Monatsh Chem 139, 1103–1108 (2008)
DOI 10.1007/s00706-008-0901-9
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Thionation of tetrakis[(ethoxycarbonyl)methoxy]tetrathiacalix[4]arenes with *Lawesson*'s reagent

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Received 15 January 2008; Accepted 24 February 2008; Published online 29 April 2008

Abstract Tetra- and tri-thioated derivatives of tetrakis[(ethoxycarbonyl)methoxy]tetrathiacalix[4]arenes were synthesized by thionation with *Lawesson*'s reagent in dry toluene. The prepared compounds' structures were investigated by FT-IR, ^{1}H NMR, 2D-NMR, MALDI-TOF-MS, and X-ray crystallography.

Keywords Calixarene; Thiacalixarene; *Lawesson*'s reagent; Thionation; Synthesis.

Introduction

Ever since calixarenes have been presented to the supramolecular chemistry research community [1], they have met a great interest due to their wide range of applications within catalysis, molecular recognition, and ion separation [2–4]. These macrocycles can be synthesized from cheap and commercially available starting materials, *e.g.*, 4-*tert*-butylphenol and formaldehyde. A wide variety of calixarenes has been prepared [5, 6]. These differ in ring size, in the substitutions on the upper and/or lower rims, and on the CH_2 bridge groups. Recently, thiacalixarenes [7–9] have been prepared. In these members of the calixarene family [6] the CH_2 bridges are replaced by sulfur atoms. Owing to the coordination of the bridging sulfur atoms with metal ions, thiacalix[4]-arenes were found to bind transition metal ions very well without the introduction of supplementary ligating groups at the lower or upper rims [10, 11]. The optimization of calixarenes and thiacalixarenes for different application purposes is usually achieved by derivatization. Therefore, our attention has been focused on the preparation of thiacalixarenes with a higher number of sulfur atoms. This modification is expected to additionally increase metal complexation properties. Previously, attempts have been undertaken to increase the number of sulfur atoms by preparing tetramercaptotetrathiacalixarene [12].

Here, we report the synthesis and structure determination of five new thiacalix[4]arene derivatives containing four and/or three sulfur atoms in O-ethyl-thioate groups **2**–**6**.

Results and discussion

Compounds **1a**–**1c** in three different conformers *cone*, *partial cone*, and *1,3-alternate* (Fig. 1), were prepared following the procedure given by *Hosseini et al.* [13] and refluxed with *Lawesson*'s reagent in dry toluene. In addition to the tetrathioated thiacalix[4]arenes **2**, **4**, and **6** in *cone*, *partial cone*, and 1,*3-alternate* conformation, we also observed the formation of trithioated thiacalixarenes **3** and **5** (in *cone* and *partial cone* conformation) (Scheme 1).

