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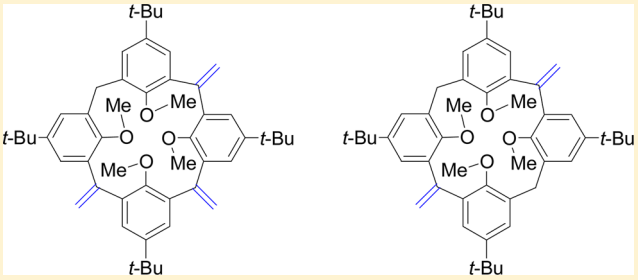
Incorporation of Three or Two Distal Double Bonds at the Methylene Bridges of the Calix[4]arene Scaffold

Ori Shalev and Silvio E. Biali*

Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Supporting Information

ABSTRACT: Partial oxidation of the 1,3-*alternate* atropisomer of *p*-*tert*-butylcalix[4]arene tetraacetate with CrO_3 afforded mainly a mixture of trioxo- and tetraoxo-calix[4]arene tetraacetate derivatives. The trioxotetrahydroxy derivative **6** was isolated from the mixture after hydrolysis of the crude product, followed by trituration with ethanol. Trioxocalix[4]-arene adopts in the crystal a 1,2-*alternate* conformation. Acetylation or alkylation of the tetrahydroxytrioxocalix[4]arene **6** with acetic anhydride and 1-bromobutane, respectively, afforded exclusively a single atropisomer of the product, which in both cases were characterized as the 1,3-*alternate* form. Addition of MeLi to the tetramethyl and tetrabutyl ether of the trioxocalix[4]arenes followed by 3-fold elimination of water yielded calixarene derivatives possessing three exocyclic double bonds at the bridges. Reaction of the dioxotetramethoxy calix[4]arene **9b** with MeLi followed by 2-fold elimination of water afforded calixarene **11** with a pair of distal exocyclic double bonds at the bridges. Both the tetramethyl ether derivatives **9b** and **11** exist in solution as a mixture of the 1,2-*alternate* and 1,3-*alternate* conformers, but in the crystal both adopt a 1,2-*alternate* conformation.



INTRODUCTION

"Ketocalixarenes" are calixarene derivatives where part or all of the methylene groups of the parent system have been replaced by carbonyl groups.[1,2] The parent tetrahydroxy tetraooxocalix-[4]arene **1a** was first reported by Görmar and co-workers.[3] The preparation of the system involved acetylation of tetrahydroxycalix[4]arene **2a** to yield the tetraacetate derivative **2b**, followed by oxidation with CrO_3, and hydrolysis of the acetate groups.[4]

A reinvestigation of the oxidation step indicated that the reaction is sensitive to the stereochemistry of the starting material.[5] Tetraacetate **2b** is conformationally rigid (the acetate groups effectively block the "rotation through the annulus" of the rings), and the four forms resulting from the possible "up" or "down" arrangement of the rings (Figure 1) represent atropisomers which can be separated.[6,7] Acetylation of *p*-*tert*-butylcalix[4]arene under acidic conditions usually results in a mixture of the 1,3-*alternate*, *partial cone*, and 1,2-*alternate* forms. Methylene groups located in between rings oriented *anti* are oxidized faster than those methylenes located in between rings oriented *syn* (Figure 2). As we have shown previously, this feature enables a synthetic entry into the preparation of proximal or distal dioxocalixarenes derivatives (via oxidation of the *partial-cone* and 1,2-*alternate* atropisomers, respectively),[8] in addition to the tetraoxocalixarene derivative (obtained from the oxidation of the 1,3-*alternate* atropisomer).[5]

A structural modification of interest is the introduction of exocyclic double bonds to the bridges of the calixarenes. In the resulting systems ("calixradialenes") the cross-conjugated

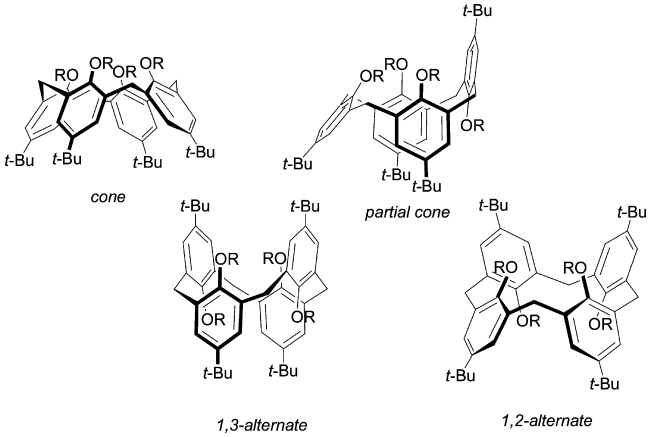


Figure 1. Four atropisomeric forms of *p*-*tert*-butylcalix[4]arene tetraacetate (R= Ac).

double bonds can in principle undergo a vast array of reactions and therefore provide a platform for the attachment of a large variety of functionalities. We have shown recently that reaction of the methyl ethers of ketocalixarenes **3a**–**c**[9] with excess of MeLi followed by multifold acid-catalyzed elimination of water, affords the corresponding calix[*n*]radialenes **4a**–**c**.[9a,10] A calix[4]arene derivative possessing only two exocyclic[11] double bonds at adjacent bridges (**5**) was also synthesized, starting

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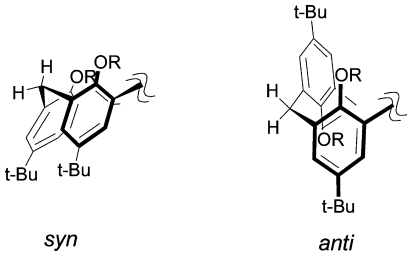
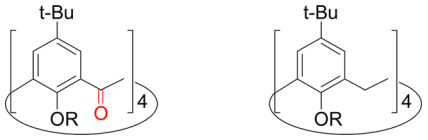


Figure 2. *Syn* and *anti* orientation of a pair of geminal rings. Methylene groups located between rings oriented *anti* are oxidized faster.

from the corresponding dioxocalix[4]arene. This calixarene exists in tetrachloroethane-d_2 solution at rt, as a 2.3:1 mixture of the 1,3-*alternate* and *partial cone* conformers.[9a]



