Tetrahedron 67 (2011) 7027–7034

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and 'click' cycloaddition reactions of tetramethoxy- and tetrapropoxy-2-(ω-azidoalkyl)calix[4]arenes

Michael J. Hardman [a], Ashley M. Thomas [a], Louise T. Carroll [a], Linus C. Williams [a], Sean Parkin [b], Jordan L. Fantini [a,*]

[a] Department of Chemistry and Biochemistry, Ebaugh Laboratories, Denison University, Granville, OH 43023, USA
[b] Department of Chemistry, University of Kentucky, Lexington, KY 40536, USA

ARTICLE INFO

Article history:
Received 31 May 2011
Received in revised form 8 July 2011
Accepted 8 July 2011
Available online 19 July 2011

Keywords:
Atropisomerism
Azides
Calixarenes
Click chemistry

ABSTRACT

2-(ω-Chloroalkyl)tetramethoxycalix[4]arenes are converted to 2-(ω-azidoalkyl)tetramethoxy- and *cone*-2-(ω-azidoalkyl)tetrapropoxycalix[4]arenes, the former by substitution and the latter by demethylation to 2-(ω-chloroalkyl)tetrahydroxycalix[4]arenes, which are *O*-propylated before substitution of azide for chloride. The azide-terminated calixarenes undergo Cu(I)-catalyzed 1,3-cycloaddition to terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles, demonstrating the potential to couple calixarenes from a tether at the 2-position (methylene bridge) to substrates that bear a terminal alkyne group. The cone conformation of *cone*-2-(4-chlorobutyl)tetrapropoxycalix[4]arene has been confirmed by X-ray diffraction.

1. Introduction

Calix[*n*]arenes are cyclic oligomers obtained from the base-catalyzed condensation of *para*-substituted alkyl phenols (typically *p*-*tert*-butylphenol) with formaldehyde, where *n* denotes the number of repeating units in the molecules.[1] The preferred conformation of tetrahydroxy-*p*-*tert*-butylcalix[4]arene (**1**, Fig. 1)[2] is the so-called cone conformation, stabilized by intramolecular hydrogen bonds[3] of the phenolic groups at the narrow rim (or lower rim). The *C*-alkyl groups occupy the wide rim (or upper rim). *O*-Alkylation of the phenols imparts comparable stability to the conformations shown in Fig. 1—the partial cone (paco), 1,2-alternate (1,2-alt), and 1,3-alternate (1,3-alt).[4]

In the series of tetra(alkyl)calixarenes **2**-R, accessed by *O*-alkylation of **1** (Fig. 2), the rate of interconversion of atropisomers depends on the size of the alkyl group. Interconversion is swift for **2**-Me, occurs at elevated temperatures for **2**-Et, and is effectively prohibited for **2**-Pr (and similar species with larger R groups).[5] For this project, we studied calixarene derivatives where interconversion would either be facile (derivatives of **2**-Me) or not occur at all (derivatives of **2**-Pr). Syntheses of derivatives of **2**-Pr by tetrapropylation of a tetrahydroxycalixarene can lead to mixtures of atropisomers because the bulk of the propyl group prevents aryl group rotation through the annulus of the calixarene.[6]

Calixarene-forming condensation works with formaldehyde and no other aldehydes and is only high-yielding with *p*-*tert*-butylphenol.[7] As a result, a rich body of chemistry has developed around the modification of **1**. Typical transformations at the upper rim involve electrophilic aromatic substitution, for example, dealkylation[8] or nitration[9] of the aryl ring. Entry to modifications at the lower rim often start with *O*-alkylation of the phenolic groups.[10] The chemistry of the methylene group linking the calixarene aromatic rings is much less developed even though selective substitution at that position could alter calixarene solubility or flexibility and provide a point for connection to surfaces and other molecules. Early efforts to incorporate alkyl groups at one or more bridge positions were by a 'fragment-condensation' pathway in which smaller units—at least one bearing a bridge substituent—were independently synthesized then brought together by condensation.[11] In contrast, our research has centered on the direct, selective installation of a single substituent at the methylene-bridge position of the calix[4]arene by a deprotonation–alkylation sequence.[12] Our first report detailed the installation of an alkyl or carboxy group at the 2-position of tetramethoxycalix[4]arene.[12a] Recently we have described the synthesis and characterization of a series of functional group tether calixarenes—compounds with a 3–6 methylene chain terminating in a functional group (chloro, iodo, alkyl or aryl amine) starting from tetramethoxycalix[4]arene and a 1-bromo-ω-chloroalkane.[12b] Other

