Pergamon

Tetrahedron 58 (2002) 5591–5597

TETRAHEDRON

Synthesis of selectively formylated calixarene ethers

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Received 14 March 2002; revised 7 May 2002; accepted 30 May 2002

Abstract—By careful choice of a catalyst ($TiCl_4$ or $SnCl_4$), temperature, reaction time and mole ratio of the substrate to dichloromethylmethylether, it has been possible to obtain new functionalized formylated calix[*n*]arenes in the cone or partial cone conformation. Optimized general reaction procedures for obtaining mono-, di-, tri- and tetraformylated derivatives of calix[4]arenes as exemplified by formylation of tetramethoxy-, tetrakis(2-ethoxyethoxy)-, bis(ethoxycarbonylmethoxy)- and bis(hexadecyloxy)-calix[4]-arenes have been reported. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Calix[*n*]arenes are phenolic metacyclophanes, which possess a cavity and distinct hydrophilic (lower rim) and hydrophobic (upper rim) regions in their molecular architecture. They can be present in numerous interconvertible conformations[1] some of which can be immobilized via etherification of the lower rim or functionalization of the upper rim[2] for innovative applications.[3,4] Selectively formylated calix[*n*]arenes constitute important intermediates for obtaining a variety of molecular receptors for ionic and molecular recognition. Recently we have reported the reaction conditions for exhaustive formylation of calix[*n*]arenes.[5] In this paper, we report our attempts to achieve general optimized procedures for obtaining mono-, di-, tri- and tetraformyl calix[*n*]arene ethers by varying reaction parameters and catalysts.

1.1. Formylation of calixarenes

The formylation of calix[*n*]arenes can be achieved in a variety of ways as reported earlier[6–9] but the reaction usually results in low yields and uncertain conformations. In some cases the reaction results in a complicated mixture of products which is difficult to separate. The formylation of calixarenes using hexamethylenetetraamine (HMTA) in trifluoroacetic acid (TFA)[8] requires long reaction times and is considered good only for exhaustive formylation of calixarenes with no regio-selectivity. Likewise chloromethylation or hydroxymethylation followed by mild oxidation of the product to formyl calixarenes gives poor yields. Claisen migration of allylated calixarenes followed by ozonolysis or oxidative double bond cleavage also suffers from similar disadvantages. Recently, Pochini and coworkers[10] have successfully used dichloromethylmethyl ether and titanium tetrachloride for formylation of tetrakis(2-ethoxyethyl)calix[4]arene but they have not examined the case of other calixarenes and conformational selectivity. The outcome of reaction under different parameters has also not been elaborated so far. Since we required selectively formylated calix[*n*]arene ethers and esters with long alkyl chains, we had to optimize the reaction parameters to achieve desired derivatives since reported reaction conditions were not useful. During the execution of present work, characterization of products and conformational analysis was achieved by well-documented NMR methods. Direct comparison with authentic samples prepared by known routes confirmed the identity of products. New information gathered on the formylation of calixarenes is given in the ensuing discussion.

2. Results and discussion

The required alkoxycalixarenes were obtained from respective calix[*n*]arenes by reaction with alkyl halides in NaH/DMF.[7,12,13] These alkoxycalix[*n*]arenes were then subjected to reaction with dichloromethylmethylether in the presence of titanium tetrachloride and stannic chloride to yield formylated calix[*n*]arene ethers (Scheme 1). The choice of titanium tetrachloride and stannic chloride was based upon our earlier success in obtaining formylated calix[*n*]arene methyl ethers[5] and also because other Lewis acids often led to partially dealkylated calixarenes. It was observed that the Lewis acid catalysts employed in the present work did not change the conformation of the starting calixarenes during formylation. For example, formylation of partial cone conformer of tetramethoxycalix[4]arene under the conditions being reported provided a partial cone conformer of tetraformyl-tetramethoxycalix[4]arene in 61% yield. Stannic chloride being a milder Lewis acid was used for mono- and diformylation of tetraalkylated calixarenes

Keywords: selective; calix[4]arene; formylation.