1a R = OH
1b R = OAc

2a R = OH
2b R = OAc

In this paper we report the preparation of calix[4]arene derivatives possessing three exocyclic double bonds. This is particularly challenging since only few calixarenes derivatives modified at only three bridges are known, and these have been prepared by reaction of diynes with bis-carbenes complexes.[12] In addition, we report the preparation and characterization of a system with only two distal exocyclic double bonds.[13]

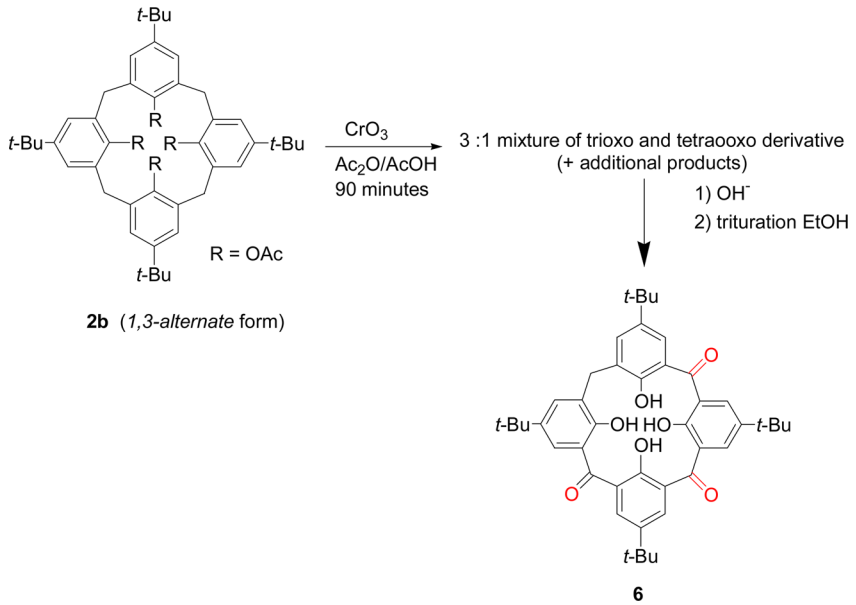
RESULTS AND DISCUSSION

Preparation of Trioxocalix[4]arene. For the preparation of a calix[4]arene with three exocyclic double bonds and a single methylene group at the bridges we needed a trioxocalixarene derivative as the starting material. In principle, such a derivative may be obtained by partial oxidation of the 1,3-*alternate* atropisomer of *p-tert*-butylcalix[4]arene tetraacetate **2b** (the atropisomer where all methylenes can be readily oxidized since all groups are located between a pair of geminal rings with an *anti* orientation). After several attempts involving reducing the reaction time and the amount of CrO_3, we found reaction conditions affording the desired trioxo derivative, albeit as a 3:1 mixture with the known tetraoxo derivative, and together with small amounts of additional products. Since the compounds displayed in the TLC (silica) similar R_f values, separation of the desired trioxocalixarene was attempted via repeated recrystallization from $CHCl_3$/MeOH, but this yielded only minute amounts of the pure trioxo tetraacetate derivative. For practical purposes, we found it more convenient to proceed to the hydrolysis stage with the crude mixture and to subsequently separate the trioxo derivative in its tetrahydroxy form **6**. This was achieved by trituration of the hydrolyzed product with cold EtOH followed by filtration, giving nearly pure tetrahydroxy trioxocalix[4]arene **6** (Scheme 1).

Crystal Structure of Trioxocalixarene 6. A single crystal of **6** was grown from acetonitrile and submitted to X-ray diffraction analysis. The trioxocalixarene adopts a 1,2-*alternate* (C_1) conformation[14] and is disordered in the crystal resulting in an average structure of crystallographic C_i symmetry. The O4, H11a′, and H11b′ atoms (these are atoms at the carbonyl and methylene bridge which are "exchanged" by the symmetry operation) were refined as half atoms at the two symmetry-related positions (only one position is shown in Figure 3). The OH groups are not involved in intramolecular hydrogen bonding with the carbonyl groups. Pairs of geminal rings mutually oriented in a *syn* fashion are intramolecularly hydrogen bonded (O···O distance of 2.732 Å), where the OH, which serves as acceptor of the hydrogen bond, serves also as a donor of a hydrogen bond with an acetonitrile molecule (O···N distance of 2.733 Å).

Trioxocalix[4]arene **6** displays in the ^{13}C NMR spectrum two low-field signals (at δ 192.2 and 191.1 ppm) characteristic of carbonyl groups. In the ^1H NMR spectrum (400 MHz, $CDCl_3$, rt) two singlets are observed for the OH groups (at δ 5.87 and 5.38 ppm). These signals resonate at a significantly higher field than the OH signals of the parent **2a** (10.34 ppm)[15]

Scheme 1



2b (*1,3-alternate* form)

6

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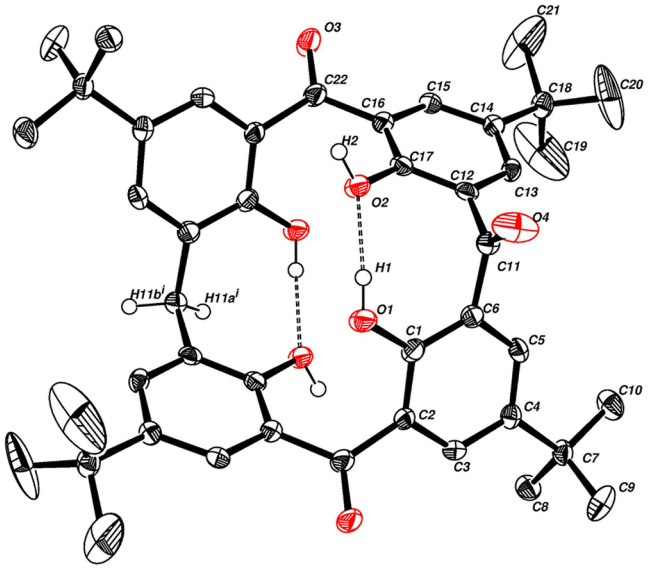
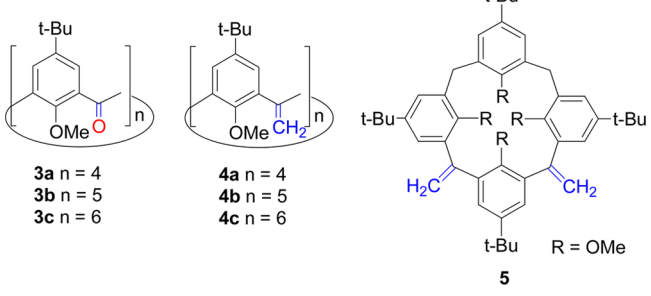


