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ORIGINAL ARTICLE

Bis-calix[4]arene-based podants using the bridge position as a constructive mode of subunit connection

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Abstract Synthetic pathways for a bridge type connection of two calixarenes by a flexible alkylene chain or a more rigid bistriazole modified connection element of different length are presented. NMR measurements as well as MM calculations point to rather flexible conjugates showing suitable requirements for a potential formation of inclusion complexes with neutral and anionic guests of appropriate size.

Keywords Calixarene · Bridge connection · Methylene bridge · Click reaction · MM calculation

Introduction

The availability of no fewer than twelve sites for substitution within a rather small highly preorganized molecule in combination with a tuneable conformational flexibility make calixarenes to an ideal target in different fields of organic and supramolecular chemistry [1]. With reference to their synthesis, being broadly investigated since several decades, the lion's share is focussed on the vertical substitution of the calixarene framework, i.e. the modification of the *upper* and *lower rim* [1], while the horizontal expansion including a functionalization of at least one methylene bridge has recently become a challenging new substitution mode [2–4].

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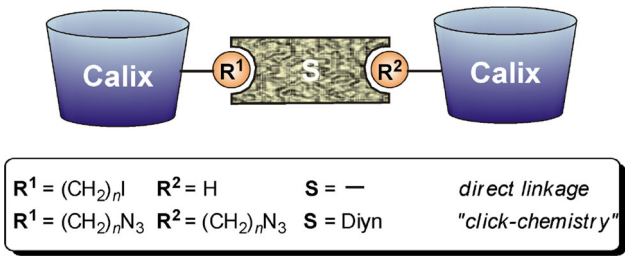
Moreover, the linkage of two or more calixarenes by means of flexible alkyl or triazole units enabled access to promising hybrid compounds, applicable as chemosensing materials for neutral gas molecules as well as anions [5]. Referring to "click" chemistry, only calix[4]arene nanotubes linked via the *upper* [6] and *lower rim* [7] have been explored so far. However, to the best of our knowledge no reports are available aiming at the bridge site linkage of two calix[4]arenes. Here, we demonstrate the first examples of corresponding biscalix[4]arenes as illustrated in Scheme 1 featuring a linkage by using alkyl or triazole connection elements of different flexibility. We present a conformational analysis study in solution and discuss these data compared with theoretical calculations of isolated molecules in order to show potential opportunities of this particular connection mode made for a future development of new chemical sensor types.

Experimental

Melting points were determined on a microscope heating stage and are uncorrected. IR spectra were measured as KBr pellets and can be found in the supplementary data (S1). NMR spectra were recorded at 500.1 MHz (^{1}H NMR) and 125.7 MHz (^{13}C NMR), respectively, in $CDCl_3$/CD_3CN solution (9:1) with small amounts of NaI. Chemical shifts δ are reported in ppm relative to the internal reference TMS. The COSY spectrum for assignment of resonances in compound **2** was taken using the cosygpsw pulse sequence with a relaxation delay of 1.48 s including 12 scans and 400 increments of 2048 points each. Reagents and chemicals for the synthesis were used as purchased from chemical suppliers. The solvents used were purified or dried according to common literature procedures.



Scheme 1 Envisaged linking modes of biscalix[4]arene-based podants

Syntheses

Starting compound **1** [8], the basic ω-chloroalkyl substituted calixarenes **2–6** [9], as well as the ω-iodoalkyl modified calixarenes **7–9** [9] were prepared according to described protocols. For the preparation of the ω-azidoalkyl substituted calixarenes **10–12** the corresponding ω-chloroalkyl calixarenes and NaN_3 were treated in DMF at 80 °C for 24 h following a reported protocol [10] but addition of the NaN_3 was modified. While compounds **21** and **22** were used as commercially available substances, 3,6-diethynylfluoren-9*H*-one (**23**) was synthesized following a literature known pathway [11] from 3,6-dibromophenanthren-9,10-dione [12].

*2-Chloromethyl-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**2**, cone)*

Reagents: 1.4 g (2.0 mmol) calix[4]arene **1** in 190 ml dry THF, 5 ml (8.0 mmol) *n*-BuLi (1.6 M in *n*-hexane) and 0.5 ml (1.15 g, 8.0 mmol) bromochloromethane were used. Yield: 1.1 g (74 %), mp 176–177 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.21 (d, 2H, $^4J_{HH}$ = 2.1 Hz, ArH), 7.17 (s, 4H, ArH), 7.14 (d, 2H, $^4J_{HH}$ = 2.1 Hz, ArH), 5.11 (t, 1H, $^3J_{HH}$ = 8.5 Hz, C<u>H</u>CH_2Cl), 4.31 (d, 3H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 4.25 (s, 6H, OCH_3), 4.21 (s, 6H, OCH_3), 4.20 ("m", 2H, C<u>H</u>$_2$Cl), 3.44 (d, 3H, $^2J_{HH}$ = 12.2 Hz, $ArCH_2Ar$), 1.21 (s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.8, 150.7, 149.0, 148.8, 135.0, 134.8, 134.5, 134.4, 126.5, 126.0, 125.9, 121.6, 65.5, 65.0, 45.5, 38.4, 34.4, 34.2, 31.2, 30.0. LC–MS (ESI): calcd. for $C_{49}H_{65}O_4Cl$ (752.5); found: 775.4 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 78.11 H%: 8.70; found: C%: 78.16 H%: 8.62.

*2-(ω-Chloroethyl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**3**, cone)*

Reagents: 1.4 g (2.0 mmol) calix[4]arene **1** in 190 ml dry THF, 5 ml (8.0 mmol) *n*-BuLi (1.6 M in *n*-hexane) and 1.15 ml (1.15 g, 8.0 mmol) 1-bromo-2-chloroethane were used. Yield: 1.15 g (75 %), mp 160–162 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.18 (d, 2H, $^4J_{HH}$ = 2.0 Hz, ArH), 7.17 (m, 6H, ArH), 5.05 (t, 1H, $^3J_{HH}$ = 8.0 Hz, $CHCH_2CH_2Cl$), 4.31 (d, 3H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 4.24 (s, 6H, OCH_3), 4.21 (s, 6H, OCH_3), 3.57 (t, 2H, $^3J_{HH}$ = 6.5 Hz, CH_2CH_2Cl), 3.42 (d, 3H, $^2J_{HH}$ = 12.2 Hz, $ArCH_2Ar$), 2.62 (q, 2H, CH_2CH_2Cl), 1.20 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 151.0, 150.8, 148.9, 148.7, 136.7, 134.8, 134.6, 134.4, 126.1, 126.0, 125.9, 122.1, 65.5, 65.2, 42.8, 37.0, 34.4, 34.2, 32.4, 31.1 (2C), 30.0, 29.9. LC–MS (ESI): calcd. for $C_{50}H_{67}O_4Cl$ (766.5); found: 767.5 $(M + H)^+$ *m/z*. Anal. calcd. C%: 78.24 H% 8.80; found: C%: 78.49 H%: 8.87.