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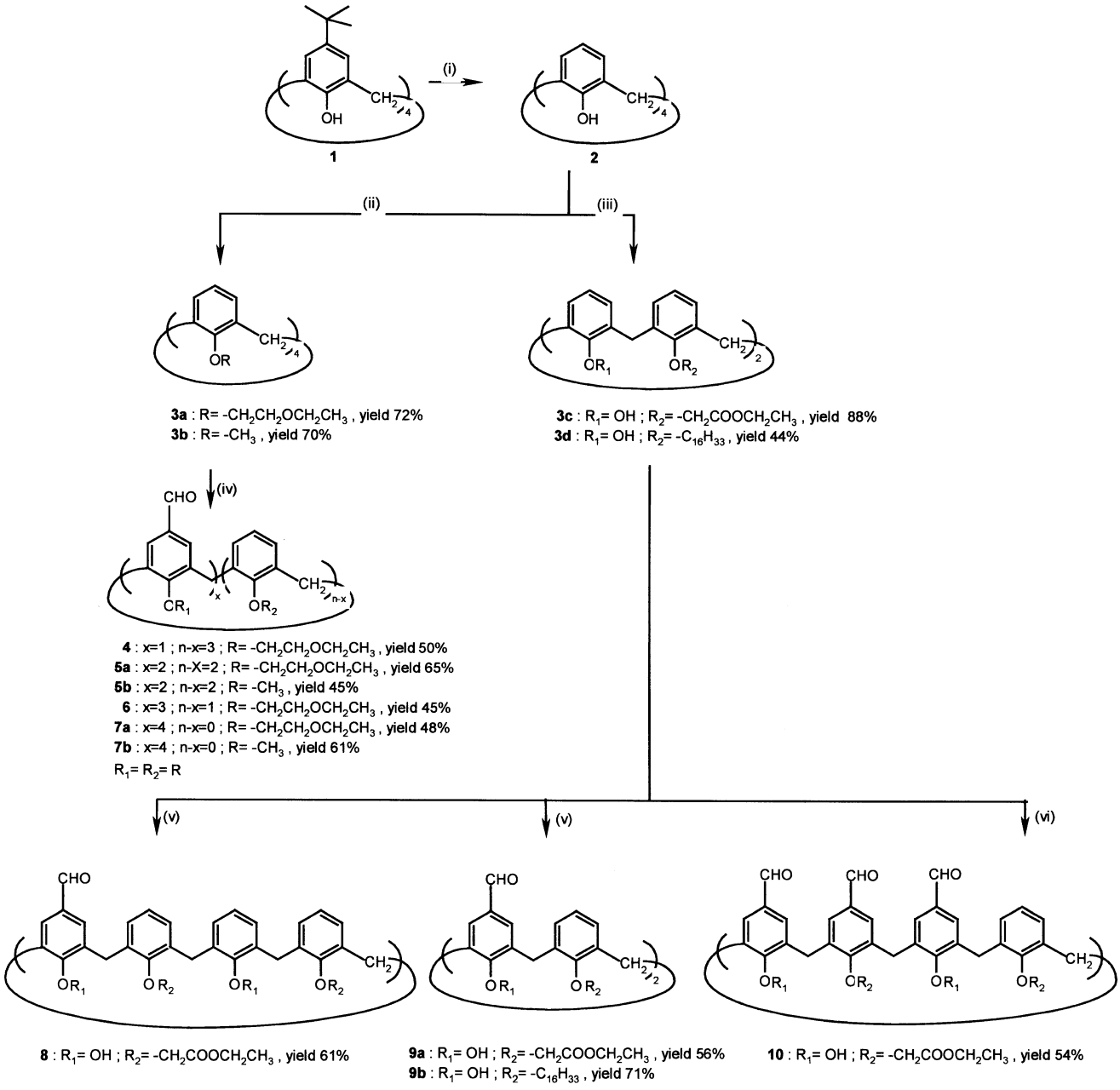
0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)00551-3



Scheme 1. (i) $AlCl_3$, PhOH, toluene, rt; (ii) RX, NaH, THF/DMF, reflux; (iii) RX, K_2CO_3, acetonitrile/acetone, reflux; (iv) Cl_2CHOCH_3, $TiCl_4/SnCl_4$, $CHCl_3$; (v) Cl_2CHOCH_3, $TiCl_4$, $CHCl_3$; (vi) HMTA, TFA, reflux.

while titanium tetrachloride was used for tri- and tetra-formylation of tetraalkylated calixarenes as well as for mono- and diformylation of dialkylated calixarenes.

2.1. Effect of the nature and length of alkoxy chains

Since titanium tetrachloride is known to complex with different alkylaryl ethers to a different extent, it was decided to examine the formylation of calixarene ethers with variable alkyl groups. Different calixarene ethers were prepared by alkylating calix[4]arene with methyl iodide, 2-ethoxyethoxybromide, 2-ethylbromoacetate and hexadecyloxybromide, respectively, under conditions known to effect selective as well as exhaustive alkylation. The synthesized fully alkylated and partially alkylated calix[4]arenes were formylated by using dichloromethylmethylether in the presence of $TiCl_4/SnCl_4$ and the products obtained were analyzed by TLC and NMR. It was observed that formylation of tetrakis(2-ethoxyethoxy)calix[4]arene only gave a diametrically (1,3) diformylated calix[4]arene (Fig. 1a) with a very negligible amount of proximal (1,2) diformylated calix[4]arene (Fig. 1b). This revealed that alkoxy chains potentially divert substituents to a diametrically opposite aryl residue as observed earlier.[11] When the length of chain was extended to hexadecyl, it was observed that formylation reactions predominantly gave the diformyl derivative only. For instance, bis(hexadecyloxy) calix[4]-arene (**3d**) (prepared by refluxing equivalent amounts of tetrahydroxycalix[4]arene (**2**), hexadecyl bromide and potassium carbonate in acetonitrile) gave the diformylated

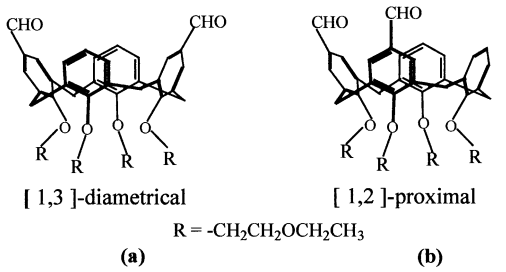


Figure 1. Positional isomers of diformyl calix[4]arene ethers.

bis(hexadecyloxy)calix[4]arene on formylation with dichloromethylmethylether and titanium tetrachloride at room temperature. It was observed that monoformyl, triformyl and tetraformyl derivatives of bis(hexadecyloxy)-calix[4]arene (**3d**) were not obtained even when a large excess of reagents or change in temperature was employed. ^{1}H NMR spectrum of diformyl-bis(hexadecyloxy)calix[4]-arene (**9b**) revealed that the compound was indeed present in the fixed cone conformation.