* Corresponding author. Tel.: +1 740 587 6491; fax: +1 740 587 6673; e-mail addresses: s.parkin@uky.edu (S. Parkin), fantinij@denison.edu (J.L. Fantini).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.07.022

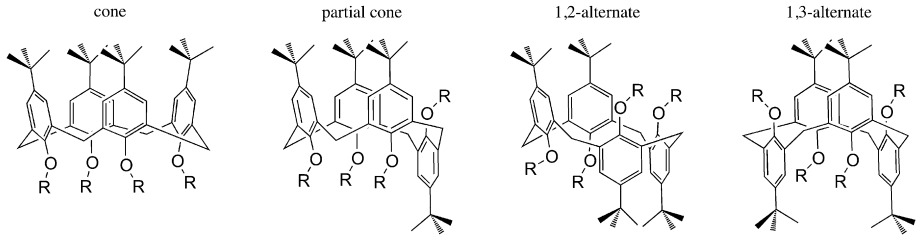

Fig. 1. The four major conformations of *p-tert*-butylcalix[4]arenes (**1**: R=H).

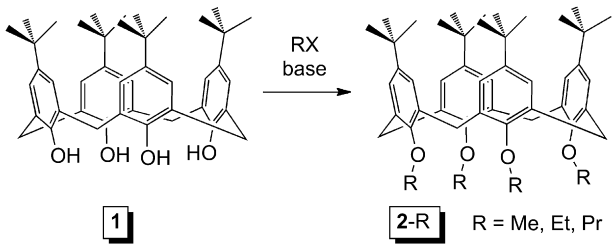

Fig. 2. Alkylation of tetrahydroxy-*p-tert*-butylcalix[4]arene (1) with excess alkyl halide (methyl or 1°) and strong base (e.g., NaH) yields tetraalkylcalix[4]arenes. Mixtures of atropisomers are possible for R≠Me.

reactions that install groups at the bridge position include the anionic *ortho*-Fries rearrangement,[13] addition to a spirodienone calixarene derivative,[14] and tetrabromination[15] followed by nucleophilic substitution.[16] The bridge position can also be oxidized to a ketone,[17] then further transformed by an addition reaction at that site.[18]

The Huisgen[19] 1,3-dipolar cycloaddition of azides and terminal alkynes to give 1,2,3-triazoles is widely considered the prototypical 'click' reaction.[20] The cycloaddition is regiospecific when catalyzed by Cu(I), affording 1,4-substituted triazoles under mild conditions.[21] Calixarenes with upper- or lower- rim azide[22] and alkyne[23] groups have been employed in this click reaction. In this paper we extend calixarene click chemistry to the methylene bridge with the synthesis of flexible (tetramethoxy) and rigid (*cone*-tetrapropoxy) ω-azidoalkyl calixarenes. Calixarenes with azide tethers provide the potential for anchoring a calixarene to a solid support, attaching a chromophore or reactive species, or a complementary element at a position that does not occupy the upper or lower rims. The azide element is 'orthogonal' to many chemical transformations,[20] and should allow for modifications at the calixarene. We demonstrate the cycloaddition of ω-azidoalkyl calixarenes with terminal alkynes to give 1,4-substituted 1,2,3-triazoles as shown in Fig. 3.