*2-(ω-Iodoethyl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**7**, cone)*

Reagents: 1.0 g (1.3 mmol) calix[4]arene **3** in 30 ml butanone and 0.38 g (2.5 mmol) NaI were used. Yield: 0.74 g (66 %), mp 146–148 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.17 (d, 2H, $^4J_{HH}$ = 2.4 Hz, ArH), 7.16 (s, 4H, ArH), 7.15 (s, 2H, ArH), 4.88 (t, 1H, $^3J_{HH}$ = 8 Hz, C<u>H</u>CH_2 CH_2I), 4.30 (d, 3H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 4.26 (s, 6H, OCH_3), 4.21 (s, 6H, OCH_3), 3.43 (d, 2H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 3.41 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2$ Ar), 3.16 (t, 2H, $^3J_{HH}$ = 7 Hz, CH_2C<u>H</u>$_2$I), 2.72 (q, 2H, $^3J_{HH}$ = 7.3 Hz, C<u>H</u>$_2CH_2I$), 1.20 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 151.0, 150.8, 149.0, 148.7, 136.6, 134.7, 134.6, 134.4, 126.1, 126.0, 125.9, 122.1, 65.9, 65.2, 38.4, 36.0, 34.4, 34.3, 31.2, 31.1, 30.0, 29.9, 29.6, 2.8. LC–MS (ESI): calcd. for $C_{50}H_{67}O_4I$ (858.4); found: 881.5 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 69.65 H%: 7.75; found: C%: 70.10 H%: 7.90.

*2-(ω-Iodohexyl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**9**, cone)*

Reagents: 0.9 g (1.0 mmol) calix[4]arene **6** in 30 ml butanone and 0.3 g (2.0 mmol) NaI were used. Yield: 0.58 g (57 %), mp 149–150 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.21 (d, 2H, $^4J_{HH}$ = 2.2 Hz, ArH), 7.18 (s, 4H, ArH), 7.15 (d, 2H, $^4J_{HH}$ = 2.2 Hz, ArH), 4.66 (t, 1H, $^3J_{HH}$ = 8.2 Hz, C<u>H</u>$CH_2(CH_2)_4CH_2I$), 4.30 (d, 3H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 4.19 (s, 6H, OCH_3), 4.17 (s, 6H, OCH_3), 3.42 (d, 2H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 3.41 (d, 1H, $^2J_{HH}$ = 12.5 Hz, $ArCH_2Ar$), 3.19 (t, 2H, $^3J_{HH}$ = 7.0 Hz, $CH_2(CH_2)_4C$<u>H</u>$_2$I), 2.11 (q, 2H, $^3J_{HH}$ = 7.5 Hz, C<u>H</u>$_2(CH_2)_4CH_2I$), 1.81 (m, 2H, $CH_2(C$<u>H</u>$_2)_4CH_2I$), 1.42 (m, 4H, $CH_2(C$<u>H</u>$_2)_4CH_2I$), 1.37 (m, 2H, $CH_2(C$<u>H</u>$_2)_4CH_2I$), 1.21 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.7, 148.7 (2C), 138.1, 134.5 (2C), 134.3, 125.9 (2C), 125.5, 122.3, 65.1, 65.0, 35.5, 34.3, 34.2, 33.9, 31.1, 31.0, 30.0 (2C), 29.9, 28.6, 7.0. LC–MS (ESI): calcd. for $C_{54}H_{75}O_4I$

(914.5); found: 937.5 $(M+Na)^+$ *m/z*. Anal. calcd. C %: 70.88 H%: 8.26; found: C%: 70.99 H%: 8.45.

*2-(ω-Azidoethyl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**10**, cone)*

Reagents: 1.53 g (2.0 mmol) calix[4]arene **3** in 50 ml dry DMF and 0.5 g (8.0 mmol) NaN_3 were used. Yield: 1.12 g (73 %), mp 156–158 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.18 (s, 6H, ArH), 7.14 (s, 2H, ArH), 4.88 (t, 1H, $^3J_{HH} = 8.2$ Hz, $C\underline{H}CH_2CH_2N_3$), 4.30 (d, 3H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 4.21 (s, 6H, OCH_3), 4.20 (s, 6H, OCH_3), 3.44 (d, 2H, $^2J_{HH} = 12.4$ Hz, $ArC\underline{H}_2Ar$), 3.42 (d, 1H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 3.39 (t, 2H, $^3J_{HH} = 6.5$ Hz, $CH_2C\underline{H}_2N_3$), 2.43 (q, 2H, $^3J_{HH} = 7.7$ Hz, $C\underline{H}_2CH_2N_3$), 1.19 (s, 36H, $C(CH_3)_3$);.^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.8 (2C), 148.8, 148.6, 136.7, 134.7, 134.6, 134.4, 126.0 (2C), 125.1, 122.0, 65.3, 65.2, 49.6, 34.4, 34.2, 33.0, 32.3, 31.2, 31.1, 30.0, 29.9. LC–MS (ESI): calcd. for $C_{50}H_{67}O_4N_3$ (773.5), found: 774.5 $(M+H)^+$ *m/z*. Anal. calcd. C%: 72.75 H%: 8.17 N%: 5.04; found: C%: 72.60 H%: 8.31 N%: 4.69 ($C_{50}H_{67}O_4N_3$·0.5 $CHCl_3$).

General Procedure for the synthesis of biscalixarenes **13–15**

To a solution of calixarene **1** in dry THF is added 1.1 equiv. *n*-BuLi (1.6 M in *n*-hexane). The cherry-red solution which has formed is stirred at room temperature for 45 min. While stirring, a solution of the corresponding 2-ω-iodo-alkyl derivative in 5 ml dry THF is added, changing the colour of the solution gradually to grey and later yellow. After 12 h of stirring, all volatiles are removed and the residue is partitioned between dichloromethane and water (50 ml each). The organic phase is washed several times with brine and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow sliffy product, which is transformed to a white microcrystalline solid by crystallization from MeOH.

*2,2′-(Ethane-1,2-diyl)bis(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**13**, cone)*

Reagents: 105 mg (0.15 mmol) calix[4]arene **1** in 15 ml dry THF, 0.11 ml (0.17 mmol) *n*-BuLi (1.6 M in *n*-hexane) and 130 mg (0.15 mmol) 2-iodoethylcalix[4]arene **7** in 5 ml dry THF were used. Yield: 110 mg (52 %), mp 188–190 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.22 (d, 4H, $^4J_{HH} = 2.2$ Hz, ArH), 7.16 (s, 8H, ArH), 7.13 (d, 4H, $^4J_{HH} = 2.1$ Hz, ArH), 4.72 (br, 2H, $C\underline{H}(CH_2)_2R$), 4.28 (d, 6H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 4.18 (s, 12H, OCH_3), 4.16 (s, 12H, OCH_3), 3.41 (d, 6H, $^2J_{HH} = 12.4$ Hz, $ArC\underline{H}_2Ar$), 2.16 (m, 4H, $CH(C\underline{H}_2)_2CH$), 1.19 (s, 36H, $C(CH_3)_3$), 1.17 (s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.6, 150.5, 149.1, 148.8, 148.7, 137.6, 134.5, 134.4 (2C), 126.0, 125.9, 125.7, 122.1, 65.1, 65.0, 35.9, 34.4, 34.2, 31.2, 31.0 (2C), 29.9, 29.8. LC–MS (ESI): calcd. for $C_{98}H_{130}O_8$ (1435.0); found: 1457.5 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 80.99 H%: 9.20; found: C%: 80.66 H%: 9.29 ($C_{98}H_{130}O_8$·MeOH).