2.2. Effect of time of contact of substrate and the catalyst

The product of formylation was also observed to be affected by the time of contact of the catalyst and the substrate. This observation allowed us to optimize procedures and yields of specific formylated derivatives (Table 1) by adjusting only the reaction time while maintaining all other reaction parameters unchanged. For example, when formylation of bis(ethoxycarbonylmethoxy)calix[4]arene was carried out for 40 min at 25°C using $TiCl_4$ and Cl_2CHOCH_3, it yielded 61% of the monoformylated derivative with only 12% of the diformylated derivative. When the same reaction was repeated at the same temperature for 2 h, it yielded 56% of the diformylated derivative with only 8% of the monoformylated derivative. The diformylated product (**9a**) was confirmed to be present in the cone conformation by detailed study of the ^{1}H NMR spectrum (doublets at δ 3.51 and δ 4.46 (J=13.2 Hz) for $ArCH_2Ar$ protons). The monoformylated product (**8**) showed two pairs of doublets for methylene protons at δ 3.33 and δ 3.40 and δ 4.36 and δ 4.44 (J=13.2 Hz) indicating that it was either present in the cone conformation or in the partial cone conformation. Two-dimensional NMR spectral analysis of the monoformylated calix[4]arene showed that it was in fact present in the cone conformation as no cross-peaks were observed in its NOESY spectrum due to interaction of aromatic protons and the protons at the lower rim (i.e. the OH protons or $OCH_2COOCH_2CH_3$ protons). The above observations reveal that the reaction is sequential in nature, i.e. the substrate undergoes monoformylation followed by further reaction to diformylation. Further formylation does not take place under these conditions. When the reaction was carried out for a longer duration it gave a mixture which could not be analyzed completely. Such an effect of time of contact of catalyst and the substrate is reminiscent of the observations made in the reactivity of sharpless catalyst for epoxidation.

2.3. Effect of temperature of the reaction

The formylated product obtained was also observed to be strongly dependent on the reaction temperature. For instance, the partial cone conformer of tetramethoxycalix[4]arene gave the tetraformyl derivative (**7b**) in 61% yield when formylated at 25°C, while the yield was considerably reduced (32%) when the reaction was performed at a higher temperature (40°C). On the other hand, when the reaction was repeated at −10°C using Cl_2CHOCH_3 and $SnCl_4$ it gave the diformyltetramethoxycalix[4]arene (**5b**) in 45% yield. The conformation of the tetraformyl product was determined as partial cone by ^{1}H NMR spectrum which exhibited two pairs of doublets at δ 3.30 and δ 4.08 (J=14.0 Hz) and δ 3.4 and δ 4.42 (J=13.6 Hz) for methylene protons and four singlets in the ratio 1:1:1:1 for aromatic protons. The ^{1}H NMR spectrum of diformyl-tetramethoxycalix[4]arene (Fig. 2) exhibited multiplets at δ 2.95–4.4 for methylene protons as well as multiplets at δ 6.44–7.84 for aromatic protons. This indicated that the diformyl derivative was present in more than one unresolvable conformation. A similar temperature effect could also be observed in the case of other calix[4]arene ethers. Formylation of tetrakis(2-ethoxyethoxy)calix[4]arene (**3a**) when carried out by a slight modification of the published procedure (using Cl_2CHOCH_3 and titanium tetrachloride), it resulted in better yields of the products. For instance when **3a** was formylated at 40°C, it gave tetraformyltetrakis(2-ethoxyethoxy)calix[4]arene (**7a**) in 48% yield but when the temperature was lowered to 25°C, the same substrate with the same catalyst gave triformyltetrakis(2-ethoxyethoxy)calix[4]arene (**6**) in 45% yield. Change of the catalyst to a still milder stannic chloride and lower temperatures (−10°C) provided a mixture of mono- and diformyltetrakis(2-ethoxyethoxy)calix[4]arene which could be easily separated by column chromatography to provide monoformyltetrakis(2-ethoxyethoxy)calix[4]arene (**4**) (30% yield) and diformyltetrakis(2-ethoxyethoxy) calix[4]-arene (**5a**) (65% yield).

