Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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Ghada Merhi[a]; Marc Munoz[b]; Anthony W. Coleman[b]; Gillian Barrat[a]
[a] Laboratoire de Pharmacie Galénique, URA CNRS 1218, Centre pharmaceutique, Université de Paris XI, Chtenay-Malabry, France [b] IBCP, Lyon, France

To cite this Article Merhi, Ghada , Munoz, Marc , Coleman, Anthony W. and Barrat, Gillian(1995) 'Amphiphilic calixarenes: Probing monolayer stability by selective modification of the hydrophobic-hydrophilic balance', Supramolecular Chemistry, 5: 2, 173 — 177

To link to this Article: DOI: 10.1080/10610279508029491

URL: http://dx.doi.org/10.1080/10610279508029491

SUPRAMOLECULAR CHEMISTRY, Vol. 5, pp. 173–177
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Amphiphilic calixarenes: probing monolayer stability by selective modification of the hydrophobic-hydrophilic balance

GHADA MERHI[‡], MARC MUNOZ[†], ANTHONY W. COLEMAN[†]* and GILLIAN BARRAT[‡]

[‡]*Laboratoire de Pharmacie Galénique, URA CNRS 1218, Centre pharmaceutique, Université de Paris XI, Châtenay-Malabry (France) and* [†]*IBCP, URA CNRS 412, 7 passage du Vercors, F69367, Lyon 07, (France)*

(Received August 4, 1994)

The synthesis of calix[4]arenes permuting 1 or 4 C12 acyl chains at the upper rim and 1 or 4 methylene ethyl ester groups at the lower rim is described. The Langmuir compression isotherms of the compounds show that in the case of 1 acyl + 1 ester, there is probably orientation parallel to the air-water interface. For the other systems, orientation is orthogonal to the interface, and for the 4+4 compound a pseudo collapse with reorientation of the hydrophilic ester groups is observed.

INTRODUCTION

Of the large structural motifs available to supramolecular chemistry, the calixarenes[1] and the cyclodextrins[2] are available at industrial scales and costs. Hence development of molecular self-assembly systems for a wide range of applications is likely to be based on these molecules.

For the preparation of such organised polymolecular assemblies, the application of Langmuir-Blodgett techniques seems an obvious strategy.[3] The controlled synthesis of amphiphilic derivatives should be coupled with studies into how such synthetic modifications change the organizational properties of these molecules. This feedback approach will be a determinant factor in the conception and the elaboration of new materials based on these molecules.

In the case of the cyclodextrins, a wide range of amphiphilic molecules are now available[4] and the self-assembly properties both as monolayers[5] and as dispersed nanostructures[6] have been studied. In contrast, for the calixarenes apart from the in-depth study of certain systems by Regen,[7] this subject has so far received much less attention.[8]

In this paper, we report the synthesis and self-assembly properties of a series of calix[4]arenes in which either one or four hydrophobic C12 acyl moieties are grafted at the para positions, with permutation at the phenolic function of one or four hydrophilic methylene ethyl ester moieties. All the compounds form relatively stable Langmuir layers at the air-water interface. The stability of these systems varied as a function of the sum of the hydrophobic and the hydrophilic groups. Thus, with regard to monolayer stability, (1acyl + 1ester) < (1acyl + 4ester) = (4acyl + 1ester) << (4acyl + 4ester): **4** < **6** = **5** << **7**. Apparently both **7** and **4** show reorganisation within the layers as a function of applied pressure. The shapes of the observed isotherms imply different organisational behaviour for each compound. As the compression isotherms show strongly divergent shapes, deriving apparent molecular areas for these systems is a nontrivial problem, but for **5**,**6** and **7** extrapolation suggests a value of ca. 100 Å^2, whilst for **4** a value of ca. 75 Å^2 is observed.

RESULTS AND DISCUSSION

The synthetic routes to compounds **2** through **7** are given below in Figure **1**.

Synthesis of **3** was acheived by Friedel-Crafts acylation of the "naked" calix[4]arene **1**, in which 4 equivalents of dodecanoyl chloride and 8 equivalents of $AlCl_3$

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*To whom correspondence should be addressed.

