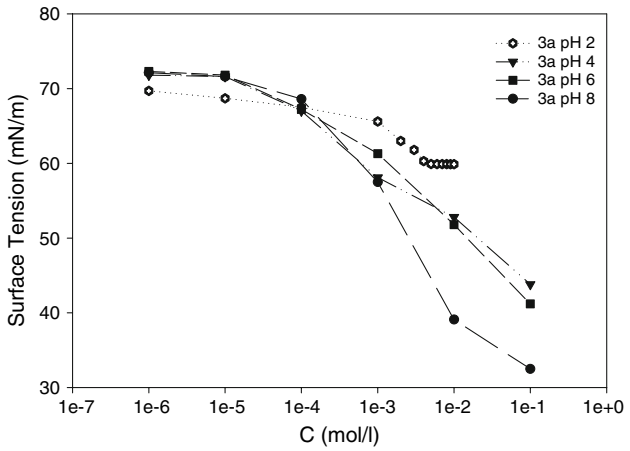

Fig. 4 Surface pressure-concentration isotherms for **3a** at pH 2, 4, 6 and 8

isotherms. Only at pH 2 are the dimethylaminomethylene polar head groups expected to be fully protonated [24].

Two different types of aggregation behaviour are observed, and these are shown in Figs. 3 and 4, for compounds **3d** and **3a** respectively. The Critical Micellar Concentrations and the observed surface tension at the CMC values are given in Tables 3. Observed aggregate sizes are given in Table 4. All the molecules give rise to surface tension concentration dependent isotherms typical of the formation of micellar aggregates at pH 2.

For compounds **3d** and **3h–k** the molecules show expected behaviour for the formation of micellar type aggregates, with CMC values varying between 10^{-6} M and 10^{-2} M, however there is no dependence of the CMC on the length of the alkyl chain attached at the phenolic face of the calix[4]arene skeleton. This is in contrast to the behaviour of simple surfactant molecules where there is a direct dependence of the CMC on the hydrophobic chain [26]. Similarly, there is no direct relation between the chain length of the substituent for molecules **3d** and **3h–k** and the surface tension values observed at the CMC concentrations, again this is in contrast to the behaviour observed for simple surfactant systems.

It is of note that while this CMC like aggregation behaviour is observed for molecules with chain lengths of 8 carbon atoms or longer, **3d** with only four carbon atoms in the alkyloxy chain also behaves in this way, as shown in Fig. 3.

A second type of behaviour is observed for molecules **3a–c** and **3e–g**, as shown for **3a** in Fig. 4. For these molecules there are pH values at which the surface tension continues to decrease with concentration and does not show the plateau expected, it should be noted that at concentrations above 100 mM there is clear precipitation observed in all cases.

Table 3 Values for the Critical Micellar Concentration and values for the surface tension on an aqueous subphase at pH 2, 4, 6 and 8

Compound	Critical Micellar Concentration (M)				Surface tension (mN/m)			
	pH 2	pH 4	pH 6	pH 8	pH 2	pH 4	pH 6	pH 8
3a	5×10^{-4}	n.d[a]	n.d[a]	n.d[a]	59.91	n.d[a]	n.d[a]	n.d[a]
3b	2×10^{-4}	n.d[a]	n.d[a]	n.d[a]	64.39	n.d[a]	n.d[a]	n.d[a]
3c	2×10^{-4}	n.d[a]	n.d[a]	n.d[a]	64.85	n.d[a]	n.d[a]	n.d[a]
3d	3×10^{-4}	4×10^{-4}	1.1×10^{-3}	1.2×10^{-3}	60.57	61.9	39.5	39.1
3e	1.1×10^{-4}	1.2×10^{-2}	6.3×10^{-2}	n.d[a]	54	29.87	58	n.d[a]
3f	4×10^{-4}	5.1×10^{-2}	n.d[a]	n.d[a]	55.7	31.81	n.d[a]	n.d[a]
3g	1.2×10^{-2}	5×10^{-3}	7×10^{-6}	n.d[a]	48.16	33.46	31.17	n.d[a]
3h	6×10^{-5}	8×10^{-3}	3×10^{-6}	7×10^{-6}	47	51.4	61	55.11
3i	1.1×10^{-3}	1.1×10^{-2}	7.1×10^{-2}	1.3×10^{-3}	50.9	51.4	63.6	57.81
3j		4.8×10^{-2}	1.1×10^{-4}	1.1×10^{-3}		40.1	50.2	29.5
3k	1.2×10^{-3}	4.5×10^{-2}	5.3×10^{-3}	1.2×10^{-3}	46.48	49.83	23.1	46.35

[a] No minimum value observed.

Table 4 Aggregate diameters for colloidal suspensions of **3a–k** at pH values 2, 4, 6, and 8, measured at 298 K

Compound	Apparent diameter (nm)			
	pH 2	pH 4	pH 6	pH 8
3a	80, 450	>500	>500	500
3b	84, 400	>500	>500	>500
3c	90, 490	73, >500	156, >500	140, >500
3d	90, 450	100, 250	4, 150, >500	4, 150, >500
3e	24, 200	4, 10, 250	150, >500	>500
3f	440	>500	90, >500	240, >500
3g	90, 480	120, >500	>500	320
3h	90, 500	400	>500	>500
3i	25, 80	40, >500	20, >500	40, >500
3j	15, 80	100, >500	100, >500	200, >500
3k	8, 60	8, 60, >500	6, 20, >500	7, 60, >500

The group may be divided into two sub-groups, for **3a–c** i.e. for those derivatives with short alkyloxy chains, no CMC is observed at pH values of 4 or superior, whereas for **3e–g** with intermediate chain lengths at the substituent it in general only at pH 8 that no CMC like behaviour is observed.

The observed aggregate sizes as determined by Dynamic Light Scattering are given, below in Table 4.

There is a clear correlation between the aggregate sizes as determined by Dynamic Light Scattering and the CMC measurements. Thus, **3d** and **3k**, both of which show CMC type behaviour at all pH values are characterised by the presence of small aggregate species, in particular the presence of objects of ca 6–8 nm is consistent with the presence of true micellar species. It is clear, also, that there are geometrical constraints on how these surfactant calix-arenes assemble, which do not follow the same rules as for simple one-dimensional surfactants.

Indeed for virtually all systems showing CMC type isotherms there are aggregates of less than 200 nm present. Conversely, for systems in which the surface tension shows a simple decrease with concentration and with no plateau present, are characterised by the presence of aggregates of at least 400 nm in diameter and generally with objects in the range >500 nm.

Thus two types of aggregate appear to be present and the CMC isotherm behaviour can be correlated with the aggregate diameter determined from Dynamic Light Scattering.

Conclusions

In conclusion, a series of 11 novel calix[4]arene derivatives has been synthesised, based on the rational design of molecular species capable of forming micellar aggregates and where the presence of only three substituents at the para-position will not block inclusion of molecules or more interestingly amino-acid side chains. The design principles are confirmed by the surfactant behaviour of these molecules and the formation of micellar aggregates.

Work is currently underway to investigate the biological properties of these molecules.

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