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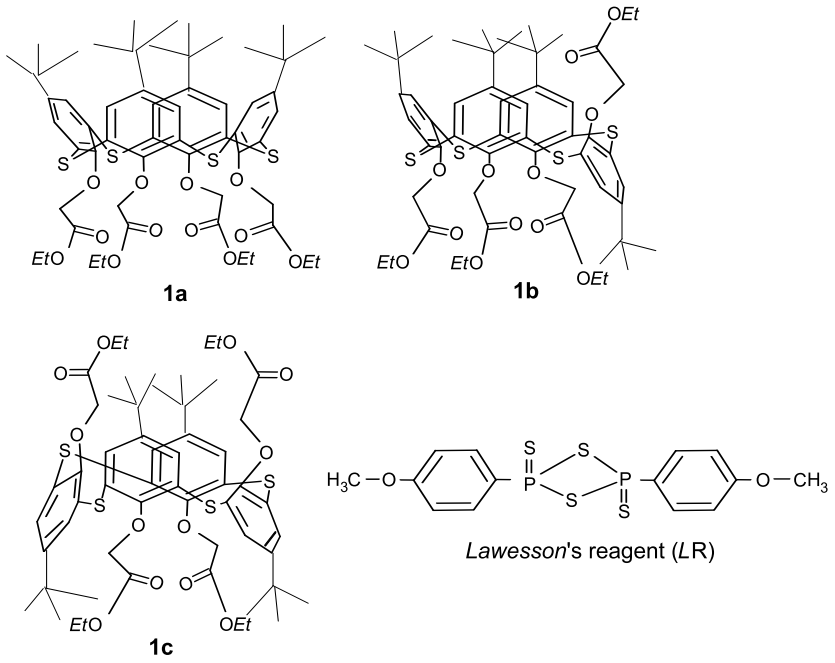
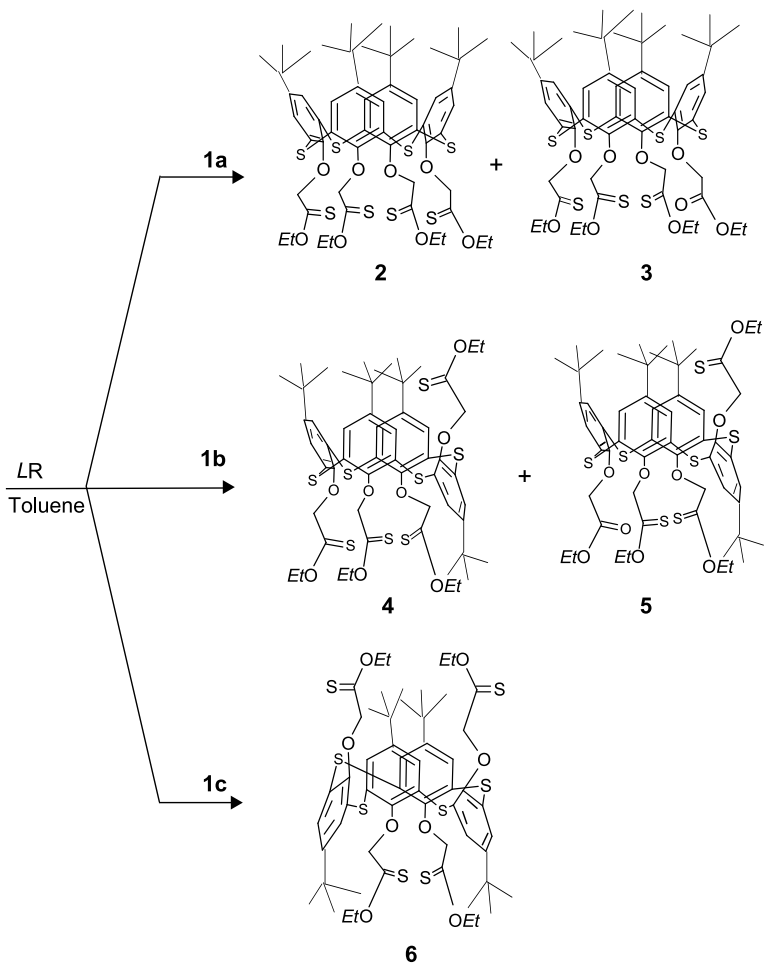


Fig. 1 Tetrakis[(ethoxycarbonyl)methoxy]tetrathiacalixarenes **1a**–**1c** and *Lawesson*'s reagent



