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Alkylation of Narrow Rim Calix[4]arenes in a DMSO-NaOH Medium

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Abstract

An effective method of 5,11,17,23-tetra-*tert*-butyl-25,26-dialkoxy-27,28-dihydroxy-calix[4]arenes and 25,26,27,28-tetraalkoxycalix[4]arenes synthesis by alkylation of tetrahydroxycalix[4]arenes in a DMSO–NaOH medium was developed.

Introduction

Calixarenes [1, 2] are bowl-shaped macrocyclic compounds synthesized by the condensation of para-substituted phenols with formaldehyde. They are widely used as building blocks for synthesis of host molecules with different supramolecular functions, due to their capability to recognize, bind and separate cations similar in properties or anions or neutral organic molecules. Utilization of calixarenes as chemical sensors, extractants for radioactive waste processing, materials for non-linear optics, bio-active compounds has been reported [3a–c].

Alkylation of hydroxyl groups at the narrow (lower) rim of calix[4]arenes is a relevant stage in the design of these materials.

Preparative syntheses of monoalkoxy-, 25,26-dialkoxy-, 25,27-dialkoxy -, trialkoxy - and tetraalkoxycalix[4]arenes in miscellaneous conformations like *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* [4] are being developed.

Alkylation of tetrahydroxycalix[4]arenes with excess of alkyl halides in the presence of mild bases (Na_2CO_3, K_2CO_3, CsF) results in high yields of monoalkoxy- [5–7] or distally substituted 25,27-dialkoxycalix[4]arenes [8–10]. Use of two equivalents of the alkylating agent and excess of strong bases such as NaH in DMF medium allows the receiving of proximally substituted 25,26-dialkoxycalix[4]arenes with 15–55% yield [11]. The maximum yield of 25,26-regioisomere (70% after column chromatography) was reached by alkylation of *para-tert*-butylcalix[4]arene **1a** with specific reactant – 2-chloromethylpyridine [12]. Trialkoxycalix[4]arenes were synthesized by alkylation of tetrahydroxycalix[4]arenes in DMF solution in the presence of BaO as the base [13]. Tetraalkylated calix[4]arenes were prepared with high yields by using both alkyl halides and NaH excess in DMF medium [14, 15]. Monoalkylated, 25,26-dialkylated, 25,27-dialkylated, tri- and tetraalkylated calix[4]arenes were obtained predominantly in the *cone* conformation in the indicated conditions.

The diversity of the alkylation ways is explained by the drastic decrease of the OH groups acidity [16] ($\Delta pK > 14$) during their step-by-step deprotonation resulted in a formation of strong intramolecular hydrogen bonds [17] at the narrow rim.

In this article we investigate alkylation of OH groups of calix[4]arenes in a DMSO–NaOH system. This medium has been successfully used for alkylation of primary or secondary phosphines and phosphine oxides possessing low acidic P–H functional groups [18]. The success of the P-alkylation is explained by the lower acidity of water (pK = 31.4) in the DMSO medium [19] compared with P–H proton acidity in the DMSO solution. Although pK parameters of tetrahydroxycalix[4]arene in DMSO solution were not determined [16], it was interesting to examine the DMSO–NaOH medium for the lower rim alkylation as an alternative to the classic DMF–NaH system which is widely used for preparation of 25,26-dialkyl or tetraalkylcalix[4]arenes.

Results and discussion

para-tert-butylcalix[4]arene **1a** is easily alkylated by alkyl bromides in the presence of an excess of 40% sodium hydroxide water solution at 70 °C within 4 h. The reaction is regio- and stereoselective and leads to proximally 25,26-disubstituted products **2a–c** in the *cone* conformation with high yields (Scheme 1).

