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Building Triazolated Macrocycles from Bis-Propargylated Calix[4]arenes and Bis-Azidomethylated Azobenzene or Stilbene

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Abstract: Copper(I)-catalyzed azide-alkyne cycloaddition was employed to construct biscalixarene assemblies from the calix[4]arene dipropargyl ethers and 4,4′-bis-azidomethylated azobenzene or stilbene. Three bis(calixarenes) having the calix[4]arene cores linked to each other by pairs of (*E*)-azobenzene/stilbene units through four triazole groups were obtained as confirmed by NMR, HRMS and X-ray diffraction data. Nevertheless, the formation of larger macrocycles and polymeric/oligomeric products was found to be the major competing process that seriously limited the applicability of the one-step macrocyclization approach for the construction of photoresponsive biscalixarene assemblies linked by pairs of azobenzene/stilbene units.

Keywords: calixarenes; triazoles; azobenzenes; stilbenes; macrocyclization; CuAAC

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1. Introduction

Covalent linking of several calixarene-type macrocycles is one of the modern synthetic strategies towards multitopic receptor systems, which possess unique properties that cannot be achieved using a single macrocyclic core [1–13]. In particular, the involvement of more than one linker into the connection of pairs of the cores is widely used in calixarene chemistry to obtain various multi(macrocycles) having tubular or semi-tubular shapes [14–31], which have special receptor properties provided by the new receptor holes formed during macrocyclization. We have recently shown that two calix[4]arene cores could be readily linked to each other by two azobenzene or stilbene units using the K_2CO_3-promoted alkylation of parent calixarene tetrols with 4,4′-bis-bromomethylated azobenzene or stilbene, which furnished semi-tubular bis(calix[4]arenes) capable of shape changes upon irradiation/heating [32]. On the other hand, our ongoing studies on the features [33,34] and applications [35,36] of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) in calixarene chemistry showed the great potential of this reaction for the preparation of diverse receptor molecules including bis- and triscalixarene semi-tubular assemblies [37,38] comprising 1,4-disubstituted 1,2,3-triazoles as the key linking or/and receptor units. Within a reasonable extension of the above studies, herein we investigated the applicability of the CuAAC approach for the one-step construction of biscalixarene molecules from the calix[4]arene dipropargyl ethers and bis-azidomethylated azobenzene or stilbene.

2. Results and Discussion

Cone calix[4]arene **1** [39] having two propargyl and two propyl groups at the narrow rim (Figure 1) was selected as the alkyne component of the CuAAC-macrocyclization to be reacted with 4,4′-bis-azidomethylated (*E*)-azobenzene **2** [40] and (*E*)-stilbene **4**. The latter was prepared for the first time upon reacting 4,4-bis-bromomethylated (*E*)-stilbene **3** [41] with sodium azide (Scheme 1).

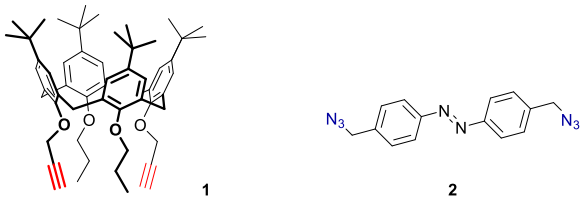
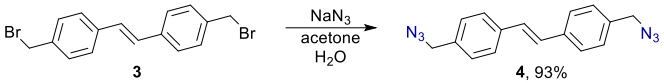
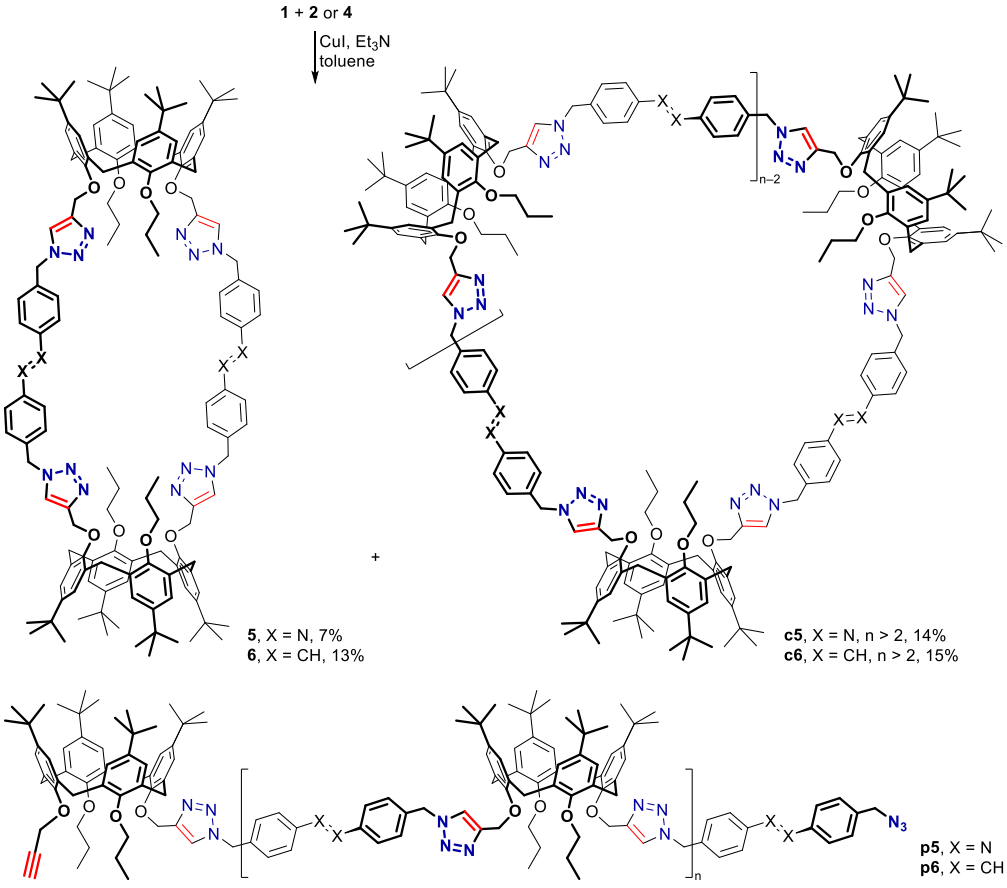