Scheme 1

FT-IR, ^{1}H NMR, MALDI-TOF-MS, and X-ray crystallography were used to determine and verify the structures of the thiacalixarenes **2**–**6**. FT-IR analysis of the tetrathioated thiacalixarenes **2**, **4** and **6** showed a complete disappearance of the carbonyl stretching band, whereas the trithioated thiacalixarenes **3** and **5** featured a stretching band of the carbonyl group at $\bar{\nu} = 1769\,\mathrm{cm}^{-1}$. Compounds **2**, **4** and **6** showed an intense peak in the MALDI-TOF-MS spectrum at $m/z = 1129.69$, whereas **3** and **5** showed an m/z of 1113.62. The C=S group causes a stronger deshielding of neighboring ^{1}H resonances than the C=O group. Apart from this additional deshielding by approximately $\delta = 0.25$ ppm ^{1}H NMR spectra of **2**, **4** and **6** in $CDCl_3$ were very similar to those of the parent thiacalixarenes **1a**, **1b**, and **1c**. The trithioated thiacalixarenes **3** and **5**, in the *cone* and *partial cone* conformation, have the same symmetry (point group C_S) and hence similar NMR signal patterns as the *partial cone* thiacalixarenes **1a** and **4**. The hydrogen atoms of the $-OCH_2CO$-moiety and the $-OCH_2CS$-moieties located at opposite sides of the macrocycle are enantiotopic and, hence, only yield a single (singlet) NMR resonance. The hydrogen atoms of the $-OCH_2CS$-moieties adjacent to the $-OCH_2CO$-moiety, however, are diastereotopic, as the replacement of either of them (by an arbitrary test substituent) would lead to the formation of diastereomers. Hence, the two hydrogen atoms in the latter CH_2 groups will potentially yield different signals. However, due to the C_S symmetry, they will be pairwise equivalent, so that we can expect two doublet signals arising from these two CH_2 groups. Altogether, we expect two singlet and two doublet resonances for the $-OCH_2CO$- and $-OCH_2CS$-moieties in **3** and **5**.

The aromatic protons of **3** and **5** yield four NMR signals, one for the aromatic ring bearing the $-OCH_2CO$-moiety, one for the aromatic ring opposite to it, and two identical pairs of weakly ($^4J = 4.2$ Hz) scalarly coupled resonances from the remaining two rings. According to the above discussion **3** has only one possible conformer. However,