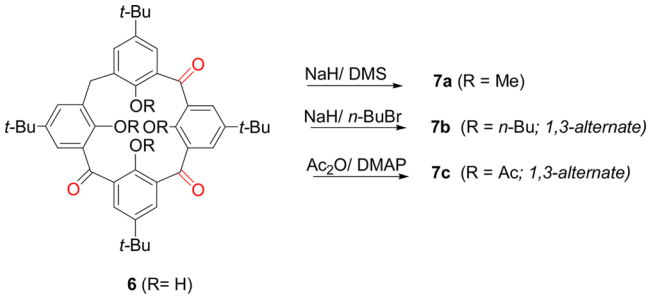
Figure 3. Top view of the molecular structure of trioxocalix[4]arene **6**. O4 and H11a′ and H11b′ were refined as half atoms at the two symmetry-related positions (only one position shown).

in agreement with a preferred conformation in solution where there is no circular array of hydrogen bonds. The methylene protons resonate as a singlet, which do not decoalesce even upon cooling to 183 K. This may indicate that either the rotational barrier of **6** is substantially lower than the barrier of the parent tetraoxocalixarene **1a** (15.2 kcal mol^{-1}),[16] and therefore only an average geometry is observed, and/or that the preferred conformation in solution is either the 1,2-*alternate* (C_2) or the 1,3-*alternate*. In both of these conformations the two methylene protons are homotopic (they are related by the C_2 axis bisecting the methylene and the unique carbonyl group distal to the methylene), and therefore if any of these conformations is adopted, no decoalescence of the methylene protons should be observed.



Acetylation and Alkylation of 6. Since the oxidation of the methylene groups to carbonyls should not affect the relative up−down disposition of the aromatic rings of tetraacetate **2b**, it can be safely assumed that in all the products obtained in the oxidation step, the aryl rings adopt a frozen 1,3-*alternate* arrangement. To obtain the 1,3-*alternate* form of the tetraacetate derivative of **6** in a pure form, we attempted the acetylation of **6** with Ac_2O, using 4-dimethylaminopyridine (DMAP) as the nucleophilic catalyst. Since acetylation of the parent *p-tert*-butylcalix[4]arene **2a** under acid catalysis affords a mixture of the atropisomeric tetraacetates, it was not clear to us whether the acetylation of **6** will proceed in stereoselective fashion, and if so, whether the 1,3-*alternate* form will be obtained. Fortunately, we found that the DMAP-catalyzed reaction proceeded in a stereoselective fashion and that the ^{1}H NMR spectrum of the product obtained (**7c**) was identical to the spectrum observed in the product mixture obtained in the oxidation step (Scheme 2). On this basis, we ascribe to the product of the acetylation (**7c**) a 1,3-*alternate* geometry.

Scheme 2



We also examined the stereoselectivity of the tetraalkylation reaction of **6** with 1-bromobutane. The expected product was expected to be rigid since the bulky *n*-butyl groups should effectively hinder the rotation through the annulus of the rings.[17] In the ^{1}H NMR spectrum of the product **7b** (400 MHz, $CDCl_3$, rt) four multiplets were observed for the OCH_2 groups (Figure 4). The diastereotopicities of pairs of protons on a

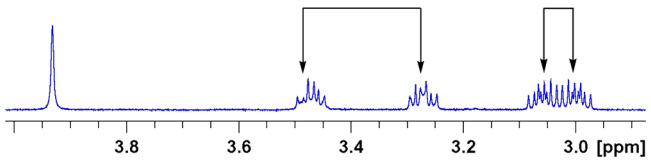


Figure 4. ^{1}H NMR spectrum of the low-field methylene region of **7b** (400 MHz, $CDCl_3$, rt). The protons at the methylene bridge appear as a singlet, at 3.93 ppm. Pairs of diastereotopic protons on a given OCH_2 group are marked with arrows.

given OCH_2 group are in agreement with a frozen conformation in solution (on the NMR time scale) since rapid rotation though the annulus of the rings should render a given pair of protons isochronous. Notably, the methylene protons at the bridge appeared as a singlet indicating that in the conformation adopted, these protons are related by a C_2 axis.

The pattern of NMR signals observed is in agreement with either frozen 1,2-*alternate* (C_2) or 1,3-*alternate* conformations. To distinguish between the two possibilities we conducted a NOESY experiment. Each of two diastereotopic OCH_2 protons displayed NOE cross peaks with aromatic protons at two different neighboring rings (cf. Figure 5, NOE interactions are

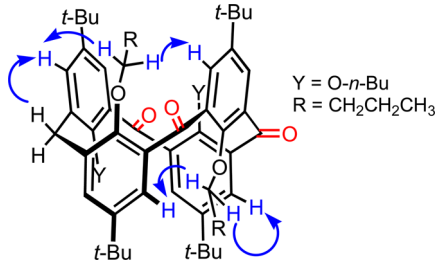


Figure 5. NOE interactions in **7b**.

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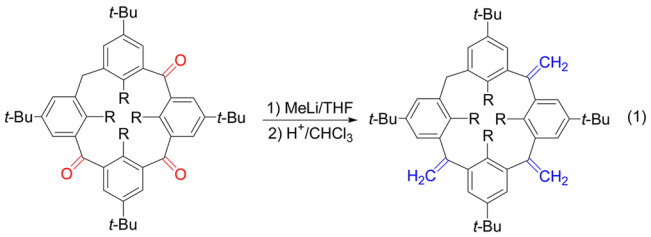
designated by blue curved arrows). The NOE interactions (indicating *anti* arrangements of geminal rings) suggest that **7b** possess a 1,3-*alternate* arrangement of the rings.

The stereoselectivity observed in the acetylation and butylation reactions may be a reflection of the intrinsic conformational preferences of the macrocycle, and on this basis, we ascribe the 1,3-*alternate* form as the preferred conformation of **6**. This assignment is in line with the conformational preferences previously observed for other ketocalix[4]arenes where a pair of germinal rings attached to a carbonyl prefer an *anti* over a *syn* arrangement.[5] The 1,2-*alternate* (C_1) conformation observed in the crystal of **6** most likely does not correspond to the lowest energy form, and its presence may be due to packing forces in the crystal.