In the case of bis(ethoxycarbonylmethoxy)calix[4]arene

Table 1. Optimized reaction conditions for obtaining cone and partial cone conformers of calix[4]arene ethers

Starting material	Reagents	Temperature (°C)	Time (min)	Product	Yield (%)	Conformation
3a	$Cl_2CHOCH_3/SnCl_4$	−10	30	**4**	50	Cone
3a	$Cl_2CHOCH_3/SnCl_4$	−10	60	**5a**	65	Cone
3b	$Cl_2CHOCH_3/SnCl_4$	−10	30	**5b**	45	–
3a	$Cl_2CHOCH_3/TiCl_4$	25	60	**6**	45	Cone
3a	$Cl_2CHOCH_3/TiCl_4$	40	30	**7a**	48	Cone
3b	$Cl_2CHOCH_3/TiCl_4$	25	60	**7b**	61	Partial cone
3c	$Cl_2CHOCH_3/TiCl_4$	25	40	**8**	61	Cone
3c	$Cl_2CHOCH_3/TiCl_4$	25	120	**9a**	56	Cone
3d	$Cl_2CHOCH_3/TiCl_4$	25	90	**9b**	71	Cone
3c	HMTA/TFA	Reflux	1440	**10**	54	Cone

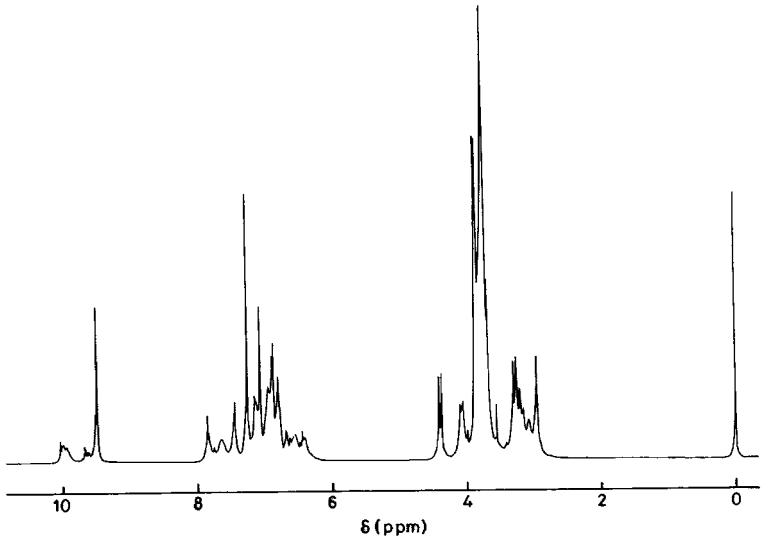


Figure 2. ^{1}H NMR spectrum of 5,17-diformyl-25,26,27,28-tetramethoxycalix[4]arene in $CDCl_3$ at 25°C.

(**3c**), although optimized yields of the mono- and diformyl derivatives could be obtained at room temperature by adjusting the reaction time, the triformylated bis(ethoxycarbonylmethoxy)calix[4]arene (**10**) could be isolated only in low yields (~29%) from the complicated mixture obtained when the reaction was carried out at 40°C. An optimized yield of triformylbis(ethoxycarbonylmethoxy)-calix[4]arene (54%) was obtained when the formylation of **3c** was carried at reflux temperature using HMTA in TFA (conditions known for exhaustive formylation).[8] The conformation of triformylbis(ethoxycarbonylmethoxy)-calix[4]arene (**10**) obtained was determined from its ^{1}H NMR spectrum (pair of doublets at δ 3.53 and δ 3.60 and δ 4.42 and δ 4.56 (J=13.5 Hz) for methylene protons) indicating that it was present in a cone conformation.

3. Conclusion

Various combinations of reaction parameters (mole ratios of reactants, time, catalyst, temperature, etc.) for the formylation of calixarene ethers were examined and the procedures were optimized for obtaining selectively formylated alkoxy calixarenes in the cone or partial cone conformation. These procedures are given in Section 4. Table 1 gives a summary of the standardized reaction conditions for obtaining mono-, di-, tri- and tetraformylated calixarenes in yields indicated. Conformational analysis of the products was arrived at mainly by NMR and comparison of data obtained with literature precedents.

In conclusion, we can state that by careful choice of catalyst, temperature, reaction time and mole ratio of the substrate to reagent, one can obtain regioselectively formylated calixarene ethers in good yields.

4. Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300DPX instrument. IR spectra were recorded on a Nicolet 5DX spectrometer. Column chromatography was performed on silica gel (Qualigens, 60–120 mesh). Chloroform was dried over phosphorus pentoxide before use. $SnCl_4$ was prepared by passing dry chlorine gas over tin granules followed by vacuum distillation of crude stannic chloride. $TiCl_4$ and Cl_2CHOCH_3 were commercially procured from Merck. $TiCl_4$ was re-distilled before use in the formylation reactions.

4.1. Synthesis of 1, 2, 3a–d

Compounds **1**,[1] **2**,[1] **3a**,[12] **3b**[7] and **3c**[13] were synthesized by the procedures reported in the literature.