The structure of calixarenes **2a–c** was approved by spectral data. In the ^{1}N NMR spectrum of **2a** ($CDCl_3$ solution) the equatorial protons of the methylene groups of the macrocyclic skeleton give a complicated superposition of three overlapping doublets at 3.33 ppm. The axial protons display three doublets at 4.32, 4.33, 4.48 ppm (2H, 1H, 1H $^2J_{H-H}$ = 12.9, 13.4, 12.5 Hz respectively). It should be noted that the doublet at 4.33 ppm of the methylene group, linking with two non-alkylated phenol fragments (identified by COSY

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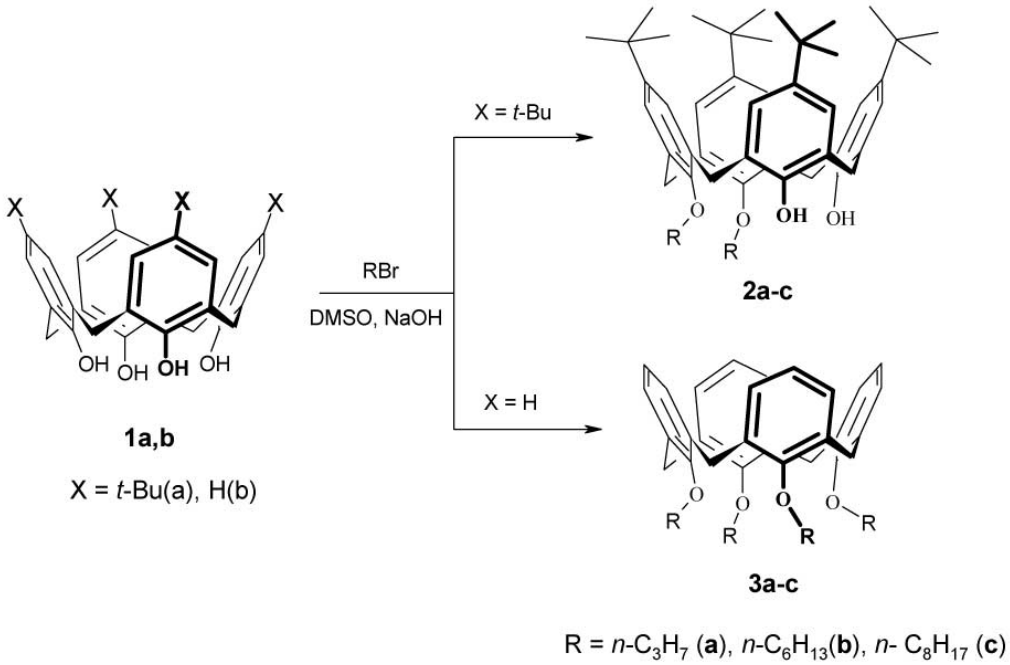


Scheme 1.

experiment), is shifted to 4.29 ppm when concentration of **2a** is decreased from 0.1 M to 0.00625 M (see Figure 1). The concentration dependence of other signals is less expressed.

The aromatic protons show four doublets of identical intensity at 6.97, 6.99, 7.02, 7.05 ppm ($^2J_{H-H} = 2.2$, 2.5, 2.2, 2.5 Hz respectively). The protons of OCH_2 groups, due to their diastereotopicity, are registered by two doublets at 3.79 and 3.98 ppm ($^2J_{H-H} = 7$ Hz) of *AB* spin system in ^{1}H NMR spectra under decoupling of the spin–spin interaction of the protons of the nearest methylene group.

The narrow rim hydroxyl groups of calixarenes **2** form strong intramolecular hydrogen bonds. As a result, the IR spectrum (KBr pellet) of **2a** shows two bands of OH groups at 3193 cm^{-1} (stretch, O–*H*· · ·O–H)) and 3365 cm^{-1} (stretch, O–*H*· · ·O–C_3H_7) [20, 21].

However, in contrast to the DMF–NaH system the alkylation in DMSO–NaOH medium is finished at the stage of dialkylated calixarenes **2a-c**. Simultaneous increase of the temperature up to 100 °C and the reaction time to 72 h as well as an increase of the concentration of the reactants does not result in further alkylation of compounds **2a–c**. An attempt to use alkyl tosylates as more active reactants did not lead to more alkylated products. Yields of compounds **2a–c** have strongly decreased, in this case due to the hydrolysis of the tosylates.