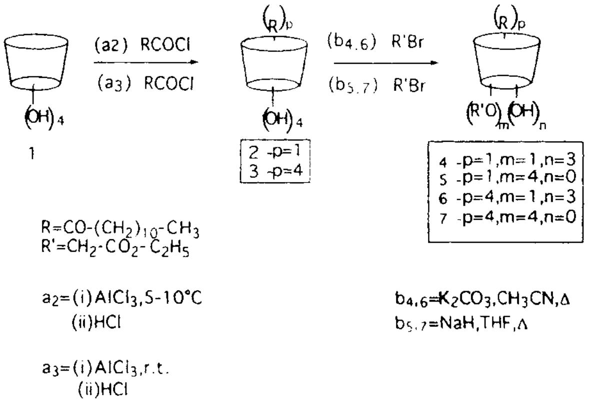

Figure 1

were reacted with **1** in nitrobenzene at room temperature during 3h.[9] Excess hydrochloric acid was used to stop the reaction and aqueous/chloroform extraction followed by crystallisation from acetone afforded **3** in 83% yield. Compound **2** was prepared by an analogous route in which 1 equivalent of **1** was treated with 1 equivalent of dodecanoyl chloride and 2 equivalents of $AlCl_3$ in nitrobenzene for 3h at 5–10°C. The reaction was stopped with hydrochloric acid and an aqueous/chloroform extraction followed by recrystallisation from propanol gave **2** in 50% yield.

The synthesis of **5** and **7** was achieved by etherification of the phenolic functions under forcing conditions[10] with 5 equivalents NaH per phenol. Workup via chromatography lead to pure **5** and **7** in high yields; 70% and 92%, respectively.

For the monoalkyl ester derivatives **4** and **6**, a synthesis analogous to that of Reinhoudt[11] was used. This involved treatment of the corresponding acyl compounds **2** and **3** with an excess of bromoethyl acetate and 0.6 equivalents of K_2CO_3 under reflux in acetonitrile during 24h. Subsequent work up and chromatography gave the tetraacyl monoalkyl ester derivative **6** and the monoacyl monoalkyl ester **4** in relatively low yields, 25% and 20%, respectively, as compared to the literature reactions.[11] Purification of **4** and **6** is complicated by the obtention of positional isomers, and compounds with more than one alkyl ester substituent, isolation and identification of these other compounds is being undertaken.

The infrared spectra of **2–7** show a characteristic νCO at 1679cm^{-1} for the aryl acyl group. The monoalkyl ester compounds **4** and **6** show νCO_2 at 1749 cm^{-1} whereas for the tetra substituted derivatives, the band is shifted to 1755 cm^{-1}. The OH stretch for the unsubstituted compounds has a maximum at 3194 cm^{-1}, but for the mono substituted compounds, this is strongly shifted to 3340 cm^{-1}. This shift no doubt arises from a breakdown of the H-bonding pattern in the unsubstituted compounds.[1]

The UV-Visible spectra of **2** and **3** show single absorptions with maxima at 275.5 and 278.4 nm, respectively; for **7** the maximum is shifted to higher wavelength at 309.5 nm, with a shoulder at 325 nm.

For both **2** and **3**, the methylene bridge protons in the ^{1}H NMR spectra appear as broad, unresolved signals at 3.4 and 4.1 ppm and 3.5 and 4.1 ppm, respectively. As no blocking groups are present at the phenolic rim, these compounds showing the expected fluxional behaviour of unsubstituted calix[4]arenes.[1]

Compounds **4,5,6** and **7** all show sharp signals for the axial and equatorial protons, (Figure **2**), implying that for all these compounds the conformation has been locked in place. In all cases, the axial-equatorial coupling constants are approximately 13 Hz. The highly symmetrical spectrum of **7** is consistent with a cone conformation. For compound **6**, the equatorial protons present at 3.56 ppm as a doublet suggest a fixed cone conformation, arising from a configuration in which all these protons would be effectively equivalent.

For compound **5**, two sets of axial and equatorial protons are present at 3.14 and 4.8 ppm and 3.26 and 4.92 ppm, as shown by a COSY spectrum. This is effectively consistent with either a cone or a strict semi-cone conformation. However, by analogy with previously obtained tetraester systems, we consider that a locked cone conformation is again present, in agreement with the molecular areas obtained from the Langmuir isotherms. Similarily, two sets of axial and equatorial protons are present for **4**, at 3.35 and 4.15 ppm and 3.45 and 4.48 ppm. By analogy with **5**, this system represents a cone conformation. The Langmuir compression isotherms for **4,5,6** and **7** are presented in Figure **3a–d**.