4.1.1. Synthesis of 25,27-bis(hexadecyloxy)calix[4]arene (3d). A mixture of tetrahydroxycalix[4]arene (**2**) (1.0 g, 2.4 mmol), hexadecylbromide (6.0 g, 19.6 mmol) and anhydrous potassium carbonate (2.76 g, 20 mmol) was refluxed in dry acetone (28 ml) for 24 h. The reaction mixture was filtered to remove insoluble particles and the filtrate concentrated to one-quarter of its initial volume under reduced pressure beyond which no further concentration took place. The thick viscous liquid solidified on standing for 1 day, after which it was column-chromatographed over silica gel. The product was obtained when the column was eluted with 90% hexane/chloroform as a white solid. Mp 42–43°C, yield 0.19 g (44%); Anal. Calcd for $C_{60}H_{88}O_4$: C, 82.51; H, 10.15; Found: C, 82.3; H, 9.97; IR(ν_{max}, KBr): 2917(s), 2850(m), 1467(s), 1386(s), 1258(m), 1213(m), 1095(s), 990(m), 785(m), 719(m), 639(m) cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 0.81 (t, J=6.8 Hz, 6H, CH_3), 1.19 (bs, 48H, $-C_{12}H_{24}$), 1.59 (quintet, J=7.2 Hz, 4H, $-OCH_2CH_2CH_2C_{12}H_{24}$), 2.02 (quintet, J=7.1 Hz, 4H, $-OCH_2CH_2CH_2C_{12}H_{24}$), 3.92 (t, J=6.6 Hz, 4H, OCH_2), 3.29 (d, J=12.9 Hz, 4H, $ArCH_2Ar$), 4.24 (d, J=12.9 Hz, 4H, $ArCH_2Ar$), 6.56 (t, J=7.5 Hz, 4H, ArH), 6.66 (t, J=7.7 Hz, 4H, ArH), 6.84 (d, J=7.5 Hz, 2H, ArH), 6.97 (d, J=7.4 Hz, 2H, ArH), 8.16 (s, 2H, D_2O exchangeable OH).

4.2. General method for the synthesis of monoformyltetraalkoxycalix[4]arenes

1,1-Dichloromethylmethylether (1.13 g, 9.8 mmol) and tetraalkoxycalix[4]arene (0.70 mmol) were dissolved in chloroform (50 ml) and cooled to −10°C, tin tetrachloride (2.55 g, 9.8 mmol) was added and the reaction mixture was stirred for 30 min and then treated with water (100 ml). The organic layer was separated, washed twice with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the product was subjected to column chromatography.

4.2.1. Synthesis of 5-formyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (4). Purification by column chromatography (hexane/ethyl acetate 85:15) afforded 0.37 g of 5-formyl-25,26,27,28-tetrakis(2-ethoxyethoxy)-calix[4]arene (**4**) as a viscous oil (yield 50%); MS *m/e* 741 ($M+H^+$); Anal. Calcd for $C_{45}H_{56}O_9$: C, 72.94; H, 7.61; Found: C, 73.02; H, 7.70; IR(ν_{max}, KBr): 2966(m), 2866(m), 1691(s), 1595(m), 1451(m), 1260(s), 1108(bs), 1023(bs), 800(s) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.12 and 1.27 (2t, J=7.0 Hz, 12H, OCH_2CH_3), 3.14 and 3.22 (2d, J=13.5 Hz, 4H, $ArCH_2Ar$), 3.53 (q, J=7.2 Hz, 8H, OCH_2CH_3), 3.81 (t, J=7.1 Hz, 8H, OCH_2CH_2O), 4.12 (t, J=7.1 Hz, 8H, OCH_2CH_2O), 4.47 and 4.56 (2d, J=13.5 Hz, 4H, $ArCH_2Ar$), 6.52 (t, J=7.1 Hz, 3H, ArH), 6.65 (d, J=7.2 Hz, 6H, ArH), 7.11 (s, 2H, ArH), 9.61 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, δ): 15.2, 30.8, 66.3, 69.6, 69.8, 73.2, 73.6, 122.2, 122.5, 128.1, 128.2, 128.6, 130.0, 131.1, 134.3, 135.3, 136.8, 157.7, 156.9, 162.6, 191.6.

4.3. General method for the synthesis of diformyltetraalkoxycalix[4]arenes

A solution of the appropriate tetraalkoxycalix[4]arene (1.04 mmol) in chloroform (30 ml) was cooled to −10°C. A solution of 1,1-dichloromethylmethylether (1.43 g, 12.5 mmol) in chloroform and a solution of tin tetrachloride (3.25 g, 12.5 mmol) in chloroform were added to it. The reaction mixture was stirred at −10°C for 30 min and then water (100 ml) was added. The organic layer was separated and washed twice with saturated Na_2CO_3 solution, twice with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product obtained was subjected to column chromatography to get specific compounds in good yields as given below.

4.3.1. 5,17-Diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (5a). Column chromatographic separation of the crude product (obtained by subjecting tetra(2-ethoxyethoxy)calix[4]arene (**3a**) according to the general methods described above) by using hexane/ethyl acetate (8:2) as the eluent afforded 5,17-diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (**5a**) (0.52 g, yield 65%); mp 64–66°C; MS *m/e* 769 ($M+H^+$); Anal. Calcd for $C_{46}H_{56}O_{10}$: C, 71.85; H, 7.34; Found: C, 72.0; H, 7.52; IR(ν_{max}, KBr): 2850(m), 2791(m), 1694(s), 1594(s), 1450(m), 1381(w), 1262(s), 1110(bs), 1025(bs), 812(s) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.17 and 1.20 (2t, J=6.9 Hz, 12H, OCH_2CH_3), 3.26 (d, J=13.7 Hz, 4H, $ArCH_2Ar$), 3.51 and 3.54 (2q, J=6.9 Hz, 8H, OCH_2CH_3), 3.81–3.84 (m, 8H, OCH_2CH_2O), 4.14 and 4.18 (2t, J=5.3 Hz, 8H, OCH_2CH_2O), 4.58 (d, J=13.7 Hz, 4H, $ArCH_2Ar$), 6.68–6.76 (m, 6H, ArH), 7.05 (s, 4H, ArH), 9.48 (s, 2H, CHO); ^{13}C NMR ($CDCl_3$, δ): 15.3, 30.7, 66.3, 69.6, 69.7, 73.4, 73.6, 122.8, 128.5, 130.0, 131.2, 134.2, 136.4, 156.0, 162.3, 191.6.