Figure 1. Structures of calix[4]arene **1** and 4,4′-bis-azidomethylated (*E*)-azobenzene **2**.



Scheme 1. Preparation of 4,4′-bis-azidomethylated (*E*)-stilbene **4**.

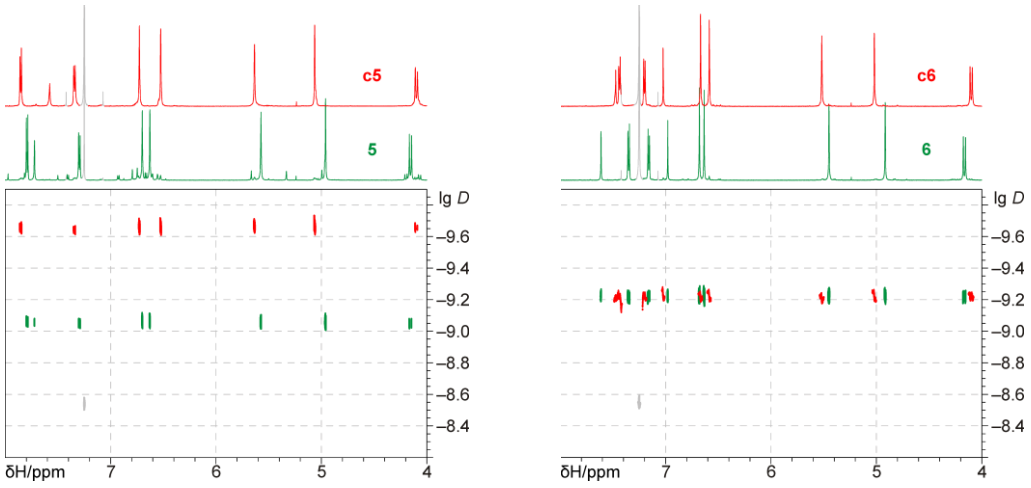
Following our previous study on the CuAAC-assembling of triazolated calix[4]semitubes from the calix[4]arene bis(azide) and bis(alkyne) counterparts [37], several catalytic systems were tested in the reactions between calixarene **1** and bis(azides) **2** or **4** taken in a 1:1 molar ratio (Scheme 2).



Scheme 2. Reactions between calixarene dipropargyl ether **1** and bis(azides) **2** or **4** under CuAAC conditions.

Neither $CuSO_4 \cdot 5H_2O$/sodium ascorbate in THF/H_2O mixture at 60 °C nor CuI·$P(OEt)_3$ in toluene at 90 °C were found efficient to complete the cycloaddition within 24 h, as it was concluded from the presence of signals from the starting material in the ^{1}H NMR spectra of the treated reaction mixtures. Nevertheless, in both reactions, which were carried out in toluene at 60 °C in the presence of CuI (30 mol. %) activated with triethylamine (20 equiv. per CuI), a complete conversion of the starting bis(azides) and bis(alkynes) was achieved. Due to the bifunctionality of both the azide and alkyne components of CuAACs, the formation of polymeric products **p5** and **p6** along with the desired bis(calixarenes) **5** and **6** was expected in the reactions of calix[4]arene **1** with bis(azides) **2** or **4**. Indeed, the ^{1}H NMR spectra of the reaction mixtures, from which copper salts were removed upon extraction in a dichloromethane/HCl mixture, contained broadened signals from the polymeric products along with much less intensive sharp resonances arisen from the non-polymeric assemblies. Unexpectedly, not a single, but two sets of these sharp resonances were observed in the spectra of both reaction mixtures.