*2,2′-(Propane-1,3-diyl)bis(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**14**, cone)*

Reagents: 105 mg (0.15 mmol) calix[4]arene **1** in 15 ml dry THF, 0.11 ml (0.17 mmol) *n*-BuLi (1.6 M in *n*-hexane) and 130 mg (0.15 mmol) 2-iodopropylcalix[4]arene **8** in 5 ml dry THF were used. Yield: 120 mg (56 %), mp 171–175 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.20 (d, 4H, $^4J_{HH} = 2.2$ Hz, ArH), 7.18 (s, 8H, ArH), 7.17 (d, 4H, $^4J_{HH} = 2.3$ Hz, ArH), 4.57 (t, 2H, $^3J_{HH} = 8.1$ Hz, $C\underline{H}(CH_2)_3R$), 4.29 (d, 2H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 4.28 (d, 4H, $^2J_{HH} = 12.4$ Hz, $ArC\underline{H}_2Ar$), 4.18 (s, 12H, OCH_3), 4.05 (s, 12H, OCH_3), 3.44 (d, 4H, $^2J_{HH} = 12.4$ Hz, $ArC\underline{H}_2Ar$), 3.41 (d, 2H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 2.21 (m, 4H, $CHC\underline{H}_2CH_2C\underline{H}_2CH$), 1.30 (m, 2H, $CHCH_2C\underline{H}_2CH_2CH$), 1.21 (s, 36H, $C(CH_3)_3$), 1.20 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.7, 150.6, 148.8, 148.7 (2C), 137.7, 134.5 (2C), 126.0, 125.9 (2C), 122.0, 65.0 (2C), 35.4, 34.4, 34.2, 31.3, 31.2, 31.0, 30.0, 29.9. LC–MS (ESI) calcd. for $C_{99}H_{132}O_8$ (1449.0); found: 1473.5 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 81.04 H%: 9.25; found: C%: 79.83 H%: 9.35 ($C_{99}H_{132}O_8$·MeOH).

*2,2′-(Hexane-1,6-diyl)bis(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**15**, cone)*

Reagents: 105 mg (0.15 mmol) calix[4]arene **1** in 15 ml dry THF, 0.11 ml (0.17 mmol) *n*-BuLi (1.6 M in *n*-hexane) and 140 mg (0.15 mmol) 2-iodo-*n*-hexylcalix[4]aren **9** in 5 ml dry THF were used. Yield: 80 mg (36 %); mp 249–251 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.20 (s, 4H, ArH), 7.17 (s, 8H, ArH), 7.14 (s, 4H, ArH), 4.64 (t, 2H, $^3J_{HH} = 8.0$ Hz, $C\underline{H}(CH_2)_6R$), 4.29 (d, 6H, $^2J_{HH} = 12.3$ Hz, $ArC\underline{H}_2Ar$), 4.19 (s, 12H, OCH_3), 4.15 (s, 12H, OCH_3), 3.42 (d, 6H, $^2J_{HH} = 12.4$ Hz, $ArC\underline{H}_2Ar$), 2.10 (m, 4H, $CHC\underline{H}_2(CH_2)_4C\underline{H}_2CH$), 1.41–1.28 (m, 8H, $CHCH_2(C\underline{H}_2)_4CH_2CH$), 1.20 (s, 36H, $C(CH_3)_3$), 1.19 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.7, 148.7, 138.1, 134.6, 134.3, 126.0, 125.5, 122.3, 65.1, 65.0, 35.6, 34.4, 34.2, 31.1, 31.0, 30.0, 29.9, 29.0. IR: ν = 2956, 2928, 2868, 2821, 1481, 1461, 1432, 1361, 1302, 1284, 1245, 1204, 1174, 1121, 1023, 948, 869, 800, 642, 498. LC–MS (ESI) calcd. for $C_{102}H_{138}O_8$ (1491.0); found: 1514.0 $(M+Na)^+$ *m/z*; Anal. calcd. C%: 80.22; H%: 9.13; found: C%: 80.36 H%: 9.30 ($C_{102}H_{138}O_8$·0.5 CH_2Cl_2).

General procedure for the synthesis of **16–20**

The respective 2-ω-azidoalkylcalixarenes (**10–12**), the corresponding spacer compound (**20–23**) and 0.1 ml *N*-diisopropylethylamine (DIPEA) are dissolved in acetonitrile and the solution is degassed. After addition of CuI the reaction mixture is heated for 28 h at 60 °C. Only in the case of **20**, the reaction time is expanded to 45 h due to the low solubility of **23**. The colour of the reaction mixture gradually changes to yellow (**16–19**) and pink (**20**). The formed precipitate is filtered off and the solvent is removed under reduced pressure. The brown crude product is dissolved in 30 ml dichloromethane, washed repeatedly with 2 M HCl and water in this sequence, dried ($MgSO_4$) and evaporated. The obtained light yellow powders are purified by column chromatography (SiO_2, eluent: *n*-hexane/ethyl acetate [1:1]).

*2,2′-[1,3-Phenylenebis(1H-1,2,3-triazole-4,1-diyl-ethane-2,1-diyl)]bis-(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**16**, cone)*