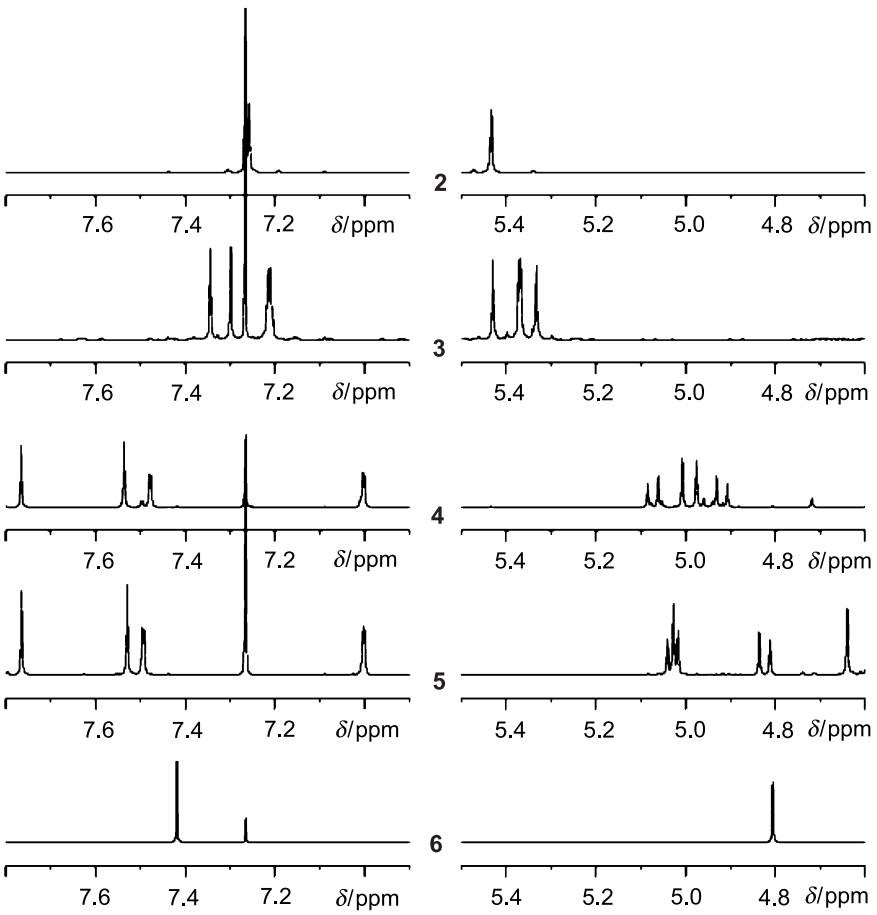


Fig. 2 Partial ^{1}H NMR spectra of **2**, **3**, **4**, **5**, and **6** ($CDCl_3$, 600 MHz). For each compound, the aromatic region and the region containing the $-OCH_2C{=}O$- and $-OCH_2{-}C{=}S$-peaks are shown

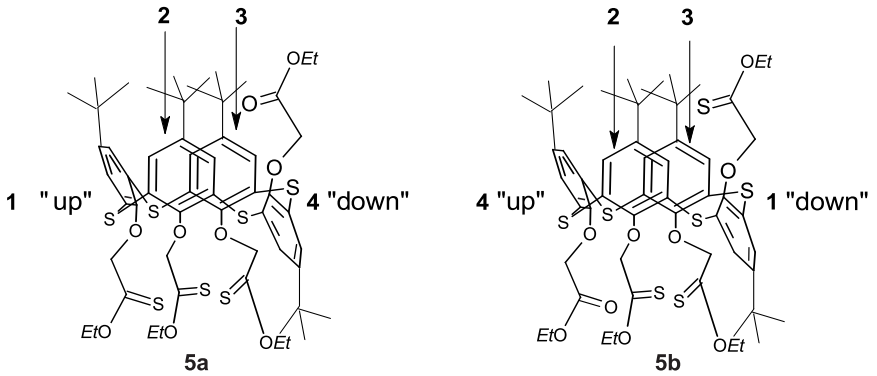


Fig. 3 The two possible isomers (labeled **5a** and **5b**) for **5**. Ring systems are numbered arbitrarily in such way, that ring 4 is always the one bearing the C=O group. ''Up'' and ''down'' are arbitrary definitions to facilitate the discussion of NMR evidence for the structure of **5**. Rings 2 and 3 are always ''up''