4.3.2. 5,17-Diformyl-25,26,27,28-tetramethoxy-calix[4]-arene (5b). Purification of the crude product (obtained from formylation of tetramethoxycalix[4]arene under general reaction conditions described above) by column chromatography using hexane/ethyl acetate (9:1) as the solvent for elution afforded 0.15 g of 5,17-diformyl-25,26,27,28-tetramethoxycalix[4]arene (**5b**) (yield 45%); mp 80–82°C; Anal. Calcd for $C_{34}H_{32}O_6$: C, 76.10; H, 6.01; Found: C, 76.31; H, 6.22; IR(ν_{max}, KBr): 1687(s), 1597(m), 1468(s), 1384(m), 1281(s), 1210(m), 1130(s), 1014(s) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.95–4.40 (m, 20H, $ArCH_2Ar$, OCH_3), 6.44–7.84 (m, 10H, ArH), 9.48–10.3 (1s and 1m, 2H, CHO); ^{13}C NMR ($CDCl_3$, δ): 30.3, 30.7, 35.2, 36.4, 59.5, 61.0, 61.4, 61.8, 122.0, 122.3, 123.1, 125.7, 128.7, 129, 129.4, 129.7, 130.0, 130.5, 132.3, 132.7, 134.7, 135.0, 135.7, 136.2, 137.6, 157.8, 159.8, 163.0, 191.5, 191.7.

4.4. General method for the synthesis of triformyltetraalkoxycalix[4]arenes

To a solution of tetraalkoxycalix[4]arene (0.28 mmol) in chloroform (20 ml) was added a solution of 1,1-dichloromethylmethylether (1.12 g, 9.8 mmol) in chloroform (5 ml) and a solution of titanium tetrachloride (1.5 g, 7.9 mmol) in chloroform (5 ml) simultaneously and as quickly as possible. The reaction mixture was stirred at room temperature for 1 h and then treated with water (50 ml). The organic layer was separated, washed twice with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel.

4.4.1. 5,11,17-Triformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (6). Column chromatographic purification of the crude product obtained through the general formylation procedure described above by using hexane/ethyl acetate (75:25) as the eluent afforded 5,11,17-triformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)-calix[4]arene (**6**) (0.1 g, 45%); mp 58–60°C; MS *m/e* 797 ($M+H^+$); Anal. Calcd for $C_{47}H_{56}O_{11}$: C, 70.8; H, 7.08; Found: C, 70.71; H, 6.98; IR(ν_{max}, KBr): 1692(s), 1596(m), 1452(m), 1384(m), 1261(s), 1109(bs), 1024(bs), 800(s) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.07–1.18 (m, 12H, OCH_2CH_3), 3.18 and 3.25 (2d, J=13.4 Hz, 4H, $ArCH_2Ar$), 3.39–3.49 (m, 8H, OCH_2CH_3), 3.67–3.79 (m, 8H, OCH_2CH_2O), 4.01 (t, J=5.3 Hz, 2H, OCH_2CH_2O), 4.10–4.23 (m, 6H, OCH_2CH_2O), 4.47 (d, J=13.4 Hz, 2H, $ArCH_2Ar$), 4.56 (d, J=13.4 Hz, 2H, $ArCH_2Ar$), 6.45 (s, 3H, ArH), 7.01 (s, 2H, ArH), 7.16 (s, 4H, ArH), 9.54 (s, 1H, CHO), 9.56 (s, 2H, CHO); ^{13}C NMR ($CDCl_3$, δ): 15.1, 30.7, 66.3, 69.3, 69.5, 69.7, 73.4, 73.8, 74.0, 122.7, 128.4, 130.0, 130.1, 130.4, 131.2, 131.4, 134.0, 135.5, 136.0, 156.0, 162.2, 191.2, 191.4.

4.5. General method for synthesis of tetraformyltetraalkoxycalix[4]arenes

A solution of tetraalkoxycalix[4]arene (0.5 g, 0.7 mmol) in chloroform (12 ml) and a solution of titanium tetrachloride (3.32 g, 17.5 mmol) in chloroform (12 ml) were added simultaneously through dropping funnels to a stirred solution of 1,1-dichloromethylmethylether (4.0 g, 35.0 mmol) in chloroform (12 ml) at 40°C over a period of 10 min. The reaction mixture was stirred for additional 20 min and then treated with water (150 ml). The organic layer was separated and worked up in a similar manner as described above. The residue obtained was purified by column chromatography.