Methylation of **6** was conducted with NaH/DMS to afford the tetramethoxy derivative **7a**, which displayed a simple spectrum, indicating either a conformationally flexible structure on the NMR time scale or the adoption of a single conformation. The ^{1}H NMR spectrum did not change upon cooling in $CDCl_3$ to 183 K, and therefore it seems likely that the relative simplicity of the spectrum at room temperature (rt) is due to the presence of essentially a single conformation and not the result of averaging several rapidly interconverting conformers.

Incorporation of Three Exocyclic Double Bonds at the Bridges. The reaction of ketocalixarenes **3a**–**c** with excess MeLi proceeds in nonstereoselective fashion and mixtures of isomeric products are obtained.[9a] Reaction of trioxocalixarene **7a** with MeLi also afforded, as judged by NMR, a mixture of isomeric triaddition products. Without purification, this mixture was dehydrated with *p*-toluenesulfonic acid to yield **8a** (eq 1).



7a R = OMe
7b R = O-*n*-Bu (*1,3-alternate*)

8a R = OMe
8b R = O-*n*-Bu (*1,3-alternate*)

In contrast to **7a**, trioxocalixarene **7b** is conformational rigid, and it could be expected that its reaction with MeLi will show some stereoselectivity. However, since ^{1}H NMR analysis of the product also indicated the presence of a mixture of isomeric products, the crude mixture without prior purification was dehydrated to afford **8b**. Since the addition–elimination sequence at the bridges should not affect the conformationally frozen "up-down" disposition of the rings, **8b** should also possess the rigid 1,3-*alternate* conformation of the starting material **7b**.

Calixarenes **8a** and **8b** display in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, rt) a pair of doublets and a singlet for the vinyl protons, with the separation between the pair of doublets being larger for **8b** than for **8a** (Figure 6). In both molecules the methylene protons at the saturated bridge resonate as a singlet at δ 3.82 ppm.

To determine the preferred conformation of **8a** we conducted a NOESY experiment. NOE cross peaks were observed between each of the methoxy signals and two aromatic protons located at different rings, a pattern analogous

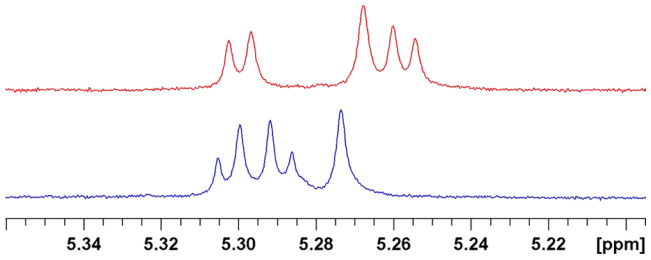
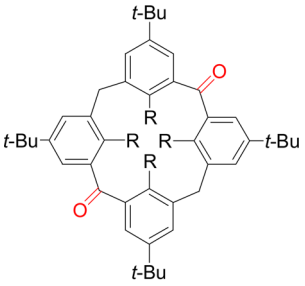


Figure 6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, rt) of the vinylic region of **8a** (bottom) and **8b** (top).

to the one depicted in Figure 5. On this basis, we assign to **8a** a 1,3-*alternate* conformation.

Incorporation of Two Exocyclic Double Bonds at Distal Bridges. For the preparation of a system with two distal exocyclic double bonds it was necessary to protect the OH groups of the dioxocalixarene **9a**, which was synthesized as described previously[5] via oxidation of the 1,2-*alternate* form of **2b** followed by hydrolysis of the acetate groups. However, initial methylation experiments afforded unexpectedly only very low yields of the tetramethoxy derivative. We observed previously in the methylation of a ketocalix[6]arene a competing intramolecular reaction involving an S_NAr attack of the intermediate phenolate to a neighboring ring, resulting in the formation of a xanthone ring.[9b] Since we suspected that the low yields were due to a similar competing intramolecular reaction, the reaction was repeated at a lower temperature (0 °C) with the hope to increase the chemoselectivity of the reaction. Fortunately, examination of the crude product by NMR indicated that under these conditions the desired tetramethoxy derivative **9b** is obtained as the major product.



9a R = OH
9b R = OMe

Compound **9b** displays in the NMR spectrum ($CDCl_3$, rt) two sets of signals, indicating the presence of two conformers in a 3:1 ratio under slow mutual exchange on the NMR time scale. Both conformers display a pair of signals for the aromatic protons and single signals for the methoxy and *t*-Bu groups. However, the major conformer displayed a pair of well-separated doublets for the methylene groups, while the minor conformer displayed a singlet for these groups (Figure 7). On the basis of the signal pattern we assign the 1,2-*alternate* (of C_{2h} symmetry) and a chiral 1,3-*alternate* conformations (of D_2 symmetry) to the major and minor conformers present in $CDCl_3$ (Figure 8).[18] The chirality of the minor conformation could be corroborated by the addition of a chiral solvating agent ((*R*)-(−)-α-(trifluoromethyl)benzyl alcohol) which resulted in splitting of its methylene singlet into two signals, indicating the presence of two enantiomers in solution. The relative population of the two conformers is dependent on the

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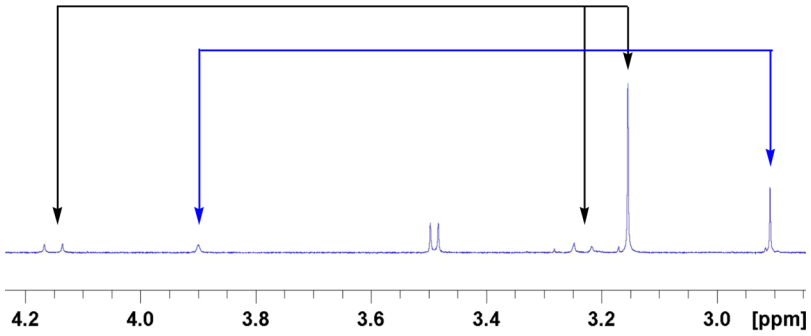


Figure 7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the methylene and methoxy region of **9b**. Arrows in black and blue denote signals of the major (1,2-*alternate*) and minor (1,3-*alternate*) conformers, respectively. The doublet at 3.48 ppm is due to residual MeOH.