Reagents: 0.77 g (1.0 mmol) 2-azidoethylcalix[4]arene **10** in 30 ml dry THF, 0.063 g (0.5 mmol) 1,3-diethynylbenzene, 0.1 ml (0.6 mmol) DIPEA and 0.06 g (0.3 mmol) CuI were used. Yield: 0.32 g (39 %); mp 203–205 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 8.21 (s, 1H, ArH^{Phen}), 8.16 (s, 2H, ArH^{TA}), 7.90 (d, 2H, $^3J_{HH} = 7.7$ Hz, ArH^{Phen}), 7.48 (t, 1H, $^3J_{HH} = 7.7$ Hz, ArH^{Phen}), 7.17–7.14 (m, 16H, ArH), 4.74 (t, 2H, $^3J_{HH} = 8.0$ Hz, $C\underline{H}CH_2CH_2R$), 4.55 (t, 4H, $^3J_{HH} =$! 7.0 Hz, $CHCH_2\underline{CH_2}R$), 4.30 (d, 6H, $^2J_{HH} = 12.3$ Hz, $ArCH_2Ar$), 4.20 (s, 12H, OCH_3), 4.18 (s, 12H, OCH_3), 3.42 (d, 6H, $^2J_{HH} = 12.4$ Hz, $ArCH_2Ar$), 2.20 (m, 4H, $CHC\underline{H_2}CH_2R$), 1.19 (s, 36H, $C(CH_3)_3$), 1.17 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.7, 148.8, 148.6, 136.7, 136.2, 134.7, 134.5, 134.3, 131.6, 129.1, 128.8, 126.3, 126.0, 125.9, 122.6, 122.0, 65.0 (2C), 49.4, 34.4, 34.3, 34.2, 33.2, 31.1 (2C), 29.5. LC–MS (ESI) calcd. for $C_{110}H_{140}O_8N_6$ (1673.1); found: 1697.3 $(M+Na)^+$ *m/z*. Anal. calcd.: C%: 78.91 H%: 8.43 N%: 5.02; found: C%: 78.52 H%: 8.29 N%: 4.68 ($C_{110}H_{140}O_8N_6$·MeOH).

*2,2′-[1,3-Phenylenebis(1H-1,2,3-triazole-4,1-diyl-propane-3,1-diyl]bis-(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**17**, cone)*

Reagents: 0.79 g (1.0 mmol) 2-azido-*n*-propylcalix[4]arene **11** in 30 ml dry THF, 0.063 g (0.5 mmol) 1,3-diethynylbenzene, 0.1 ml (0.6 mmol) DIPEA and 0.06 g (0.3 mmol) CuI were used. Yield: 0.36 g (42 %); mp 196–199 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 8.21 (s, 1H, ArH^{Phen}), 8.11 (s, 2H, ArH^{TA}), 7.89 (d, 2H, $^3J_{HH} =$ 7.8 Hz, ArH^{Phen}), 7.49 (t, 1H, $^3J_{HH} = 7.8$ Hz, ArH^{Phen}), 7.17–7.15 (m, 16H, ArH), 4.75 (t, 2H, $^3J_{HH} = 8.0$ Hz, $C\underline{H}CH_2CH_2CH_2R$), 4.55 (t, 4H, $^3J_{HH} = 6.6$ Hz, $CHCH_2$ $CH_2C\underline{H_2}R$), 4.29 (d, 6H, $^2J_{HH} = 12.3$ Hz, $ArCH_2Ar$), 4.20 (s, 12H, OCH_3), 4.18 (s, 12H, OCH_3), 3.42 (d, 4H, $^2J_{HH} =$ 12.4 Hz, $ArCH_2Ar$), 3.41 (d, 2H, $^2J_{HH} = 12.4$ Hz, $ArCH_2$ Ar), 2.20 (m, 4H, $CHC\underline{H_2}CH_2CH_2R$), 2.08 (m, 4H, $CHCH_2$ $C\underline{H_2}CH_2R$), 1.19 (s, 36H, $C(CH_3)_3$), 1.17 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 148.8, 148.7, 147.3, 137.9, 134.5, 134.3, 134.1, 132.5, 132.2, 128.3, 126.1, 126.0, 125.9, 125.8, 125.4, 124.9, 122.3, 121.9, 65.2, 65.0, 53.4, 42.3, 34.5, 34.1, 33.2, 31.2, 31.1, 29.5. LC–MS (ESI) calcd. for $C_{112}H_{144}O_8N_6$ (1701.1); found: 1725.3 $[M+Na]^+$ *m/z*. Anal. calcd. C%: 78.25 H%: 8.60 N%: 4.85; found: C%: 78.21 H %: 8.44 N%: 4.41 ($C_{112}H_{144}O_8N_6$·MeOH).

*2,2′-[1,3-Phenylenebis(1H-1,2,3-triazole-4,1-diyl-pentane-5,1-diyl)]bis-(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**18**, cone)*

Reagents: 0.82 g (1.0 mmol) 2-azido-*n*-pentylcalix[4]arene **12** in 30 ml dry THF, 0.063 g (0.5 mmol) 1,3-diethynylbenzene, 0.1 ml (0.6 mmol) DIPEA and 0.06 g (0.3 mmol) CuI were used. Yield: 0.37 g (42 %); mp 190–193 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 8.29 (s, 1H, ArH^{Phen}), 7.95 (s, 2H, ArH^{TA}), 7.82 (d, 2H, $^3J_{HH} = 7.5$ Hz, ArH^{Phen}), 7.49 (t, 1H, $^3J_{HH} = 7.6$ Hz, ArH^{Phen}), 7.20–7.15 (m, 16H, ArH), 4.66 (t, 2H, $^3J_{HH} = 8.0$ Hz, $C\underline{H}CH_2(CH_2)_3CH_2R$), 4.42 (t, 4H, $^3J_{HH} = 6.6$ Hz, $CHCH_2(CH_2)_3C\underline{H_2}R$), 4.30 (d, 6H, $^2J_{HH} = 12.3$ Hz, $ArCH_2Ar$), 4.18 (s, 12H, OCH_3), 4.16 (s, 12H, OCH_3), 3.41 (d, 2H, $^2J_{HH} = 12.4$ Hz, $ArCH_2Ar$), 3.40 (d, 4H, $^2J_{HH} = 12.3$ Hz, $ArCH_2Ar$), 2.12 (m, 4H, $CHC\underline{H_2}(CH_2)_3CH_2R$), 1.98 (m, 4H, $CHCH_2$ $(C\underline{H_2})_3CH_2R$), 1.48–1.39 (m, 8H, $CHCH_2(C\underline{H_2})_3CH_2R$), 1.20 (s, 36H, $C(CH_3)_3$), 1.19 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$/CD_3CN 9:1): 150.6 (2C), 148.8, 148.7, 147.2, 137.9, 134.4, 134.3, 131.1, 125.9, 125.5, 125.1, 122.7, 122.2, 119.9, 65.1, 64.9, 50.2, 35.4, 34.3, 34.2, 31.1 (2C), 30.0, 29.8, 29.5, 28.4, 26.7, 22.5. LC–MS (ESI) calcd. for $C_{116}H_{152}O_8N_6$ (1757.2); found: 1781.4 $(M+Na)^+$ *m/z*. Anal. calcd.: C%: 78.48 H%: 8.78 N%: 4.69; found: C%: 78.19 H%: 8.62 N %: 4.30 ($C_{116}H_{152}O_8N_6$ · MeOH).