In this system, the attachment of the tether, whose length is easily varied, is accomplished without taking up a position on the upper or lower rims of the calixarene. At the methylene-bridge position, the tether is not expected to appreciably perturb the conformation of a calixarene vis a vis its unsubstituted analog.[24]

2. Results and discussion

The flexible ω-azidoalkyl calixarenes (**6**) were prepared by routine transformations at the ω-carbon of the methylene-bridge substituent, as described below. The preparation of rigid tetrapropoxy bridge-substituted calixarenes (**8**) was complicated by the failure of direct deprotonation–alkylation of **2**-Pr, which yielded no *C*-alkylated products. The products recovered when **2**-Pr in THF was treated with a solution of *n*-butyllithium in hexanes followed by attempted alkylation with MeI were ca. 95% **2**-Pr and ca. 5% *cone*-25,26,27-tripropoxy-28-hydroxy-*p-tert*-butylcalix[4]arene (**3**).[25] The conversion of **2**-Pr to **3** increased to 81% (19% unreacted **2**-Pr) when the reaction was carried out in hexanes. The appearance of **3** in these reactions likely begins with formation of the bridge-lithiated calixarene, followed by intramolecular β-elimination (Fig. 4). Modifications to the solvent or base were not likely to prevent this undesired reaction, thus we prepared bridge-substituted tetrapropoxycalixarenes by an *O*-dealkylation–realkylation sequence on bridge-substituted tetramethoxycalixarenes.

2.1. Lower-rim reactions of (chloroalkyl)calixarenes

To prepare bridge-substituted tetrapropoxycalixarenes from analogous tetramethoxycalixarenes requires that the bridge substituent react with neither the reagents for *O*-dealkylation (strong Lewis acid)[26] nor the reagents for ether synthesis (strong Brønsted base).[8] The alkyl chloride tether **4** was expected to fulfill these conditions as shown in Fig. 5.

2.2. Demethylation of tetramethoxy(chloroalkyl)calixarenes

The tetramethoxycalixarene **4** was demethylated by treatment with the strong Lewis acid BBr_3 (CH_2Cl_2, −78 °C).[26] Colorless, microcrystalline tetrahydroxycalixarenes with chloroalkyl chain lengths of 3–5 (**5a**–**c**) were obtained after workup and recrystallization from methanol. The NMR spectra ($CDCl_3$) of **5a** to **5c** were consistent with the expected cone conformation, which is stabilized preferentially by intramolecular hydrogen bonding,[3] with the tether group in an equatorial position.[27] Two signals, rather than four, are observed for the *tert*-butyl groups, indicating molecular C_s symmetry. (In some bridge-substituted calixarenes, the signals for all the *tert*-butyl groups are accidentally equivalent.) The equatorial disposition of the tether is confidently inferred by the ^{1}H NMR signal of the methyne hydrogen residing on the same carbon. The tether occupies the equatorial position in all of the cone calixarenes described herein. These calixarenes have very similar NMR signals arising from the calixarene moiety, but distinctions are noted for signals from the tether, especially at the ω-position.[12b]

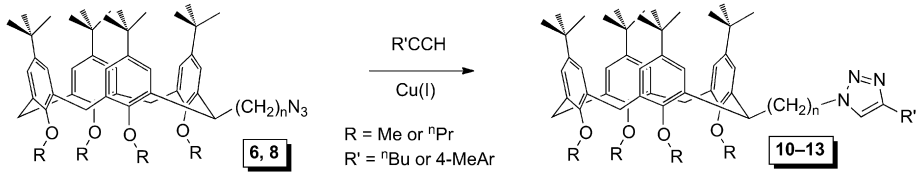

Fig. 3. Desired ω-azidoalkyl calixarenes and expected reaction products from Cu(I)-catalyzed cycloaddition to terminal alkynes.

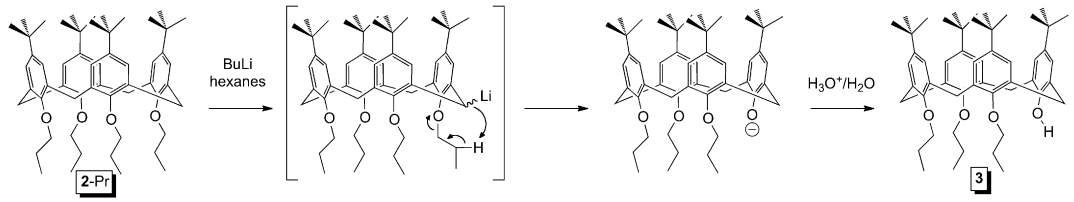

Fig. 4. The deprotonation of tetrapropoxy-*p*-*tert*-butylcalix[4]arene (**2**-Pr) generates a lithium-stabilized carbanion, which intramolecularly attacks a lower rim substituent. The net result is a selective single dealkylation at the lower rim.