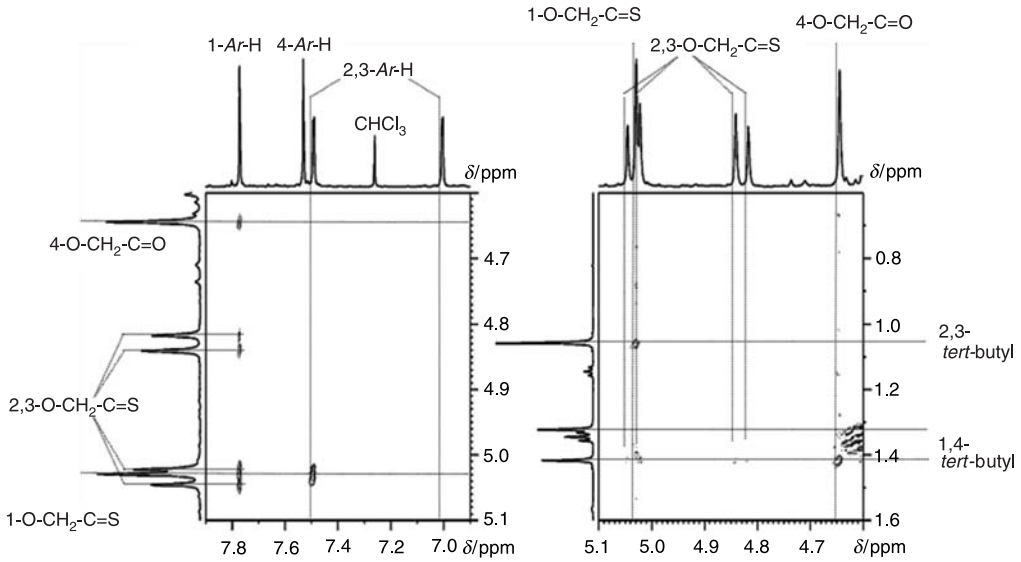


Fig. 4 2D ROESY NMR of **5**. Assignments written in normal type can be done without knowing the correct structure, based on symmetry, chemical shift, and multiplicity considerations. Assignments shown in bold can be done with knowledge of the correct structure of **5**

the spectroscopic evidence for **5** could be consistent with the two isomeric structures shown in Fig. 3. The effect of the shielding calixarene cavity [13, 14] for the asymmetric structures and 2D ROESY NMR (Fig. 4a and b) were used to find the conformation of **5**.

Comparing the ^{1}H NMR signals of **4** and **5** shows that changing one C=S to C=O leads to an upfield shift of one singlet O–CH_2–C=O/S signal by $\delta = 0.35$ ppm. Since compounds **4** and **5** both have the *partial cone* conformation, this change can only be ascribed to the lesser deshielding of the C=O group as compared to the C=S group, hence the singlet O–CH_2–C=O/S signal with the lower shift ($\delta = 4.64$ ppm) is assigned to the O–CH_2–C=O group, and hence to ring 4.

Figure 4a shows the ROESY cross peaks from the O–CH_2–C=O/S groups to the aromatic hydrogen atoms: the CH_2 group of ring 1 (C=S) shows a cross peak to an aromatic doublet. That is only possible if ring 1 points ''down'' (see Fig. 3 for the definition of ''down'' and ''up''). If ring 4 were pointing ''down'', then there should be a cross peak from the signal at $\delta = 4.64$ ppm to the aromatic doublet. On the contrary, the –O–CH_2–C=O signal at $\delta = 4.64$ ppm has a cross peak to the same aromatic singlet as the

O–CH_2–C=S signals from rings 2 and 3, which means, they have to point towards the same side.

For the *tert*-butyl groups, the argument is essentially the same. Figure 4b shows the ROESY cross peaks from the *tert*-butyl groups to the O–CH_2–C=O/S groups. Also here, the O–CH_2–C=O group shows a cross peak to either the 1 or 4 *tert*-butyl group, and not to the 2,3-*tert*-butyl groups. If ring 4 pointed ''down'', the –O–CH_2–C=O group should give a cross peak to the 2,3-*tert*-butyl groups. However, the O–CH_2–C=S group of ring 1 gives a cross peak to the 2,3-*tert*-butyl groups. This is only possible if ring 1 points ''down''. Altogether, there is compelling evidence that ring 1 points ''down'', and the correct structure of **5** is **5b** as shown in Scheme 1. Compounds **2**, **3**, **4**, **5,** and **6** were obtained in 50, 25, 45, 25, and 85% yields and their interactions with different chemical species are under investigation.

Single crystals of **6** were prepared from a solution in methylene chloride:acetonitrile (2:1) and its crystal structure is shown in Fig. 5. The crystallographic data in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC299162. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. X-ray data: $C_{56}H_{72}O_8S_8$, $M=1129.79$, tetragonal, $a=19.038$ Å, $b=19.038$ Å, $c=16.870$ Å, $\alpha=\beta=\gamma=90.00°$, $V=6114.2$ Å^3, and $Z=4$.