*2,2′-{Carbonylbis[4,1-phenylene(1H-1,2,3-triazole-4,1-diyl)-propane-3,1-diyl]}bis(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**19**, cone)*

Reagents: 0.50 g (0.63 mmol) 2-azido-*n*-propylcalix[4]arene **11** in 30 ml dry THF, 0.071 g (0.31 mmol) 4,4′-diethynylacetophenone, 0.09 ml (0.5 mmol) DIPEA and 0.05 g (0.25 mmol) CuI were used. Yield: 0.38 g (67 %); mp 183–185 °C. ^{1}H NMR ($CDCl_3$/CD_3CN 9:1): 7.98 (d, 4H, $^3J_{HH} = 8.5$ Hz, ArH^{Phen}), 7.88 (d, 4H,

$^{3}J_{HH}$ = 8.5 Hz, ArH^{Phen}), 7.17–7.14 (m, 16H, ArH), 4.73 (t, 2H, $^{3}J_{HH}$ = 8.1 Hz, $C\underline{H}CH_2CH_2CH_2R$), 4.56 (t, 4H, $^{3}J_{HH}$ = 6.5 Hz, $CHCH_2CH_2C\underline{H}_2R$), 4.30 (d, 2H, $^{2}J_{HH}$ = 12.2 Hz, $ArCH_2Ar$), 4.29 (d, 4H, $^{2}J_{HH}$ = 12.3 Hz, $ArCH_2Ar$), 4.20 (s, 12H, OCH_3), 4.18 (s, 12H, OCH_3), 3.43 (d, 2H, $^{2}J_{HH}$ = 12.2 Hz, $ArCH_2Ar$), 3.42 (d, 4H, $^{2}J_{HH}$ = 12.3 Hz, $ArCH_2Ar$), 2.22 (m, 4H, $C\underline{H}_2CH_2CH_2R$), 2.03 (m, 4H, $CH_2C\underline{H}_2CH_2R$), 1.20 (s, 36H, $C(CH_3)_3$), 1.17 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3/CD_3CN$ 9:1): 195.4, 150.6, 149.0, 148.7 (2C), 146.8, 137.1, 136.8, 135.1, 134.5 (2C), 134.4, 130.6, 126.0, 125.9, 125.3, 125.0, 121.9, 120.4, 65.3, 65.0, 50.2, 35.0, 34.3, 34.2, 31.0, 30.9, 30.8, 30.0, 29.8. LC–MS (ESI) calcd. for $C_{119}H_{148}O_9N_6$ (1805.1); found: 1829.2 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 79.12 H%: 8.26 N%: 4.65; found: C%: 79.53 H%: 8.35 N%: 4.59.

*2,2′-{Fluoren-9H-one-3,6-diylbis[(1H-1,2,3-triazole-4,1-diyl)-propane-3,1-diyl]}bis(5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene) (**20**, cone)*

Reagents: 0.55 g (0.7 mmol) 2-azido-*n*-propylcalix[4]arene **11** in 30 ml dry THF, 0.080 g (0.35 mmol) 3,6-diethynyl-9-fluorenone, 0.1 ml (0.6 mmol) DIPEA and 0.06 g (0.3 mmol) CuI were used. Yield: 0.34 g (54 %); mp 195–198 °C. ^{1}H NMR ($CDCl_3/CD_3CN$ 9:1): 8.25 (s, 2H, ArH^{Flu}), 8.24 (s, 2H, ArH^{TA}), 7.83 (d, 2H, $^{3}J_{HH}$ = 7.6 Hz, ArH^{Flu}), 7.69 (d, 2H, $^{3}J_{HH}$ = 7.6 Hz, ArH^{Flu}), 7.21–7.18 (m, 16H, ArH), 4.75 (t, 2H, $^{3}J_{HH}$ = 8.0 Hz, $CHCH_2CH_2C\underline{H}_2R$), 4.60 (t, 4H, $^{3}J_{HH}$ = 6.4 Hz, $CHCH_2CH_2CH_2R$), 4.28 (m, 6H, $ArCH_2Ar$), 4.19 (s, 12H, OCH_3), 4.17 (s, 12H, OCH_3), 3.45 (d, 2H, $^{2}J_{HH}$ = 12.1 Hz, $ArCH_2Ar$), 3.44 (d, 4H, $^{2}J_{HH}$ = 12.2 Hz, $ArCH_2Ar$), 2.22 (m, 4H, $C\underline{H}_2CH_2CH_2R$), 2.10 (m, 4H, $CH_2C\underline{H}_2CH_2R$), 1.20 (s, 36H, $C(CH_3)_3$), 1.18 (s, 36H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3/CD_3CN$ 9:1): 192.1, 150.3 (2C), 148.6, 148.5, 148.4, 148.3, 146.3, 144.3, 137.1, 137.0, 136.6, 134.2, 134.1, 133.4, 133.3, 133.2, 132.9, 125.6, 125.5, 125.3, 125.1, 124.7, 124.1, 121.8, 121.0, 64.9, 64.4, 50.9, 34.9, 34.7, 34.0 (2C), 33.5, 30.9, 30.8, 29.6, 29.5, 27.9. LC–MS (ESI) calcd. for $C_{119}H_{146}O_9N_6$ (1803.1); found: 1827.1 $(M+Na)^+$ *m/z*. Anal. calcd. C%: 79.21 H%: 8.16 N%: 4.66; found: C%: 79.64 H%: 8.08 N%: 4.72.