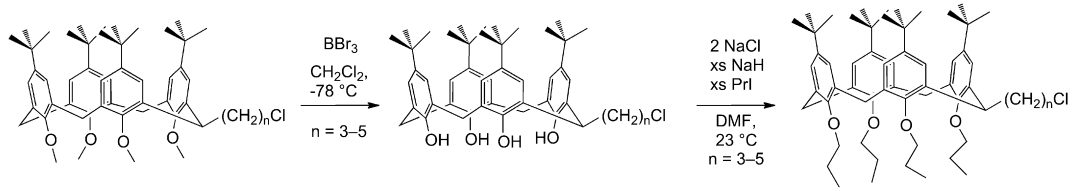

Fig. 5. Dealkylation of the calix[4]arene **4**, followed by realkylation with sodium hydride and propyl iodide gives a tetrapropoxycalixarene with a cone conformation and the tether in the equatorial position. The letter indicates the length of the alkyl chain (a: n=3; b: n=4; c: n=5).

2.3. Tetrapropylation of tetrahydroxy(chloroalkyl)calixarenes

Exhaustive alkylation of a tetrahydroxycalix[4]arene with propyl iodide can give different atropisomers because the propyl group is too large to fit through the annulus of the calixarene.[6] Literature precedent for direct and selective synthesis of the cone atropisomer of **2**-Pr is inconsistent. For example, Reinhoudt[28] reported 100% selectivity for the cone atropisomer while Shinkai[25] obtained a 55:45 paco/cone mixture under ostensibly similar conditions. We attempted propylations of **5a**–**c** using a literature procedure for the propylation of 25,26,27,28-tetrahydroxycalix[4]arene (no *para tert*-butyl groups), which yields the cone atropisomer of 25,26,27,28-tetrapropoxycalix[4]arene.[8] In our hands, this procedure for alkylation applied to **5a**–**c** gave predominantly the cone atropisomer of **6a**–**c** with variable amounts (10–30%) of other atropisomers, as judged by the signals in the ^{1}H NMR spectra of the products. The major signals were consistent with the C_s-symmetric cone atropisomer with an equatorial tether. (Percent cone atropisomer was estimated by integrations of signals in the aromatic region of the ^{1}H NMR spectra of the products.) Because the cone conformation of calix[4]arenes is templated by the Na^+ ion,[29] we modified the literature protocol, adding 2 equiv of Na^+ (from NaCl) to the reaction mixture prior to the addition of calixarene. Percent cone atropisomer of tetrapropoxycalix[4]arenes **6a**–**c** increased from 75–92% without extra Na^+ to 92–95% cone with extra Na^+. Products obtained with the modified process were carried forward in syntheses. No products arising from intramolecular *O*-alkylation with the alkyl chloride tether moiety were detected. The tetrapropoxy compounds are colorless powders obtained by precipitation from a DMF/methanol solvent mixture; samples recrystallized from methanol/dichloromethane were not further enriched in cone atropisomer.

As described above, the cone conformation for **6a**–**c** was inferred from ^{1}H and ^{13}C NMR spectra; it was verified for **6b** by a single crystal X-ray diffraction structure determination (Fig. 6). The crystal structure of **6b** exhibits substantial disorder of *tert*-butyl groups and of the chlorobutyl group with chloroform solvent molecules. Because of this disorder, manifest in poor observation of high-angle reflections, little confidence is placed on individual bond lengths or angles in the structure solution. Nevertheless, the connectivity and gross geometry (cone conformation) of **6b** is unequivocally confirmed by the X-ray crystal structure.