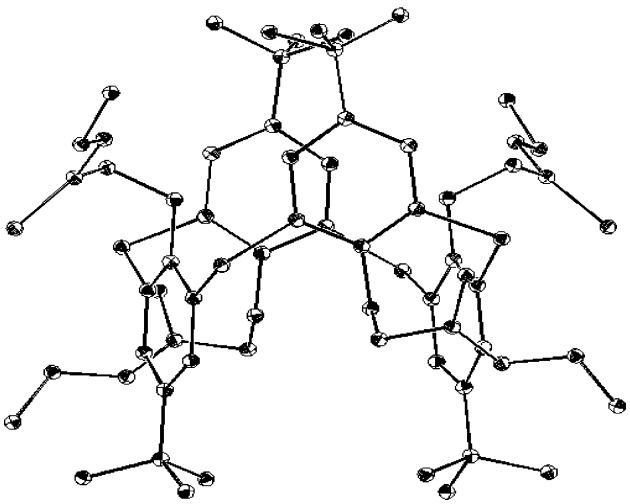


Fig. 5 X-ray structure of **6** in *1,3-alternate* conformation. For the sake of clarity, H atoms are not represented

Conclusion

By using *Lawesson*'s reagent, successful thionation of tetrakis((ethoxycarbonyl)methoxy)tetrathiacalix-[4]arene was obtained. For *cone* and *partial cone* conformers of thiacalix[4]arenes, both tetra- and trithiated products were found due to the steric hindrance at the lower rims. For the *1,3-alternate* conformer, only the tetrathioated product was obtained.

Experimental

All NMR spectra were recorded on a BRUKER DRX600 NMR spectrometer equipped with a triple-gradient TXI (H/C/N) probe operating at a magnetic field strength of 14.1 T. A 2D-ROESY spectrum was recorded with a mixing time of 250 msec. Mixing was achieved by a 1.3 kHz continuous wave spin-lock. Mass spectrometric analysis was carried out on a MALDI-TOF-MS REFLEX III (Bruker-Daltonics, Germany).

General procedure for the synthesis of ***2–6***

A mixture of 1.0 g **1a**–**1c** (0.94 mmol) with 1.52 g *Lawesson*'s reagent (3.75 mmol) was refluxed for 7 days in 50 cm^3 dry toluene. After cooling *Me*OH was added. The solid residue was separated and purified by column chromatography (*n*-hexane-methylene chloride as eluent).

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(ethoxythiocarbonyl)methoxy]thiacalix[4]arene (cone) (**2**, $C_{56}H_{72}O_8S_8$)
Yield 50%; Colorless crystals, Mp 185°C; MS: $m/z=1129.69$ $[MH]^+$; IR (KBr): $\bar{\nu}=2967$ (CH) cm^{-1}; ^{1}H NMR (600 MHz, *TMS*, $CDCl_3$): $\delta=1.09$(36H, s, Bu^t), 1.33 (12H, t, OCH_2CH_3), 4.54 (8H, q, $J=4.0$ Hz, OCH_2CH_3), 5.43 (8H, s, OCH_2CS), 7.26 (8H, s, *Ar*–H) ppm.

5,11,17,23-Tetra-tert-butyl-25,26,27-tris[(ethoxythiocarbonyl)-methoxy]-28-[(ethoxycarbonyl)methoxy]thiacalix[4]arene (cone) (**3**, $C_{56}H_{72}O_9S_7$)
Yield 25%; Colorless crystals, Mp 181°C; MS: $m/z=1113.62$ $[MH]^+$; IR (KBr): $\bar{\nu}=2960$ (CH) and 1769 (CO) cm^{-1}; ^{1}H NMR (600 MHz, *TMS*, $CDCl_3$): $\delta=1.05$ (18H, s, Bu^t), 1.11 (9H, s, Bu^t), 1.13 (9H, s, Bu^t), 1.27 (3H, t, OCH_2CH_3), 1.32–1.37 (9H, m, OCH_2CH_3) 4.20 (2H, q, OCH_2CH_3), 4.52–4.58 (6H, m, OCH_2CH_3), 5.33 (2H, d, OCH_2CS), 5.37 (4H, 2d, AB-system, OCH_2CS), 5.43 (2H, s, OCH_2CO), 7.21(2H, d, *Ar*–H), 7.22 (2H, d, *Ar*–H), 7.3 (2H, s, *Ar*–H), 7.34 (2H, s, *Ar*–H) ppm.