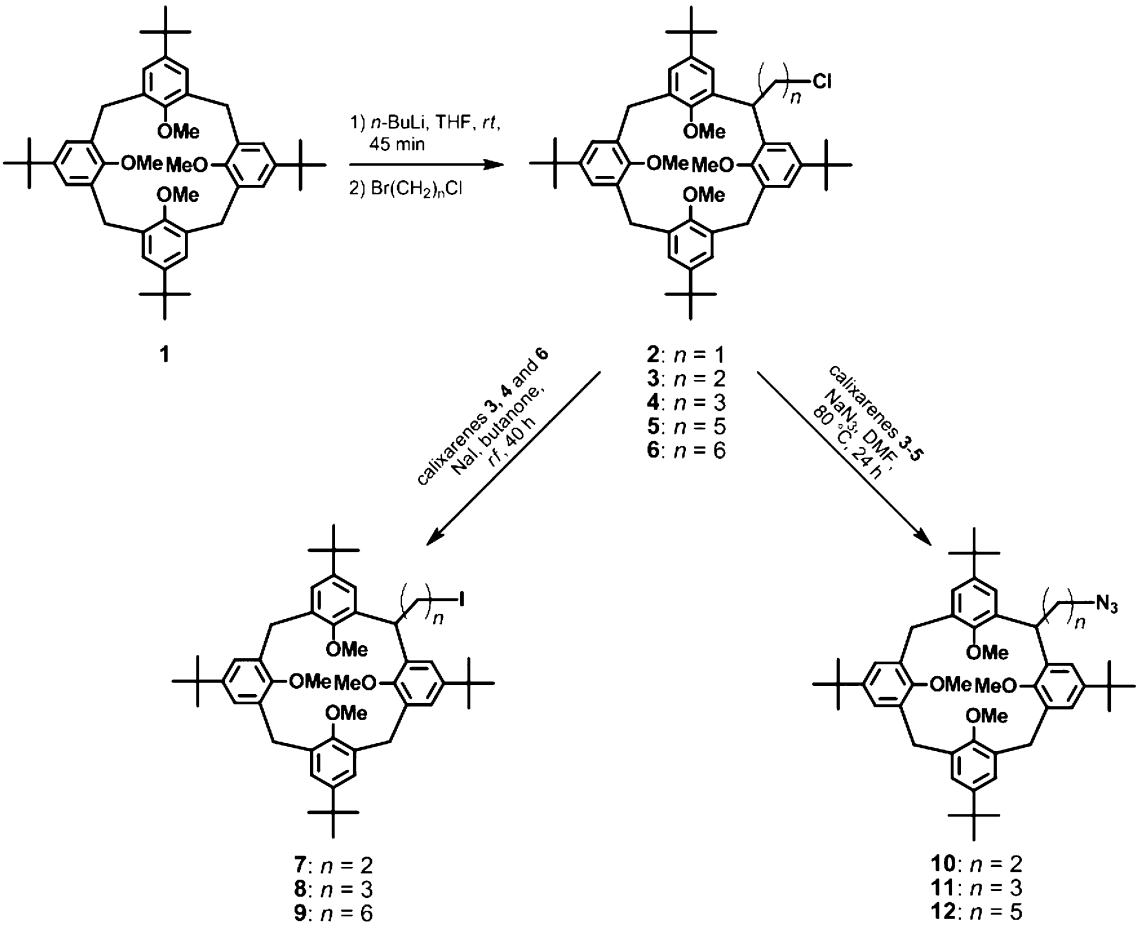
Computional methods

Molecular mechanistic calculations of gas phase molecules were performed using the MMFF94 force field as implemented in MACROMODEL 9.1 (Schroedinger, New York). The starting geometry of the single conformers are minimized with the help of the dipolar effects and ion pair repulsion sensitive PRCG method (ε = 4, 10000 steps, convergence criterion: 0.005) and the optimized geometries were submitted to a conformational search. Each search was repeated until convergence using the "mixed torsional/low-mode sampling method" (1000 steps, 50 steps per rotatable bond, $\Delta E < 5.02$ kcal mol^{-1}, RMSD cutoff: 0.3 Å).

Results and discussion

After having established the structural conditions required for the bridge lithiation of a basic calix[4]arene [13] and giving a systematic structural characterization of the conformational behaviour of corresponding lateral mono- [2–7] and disubstituted [14–16] tetramethoxycalixarenes, preconditions should be met to carry out a potential bridge connection of two laterally functionalized calix[4]arenes as outlined in Scheme 2. To realize the chain of reasoning there, starting from **1** the corresponding bridge -chloroalkyl substituted calixarenes **2–6** were synthesized by the common lithiation and substitution technique [9] with 1-bromo-ω-chloroalkanes as electrophiles (Scheme 2). Although an excess of electrophile was used, the chloro function remains stable against *n*-BuLi and no dimeric products are obtained. Subsequent nucleophilic substitution of **2–6** with NaI in butanone yielded the respective ω-iodo-calixarenes **7–9**, while convenient substitution with NaN_3 in DMF [10] gave the respective azides **10–12** in good yield as white powders after recrystallization from methanol (Scheme 2). In accordance with previous reports [2–7], all bridge monosubstituted calixarenes **2–12** are flexible in solution and show complex NMR-spectra with signal overlap. However, complexation of Na-cation by addition of NaI and acetonitrile-d_3 forces all calixarenes in a pure *cone* conformation, leading to clear and interpretable NMR-spectra. Worthy of note, for both cases of nucleophilic substitution, no conversion for the chloromethyl derivative **2** was observed, even after expanding the reaction conditions, i.e. doubling of reaction time and raising the temperature. This behaviour can be attributed to a shielded back site of the lateral CH_2-group due to the proximity of the neighbouring arene units (Fig. 1, Figs. S2–S4), which hampers the S_N2-attack of the large iodide nucleophile. In addition, the reaction centre shows a highly reduced electrophilic character as result of the -I-effect of the neighbouring phenyl rings as well as the chloromethyl substituent indicated by a strong deshielding of the lateral CH_2 protons compared to the higher homologues **3–6** (4.20 ppm, Fig. S2). The assignment of resonances in compound **2** was done by a HSQC experiment since the CH_2 proton signal overlaps with those of the $ArCH_2Ar$ protons (Fig. S4).

Using the direct linkage process indicated in Scheme 2, the alkyl-bridged calixarenes **13–15** are easily accessible



Scheme 2 Pathways to the intermediate calixarenes possessing lateral ω-chloroalkyl (**2–6**), ω-iodoalkyl (**7–9**) and ω-azidoalkyl (**10–12**) substituents

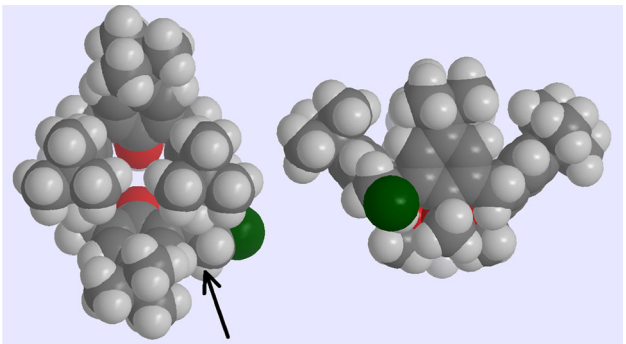
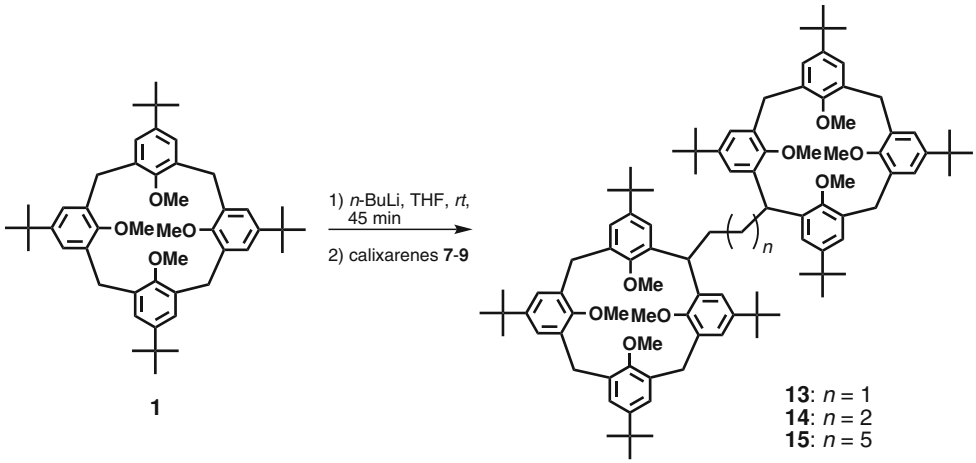