It should be noted that the proximal OH groups of calixarenes can be alkylated under stronger conditions. For example, reaction of 25,26-dipropoxycalix[4]arene **2a** with methylmonobromacetate in DMF in the presence of a strong base such as NaH gives 25,26-dipropoxy-27,28-bis(methoxycarbonylmethoxy)calix[4]arene **4** (Scheme 2) which is a promising synthon for the design of host molecules.

There is a great difference in the reactivity of the proximal (25,26-disubstituted) and distal (25,27-disubstituted) regioisomers of dialkylated *tert*-butylcalix[4]arenes in DMSO-NaOH system. 25,27-Dipropoxycalix[4]arene **5** [10] was easily alkylated in the DMSO–NaOH medium by propyl bromide with formation of tetrapropoxycalix[4]arene **6** in the *cone* conformation (Scheme 3).

The substituents at the *para*-positions of benzene rings (upper or wide rim) drastically influence the reactivity of tetraxydroxycalix[4]arenes in the DMSO–NaOH medium. The reaction of tert-butyl depleted calix[4]arene **1b** with a 10-fold excess of alkyl bromides and NaOH water solution in DMSO at 60–70 °C leads to tetraalkoxycalix[4]arenes **3a–c** in the *cone* conformation with high yields (Scheme 1, Experimental). Stereoselectivity of the reaction decreases at the higher temperature. Impurity (5–10%) of the *partial cone* conformation of tetraalkoxycalix[4]arenes is formed at a reaction temperature of 75–85 °C. The increase of the chain of alkyl bromide slows down the reaction. The longer alkyl chain is the higher concentration of the NaOH water solution is needed to complete the reaction (40% of NaOH water solution for propyl bromide, 50% for hexyl bromide and 60% for octyl bromide). An attempt to interrupt the reaction at the stage of the dialkylation failed. Decrease of the calixarene : alkyl bromide : NaOH ratio to 1:2:2 causes formation of a complicated mixture of mono-, di-, and tetraalkoxycalix[4]arenes similar to the DMF–NaH system [11, 12].

As a conclusion, DMSO–NaOH medium can be recommended as an alternative to the standard DMF–NaH system for preparation of tetraalkoxycalix[4]arenes and p-*tert*-butyl-25,26-dialkoxycalix[4]arenes. Simplicity and safety of the procedure, high regio- and stereoselectivity of the reaction and good yields of the desirable compounds distinguish