The apparent molecular areas (A_0) and monolayer collapse pressures are given in Table **1**.

It is evident that **4** does not orient at the air-water interface in the same manner as **5,6** and **7**. Given the presence of only one hydrophobic acyl chain and only one hydrophilic ester group, it is possible that the calixarene orients parallel to the air-water interface (Figure **4**).

This would correspond to a molecular area at 70 Å if both chain and ethyl ester are oriented at right angles to the water surface. This particular conformation is highly interesting as here the molecular cavity is parallel to the surface and not, as usually observed for macrocyclic am-

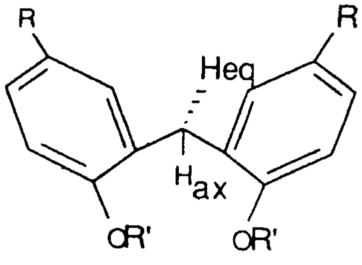

Figure 2

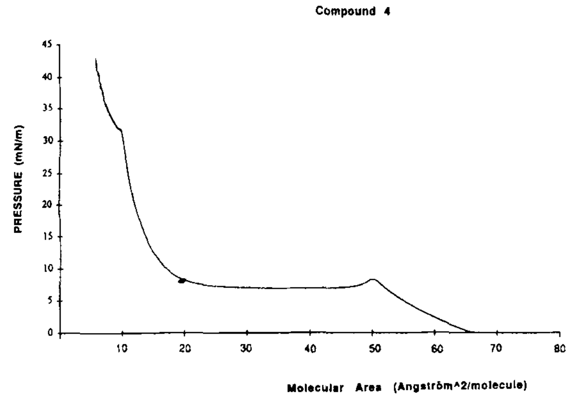

Figure 3a

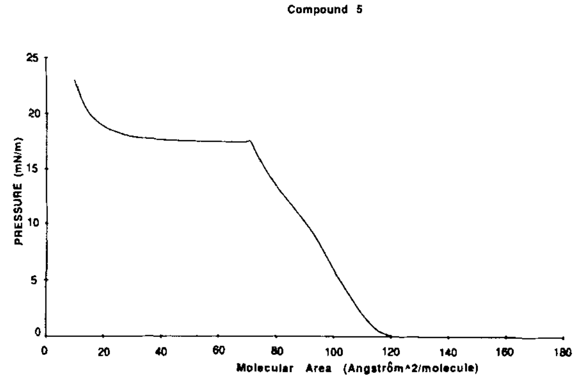

Figure 3b

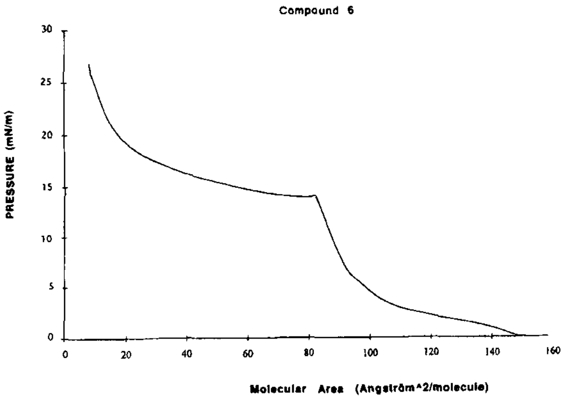

Figure 3c

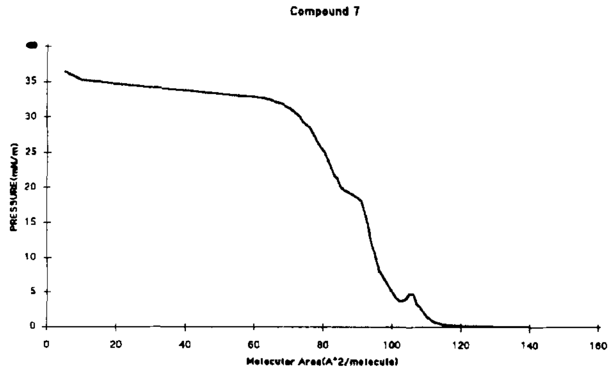

Figure 3d

phiphiles, orthogonal to it. However the low monolayer stability would tend to limit its application.