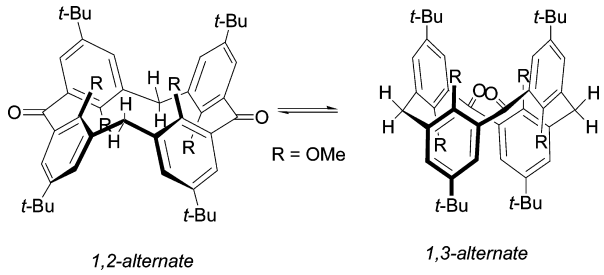


Figure 8. Two conformers of **9b** in equilibrium in $CDCl_3$ solution.

solvent, and the conformer ratio between the 1,2-*alternate* and 1,3-*alternate* forms changes from 2.75:1 in $CDCl_3$ to 1.61:1 in DMSO-d_6 and 3.28:1 in C_6D_6 (Figure 9). The larger the polarity of the solvent, the larger the population of the 1,3-*alternate* form, although in all cases the 1,2-*alternate* conformer is the predominant form.

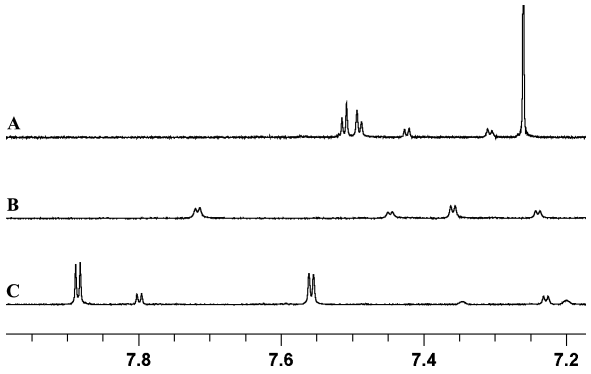


Figure 9. ^{1}H NMR spectrum of the aromatic region of **9b** in (A) $CDCl_3$, (B) DMSO-d_6, and (C) C_6D_6.

A single crystal of **9b** was grown from $CHCl_3$/MeOH and submitted to X-ray crystallography (Figure 10). The molecule adopts in the crystal a 1,2-*alternate* conformation (the major conformation observed in $CDCl_3$ solution).

Upon raising the temperature in 1,1,2,2-tetrachloroethane-d_2 solution, extensive broadening of the signals was observed, but no coalescence of the signals was observed even at the highest temperature examined (413 K). The interconversion rates between the conformers were therefore determined by means of an EXSY spectrum at 366 K.[19] From the rates for the forward (major → minor isomer: 2.1 s^{-1}) and reverse (minor → major isomer: 4.2 s^{-1}) processes, barriers of 21.0 and 20.5 kcal mol^{-1} were calculated for the two processes. These barriers

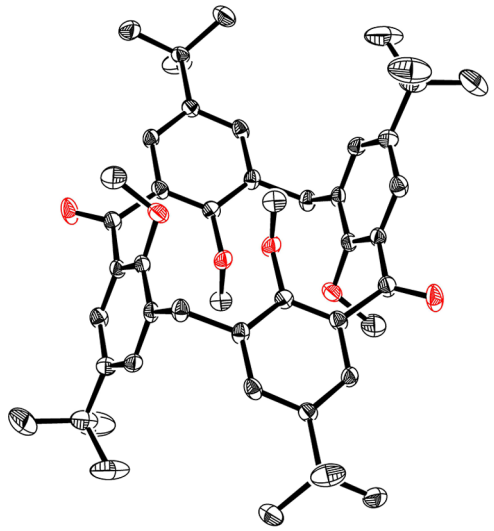
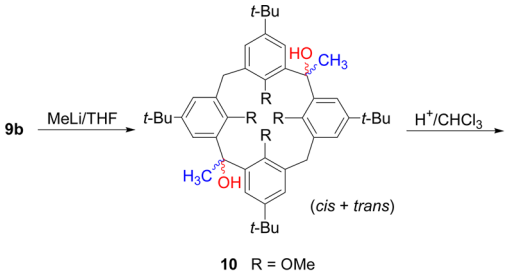


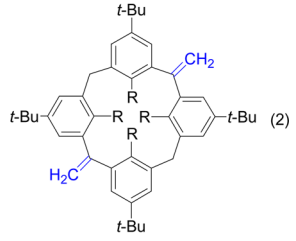
Figure 10. Crystal structure of compound **9b**.

are substantially higher than the rotational barrier of the parent **9a** (13.6 kcal mol^{-1}).

Reaction of **9b** with excess MeLi afforded the corresponding diadduct **10** (eq 2). This product displays in the ^{1}H NMR



10 R = OMe



11 R = OMe

spectrum ($CDCl_3$, rt) two sets of signals, in agreement with the presence of a mixture of both the *cis* and *trans* isomers. Whereas the signals of one set of signals were markedly broad, the

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second set was sharp. The set of sharp signals displays four doublets for the aromatic protons and two pairs of signals for the methylene protons, in agreement with a *cis* structure where the macrocyclic rings adopt a 1,2-*alternate* conformation. By exclusion, the set of broad signals is assigned to the *trans* isomer.

The mixture of addition products was not separated, but directly dehydrated under acidic conditions, to afford **11**. The ^{1}H NMR spectrum of **11** ($CDCl_3$, rt) displayed two patterns of signals (e.g., two signals were observed for the vinyl protons) indicating the presence of two major conformations in solution. Using similar arguments to those described above for **9b**, the two patterns of signals can be assigned to the 1,2-*alternate* and 1,3-*alternate* conformations of **11**. However, in contrast to **9b**, the 1,3-*alternate* form is the major form for **11** (the population ratio 1,2-*alternate*:1,3-*alternate* is 1:3.81).

A single crystal of **11** was grown from $CHCl_3$/MeOH. The macrocycle adopts in the crystal a 1,2-*alternate* conformation where the two exocyclic double bonds are located between pairs of geminal rings oriented *anti* (Figure 11). Interestingly, also for **11** the conformation present in the crystal is not the preferred conformation in solution.