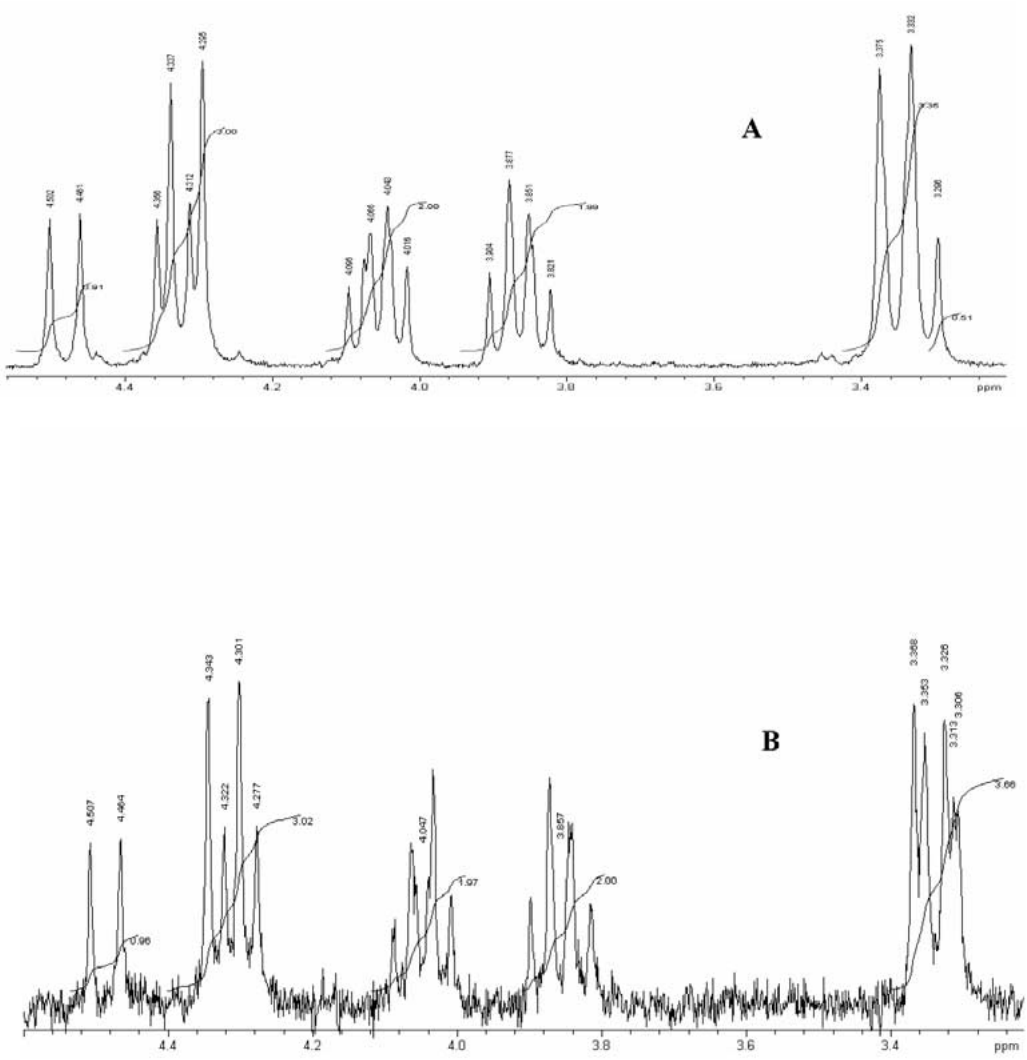
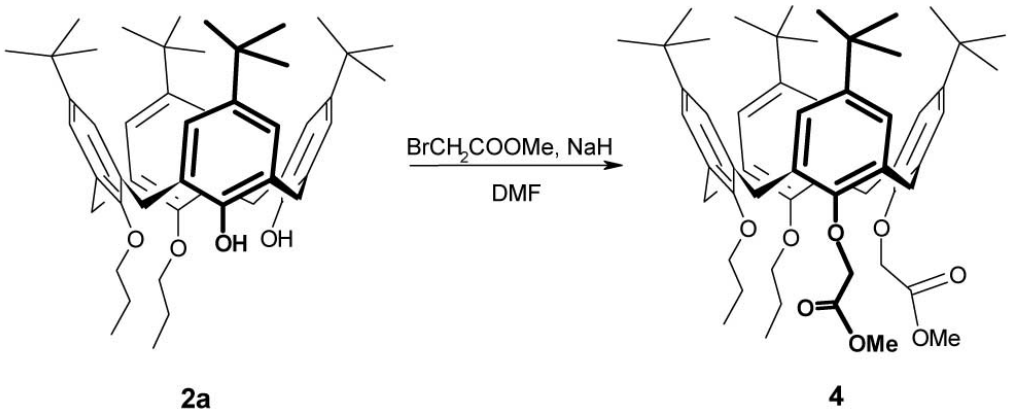
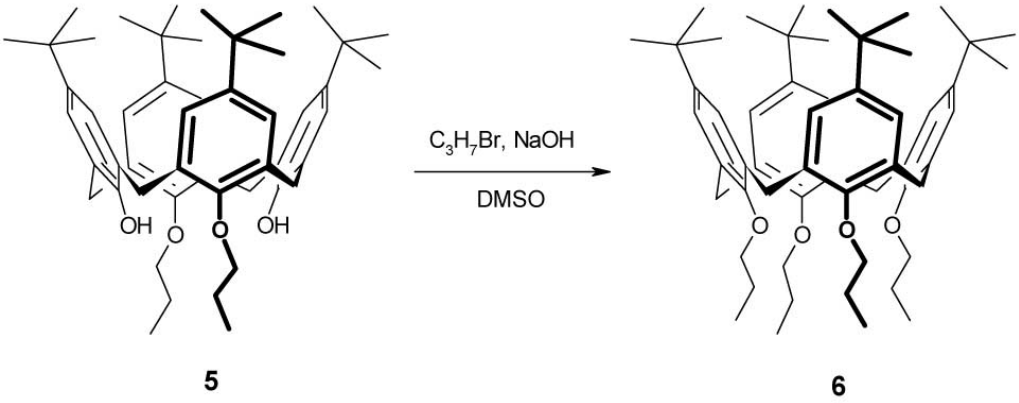