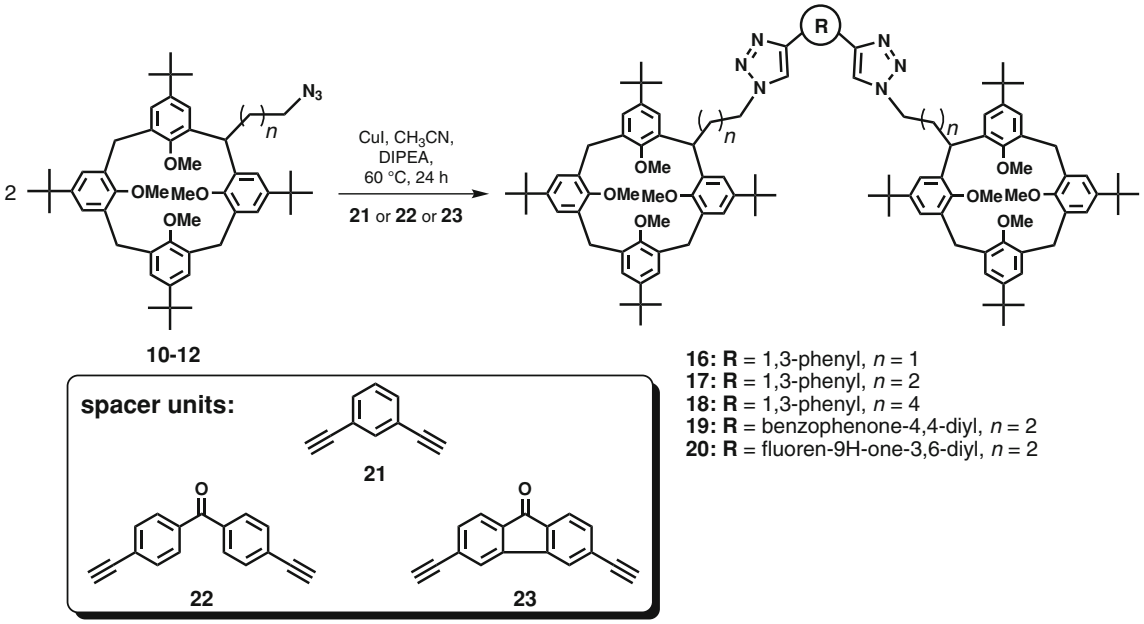
Fig. 1 Illustration of the sterically shielded methylene group regarding the bridge chloromethyl substituted calixarene **2** in front and side-view

by reaction of the obtained ω-iodo-derivatives **7–9** (S7–S10) with lithiated calixarene **1** at room temperature (Scheme 3, S13–S18). Interestingly, an alkyl chain containing at least two C-atoms is required to bridge two calixarenes (i.e. ethyl, compound **7**), thus allowing a high variability of the spacer length. As mentioned for the bridge monosubstituted calixarenes, all alkyl-bridged biscalixarenes show numerous resonances in the ^{1}H-NMR spectra representative for the coexistence of different conformers in solution. Applying the common preparation technique, that is the addition of NaI and small amounts of CD_3CN [9, 14], conversion to pure *cone* conformers is achievable. This gave access to new resonances in the alkyl region of the corresponding ^{1}H-NMR spectra (2.10–2.20 ppm, S13, S15, S17) as well as respective peaks in the mass spectra proving the successful formation of biscalixarenes **13–15**.

In another attempt, we aimed at a more rigid connection mode for bridging of two calixarenes. Along these lines and following the click-chemistry approach, the precursor calixarene azides **10–12** readily undergo 1,3-dipolar cycloaddition [17, 18] with different dialkyne spacers (**21–23**) resulting in the formation of bridge connected calixarene-conjugates **16–20** (Scheme 4). The used spacer molecules all exhibit the alkyne groups in an angled arrangement (112–120°) to each other, thus preorganizing the conjugates **16–20** in a chelate-like fashion. While the dialkynes

Scheme 3 Synthesis of calixarenes **13–15** with flexible alkyl spacer





Scheme 4 Synthesis of calixarenes **16–20** with semi-rigid bistriazole-spacers

21 and **22** are commercially available, synthesis of **23** has been done via a benzilic acid rearrangement route of 3,6-dibromophenanthren-9,10-dione [19].

Whereas flexibility of the chelate-like systems **16–18** and **20** is limited to a rotation of the spacer alkyl chains, compound **19** offers a higher degree of conformational freedom due to the possible twist of the benzophenone moiety. In the ^{1}H-NMR spectra of the *cone*-fixed biscalixarenes **16–20**, a low field shifted triplet around 4.5 ppm as well as a new singlet signal in the aromatic region indicate the successful formation of the 1,2,3-triazine systems (Figs. S19, S21, S23, S25, S27).

Since we were not successful to yield high quality crystals suitable for X-ray diffraction, MM-calculations of the gas-phase molecules were performed to elucidate the conformational behaviour and shape of the conjugate-structures **14**, **17**, **19** and **20** serving as examples. Under stochastic point of view[1] assuming independent conformations of two

Table 1 Calculated energy differences of selected conformations of compounds **14**, **17**, **19** and **20** (MMFF94, kcal mol^{-1})

	14	**17**	**19**	**20**
ConeA-coneA[a]	+0.45	+0.10	+2.24	+2.38
PacoC-coneA[a]	0	+0.57	0	0
PacoC-pacoC[a]	+0.17	0	+1.68	+1.89

[a] Conformations as designated in Fig. 2

[1] Calculated by means of combinational analysis, 10 conformations (n) of 2 individual chalices (c): $[(n + c - 1)!/(n - 1!) \cdot c!]$.

connected calix[4]arenes, the existence of 55 different conformers is possible. This number clearly raises if different geometries of the spacer elements are taken into consideration. Due to the immense CPU power needed for the calculation of such rather big molecular systems (236–282 atoms), exclusively selected conformations known to be frequently low energy conformations of bridge mono-substituted calix[4]arenes [2, 4] were calculated. The results are summarized in Table 1. Different possible conformations of bridge mono-substituted calix[4]arenes can be extracted from Fig. S29.