In the case of the synthesis involving the azobenzene bis(azide) **2**, the polymer product was eliminated using column chromatography, and then two fractions were successively eluted from the column, each containing almost pure compounds, which were thus obtained in 14 and 7% yield, respectively. In the ^{1}H NMR spectra of each of the separated products, the signal count and their relative intensities indicate the C_{2v} time-averaged symmetry of the calix[4]arene core having the 1-R-4-triazolylmethyl groups (where R is a 'half' of the azobenzene or stilbene unit) arranged in distal positions of the macrocycle (see Figure 2a for representative parts of the spectra; for the full spectra, see Figures S3 and S5 in the Supplementary Materials). Each of the acquired spectra corresponds to the structure of the desired bis(calixarene) **5** or to that of a larger assembly **c5**, though a little shape distortion is observed in the ^{1}H NMR spectrum of the first eluted product (the red trace in Figure 2a), which may be indicative of slowed conformational motions of a huge macrocycle.



(**a**) (**b**)

Figure 2. Parts of ^{1}H NMR and 2D DOSY (BPLED sequence, Δ 40 ms, joint plots from independent experiments) spectra of (**a**) macrocycles **5** (green) and **c5** (red); (**b**) macrocycles **6** (green) and **c6** (red); 600 MHz, $CDCl_3$+CD_3OD (10:1), 30 °C; residual solvent signals are colored gray.

To get more insights into the structures of the products, NMR DOSY spectra were acquired (Figure 1a; CD_3OD was added in all cases to improve solubility of the studied compounds in $CDCl_3$). The observed drastic difference in the self-diffusion coefficients indicates the much greater molecular size of the first eluted product (log D (m^2 s^{-1}) = −9.7) with respect to that of the second one (log D (m^2 s^{-1}) = −9.1). Nevertheless, these data are not sufficient to postulate the biscalixarene structure **5** of the second eluted product, since it may also be a large cyclic oligomer **c5** having just a smaller number of repeating units compared to the first eluted product.

To clarify this, both separated products were analyzed using ESI HRMS. In the case of the first eluted product, no ionization conditions were found to obtain a molecular ion in the spectrum, but for the second eluted product, a clear signal from the [**5**+H+Na]$^{2+}$ ion at 1113.1625 m/z was detected (the calculated value for the $[C_{140}H_{169}NaN_{16}O_8]^{2+}$ ion is 1113.1615 m/z). Thus, in the CuAAC reaction between the calixarene dipropargyl ether **1** and 4,4′-bis-azidomethylated azobenzene **2**, the desired bis(calixarene) **5** of moderate purity was obtained in low yield, along with the polymeric product **p5** and a cyclic oligomer **c5**, the exact structure of which could not be determined from the available data.

In the case of the synthesis involving the stilbene bis(azide) **4**, the dichloromethane solution obtained after the removal of copper salt was concentrated and the residue was treated with cold dichloromethane. This resulted in the formation of a crystalline solid, which was separated to obtain a pure (according to ^{1}H NMR spectrum; green trace in Figure 2b) compound in 13% yield. During the chromatographic purification of the evaporated mother liquid, the polymer product **p6** was eliminated, and a second non-polymeric product was obtained in 15% yield (red trace in Figure 2b; for the full spectra of both products see Figures S7 and S9 in the Supplementary Materials). Unlike compounds **5** and **c5**, these newly obtained products appear to be similar by their molecular sizes, as evidenced by their almost identical self-diffusion coefficients observed in the DOSY spectra (log D (m^2 s^{-1}) = −9.2; see Figure 2b). On the other hand, these self-diffusion coefficients are close to that of bis(calixarene) **5**. Thus, considering the shape and size similarities of the azobenzene- and stilbene-containing multi(macrocycles), the non-polymeric products of the CuAAC between calixarene **1** and bis(azide) **4** may be a cyclic oligomer **c6** having a small ring size and the desired bis(calixarene) **6**. Similar to the **5**/**c5** case, the mass spectrometry measurements were successful for only one of the two products: a clear signal from the [**6**+2H]$^{2+}$ ion was detected at 1100.1799 m/z (the calculated value for the $[C_{144}H_{174}N_{12}O_8]^{2+}$ ion is 1100.1800 m/z) in the sample of the crystalline product, which thus confirmed its biscalixarene structure.

Upon the slow evaporation of a chloroform/methanol solution of bis(calixarene) **6**, single crystals were collected and subjected to X-ray diffraction analysis. The obtained data confirmed unambiguously the structure of this compound in which two calix[4]arene macrorings were connected by two triazolated (*E*)-stilbene linkers arranged in a zigzag manner (Figure 3).

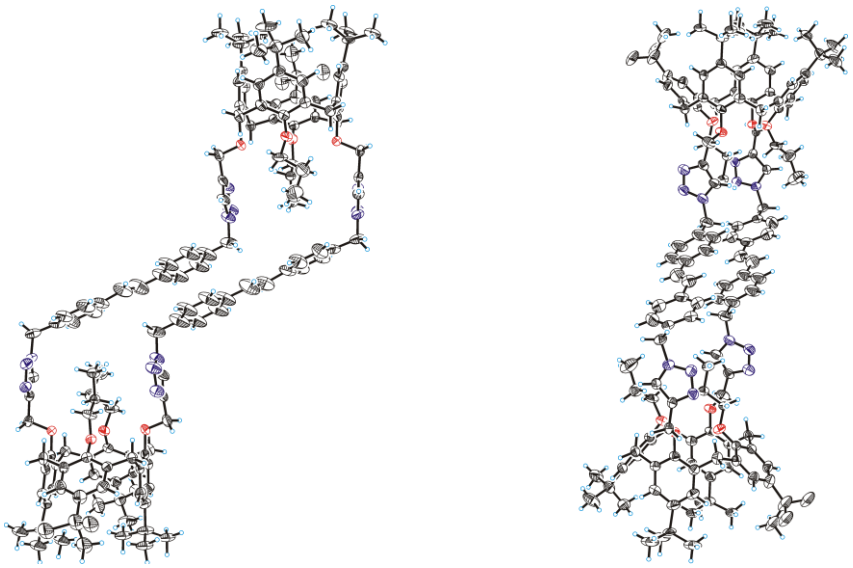


Figure 3. Molecular structure of the bis(calixarene) **6** in two projections; thermal ellipsoids are drawn at a 50% probability level.