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(ethoxythiocarbonyl) methoxy]thiacalix[4]arene (partial cone)
(**4**, $C_{56}H_{72}O_8S_8$)
Yield 45%; Colorless crystals, Mp 165.3°C; MS: $m/z=1129.69$ $[MH]^+$; IR (KBr): $\bar{\nu}=2967$ (CH) cm^{-1}; ^{1}H NMR (600 MHz, *TMS*, $CDCl_3$): $\delta=0.96$ (3H, t, OCH_2CH_3) 1.06 (18H, s, Bu^t), 1.30–1.34 (9H, m, OCH_2CH_3), 1.33 (9H, s, Bu^t), 1.43 (9H, s, Bu^t), 4.24 (2H, q, OCH_2CH_3), 4.49–4.59 (6H, m, OCH_2CH_3), 4.92 (2H, d, $^2J=14.3$ Hz, OCH_2CS), 4.98 (2H, s,

OCH_2CS), 5.01 (2H, s, OCH_2CS), 5.07 (2H, d, $^2J = 14.3$ Hz, OCH_2CS), 7.0 (2H, d, $^4J = 2.5$ Hz, *Ar*–H), 7.48 (2H, d, $^4J = 2.5$ Hz, *Ar*–H), 7.54 (2H, s, *Ar*–H), 7.76 (2H, s, *Ar*–H) ppm.

5,11,17,23-Tetra-tert-butyl-25,26,27-tris[(ethoxythiocarbonyl)-methoxy]-28-[(ethoxycarbonyl)methoxy]thiacalix-[4]arene (partial cone) (**5**, $C_{56}H_{72}O_9S_7$)
Yield 25%; Colorless crystals, Mp 132°C; MS: $m/z = 1113.62$ $[MH]^+$; IR (KBr): $\bar{\nu} = 2967$ (CH) and 1769 (CO) cm^{-1}; ^1H NMR (600 MHz, *TMS*, $CDCl_3$): $\delta = 1.06$ (18H, s, Bu^t), 1.15 (3H, t, OCH_2CH_3), 1.32 (9H, s, Bu^t), 1.35 (9H, t, OCH_2CH_3), 1.41 (9H, s, Bu^t), 4.02 (2H, q, OCH_2CH_3), 4.50–4.61 (6H, m, OCH_2CH_3), 4.64 (2H, s, OCH_2CS, OCH_2CO), 4.82 (2H, d, $^2J = 14.3$ Hz, $-OCH_2CS$), 5.03 (2H, d, $^2J = 14.3$ Hz, OCH_2CS), 5.03 (2H, s, OCH_2CS), 7.0 (2H, d, *Ar*–H), 7.49 (2H, d, $^4J = 2.6$ Hz, *Ar*–H), 7.53 (2H, s, *Ar*–H), 7.76 (2H, s, *Ar*–H) ppm.

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis[(ethoxythiocarbonyl) methoxy]thiacalix[4]arene (1,3-alternate)
(**6**, $C_{56}H_{72}O_8S_8$)
Yield 85%; Pale yellow crystals, Mp 124°C; MS: $m/z =$ 1129.69 $[MH]^+$; IR (KBr): $\bar{\nu} = 2967$ (CH) cm^{-1}; ^1H NMR (600 MHz, *TMS*, $CDCl_3$): $\delta = 1.23$ (12H, t, OCH_2CH_3), 1.25 (36H, s, Bu^t), 4.46 (8H, q, OCH_2CH_3), 4.81 (8H, s, OCH_2CS), 7.42 (8H, s, *Ar*–H) ppm.

Acknowledgments

This work was supported by the Bibliotheca Alexandrina-Center for special studies and programs under Grant No. 04041083. The NMR laboratory at Aalborg University is supported by the Obel Foundation.

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