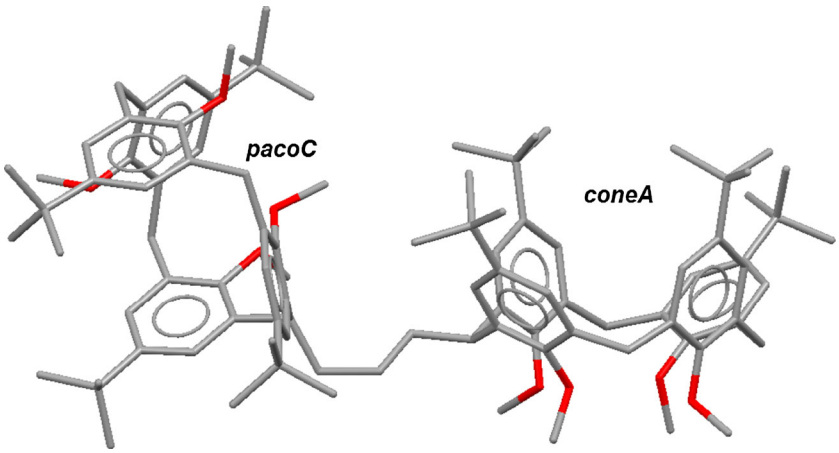


Fig. 2 Energy-minimized structure of the propyl linked biscalixarene **14** with designation of the conformations. H-atoms are omitted for clarity

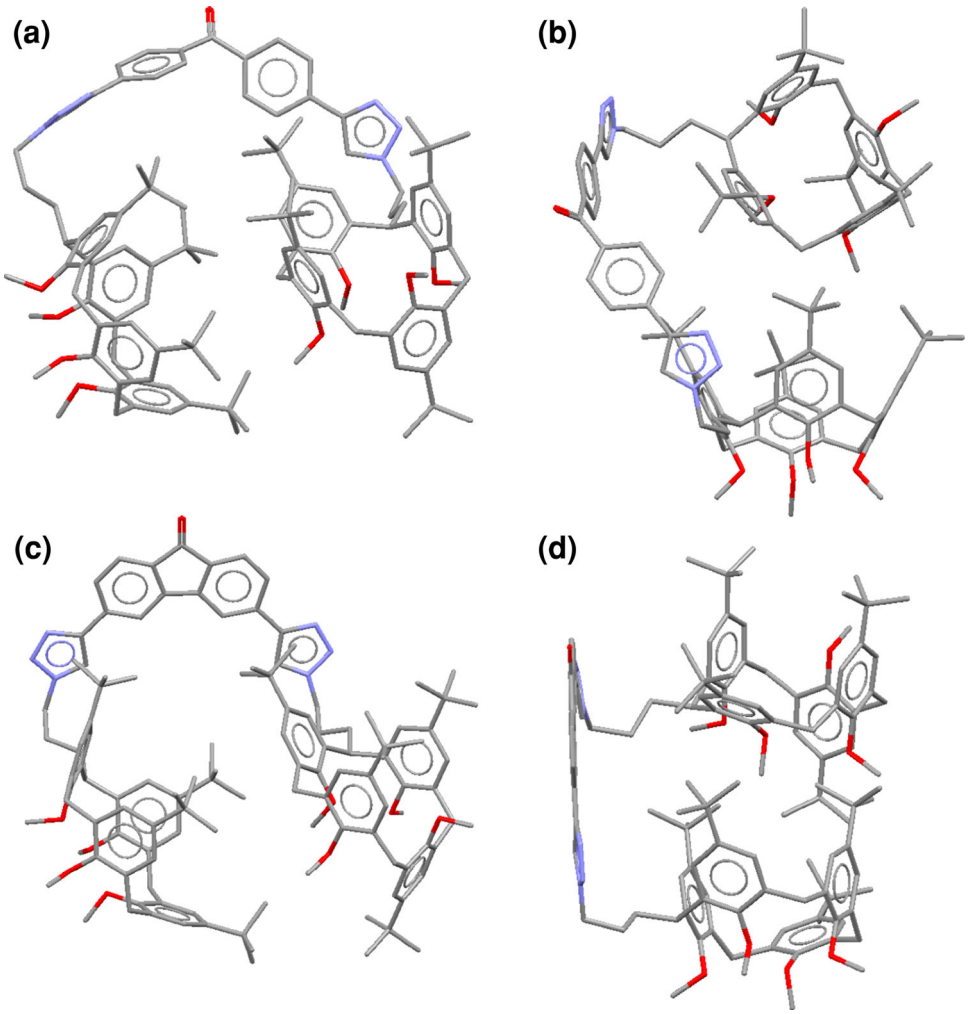


Fig. 3 Energy-minimized structures of the triazole linked biscalixarenes **19** and **20** in front- (**a**, **c**) and side perspective (**b**, **d**). H-atoms have been omitted for clarity

Regarding the most likely conformations of the propyl linked biscalixarene **14**, the *pacoC-coneA* conformer has been calculated to be the lowest energy conformer (S30), showing the bridge substituent both times in an equatorial position relative to the calixarene core. The flexibility detected in solution is reflected by similar energies of the three calculated conformations. Both chalices are twisted around the alkyl substituent thus allowing maximal interaction including *van-der-Waals* and C–H···π contacts [20, 21, 22] between the calixarenes (Fig. 2).

Elongation of the spacer as in compounds **16–20** supports higher variability with respect to conformations. Whereas in compound **17** both calixarenes adopt a *partial cone* conformation (Figs. S30, S34), for biscalixarenes **19** and **20** the *pacoC-coneA* conformer is calculated as low energy conformer (S32, S33). Raised energy levels with reference to the other two calculated conformations of about 2 kcal mol^{-1} indicate the limited flexibility of these conjugates (Table 1). The triazole units in the energy-minimized structure of **17** are arranged in *anti*-fashion.

Referring to the linked bistriazole units, the different orientation of the spacer elements in calixarenes **19** and **20** is obvious (Fig. 3). In the calculated structure of **19**, both benzene rings of the central benzophenone unit are nearly orthogonal arranged, while the conjugation in compound **20** forces a quasi planar arrangement of the fluorenone unit. Remarkably, all three calculated biscalixarenes **17**, **19** and **20** possess an inherent cavity preorganized to form secondary supramolecular interactions. Especially the *syn*-orientation of both triazole-protons in the fluorenone derivative **20** is expected to be favourable for a potential hydrogen bond-assisted inclusion of anions of appropriate size, as recently shown for related [3_4]triazolophanes[2] [23]. Their potential to include also neutral molecules due to the formed internal cavity between both chalices might be derived from the elemental analyses data, showing enclosed MeOH or methylene chloride in case of podant compounds **14–18**.

Conclusion

Summing up, for the first time, reliable synthetic pathways for a bridge mode connection of two calixarenes via an alkylene or bis-1,2,3-triazole modified linkage unit are described. A minimum of two C-atoms is required for a successful connection of this type. NMR-spectroscopic data as well as MM-calculations reveal the alkyl linked conjugates to be flexible in solution and isolated gas-phase. In contrast, the bis-triazole derivatives are more preorganized exhibiting a concave cavity which should be a beneficial fact for a potential use as shape-sensitive chemosensors [23] as well as multivalent devices [6, 7, 24].

[2] First NMR-titrations of **17** with TBAX (X = F, Cl, Br, I) show lowfield shifts of aromatic triazole protons indicative for halide ion complexation. Further studies are owing.

Acknowledgments ADDE (Cluster of Excellence "Structure Design of Novel High-Performance Materials via Atomic Design and Defect Engineering") is acknowledged for founding of the modelling software.

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