Figure 1. Fragments of the ^{1}H NMR spectra of **2a** in $CDCl_3$: C = 0.1 M (A), C = 0.00625 M (B).



2a **4**

Scheme 2.



Scheme 3.

this method. Purity of the crude compounds isolated before the stage of crystallization is satisfactorily high for synthetic purposes.

Experimental

Melting points determined on a Boëtius apparatus are uncorrected. ^{1}H, ^{13}C NMR spectra were recorded on Varian VXR-300 spectrometer (299.943 or 75.429 MHz) in $CDCl_3$ solution (TMS as internal standard).

*Alkylation of tert-butyl-calix[4]arenes **1a** and **5***

General procedure 1. Sodium hydroxide (40% water solution, 3.53 ml, 50.05 mmol NaOH) and then calixarene **1a** or **5** (5.40 mmol) were added to DMSO (25 ml). The reaction mixture was warmed to 50 °C. Alkyl bromide (21.60 mmol) was added and the mixture was stirred for 4–6 h at 70–75 °C. After cooling to 20 °C the reaction mixture was poured into the diluted hydrochloric acid. Compounds **2a**, **6** were filtered off, dried and crystallized from acetonitrile. Compounds **2b**, **c** were extracted by chloroform, dried with sodium sulfate. Chloroform was evaporated the residue was washed with methanol and crystallized from acetonitrile.

*5,11,17,23-Tetra-tert-butyl-25,26-dipropoxy-27,28-dihydroxycalix[4]arene **2a***

Yield: 93%, m.p. 118–124 °C, (119–124 °C [10]). IR (KBr), ν, cm^{-1}: 3365 (O—H$\cdots$O–C_3H_7, stretch, wide band), 3193 (O–H$\cdots$O–H, stretch, wide band), 2973 and 2888 (CH). ^{1}H NMR (δ, ppm, C = 0.1 M): 1.13 (t, s, overlapped, 24H, OCH_2–CH_2–CH_3 and t-Bu); 1.21 (s, 18 H, t-Bu), 2.1 (m, 4H, OCH_2–CH_2–CH_3); 3.33 (3 overlapped doublets, 4H, Ar–CH_2–Ar *equatorial*); 3.86 and 4.05 (2 m, 2H each, diastereotopic OCH_2); 4.48, 4.33, 4.32 (3d, 2H, 1H, 1H J^2_{H-H} = 12.5, 13.4, 12.9 Hz, respectively, Ar–CH_2–Ar *axial*); 6.97, 6.99, 7.02 and 7.05 (4 d, 2H each, J^4_{H-H} = 2.2, 2.5, 2.2, 2.5 Hz, ArH); 8.81 (s, 2H, OH). ^{13}C NMR (δ, ppm): 10.34 (CH_3 (Pr)); 23.24 (CH_2 (Pr)); 30.58, 31.44 (Ar CH_2Ar); 31.25, 31.49 (CH_3 (t-Bu)); 32.53 (Ar–CH_2–Ar); 33.84, 34.02 (C (t-Bu)); 78.01 (–OCH_2 (Pr)); 125.03, 125.31, 125.84, 125.87 (C–H (ArH)); 128.39, 128.89, 133.16, 133.89, 142.519, 146.46, 149.02, 151.36 (C (ArH)).