To improve the solubility of the CuAAC reaction products and, perhaps, to facilitate their separation using column chromatography, the calixarene dipropargyl ether **1** was replaced with the dipropargyl ether **7** [42] having additional ester functionalities. Similar to the above cases, equimolar CuAAC reactions between calixarene **7** and bis(azides) **2** or **4** conducted under the CuI/Et_3N catalysis were completed within 24 h. However, huge linear or cyclic polymeric/oligomeric compounds appeared to be the major product of the reactions, as it was concluded from the ^{1}H NMR spectra of the product mixtures obtained after the removal of copper salts. Indeed, both spectra contained mainly the broadened and highly shape-distorted signals from the huge oligomers/polymers, while signals of just minor intensities might be assigned to the desired bis(calixarenes) or at least to small cyclic oligomeric products of CuAAC (Figure 4).

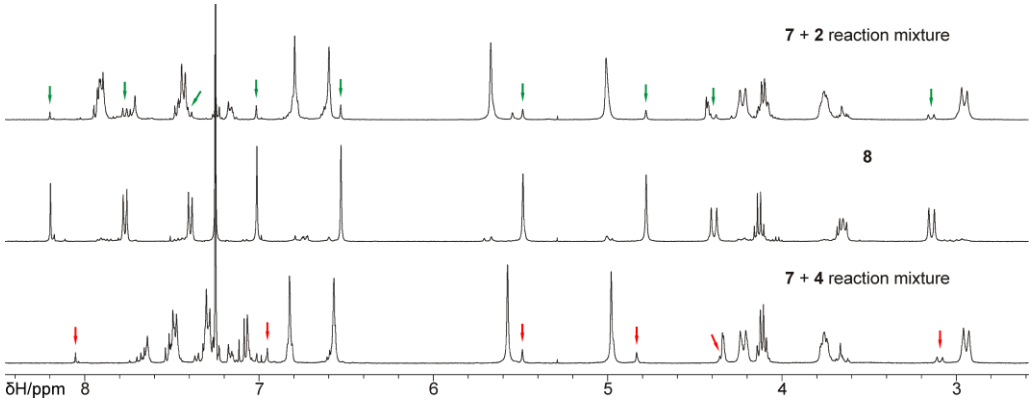
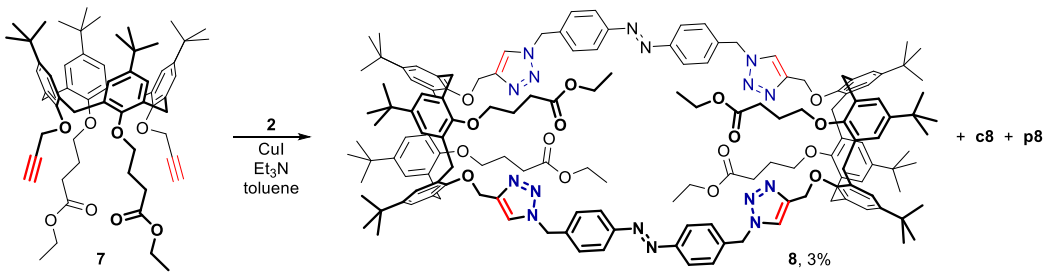


Figure 4. Representative parts of ^{1}H NMR spectra of the treated reaction mixtures obtained in the CuAACs between the calixarene dipropargyl ether **7** and bis(azides) **2** or **4** (top and bottom traces, respectively), and that of the separated compound **8** (middle trace); colored arrows indicate the signals from bis(calixarenes) or small cyclic oligomers detected in the mixtures; 400 MHz, $CDCl_3$, 20 °C.

Due to the extremely low content of the non-polymeric products in the mixtures, their chromatographic separation was attempted for only the CuAAC between calixarene **7** and bis(azide) **2** (Scheme 3). In this case, a single non-polymeric product of moderate purity was obtained in 3% yield (see middle trace in Figure 4 for the ^{1}H NMR spectrum of the separated product), which was the desired bis(calixarene) **8**, as confirmed by a clear signal from the $[\mathbf{8}+2H]^{2+}$ ion at 1246.2133 m/z in the HRMS spectrum (the calculated value for the $[C_{152}H_{186}N_{16}O_{16}]^{2+}$ ion is 1246.2128 m/z).



Scheme 3. Reaction between the propargylated calixarene ester **7** and bis(azide) **2** under CuAAC conditions.