In contrast, **5**,**6** and **7** all show approximately the same A_0 at around 100 Å^2. This is similar to the value obtained by Shinkai for p-tert-butylcalix[4]arene coupled to alkyl ester groups.[8] **5** and **6** show similar collapse pressures suggesting that the hydrophobic and hydrophilic forces stabilising the monolayer are similar for these compounds. The area of **6** at which non-zero pressure is first observed is large (>150 Å^2) and would be expected to arise from chains spreading out over the aqueous surface. Here the steric hydrophilic interactions holding the calixarene to the surface are weaker (1 ester group, 3 hydroxyls) and the phenyl groups may tilt outwards allowing the chains more freedom of movement.

Table 1

	4	5	6	7
Ao(Å^2)	75	102	100	107
Π collapse (mN. m^{-1})	9	17	15	32

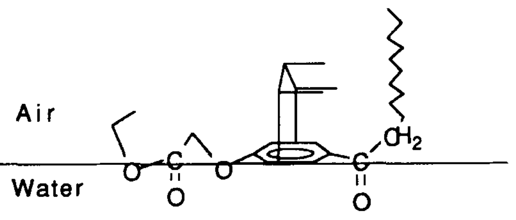

Figure 4

Compound **7** shows a quite different behaviour. There is a take-off value at ca. 120 Å^2 which undergoes a pseudo-collapse at 3 mN.m^{-1}. Similar behaviour has been observed by Regen[7] for his "octopus" molecules and, like him, we ascribe this behaviour to a rearrangement of the polar ester functions to give a more compact grouping. However, a second rearrangement is observed at 22 mN.m^{-1}. This can arise from a rearrangement of the calix itself, or from a reorientation of acyl chain carbonyl groups. The steeper curve of the compression isotherm suggest a less fluid layer organisation for **7** than for all the other systems.

EXPERIMENTAL

The "naked" calix[4]arene was synthesised via literature procedures.[1] Solvents were distilled under nitrogen over the appropriate drying agents. All chemical reagents were obtained from Aldrich Chemical Co. and used without further purification. Water for the monolayer measurements was obtained using a Milipor Milli-Q apparatus. All chromatography was carried out on silica gel S 0.032–0.063 mm (Riedel-de Haën) and thin layer chromatography was carried out on a silica gel 60F$_{254}$ plates (Merck). IR spectra were obtained as $CHCl_3$ solutions on a Perkin-Elmer 841 spectrometer. UV-Visible spectra were obtained as $CHCl_3$ solutions using a spectrometer. All ^1H (200MHz) and ^{13}C (50MHz) NMR spectra were recorded with a Bruker AC200 instrument spectrometer. Langmuir compression isotherm measurements were carried out using a KSV5000 film balance on a pure water subphase. Solutions of approximately 3.7 × 10^{16} molecules in $CHCl_3$ were spread on the surface and the solvent evaporated during 15 minutes. Compression was carried out at 25 mm.min^{-1} and all measurements repeated three times at least. Errors in the obtained values were less than ±0.5%.

5-dodecanoyl-25,26,27,28-tetrahydroxycalix[4]arene(2). 0.384 mL (1.65 mmol) of dodecanoyl chloride was dropped into a mixture of 0.7 g (1.65 mmol) of 25,26,27,28-tetrahydroxycalix[4]arene 1 and 0.44 g (3.3 mmol) of anhydrous aluminium chloride in 20mL of nitrobenzene under stirring. The mixture was continuously stirred for 3 h between 5 and 10°C. The reaction was stopped by addition of 30 mL of a solution of 1M hydrochloric acid and the water layer was extracted with chloroform (2 × 40mL). After the removal of solvent, the residue was crystallized from propanol (20 mL); 0.6 g (50%) of 2 was obtained.

^1H NMR ($CDCl_3$) : 0.8(CH_3,t,3H,7Hz), 1.2(CH_2, broad multiplet, 18H), 2.75(CH_2,t,2H,7Hz), 3.4(Ar-CH_2-Ar,broad s,4H), 4.1(Ar-CH_2-Ar,broad s,4H), 6.65(ArH,q,3H,7Hz), 7.05(ArH,broad multiplet,6H), 7.65(ArH,s,2H), 10.15(OH,s,4H).