*5,11,17,23-Tetra-tert-butyl-25,26-dihexyloxy-27,28-dihydroxycalix[4]arene **2b***

Yield: 80%, m.p. 135–140 °C. IR (KBr, ν, cm^{-1}): 3359 (O-*H*$\cdots$O–C_3H_7, stretch, wide band), 3205 (O–*H*$\cdots$O–H, stretch, wide band), 2960 and 2871 (CH). ^{1}H NMR (δ, ppm): 0.76–1.49 (m, 54H, t-Bu and OCH_2–CH_2–($\mathbf{CH_2}$)$_3$–$\mathbf{CH_3}$); 2.03 (m, 4H, OCH_2–$\mathbf{CH_2}$–$(CH_2)_3$–CH_3); 3.27 (3d overlapped, 4H, Ar–CH_2–Ar *equatorial*); 3.84, 4.01 (2 m, 2H each, $\mathbf{OCH_2}$–CH_2–$(CH_2)_3$–CH_3); 4.24, 4.27, 4.41 (3 d, 2H, 1H, 1H, J^2_{H-H} = 13.0, 13.2, 12.2 Hz, Ar–CH_2–Ar axial); 6.89, 6.92, 6.95, 6.98 (4 d, 2H each, J^4_{H-H} = 2.2, 2.5, 2.2, 2.5 Hz, ArH); 8.77 (s, 2H, OH). Calculated, %: C 82.30; H 9.87. $C_{56}H_{80}O_4$. Found, %: C 82.20; H 9.80.

*5,11,17,23-Tetra-tert-butyl-25,26-dioctyloxy-27,28-dihydroxycalix[4]arene **2c***

Yield: 76%, m.p. 120–123°C. ^{1}H NMR (δ, ppm): 0.76–1.49 (m, 62H, t-Bu and OCH_2–CH_2–($\mathbf{CH_2}$)$_5$–CH_3), 2.03 (m, 4H, OCH_2–$\mathbf{CH_2}$–$(CH_2)_5$–CH_3), 3.27 (3d overlapped, 4H, Ar–CH_2–Ar *equatorial*), 3.85, 4.00 (2 m, 2H each, $\mathbf{OCH_2}$–CH_2–$(CH_2)_5$–CH_3); 4.25, 4.27, 4.42 (3d, 2H, 1H, 1H, J^2_{H-H} = 13.0, 13.2, 12.2 Hz, respectively, Ar–CH_2–Ar *axial*), 6.88, 6.92, 6.95, 6.97 (4d, 2H each J^4_{H-H} = 2.2, 2.5, 2.2, 2.5 Hz, ArH); 8.82 (s, 2H, OH). Calculated, %: C 82.52; H 10.16. $C_{60}H_{88}O_4$. Found, %: C 82.20; H 10.11.

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrapropoxycalix[4]arene **6***

Yield: 85%, m.p. 243–245 °C. ^{1}H NMR (δ, ppm): 0.9 (t, 12H, OCH_2-CH_2-$\mathbf{CH_3}$); 1.0 (s, 36H, t-Bu); 1.95 (m, 8H, OCH_2–$\mathbf{CH_2}$–CH_3); 3.05 (d, 4H, J^2_{H-H} = 12.7 Hz, Ar–CH_2–Ar *equatorial*); 3.75 (t, 8H, $\mathbf{OCH_2}$–CH_2–CH_3); 4.35 (d, 4H, J^2_{H-H} = 12.7 Hz, Ar-CH_2-Ar *axial*); 6.7 (s, 8H, ArH).

*5,11,17,23-Tetra-tert-butyl-25,26-dipropoxy-27,28-bis(methoxycarbonylmethoxy)-calix[4]arene **4***