Single crystals of bis(calixarene) **8** suitable for X-ray diffraction analysis were obtained upon the slow evaporation of its dichloromethane/methanol solution. The obtained data confirmed the biscalixarene molecular structure of this compound having two calix[4]arene macrorings connected by two triazolated (*E*)-azobenzene linkers, and four ester residues (Figure 5). The overall zigzag shape of the obtained molecule is similar to that of the stilbene-

linked bis(calixarene) **6**, with both lacking any internal cavity between the calixarene cores and the linkers, at least in the crystalline state.

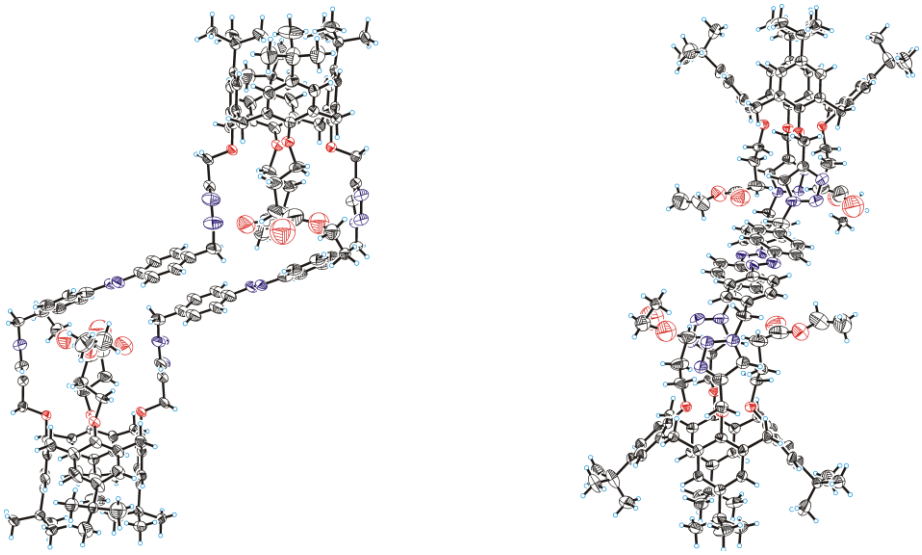


Figure 5. Molecular structure of the bis(calixarene) **8** in two projections; thermal ellipsoids are drawn at a 50% probability level.

3. Materials and Methods

Column chromatography was performed on silica gel 60 (0.063–0.200 mm). Commercial reagents were used as received. Compounds **1** [39], **2** [40], **3** [41] and **7** [42] were synthesized by the reported procedures.

^{1}H and ^{13}C (APT) NMR spectra were acquired on Bruker Avance 400 and Avance 600 spectrometers at room temperature, unless stated otherwise. Two-dimensional DOSY experiments were performed in accordance with the gradient strength G = 53.5 G/cm using standard pulse program ledbpgp2s, that is, stimulated echo sequence and LED (longitudinal eddy current delay) using bipolar gradient pulse pair and two spoiling gradients. The gradient strength was changed from 2 to 95% with linear type of ramp. Diffusion time (big delta, Δ = 40 ms), sine shaped gradient pulse length (little delta, δ = 2 ms) and relaxation delay (D1 = 2 s) were employed.

High resolution ESI mass spectra were obtained from a Sciex TripleTOF 5600+ spectrometer (AB Sciex, Singapore).

Crystallographic data were collected on a Bruker D8 Venture diffractometer using graphite monochromatized Mo–Kα radiation (λ = 0.71073 Å) using an ω-scan mode. Absorption correction based on measurements of equivalent reflections was applied [43]. The structures were solved by direct methods and refined by full matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms [44,45]. Some components of the disordered groups were refined isotropically. The hydrogen atoms were placed in calculated positions and refined using a riding model. In all structures, all or some of the highly disordered solvent molecules were not located, and their contribution was suppressed by the SQUEEZE procedure [46] included in the Olex2 package [47].

CCDC 2309204 and 2309205 contain crystallographic data for compounds **8** and **6**, respectively. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures (accessed on 21 November 2023).

3.1. (E)-1,2-bis(4-(azidomethyl)phenyl)ethene **4**

To a solution of (*E*)-1,2-bis(4-(bromomethyl)phenyl)ethene **3** (2.12 g, 5.79 mmol) in acetone (400 mL), sodium azide (1.13 g, 17.4 mmol) dissolved in water (25 mL) was added, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was parted between dichloromethane and water.

The organic layer was separated, washed with brine and concentrated to dryness. Yield 1.58 g (93%, white solid). M.p. 135–137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57–7.51 (m, 4H, ArH), 7.35–7.29 (m, 4H, ArH), 7.12 (s, 2H, CH) 4.35 (s, 4H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.18 (C_{Ar}), 134.74 (C_{Ar}), 128.61 (CH_{Ar}), 128.50 (CH), 126.92 (CH_{Ar}), 54.50 (CH_2) ppm. HRMS ESI-MS: *m*/*z*: 291.1357 $[M+H]^+$ for $C_{16}H_{15}N_6$ (291.1353).