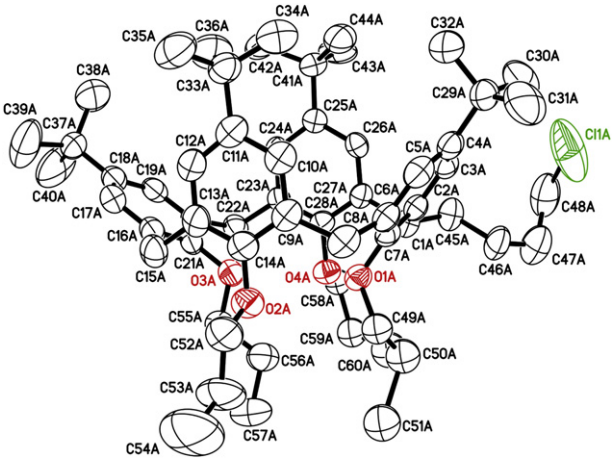

Fig. 6. Thermal ellipsoid plot (50% probability) of **6b**. Hydrogen atoms, minor components of disordered groups, and chloroform solvent of crystallization molecules are omitted to enhance clarity.

2.4. 2-(5-Iodopentyl)tetrapropoxy-*p*-*tert*-butylcalixarene (7)

Although the chloroalkyl compounds **4** and **6** are well suited for substitution at the chloride position, as described below, it will be advantageous in future work to have a better leaving group in place of the chloride at the tether's end. As an example, the 1° iodo compound 2-(5-iodopentyl)tetrapropoxy-*p*-*tert*-butylcalix[4]arene (**7**) was prepared from the corresponding chloroalkyl species **6c** by the Finkelstein reaction.[30] As expected from the similar reactions on ω-chloroalkyltetramethoxycalixarenes,[12b] treatment of **6c** with excess NaI in 2-butanone gave **7** in 61% yield after workup and recrystallization (Fig. 7).

2.5. (ω-Azidoalkyl)calixarenes

(ω-Azidoalkyl)calixarenes are easily obtained by treatment of the corresponding (ω-chloroalkyl)calixarenes with NaN_3 and NaI in warm DMF (ca. 90–120 °C; ca. 14 h; Fig. 8). The azide compounds are obtained as colorless microcrystalline solids in good yields.

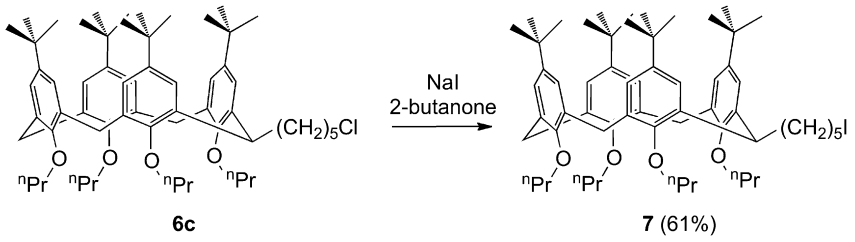

Fig. 7. The Finkelstein reaction was used to produce 2-(5-iodopentyl)tetrapropoxy-*p*-*tert*-butylcalix[4]arene (**7**).

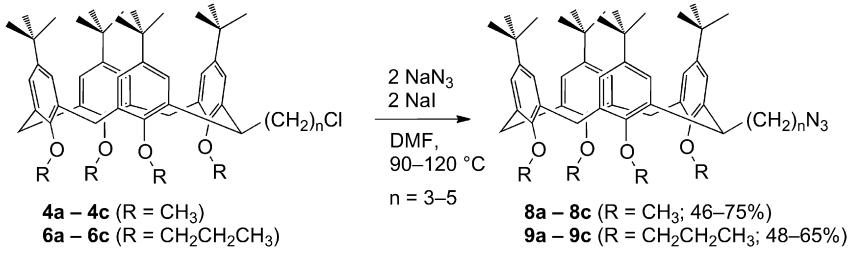

Fig. 8. Preparation of ω-azidoalkyl calixarenes by substitution. The letter indicates the length of the alkyl chain (a: n=3; b: n=4; c: n=5).

The NMR spectra of **8** and **9** (^{1}H and ^{13}C) are similar to those from the starting (ω-chloroalkyl)calixarenes. The progress and completion of this reaction (and other transformations at the ω-position) are judged by the ^{1}H NMR signals of the protons on the ω-carbon. The reactant (**8**) and product (**9**) calixarenes show virtually identical behavior in thin layer chromatography.