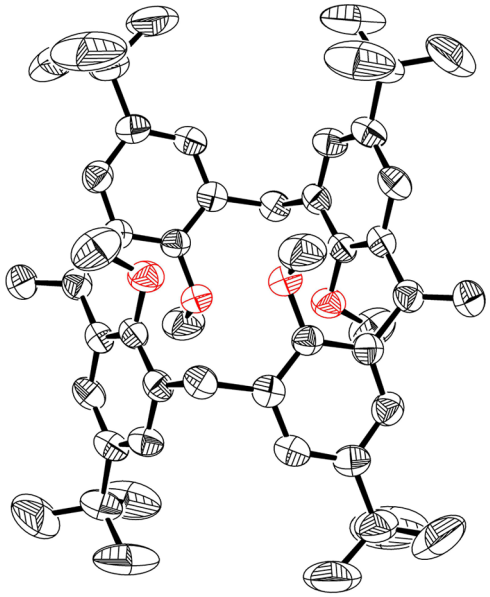

Figure 11. Crystal structure of the derivative **11**, with two exocyclic double bonds on distal bridges.

The interconversion rates between the two conformers of **11** were determined by an EXSY spectrum at 335 K (in $C_2D_2Cl_4$). From the rates of exchange of the vinyl, aromatic, and methoxy groups, barriers of 20.8 and 19.9 kcal mol^{-1} were calculated for the 1,3-*alternate* → 1,2-*alternate* and 1,2-*alternate* → 1,3-*alternate* processes. These barriers are similar to the rotational barrier of the dioxo derivative **9b**, indicating that the formal replacement of the two carbonyls of **9b** by two exocyclic double bonds has only a minute effect on the rigidity of the system.

CONCLUSIONS

Conformationally rigid and conformationally flexible calix[4]-arenes incorporating three or two (distal) exocyclic double bonds at the bridges were prepared starting from the corresponding trioxo and dioxo calix[4]arene derivatives. Since systems with one,[13] two proximal[9a] or four exocyclic bonds[9a] have been reported, the present work completes the series of calix[4]arene derivatives with part or all bridges functionalized by double bonds.

EXPERIMENTAL SECTION

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14-trioxocalix[4]arene (6). *Oxidation of Calixarene Tetraacetate.* To a mixture of the 1,3-*alternate* form of calixarene tetraacetate **2b** (2g, 2.45 mmol), acetic anhydride (170 mL), and acetic acid (0.2 mL) was slowly added CrO_3 (1.65 g, 16.5 mmol), and the mixture was heated to reflux for 90 min. After cooling, the mixture was extracted with chloroform, and the organic phase was washed twice with salt water. NMR analysis of the residue after evaporation indicated that it consisted of a 3:1 mixture of the tri- and tetraoxocalix[4]arene derivatives, together with minor amounts of some additional products.

Hydrolysis of the Trioxocalixarene Tetraacetate. A mixture of the crude product, obtained in the previous step, together with ethanol (120 mL), water (76 mL), and NaOH (2.8 g) was heated to reflux for 2 h. After cooling, conc HCl was added until the pH was acidic, and the solid that precipitated (1.6 g) was filtrated. This solid was triturated for 20 min with cold ethanol and filtrated. The solid (0.35 g, 21%) consisted of pure **6**, mp 310 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.98 (d, J = 2.7 Hz, 2H), 7. 90 (d, J = 2.7 Hz, 2H), 7.51 (d, J = 2.4 Hz, 2H), 7.47 (d, J = 2.5 Hz, 2H), 5.87 (s, 2H), 5.38 (s, 2H), 4.15 (s, 2H), 1.36 (s, 18H), 1.32 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 191.1, 152.3, 151.2, 145.5, 145.0, 132.7, 132.5, 132.2, 127.8, 127.6, 126.8, 126.1, 123.6, 36.5, 34.6, 34.4, 31.3, 31.2, 30.9 ppm. HRMS (ESI-QTOF) m/z 691.3632 (M + H$^+$), calcd for $C_{44}H_{51}O_7$: 691.3635.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14-trioxocalix[4]arene (7a). A mixture of trioxocalix[4]arene **6** (1 g, 1.44 mmol), dry THF (100 mL), NaH (1.1 g, 60% dispersion in mineral oil, 27.5 mmol), and dimethyl sulfate (2 mL, 21 mmol) was heated to reflux overnight. Methanol (20 mL) was added followed by ammonium hydroxide (5 mL), and the solvents were evaporated. After extraction with chloroform, the organic phase was washed with water and dilute HCl, dried ($MgSO_4$), and evaporated. The residue was recrystallized from $CHCl_3$/MeOH to afford 0.5 g of **7a** (46%), mp 340 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.89 (d, J = 2.7 Hz, 2H), 7.80 (d, J = 2.7 Hz, 2H), 7.36 (d, J = 2.6 Hz, 2H), 7.35 (d, J = 2.5 Hz, 2H), 3.95 (s, 2H), 3.82 (s, 2H), 3.10 (s, 6H), 2.78 (s, 6H), 1.37 (s, 18H), 1.35 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 195.5, 157.5, 155.7, 146.4, 145.5, 134.9, 133.9, 132.3, 130.4, 130.3, 123.6, 62.8, 60.3, 38.0, 34.5, 34.2, 31.4, 31.3 ppm. HRMS (ESI-QTOF) m/z 747.4264 (M + H$^+$), calcd for $C_{48}H_{59}O_7$: 747.4261.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28−tetra-*n*-butoxy-2,8,14-trioxocalix[4]arene (7b). To a mixture of trioxocalix[4]arene **6** (1g, 1.44 mmol), dry DMF (6 mL), and dry THF (1 mL) was added NaH (1.1 g, 60% dispersion in mineral oil, 27.5 mmol). After heating to reflux for 1 h, 1-bromobutane (1.25 mL, 11.6 mmol) was added. The mixture was heated for 36 h, and after cooling to rt, MeOH (20 mL) was added. After evaporation of the solvent, the residue was dissolved in chloroform, and the solution washed successively with aq HCl (1M) and water. After drying ($MgSO_4$) and evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH to yield 0.42 g (32%) **7b**, mp 253 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.83 (d, J = 2.1 Hz, 2H), 7.74 (d, J = 2.1 Hz, 2H), 7.33 (d, J = 2.1 Hz, 2H), 7.32 (d, J = 2.1 Hz, 2H), 3.93 (s, 2H), 3.49−3.44 (m, 2H), 3.29−3.24 (m, 2H), 3.08−3.03 (m, 2H), 3.02−2.97 (m, 2H), 1.35 (s, 18H), 1.32 (s, 18H), 1.12−1.045 (m, 2H), 1.04−0.95 (m, 6H), 0.85−0.77 (m, 4H), 0.74 (t, J = 5.6 Hz, 6H), 0.63 (t, J = 5.7 Hz, 6H), 0.61−0.52 (m, 2H), 0.51−0.41 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 196.3, 156.8, 155.5, 146.2, 145.1, 135.2, 134.6, 134.5, 132.5, 130.7, 130.5, 130.2, 123.6. 78.0, 74.6, 34.5, 34.2, 31.7, 31.4, 31.3, 30.6, 18.7, 18.3, 13.8, 13.6 ppm. HRMS (ESI-QTOF) m/z 915.6139 (M + H$^+$), calcd for $C_{60}H_{83}O_7$: 915.6146.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28−tetraacetate-2,8,14-trioxo-calix[4]arene (7c). A mixture of **6** (0.3 g, 0.43 mmol), 4-dimethylaminopyridine (15 mg, 0.12 mmol), and acetic anhydride (5