3.2. Bis(calixarene) **5** *and Cyclic Oligomer* **c5**

To a stirred suspension of copper(I) iodide (0.057 g, 0.30 mmol) in toluene (10 mL), triethylamine (0.835 mL, 6.00 mmol) was added, and the mixture was stirred at room temperature until a clear solution formed. A solution of calixarene **1** (0.808 g, 1.00 mmol) in toluene (35 mL) was added, followed by the solution of bis(azide) **2** (0.292 g, 1.00 mmol) in toluene (35 mL), and the mixture was stirred at 60 °C under inert atmosphere for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and washed continuously (for 2 h) with aqueous HCl (2 M) at vigorous stirring. The organic phase was separated, washed with aqueous Na_2SO_3 (5%; this optional step was applied to remove iodine resulting from the oxidation of the iodide-anion by air during the above prolonged extraction) and water, dried, and the solvent was evaporated. The residue was subjected to column chromatography (silica, gradient from dichloromethane to dichloromethane/ethanol 20:1). The cyclic oligomer **c5** was isolated upon elution with dichloromethane, followed by crystallization from the dichloromethane/methanol mixture. Further fractions containing bis(calixarene) **5** were combined, the solvent was evaporated and the product was isolated upon crystallization from the dichloromethane/methanol mixture.

Compound **5**: Yield 0.074 g (7%, orange solid). M.p. > 300 °C. ^{1}H NMR ($CDCl_3$+CD_3OD (10:1), 400 MHz): δ = 7.82–7.77 (m, 8H, ArH_{azo}), 7.73 (s, 4H, ArH_{Trz}), 7.32–7.27 (m, 8H, ArH_{azo}), 6.69 (s, 8H, ArH_{calix}), 6.64 (s, 8H, ArH_{calix}), 5.57 (s, 8H, NCH_2), 4.95 (s, 8H, OCH_2Trz), 4.15 (d, ^{2}J = 12.5 Hz, 8H, $ArCH_2Ar$), 3.56–3.48 (m, 8H, OCH_2), 2.92 (d, ^{2}J = 12.5 Hz, 8H, $ArCH_2Ar$), 1.59–1.47 (m, 8H, $C\underline{H}_2CH_3$), 1.00 (s, 36H, $C(CH_3)_3$), 0.96 (s, 36H, $(C(CH_3)_3$), 0.53 (t, ^{3}J = 7.3 Hz, 12H, $CH_2C\underline{H}_3$) ppm. ^{13}C NMR ($CDCl_3$+CD_3OD (10:1), 100 MHz): δ = 153.26, 152.06, 151.97, 145.20, 145.05, 144.21, 138.15, 134.02, 133.33 (C_{Ar}), 128.49, 124.98, 124.74, 124.03, 123.29 (CH_{Ar}), 76.98 (OCH_2), 66.95 (OCH_2Trz), 53.32 (NCH_2), 33.71, 33.64 ($\underline{C}(CH_3)_3$), 31.23 ($C(\underline{C}H_3)_3$), 31.00 ($ArCH_2Ar$), 22.76 ($\underline{C}H_2CH_3$), 9.82 ($CH_2\underline{C}H_3$) ppm. HRMS ESI-MS: *m/z*: 1113.1625 $[M+H+Na]^{2+}$ for $C_{140}H_{169}NaN_{16}O_8$ (1113.1615).

Compound **c5**: Yield 0.159 g (14%, orange solid). M.p. 250–252 °C ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95–7.88 (m, 4nH, ArH_{azo}), 7.62 (s, 2nH, ArH_{Trz}), 7.43–7.36 (m, 4nH, ArH_{azo}), 6.80 (s, 4nH, ArH_{calix}), 6.58 (s, 4nH, ArH_{calix}), 5.70 (s, 4nH, NCH_2), 5.12 (s, 4nH, OCH_2Trz), 4.18 (d, ^{2}J = 12.5 Hz, 4nH, $ArCH_2Ar$), 3.65–3.58 (m, 4nH, OCH_2), 2.93 (d, ^{2}J = 12.5 Hz, 4nH, $ArCH_2Ar$), 1.75–1.64 (m, 4nH, $C\underline{H}_2CH_3$), 1.10 (s, 18nH, $C(CH_3)_3$), 0.92 (s, 18nH, $(C(CH_3)_3$), 0.78–0.72 (m, 6nH, $CH_2C\underline{H}_3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.11, 152.30, 152.05, 145.43, 145.11, 144.06, 138.25, 134.84, 132.88 (C_{Ar}), 128.53, 125.09, 124.64, 123.96, 123.46 (CH_{Ar}), 77.03 (OCH_2), 66.66 (OCH_2Trz), 53.36 (NCH_2), 33.86, 33.64 ($\underline{C}(CH_3)_3$), 31.46, 31.26 ($C(\underline{C}H_3)_3$), 31.21 ($ArCH_2Ar$), 22.99 ($\underline{C}H_2CH_3$), 10.25 ($CH_2\underline{C}H_3$) ppm.