^{13}C NMR ($CDCl_3$) : 14.05(C-1), 22.63(C-2), 24.49(C-3), 29.45–29.57(C-4,5,6,7,8,), 31.66(C-9,10,Ar-CH_2-Ar),38.15(CH_2-CO-Ar),122.19–122.45(ArC-H),131.40(ArC-R), 148.51–148.74(ArC-OH),153.28(R-ArC-OH), 198.74(C=O).

IR: νOH=3193 cm^{-1}, νCO=1674 cm^{-1}.

Mass spectrum, *m/e* 606.60 (M$^+$, calcd 606.76).

5,11,17,23-tetradecanoyl-25,26,27,28-tetrahydroxycalix[4]arene(3). 2.63 mL (11.32 mmol) of decanoyl chloride was added dropwise into a mixture of 1.2 g (2.83 mmol) of 25,26,27,28-tetrahydroxycalix[4]arene 1 and 3g (22.64 mmol) of anhydrous aluminium chloride in 40 mL of nitrobenzene under stirring. The mixture was continuously stirred at room temperature for 3 h. The reaction was stopped by addition of 33 mL 1M hydrochloric acid, and the aqueous layer was extracted with chloroform (2 × 50 mL). After the removal of solvent, the residue was crystallized from acetone (30 mL); 2.7 g (83%) of 3 was obtained.

^1H NMR ($CDCl_3$) : 0.7(CH_3,t,12H,8Hz), 1.1(CH_2, broad multiplet,72H), 2.7(CH_2,t,8H,7Hz),3.5(Ar-CH_2-Ar, broad peak,4H), 4.1(Ar-CH_2-Ar,broad peak,4H), 7.65(ArH,s,8H), 10.05(OH,s,4H).

^{13}C NMR ($CDCl_3$: 14.02(C(R)), 22.60(C(R)), 24.31(C-3), 29.26–29.76(C-4,5,6,7,8), 31.53(C-9), 31.82(C-10,Ar-CH_2-Ar), 38.25(CH_2-CO-Ar), 129.69(ArC-R), 152.52(ArC-OH), 198.46(C=O).

IR: νOH=3195 cm^{-1}, νCO=1679 cm^{-1}.

5-decanoyl-25(ethyl ester methylene oxy)calix[4]-arene(4). A suspension of 2 (150 mg, 0.247 mmol), and K_2CO_3 (20 mg, 0.148 mmol) in acetonitrile (10 mL) was stirred at reflux temperature for 0.5 h. The ethyl acetate bromide (0.274 mL, 2.47 mmol) was added and the reaction mixture was stirred for 24 h. After cooling the solvent was removed under reduced pressure. The remaining solid was taken up in CH_2Cl_2 (50 mL) and washed with 1M HCl (2 × 50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a crude product that was purified by colunn chromatography. Rf : 0.17 (Hexane/CH_2Cl_2, 1/20). 30mg (20%) of 4 was obtained.

^1H NMR ($CDCl_3$) : 0.7 (CH_3,t,3H,7Hz), 1.1 (CH_2,CH_3,broad multiplet,21H), 2.65 (CH_2,t,2H,7Hz), 3.3 (Ar-CH_2-Ar,t,4H,13Hz), 4.15 (CH_2,7Hz,Ar-CH_2-Ar,13Hz, broad multiplet,6H), 4.85 (CH_2,s,2H), 6.55 (ArH,t,3H,7Hz), 6.9 (ArH, broad multiplet,6H) 7.65 (ArH,s,2H), 8.95 (OH,s,2H), 9.65 (OH,s,1H).

^{13}C NMR ($CDCl_3$) : 14.12(C-1,CH_3-CH_2O), 22.62 (C-2), 24.60 (C-3), 29.28–29.58 (C-4,5,6,7,8), 31.28–31.85 (C-9,10,Ar-CH_2-Ar), 38.29 (CH_2-CO-Ar), 60.46–60.62 (CH_2-CO_2), 70.96 (CH_2-O-Ar), 119.17–119.47 (ArC-H), 132.75–133.99 (R'-ArC-R), 152.78–152.91 (ArC-OH), 157.73–156.41 (R-ArC-OR'), 168.51 (CO_2), 199.76 (C=O).

IR : νOH=3340 cm^{-1}, νCO2=1747 cm^{-1}, νCO=1679 cm^{-1}.