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mL) was heated to reflux overnight under stirring. After evaporation of the solvent, the residue was dissolved in chloroform, and the solution washed successively with aq HCl (1M) and water. After drying ($MgSO_4$) and evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH to yield 0.150 g (40%) **7c**, mp 343 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.87 (d, J = 2.6 Hz, 2H), 7.77 (d, J = 2.6 Hz, 2H), 7.39 (d, J = 2.5 Hz, 2H), 7.38 (d, J = 2.4 Hz, 2H), 3.87 (s, 2H), 1.54 (s, 6H), 1.36 (s, 18 H), 1.33 (s, 18 H), 1.18 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 191.3, 167.8, 167.4, 150.2, 149.3, 144.8, 144.3, 135.9, 134.1, 132.9, 130.5, 130.0, 129.7, 123.9, 37.9, 35.1, 34.8, 31.4, 31.3, 20.6, 20.4 ppm. HRMS (ESI-QTOF) m/z 881.3875 (M + Na^+), calcd for $C_{52}H_{58}O_{11}Na$: 881.3877.

5,11,17,23-Tetra-*tert*-butyl-2,8,14-trimethylene-25,26,27,28-tetramethoxy-calix[4]arene (8a). To a solution of **7a** (0.3 g, 0.40 mmol) in dry THF (30 mL) at 0 °C under argon was slowly added MeLi (1.4 mL, 3% in 2-methyltetrahydrofuran/cumene, 1.63 mmol) under stirring. After 30 min, the ice bath was removed, and the mixture stirred for 90 min at rt. After addition of MeOH (10 mL), the solvents were evaporated, and the residue dissolved in $CHCl_3$. The solution was washed with 1 M aq. HCl, and water, dried ($MgSO_4$), and evaporated. The residue was dissolved in $CHCl_3$ (40 mL), and *p*-toluenesulfonic acid (22 mg) was added. After heating to reflux for 30 min, the solution was washed successively with aq. $NaHCO_3$ and water, and the solvent was evaporated. Recrystallization of the residue from $CHCl_3$/MeOH yielded 0.1 g (34%) of **8a**, mp 320 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.30 (d, J = 2.6 Hz, 2H), 7.24 (d, J = 2.6 Hz, 2H), 7.14 (br s, 4H), 5.30 (d, J = 2.3 Hz, 2H), 5.28 (d, J = 2.2 Hz, 2H), 5.27 (s, 2H), 3.82 (s, 2H), 2.87 (s, 6H), 2.78 (s, 6H), 1.30 (s, 18H), 1.28 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.3, 149.3, 148.9, 145.4, 144.6, 136.8, 136.0, 135.9, 133.8, 127.3, 126.0, 125.8, 125.1, 118.1, 117.1, 59.2, 58.9, 34.1, 33.9, 31.4, 30.9 ppm. HRMS (ESI-QTOF) m/z 779.4460 (M + K^+), calcd for $C_{51}H_{64}O_4K$: 779.4442.

5,11,17,23-Tetra-*tert*-butyl-2,8,14-trimethylene-25,26,27,28-tetra-*n*-butoxy-calix[4]arene (8b). To a solution of **7b** (0.9 g, 0.98 mmol) in dry THF (90 mL) at 0 °C under argon was slowly added MeLi (8 mL, 3% in 2-methyltetrahydrofuran/cumene, 3.36 mmol) under stirring. After 1 h, the ice bath was removed, and the mixture stirred overnight at rt. After addition of MeOH (20 mL), the solvents were evaporated, and the residue dissolved in $CHCl_3$. The solution was washed with 1 M aq. HCl, and water, dried ($MgSO_4$), and evaporated. The residue was dissolved in $CHCl_3$ (20 mL), and *p*-toluenesulfonic acid (100 mg) was added. After heating to reflux for 30 min, the solution was washed successively with aq. $NaHCO_3$ and water, and the solvent was evaporated. Recrystallization of the residue from $CHCl_3$/MeOH yielded 0.2 g (21%) of **8b**, mp 253 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.27 (d, J = 2.6 Hz, 2H), 7.24 (d, J = 2.6 Hz, 2H), 7.12 (d, J = 2.6 Hz, 2H), 7.05 (d, J = 2.6 Hz, 2H), 5.29 (d, J = 2.3 Hz, 2H), 5.26 (s, 2H), 5.25 (d, J = 2.2 Hz, 2H), 3.82 (s, 2H), 3.34–3.24 (m, 4H), 3.12–3.08 (m, 4H), 1.34 (s, 18H), 1.31 (s, 18H), 1.06–0.98 (m, 4H), 0.97–0.89 (m, 6H), 0.74 (t, J = 7.0 Hz, 8H), 0.72–0.65 (m, 10H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, rt) δ 153.6, 152.4, 149.9, 149.5, 144.3, 143.9, 135.3, 135.0, 134.9, 132.8, 126.5, 125.5, 125.3, 124.1, 118.0, 117.3, 72.1, 71.2, 39.2, 34.1, 34.0, 31.6, 31.0, 30.9, 30.4, 18.9, 18.7, 13.8, 13.7 ppm. HRMS (ESI-QTOF) m/z 931.6550 (M + Na^+), calcd for $C_{63}H_{88}O_4Na$: 931.6580.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,14-dioxocalix[4]arene (9b). A mixture of dioxocalix[4]arene **9a** (0.9 g, 1.22 mmol), dry DMF (4.5 mL), dry THF (225 mL), and NaH (0.9 g, 60% dispersion in mineral oil, 22.5 mmol) was heated to reflux for 5 min. After cooling the mixture, dimethyl sulfate (3 mL, 31.6 mmol) was added, and the mixture was stirred overnight at rt. Methanol (20 mL) was added followed by ammonium hydroxide (10 mL), and the solvents were evaporated. The residue was dissolved in chloroform, and the organic phase was washed successively with diluted HCl and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized from $CHCl_3$/MeOH to afford 0.44 g **9b** (45%), mp 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) *1,2-alternate conformer:* δ 7.51 (d, J = 2.6 Hz, 4H), 7.48 (d, J = 2.6 Hz, 4H), 4.15 (d, J = 12.6 Hz, 2H), 3.23 (d, J = 12.6 Hz, 2H), 3.15 (s, 12 H), 1.34 (s, 36 H) ppm. *1,3-alternate conformer:* δ 7.42 (d, J = 2.6 Hz, 2H), 7.30 (d, J = 2.5 Hz, 2H), 3.90 (s, 4H), 2.90 (s, 12H), 1.31 (s, 36 H). ^{13}C NMR (100 MHz, $CDCl_3$, rt) δ 200.0, 199.1, 155.7, 155.5, 145.5, 145.4, 135.5, 134.4, 133.7, 132.8, 130.5, 124.1, 123.9, 76.6, 62.0, 60.7, 50.9, 37.7, 34.3, 34.2, 31.4, 31.3, 29.4 ppm. HRMS (ESI-QTOF) m/z 755.4284 (M + Na^+), calcd for $C_{48}H_{60}O_6Na$: 755.4288.