3.3. Bis(calixarene) **6** *and Cyclic Oligomer* **c6**

These compounds were prepared as described for compounds **5** and **c5** from calixarene **1** (0.808 g, 1.00 mmol), bis(azide) **4** (0.290 g, 1.00 mmol), copper(I) iodide (0.057 g, 0.30 mmol) and triethylamine (0.835 mL, 6.00 mmol) in toluene (80 mL). The solution of the product mixture obtained in the extraction step was concentrated to dryness, and the residue was suspended in a small portion of dichloromethane. The suspension was cooled down to −18 °C and filtered. The collected solid was washed rapidly with cold dichloromethane and dried to give bis(calixarene) **6**. The filtrate was concentrated under reduced pressure and the cyclic oligomer **c6** was purified using column chromatography (silica, dichloromethane) followed by crystallization from the dichloromethane/methanol solvent mixture.

Compound **6**: Yield 0.142 g (13%, white solid). M.p. > 300 °C. ^{1}H NMR ($CDCl_3$+CD_3OD (10:1), 400 MHz): δ = 7.64 (s, 4H, ArH_{Trz}), 7.39–7.34 (m, 8H, ArH_{stil}), 7.20–7.15 (m, 8H,

ArH_{stil}), 7.00 (s, 4H, CH), 6.71 (s, 8H, ArH_{calix}), 6.65 (s, 8H, ArH_{calix}), 5.47 (s, 8H, NCH_2), 4.92 (s, 8H, OCH_2Trz), 4.20 (d, ^2J = 12.5 Hz, 8H, $ArCH_2Ar$), 3.59–3.51 (m, 8H, OCH_2), 2.95 (d, ^2J = 12.5 Hz, 8H, $ArCH_2Ar$), 1.61–1.49 (m, 8H, $C\underline{H}_2CH_3$), 1.03 (s, 36H, $C(CH_3)_3$), 0.97 (s, 36H, $(C(CH_3)_3)$, 0.51 (s, ^3J = 7.5 Hz, 12H, $CH_2C\underline{H}_3$) ppm. ^{13}C NMR ($CDCl_3$+CD_3OD (10:1), 100 MHz): δ = 153.57, 152.00, 145.15, 144.92, 144.25, 137.04, 134.44, 133.73, 133.71 (C_{Ar}), 128.36, 128.32, 126.85, 124.91, 124.84 (CH_{Ar}, CH_{stil}), 123.65 (CH_{Ar}), 76.62 (OCH_2), 67.11 (OCH_2Trz), 53.57 (NCH_2), 33.72, 33.71 ($\underline{C}(CH_3)_3$), 31.34, 31.24 ($C(\underline{C}H_3)_3$), 31.09 ($ArCH_2Ar$), 22.78 ($\underline{C}H_2CH_3$), 9.78 ($CH_2\underline{C}H_3$) ppm. HRMS ESI-MS: *m/z*: 1100.1794 $[M+2H]^{2+}$ for $C_{144}H_{174}N_{12}O_8$ (1100.1800). Crystal data (CCDC 2309205): temp. (K) = 150(2); cryst. system: triclinic; space group: P-1; *a* (Å) = 10.3667(5); *b* (Å) = 26.2054(13); *c* (Å) = 28.8910(13); α (°) = 75.959(2); β (°) = 79.942(2); γ (°) = 85.099(2); V ($Å^3$) = 7489.5(6); Z = 2; θ range (deg): 1.92 < θ < 25.05; collected/unique reflections: 112270/26399; completeness to θ (%) = 99.7; data/restraints/parameters: 26399/94/1525; goodness of fit on F^2 = 2.116; final R indices (I > 2σ(I)): R_1 = 0.1162, wR_2 = 0.3160; largest diff peak/hole (e/$Å^3$): 1.52/−1.05.

Compound **c6**: Yield 0.165 g (15%, white solid). M.p. 248–250 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.44 (m, 4nH, ArH_{stil}), 7.51 (s, 2nH, ArH_{Trz}), 7.29–7.21 (m, 4nH, ArH_{stil}), 7.08 (s, 2nH, CH), 6.73 (s, 4nH, ArH_{calix}), 6.64 (s, 4nH, ArH_{calix}), 5.58 (s, 4nH, NCH_2), 5.07 (s, 4nH, OCH_2Trz), 4.18 (d, ^2J = 12.5 Hz, 4nH, $ArCH_2Ar$), 3.66–3.57 (m, 4nH, OCH_2), 2.92 (d, ^2J = 12.5 Hz, $ArCH_2Ar$), 1.76–1.64 (m, 4nH, $C\underline{H}_2CH_3$), 1.06 (s, 18nH, $C(CH_3)_3$), 0.98 (s, 18nH, $(C(CH_3)_3)$, 0.77–0.69 (m, 6nH, $CH_2C\underline{H}_3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.39, 151.99, 145.22, 144.93, 144.09, 137.31, 134.55, 134.46, 133.27 (C_{Ar}), 128.56, 128.33, 127.03, 124.96, 124.72 (CH_{Ar}, CH_{stil}), 123.67 (CH_{Ar}), 76.89 (OCH_2), 66.80 (OCH_2Trz), 53.54 (NCH_2), 33.80, 33.68 ($\underline{C}(CH_3)_3$), 31.40, 31.33 ($C(\underline{C}H_3)_3$), 31.24 ($ArCH_2Ar$), 22.96 ($\underline{C}H_2CH_3$), 10.20 ($CH_2\underline{C}H_3$) ppm.