5-decanoyl-25,26,27,28-tetra(ethyl ester methylene-oxy)calix[4]arene(5). 0.5 g (4.34 mmol) of 2 was dissolved in 25 mL of THF at reflux temperature. The reaction was stirred under nitrogen. 0.346 g (8.68 mmol) of NaH (60% mineral oil dispersion was added in several times. 3.85 mL (34.72 mmol) of ethyl acetate bromide was dropped. After 5 h under these conditions, the reaction was stopped. The solvent and the ethyl acetate bromide were evaporated under vaccum. The residue was dissolved in dichloromethane and the organic layer was extracted from water (2 × 50 mL), evaporated under vaccum and purified by colunn chromatography. Yield: 70%. Rf:0.23. (Hexane/Ethyl acetate, 3/1).

^{1}H NMR (CDCl$_3$) : 0.75 (CH$_3$,t,12H,7Hz), 1.2 (CH$_2$,CH$_3$,broad multiplet, 30H), 2.6 (CH$_2$,t,2H,7Hz), 3.15 (Ar-CH$_2$-Ar,t,4H,13Hz), 4.1 (CH$_2$-CO$_2$,q,8H,7Hz), 4.6 (CH$_2$-O-Ar,Ar-CH$_2$-Ar,13Hz, broad multiplet, 12H), 6.5 (ArH,broad multiplet,3H), 6.7 (ArH,s,6H), 7.3 (ArH,s,2H).

IR : νCO2=1755 cm^{-1}, νCO=1673 cm^{-1}.

5,11,17,23-tetradecanoyl-25-(ethyl ester methylene-oxy)calix[4]arene(6). This compound is prepared via a procedure analogous to that of 4. Yield 25%. Rf:0.3. (Hexane/Ethyl acetate, 1/1).

^{1}H NMR (CDCl$_3$) : 0.8 (CH$_3$,t,12H,7Hz), 1.1 (CH$_2$,CH$_3$, broad multiplet,75H), 2.78 (CH$_2$,t,8H,7Hz), 3.56 (Ar-CH$_2$-Ar,d,4H,13Hz), 4.2 (Ar-CH$_2$-Ar,13Hz,CH$_2$-CO$_2$,7Hz, broad multiplet,6H), 4.9(CH$_2$,s,2H), 7.65(ArH, broad multiplet,8H), 9.2 (OH, broad peak,3H).

IR : νOH=3337 cm^{-1},νCO2=1749 cm^{-1},νCO=1679 cm^{-1}.

5,11,17,23-tetradecanoyl-25,26,27,28-tetra(ethyl ester methylene-oxy)calix[4]arene(7). This compound is prepared via a procedure analogous to that of 5. Yield : 92%. Rf:0.65. (Ethyl acetate/Acetone, 7/3).

^{1}H NMR (CDCl$_3$) : 0.7(CH$_3$,t,12H,7Hz), 1.1(CH$_2$,CH$_3$, broad multiplet,84H), 2.6(CH$_2$,t,8H,7Hz), 3.35(Ar-CH$_2$-Ar,d, 4H,14Hz), 4.1(CH$_2$,q,8H,7Hz), 4.7(CH$_2$,s,8H), 4.85(Ar-CH$_2$-Ar,d,4H,14Hz), 7.3(ArH,s,8H).

^{13}C NMR (CDCl$_3$) : 14.79((C-1,CH$_3$-CH$_2$O), 23.35(C-2), 24.5(C-3), 30.04–30.34(C-4,5,6,7,8), 31.45(C-9), 32.58(C-10,Ar-CH$_2$-Ar), 38.92(CH$_2$-CO-Ar), 61.51(CH$_2$-CO$_2$), 71.94(CH$_2$-O-Ar), 132.87(ArC-R), 160.28(ArC-OH), 170.16(CO$_2$), 199.73(C=O).

IR : νCO$_2$=1754 cm^{-1}, νCO=1679 cm^{-1}.

CONCLUSION

The selective synthesis of 4+4, 4+1, 1+4 and 1+1 amphiphilic calixarene derivatives has allowed the demonstration of the probable formation of layers in which the calixarene is parallel to the air-water interface for the 1+1 system. For the 4+1 and 1+4 systems, the effects of hydrophobic acyl and hydrophilic ester groups would seem to be equivalent and additive for the collapse stability of Langmuir layers. The 4+4 compound shows a more stable, compact packing accompanied by rearrangement of the head groups. The differences in behaviour should allow the tailoring of the monolayer properties of amphiphilic calixarenes to predefined uses.

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