NaH, 60% suspension in mineral oil (0.2 g, 5 mmol NaH) was placed in the dried round-bottomed flask and washed with dry benzene (5 ml). Dry DMF (10 ml) and calixarene **2a** (0.682 mmol) was added to NaH. The reaction mixture was stirred at 50 °C for 1 h. Methylmonobromacetate (3.4 mmol) was added to the reaction mixture and then mixture was stirred at 50–55 °C for 5 h. The solvent was evaporated under reduced pressure and dichlormethane (15 ml) was added to the residue. The organic layer was washed with saturated NH_4Cl (50 ml) and then with brine (2 × 75 ml), separated and dried over Na_2SO_4. Further, CH_2Cl_2 was distilled off and the solid colorless residue was crystallized from acetonitrile. Yield 85%, m.p. 181–182 °C. ^{1}H NMR (δ, ppm): 0.99 (t, 6H, –OCH_2–CH_2–C**H$_3$**); 1.07 and 1.08 (s, 18H each, t-Bu); 2.02 (m, 4H, –OCH_2–C**H$_2$**–CH_3), 3.16 (3 overlapped d, Ar–CH_2–Ar *equatorial*); 3.77 and 3.81 (s and m, 10H, OC**H$_2$**–CH_2–CH_3 and –OCH_3); 4.40; 4.59; 4.88 (3d, 1H, 2H, 1H respectively, J^2_{H-H} = 12.8 Hz, Ar–CH_2–Ar *axial*); 4.77 and 4.78 (2s, 4H, –OCH_2(C=O)–); 6.78 (m, 8H, ArH).

*Alkylation of calix[4]arene **1b***

General procedure 2. Similar to general procedure 1. Starting from calixarene **1b** (4.70 mmol), alkyl bromide (47.06 mmol), NaOH (40.1 mmol, **3a** – 40%, **3b** – 50%, **3c** – 60% water solution) in DMSO (20 ml). The reaction mixture was stirred for 2 h at 60 °C. After cooling to 20 °C the reaction mixture was poured into the diluted hydrochloric acid. Compounds **3a–c** were filtered off, dried and crystallized from acetonitrile.

*25,26,27,28-Tetrapropoxycalix[4]arene **3a***

Yield: 85%, m.p. 192–194 °C, (190.5–192.3 °C [21]). ^{1}H NMR (δ, ppm): 0.98 (t, 12H, –OCH_2–CH_2–C**H$_3$**); 1.9 (m, 8H, OCH_2–C**H$_2$**–CH_3); 3.15 (d, 4H, J^2_{H-H} = 13.4 Hz, Ar–CH_2–Ar *equatorial*); 3.84 (t, 8H, OC**H$_2$**–CH_2–CH_3); 4.46 (d, 4H, J^2_{H-H} = 13.4 Hz, Ar–CH_2–Ar *axial*); 6.59 (m, 12H, ArH).

*25,26,27,28-Tetrahexyloxycalix[4]arene **3b***

Yield: 75%, m.p. 94.5–95 °C, (94.4–94.8 °C [22]). ^{1}H NMR (δ, ppm): 0.95 (t, 12H, -CH_2-C**H$_3$**); 1.39 (m, 24H, OCH_2–CH_2–C**H$_2$**–C**H$_2$**–C**H$_2$**–CH_3); 1.94 (m, 8H, OCH_2–C**H$_2$**–CH_2–CH_2–CH_2–CH_3); 3.17 (d, 4H, J^2_{H-H} = 13.5 Hz, Ar–CH_2–Ar *equatorial*); 3.91 (t, 8H, OCH_2); 4.48 (d, 4H, J^2_{H-H} = 13.5 Hz, Ar–CH_2–Ar *axial*); 6.63 (m, 12H, ArH).

*25,26,27,28-Tetraoctyloxycalix[4]arene **3c***

Yield: 60%, m.p. 80.0–80.5 °C, (80.1–80.5 °C [23]). ^{1}H NMR (δ, ppm): 0.90 (t, 12H, CH_2–C**H$_3$**); 1.30 (m, 40H, OCH_2–CH_2–C**H$_2$**–C**H$_2$**C**H$_2$**–C**H$_2$**–CH_3); 1.90 (m, 8H, OCH_2–C**H$_2$**–CH_2–CH_2–CH_2–CH_2–CH_2–CH_3); 3.16 (d, 4H, J^2_{H-H} = 13.2 Hz, Ar–CH_2–Ar *equatorial*); 3.90 (t, 8H, OCH_2); 4.47 (d, 4H, J^2_{H-H} = 13.2 Hz, Ar–CH_2–Ar *axial*); 6.62 (m, 12H, ArH).

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