3.4. Bis(calixarene) **8**

This compound was prepared as described for compounds **5** and **c5** from calixarene **7** (0.952 g, 1.00 mmol), bis(azide) **2** (0.292 g, 1.00 mmol), copper(I) iodide (0.057 g, 0.30 mmol) and triethylamine (0.835 mL, 6.00 mmol) in toluene (57 mL). From the product mixture obtained in the extraction step, bis(calixarene) **8** was isolated using column chromatography (silica, gradient from dichloromethane to dichloromethane/ethanol 30:1). Yield 0.035 g (3%, orange solid). M.p. > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20 (s, 4H, ArH_{Trz}), 7.80–7.74 (m, 8H, ArH_{azo}), 7.42–7.36 (m, 8H, ArH_{azo}), 7.01 (s, 8H, ArH_{calix}), 6.53 (s, 8H, ArH_{calix}), 5.49 (s, 8H, NCH_2), 4.78 (s, 8H, OCH_2Trz), 4.39 (d, ^2J = 12.4 Hz, 8H, $ArCH_2Ar$), 4.13 (q, ^3J = 7.1 Hz, 8H, $O\underline{C}H_2CH_3$), 3.69–3.60 (m, 8H, $OC\underline{H}_2CH_2CH_2$), 3.14 (d, ^2J = 12.4 Hz, 8H, $ArCH_2Ar$), 1.89–1.78 (m, 8H, $OCH_2C\underline{H}_2CH_2$), 1.64–1.55 (m, 8H, $OCH_2CH_2C\underline{H}_2$), 1.30 (t, ^3J = 7.1 Hz, 12H, $OCH_2C\underline{H}_3$), 1.25 (s, 36H, $C(CH_3)_3$), 0.86 (s, 36H, $(C(CH_3)_3)$ ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.05 (C=O), 154.01, 151.99, 151.70, 144.90, 144.81, 144.72, 138.51, 134.95, 132.53 (C_{Ar}), 129.10, 125.35, 124.79, 124.33 (CH_{Ar}), 123.17 (C_{Ar}), 73.53 ($O\underline{C}H_2CH_2$), 67.94 (OCH_2Trz), 60.35 ($O\underline{C}H_2CH_3$), 53.21 (NCH_2), 33.99, 33.64 ($\underline{C}(CH_3)_3$), 31.63, 31.15 ($C(\underline{C}H_3)_3$), 31.09 ($ArCH_2Ar$), 30.44 ($\underline{C}H_2CO$), 25.10 ($OCH_2\underline{C}H_2$), 14.30 ($OCH_2\underline{C}H_3$) ppm. HRMS ESI-MS: *m/z*: 1246.2133 $[M+2H]^{2+}$ for $C_{152}H_{186}N_{16}O_{16}$ (1246.2128). Crystal data (CCDC 2309204): temp. (K) = 100(2); cryst. system: triclinic; space group: P-1; *a* (Å) = 10.1995(5); *b* (Å) = 12.2974(6); *c* (Å) = 31.3504(16); α (°) = 79.558(2); β (°) = 86.966(2); γ (°) = 84.479(2); V ($Å^3$) = 3846.6(3); Z = 1; θ range (deg): 1.69 < θ < 25.05; collected/unique reflections: 46065/13372; completeness to θ (%) = 98.0; data/restraints/parameters: 13372/83/859; goodness of fit on F^2 = 1.053; final R indices (I > 2σ(I)): R_1 = 0.0978, wR_2 = 0.2579; largest diff peak/hole (e/$Å^3$): 0.71/−0.57.

4. Conclusions

We have shown that the one-step approach involving the four-fold CuAAC reactions between the calixarene dipropargyl ethers and the respective bis(asides) can in principle be implemented for the construction of biscalixarene systems comprising pairs of azobenzene or stilbene linkers. Nevertheless, these reactions produce significant amounts of

oligomeric/polymeric by-products, which can dramatically reduce the yield of the target bis(calixarenes) and hamper their purification. In this regard, multi-step syntheses utilizing 'mono' functional reactants at the CuAAC steps may be more preferable for the preparation of such biscalixarene systems.

Supplementary Materials: The following supporting information can be downloaded online. Figure S1: ^{1}H NMR spectrum of compound **4**; Figure S2: ^{13}C NMR spectrum (APT) of compound **4**; Figure S3: ^{1}H NMR spectrum of compound **5**; Figure S4: ^{13}C NMR spectrum (APT) of compound **5**; Figure S5: ^{1}H NMR spectrum of compound **c5**; Figure S6: ^{13}C NMR spectrum (APT) of compound **c5**; Figure S7: ^{1}H NMR spectrum of compound **6**; Figure S8: ^{13}C NMR spectrum (APT) of compound **6**; Figure S9: ^{1}H NMR spectrum of compound **c6**; Figure S10: ^{13}C NMR spectrum (APT) of compound **c6**; Figure S11: ^{1}H NMR spectrum of compound **8**; Figure S12: ^{13}C NMR spectrum (APT) of compound **8**.

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