4.5.1. 5,11,17,23-Tetraformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (7a). Purification of the crude product obtained by subjecting the tetrakis(2-ethoxyethoxy)calix[4]arene to the general formylation conditions described above through column chromatography (hexane/ethyl acetate 65:35) afforded 5,11,17,23-tetraformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (0.28 g, yield 48%) as a viscous oil. MS *m/e* 825 ($M+H^+$); Anal. Calcd for $C_{48}H_{56}O_{12}$: C, 69.88; H, 6.84; Found: C, 70.04; H, 6.95; IR(ν_{max}, KBr): 1691, 1591, 1470, 1384, 1268, 1152, 840 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 1.17 (t, J=7.0 Hz, 12H, OCH_2CH_3), 3.33 (d, J=13.9 Hz, 4H, $ArCH_2Ar$), 3.50 (q, J=7.0 Hz, 8H, OCH_2CH_3), 3.78 (t, J=4.7 Hz, 8H, OCH_2CH_2O), 4.20 (t, J=4.7 Hz, 8H, OCH_2CH_2O), 4.62 (d, J=13.9 Hz, 4H, $ArCH_2Ar$), 7.16 (s, 8H, ArH), 9.59 (s, 4H, CHO); ^{13}C NMR ($CDCl_3$, δ): 15.2, 30.8, 66.4, 69.6, 73.9, 130.2, 131.5, 135.7, 161.9, 191.2.

4.5.2. 5,11,17,23-Tetraformyl-25,26,27,28-tetramethoxycalix[4]arene (7b). This compound was synthesized from **3b** by employing the procedure reported earlier[10] as pale yellow crystals (yield 61%); mp 218–220°C; MS *m/e* 593 ($M+H^+$); Anal. Calcd for $C_{36}H_{32}O_8$: C, 72.96; H, 5.44; Found: C, 72.84; H, 5.18; IR(ν_{max}, KBr): 1693(s), 1597(s), 1471(m), 1428(m), 1385(m), 1283(m), 1128(s) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.96–4.44 (3s and 4d, 20H, $ArCH_2Ar$ and OCH_3), 6.82, 7.46, 7.71, 7.84 (4s, 8H, ArH), 9.50, 9.63, 9.99 (2s and 1d, J=9.8 Hz, 4H, CHO).

4.6. 11-Formyl-25,27-bis(ethoxycarbonylmethoxy)-calix[4]arene (8)

To a stirred solution of bis(ethoxycarbonylmethoxy)-calix[4]arene (**3c**) (0.1 g, 0.167 mmol) in chloroform (10 ml), was added a solution of 1,1-dichloromethylmethylether (0.635 g, 5.52 mmol) in chloroform (4.0 ml) followed by addition of a solution of titanium tetrachloride (0.865 g, 4.56 mmol) in chloroform (4.0 ml). The reaction mixture was stirred at room temperature for 40 min and then treated with water. The organic layer was washed twice with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography (hexane/ethyl acetate 8:2) to yield 11-formyl-25,27-bis(ethoxycarbonylmethoxy)calix[4]arene (**8**) as colorless needles (0.064 g, 61%); mp 168–170°C; Anal. Calcd for $C_{37}H_{36}O_9$: C, 71.14; H, 5.81; Found: C, 71.01; H, 5.90; IR(ν_{max}, KBr): 3394(bs), 2961(m), 1747(s), 1675(s), 1582(m), 1467(s), 1209(s), 1089(s), 1055(bs), 767(m) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.29 (t, J=7.2 Hz, 6H, OCH_2CH_3), 3.33 and 3.4 (2d, J=13.2 Hz, 4H, $ArCH_2Ar$), 4.28 (q, J=7.2 Hz, 4H, OCH_2CH_3), 4.36 and 4.44 (2d, J=13.2 Hz, 4H, $ArCH_2Ar$), 4.57–4.73 (AB quartet, J=15.6 Hz, 4H, OCH_2COO), 6.58 (t, J=7.5 Hz, 1H, ArH), 6.71 (t, J=7.5 Hz, 2H, ArH), 6.86 (d, J=7.2 Hz, 4H, ArH), 6.98 (d, J=7.2 Hz, 2H, ArH), 7.54 (s, 2H, ArH), 8.62 (s, 2H, OH), 9.70 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, δ): 14.0, 31.2, 31.4, 61.4, 72.4, 119.1, 125.7, 127.8, 128.4, 128.6, 129.0, 129.5, 130.9, 132.0, 133.1, 152.1, 152.8, 159.3, 168.6, 190.8.

4.7. General method for diformylation of dialkoxy-calix[4]arenes

A solution of 1,1-dichloromethylmethylether (5.5 mmol) in chloroform (10 ml) was added to a solution of dialkoxy-calix[4]arene (0.167 mmol) in chloroform (4 ml) with stirring at room temperature followed by addition of a solution of titanium tetrachloride (4.6 mmol) in chloroform (4 ml). The reaction mixture was stirred for a further period of 2 h and then worked up in a similar manner as described above. The product obtained was subjected to column chromatography to yield the formylated derivatives as given below.