5,11,17,23-Tetra-*tert*-butyl-2,14-dihydroxy-2,14-dimethyl-25,26,27,28−tetramethoxycalix[4]arene (10). To a solution of **9b** (0.44 g, 0.6 mmol) in dry THF (50 mL) at 0 °C under argon was slowly added MeLi (2 mL, 1.6 M in ether, 3.2 mmol) under stirring. After 1.5 h, the ice bath was removed, and the mixture stirred at rt for 30 min. After addition of MeOH (20 mL), the solvents were evaporated, and the residue dissolved in $CHCl_3$. The solution was washed with 1 M aq. HCl and water and dried ($MgSO_4$), and the solvent was evaporated. The residue was recrystallized from MeCN to give 0.07 g (15%) of **10**, mp 240 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) *cis* isomer: δ 7.65 (d, J = 2.4 Hz, 2H), 7.43 (d, J = 2.0 Hz, 2H), 7.37 (d, J = 2.4 Hz, 2H), 7.08 (d, J = 2.8 Hz, 2H), 4.05 (d, J = 13.6 Hz, 1H), 3.88 (d, J = 12.8 Hz, 1H), 3.42 (d, J = 14.0 Hz, 1H), 3.20 (d, J = 12.0 Hz, 1H), 3.05 (s, 6 H), 2.91 (s, 6 H), 1.91 (s, 6 H), 1.34 (s, 18H), 1.28 (s, 18H) ppm. *Trans* isomer (all signals are broad): δ 7.77, 7.3, 7.12, 3.88, 3.26, 2.46, 1.85, 1.28 ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 153.9, 152.1, 145.0, 143.6, 141.0, 137.4, 132.9, 131.9, 127.2, 126.9, 122.3, 122.0, 121.9, 76.7, 74.9, 74.8, 61.4, 61.1, 60.9, 60.5, 34.6, 34.4, 34.3, 31.7, 31.6, 31.5, 31.4, 29.2, 29.1, 28.0 ppm. HRMS (ESI-QTOF) m/z 803.4662 (M + K^+), calcd for $C_{50}H_{68}O_6K$: 803.4653.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28−tetramethoxy-2,14-dimethylenecalix[4]arene (11). The isomer mixture of **10** (35 mg, 0.04 mmol) was dissolved in $CHCl_3$ (5 mL), and *p*-toluenesulfonic acid (5 mg) was added. After heating to reflux for 20 min, the solution was washed successively with aq. $NaHCO_3$ and water, and the solvent was evaporated. Recrystallization of the residue from $CHCl_3$/MeOH yielded 8 mg (27%) of **11**, mp 240 °C. ^{1}H NMR (400 MHz, $CDCl_3$, rt) 1,2-*alternate* conformer: δ 7.38 (d, J = 2.4 Hz, 4H), 7.24 (d, J = 2.4 Hz, 4H), 5.38 (s, 4H), 4.16 (d, J = 12.4 Hz, 2H), 3.18 (d, J = 12.4 Hz, 2H), 3.13 (s, 12H), 1.34 (s, 36H) ppm. 1,3-*alternate* conformer: δ 7.16 (d, J = 2.8 Hz, 4H), 7.09 (d, J = 2.8 Hz, 4H), 5.27 (s, 4H), 3.74 (s, 4H), 2.85 (s, 12H), 1.27 (s, 36H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 153.5, 153.1, 149.7, 144.7, 136.6, 135.0, 133.7, 133.5, 127.4, 126.5, 125.4, 124.9, 116.8, 74.2, 74.0, 73.7, 60.1, 59.0, 38.5, 34.1, 33.9, 31.6, 31.5 ppm. HRMS (ESI-QTOF) m/z 729.4895 (M + H^+), calcd for $C_{50}H_{65}O_4$: 729.4883.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C spectra of compounds **6**–**11** and crystallographic data (cif files) for compounds **6**, **9b**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: silvio.biali@mail.huji.ac.il.

Notes

The authors declare no competing financial interest.

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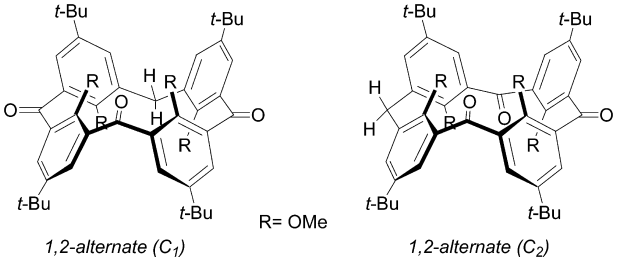

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