4.7.1. 11,23-Diformyl-25,27-bis(ethoxycarbonylmethoxy)-calix[4]arene (9a). This compound was obtained after purification of the crude product obtained by subjecting the bis(ethoxycarbonylmethoxy)calix[4]arene (**3c**) to the general formylation conditions as described above by column chromatography (hexane/ethyl acetate 7:3) (yield 0.06 g, 56%); mp 210–211°C; MS *m/e* 653 ($M+H^+$); Anal. Calcd for $C_{38}H_{36}O_{10}$: C, 69.92; H, 5.56; Found: C, 69.81; H, 5.40; IR(ν_{max}, KBr): 3373(bs), 3013(m), 2919(m), 1750(s), 1676(s), 1586(s), 1481(m), 1310(m), 1211(bs), 1159(m), 1085(s), 773(m) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.36 (t, J=7.2 Hz, 6H, OCH_2CH_3), 3.51 (d, J=13.2 Hz, 4H, $ArCH_2Ar$), 4.36 (q, J=7.1 Hz, 4H, OCH_2CH_3), 4.46 (d, J=13.2 Hz, 4H, $ArCH_2Ar$), 4.72 (s, 4H, OCH_2COO), 6.82 (t, J=7.5 Hz, 2H, ArH), 6.97 (d, J=7.5 Hz, 4H, ArH), 7.62 (s, 4H, ArH), 8.68 (s, 2H, OH), 9.78 (s, 2H, CHO); ^{13}C NMR ($CDCl_3$, δ): 14.0, 31.15, 61.5, 72.3, 125.9, 128.3, 128.5, 129.4, 130.8, 132.1, 152.0, 159.0, 168.5, 190.6.

4.7.2. 11,23-Diformyl-25,27-bis(hexadecyloxy)-calix[4]-arene (9b). This compound was obtained after chromatographic purification (hexane/ethyl acetate 9:1) of the crude product obtained when bis(hexadecyloxy)calix[4]arene (**3d**) was subjected to general formylation conditions as described above. (0.11 g, yield 71%); mp 130–132°C; MS (vapor pressure osmometry): 910 (Calcd 928); Anal. Calcd for $C_{62}H_{88}O_6$: C, 80.17; H, 9.48; Found: C, 80.21; H, 9.40; IR(ν_{max}, KBr): 2920(m), 2849(m), 1684(s), 1399(s), 1458(m), 1312(s), 1262(s), 1132(m), 1077(m), 955(s), 802(m) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.87 (t, J=6.8 Hz, 6H, $-CH_3$), 1.25 (bs, 48H, $OCH_2CH_2CH_2C_{12}H_{24}CH_3$), 1.69 (quintet, J=7.5 Hz, 4H, $OCH_2CH_2CH_2C_{12}H_{24}-$), 2.07 (quintet, J=7.3 Hz, 4H, $OCH_2CH_2CH_2C_{12}H_{24}-$), 3.49 (d, J=13.1 Hz, 4H, $ArCH_2Ar$), 4.03 (t, J=6.4 Hz, 4H, OCH_2), 4.29 (d, J=13.1 Hz, 4H, $ArCH_2Ar$), 6.79 (t, J=7.5 Hz, 2H,

ArH), 6.96 (d, J=7.5 Hz, 4H, ArH), 7.63 (s, 4H, ArH), 9.20 (s, 2H, OH), 9.78 (s, 2H, CHO).

4.7.3. 5,11,23-Triformyl-25,27-bis(ethoxycarbonylmethoxy)calix[4]arene (10). A mixture of bis(ethoxycarbonylmethoxy)calix[4]arene (**3c**) (0.1 g, 0.167 mmol) and HMTA (0.85 g, 6.064 mmol) in TFA (10 ml) was refluxed. After 24 h, the mixture was poured into 100 ml of ice/water and extracted with chloroform. The chloroform solution was washed with water and dried over Na_2SO_4. Concentration of the solution followed by dilution with hexane gave the precipitate which was recrystallized from chloroform/hexane. (0.0615 g, yield 54%); mp 182–184°C; Anal. Calcd for $C_{39}H_{36}O_{11}$: C, 68.81; H, 5.33; Found: C, 68.46; H, 5.29; IR(ν_{max}, KBr): 3375(bs), 3013(m), 2918(m), 1749(s), 1675(s), 1586(s), 1481(m), 1467(m), 1443(m), 1390(w), 1310(s), 1274(s), 1210(s), 1156(m), 1130(m), 1085(s), 1061(s), 911(w), 829(w), 773(m), 687(w), 588(w) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.36 (t, J=7.2 Hz, 6H, CH_2CH_3), 3.53 (d, J=13.5 Hz, 2H, $ArCH_2Ar$), 3.60 (d, J=13.5 Hz, 2H, $ArCH_2Ar$), 4.38 (q, J=7.1 Hz, 4H, OCH_2CH_3), 4.42 (d, J=13.5 Hz, 2H, $ArCH_2Ar$), 4.55 (d, J=13.5 Hz, 2H, $ArCH_2Ar$), 4.72 and 4.78 (2s, 4H, OCH_2CO), 6.81 (t, J=7.2 Hz, 1H, ArH), 6.97 (d, J=7.5 Hz, 2H, ArH), 7.48 (s, 2H, ArH), 7.67 (s, 4H, ArH), 8.50 (s, 2H, D_2O exchangeable OH), 9.68 (s, 1H, CHO) and 9.81 (s, 2H, CHO).

Acknowledgements

Authors are thankful to CSIR, New Delhi for research fellowship (to A. S. and V. A.) and Department of Science and Technology, Government of India for financial assistance.

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