2.6. Click reactions of (ω-azidoalkyl)calixarenes

The ω-azidocalixarenes **8** and **9** are easily converted to triazoles by the Cu(I)-catalyzed Staudinger ligation with both aryl and alkyl terminal alkynes. Calixarenes **8** and **9** showed adequate solubility in a *tert*-butyl alcohol–water mixture (4:1) at 75 °C so that the reaction catalyzed by Cu(I) (generated from Cu powder and $CuSO_4$) proceeded smoothly and was complete in about 16 h. Despite the elevated temperature used to dissolve the calixarene, only the 1,4-disubstituted triazole was detected by ^{1}H NMR spectroscopy. The triazoles were reluctant to crystallize and were usually obtained and purified by trituration with methanol. The yields were fair, typically 40–70%; the exceptionally low yield for **11a** reflects material loss during recrystallization. The products and yields are summarized in Fig. 9. The ^{1}H NMR spectra of **10**–**13** show signals indicative of molecular C_s symmetry and the presence of the triazole ring with a characteristic signal for the 5-hydrogen around δ 7.9 ppm.

3. Conclusion/summary

The utility of alkyl-tethered functional groups at a single methylene bridge of a calix[4]arene has been extended to include the (ω-azido)alkyl group on tetramethoxy- and *cone*-tetrapropoxycalixarenes, thus broadening the scope of how a bridge tether can be used. Tether calixarenes with all upper- and lower-rim sites available for elaboration will allow for connection to a solid support or to various biologically relevant molecules functionalized with an alkyne group. By virtue of the 'orthogonal nature' of the azide group, these azido-terminated species will allow for a range of transformations at the other reactive sites on the

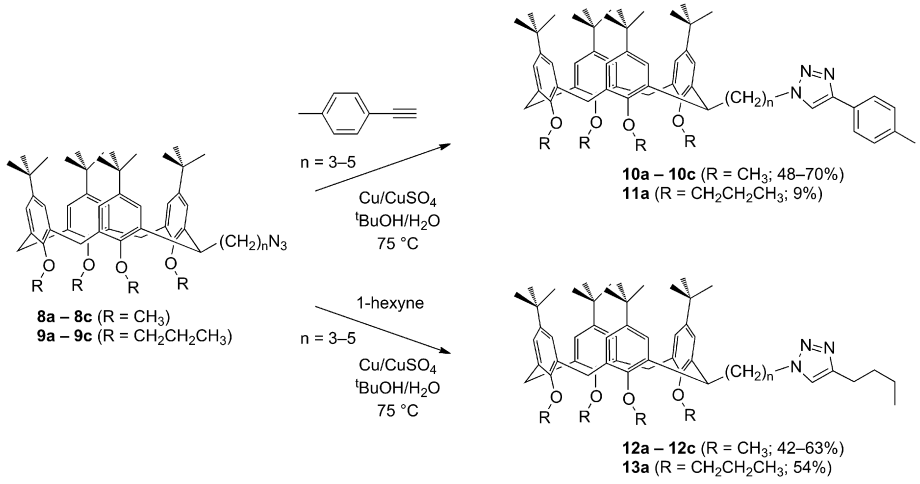

Fig. 9. Copper(I)-catalyzed 1,3-cycloaddition of calixarene azides to terminal alkynes yields 1,4-substituted 1,2,3-triazoles. The letter indicates the length of the alkyl chain (a: n=3; b: n=4; c: n=5).

calixarene before the azide group engages in a 'click' reaction with a terminal alkyne. The potential utility of these species has been demonstrated with representative click couplings of the (ω-azido) alkylcalixarenes with both aryl and alkyl terminal alkynes.

4. Experimental section

4.1. General considerations

Compounds **7**–**13** were synthesized under ambient atmosphere while compounds **5** and **6** were synthesized using standard Schlenk techniques. The solvents and reagents were purchased from commercial suppliers and used as received. CD_3CN and $CDCl_3$ (with 0.03% $SiMe_4$) were purchased from Aldrich or Fisher and used as received. ^1H and ^{13}C NMR data were obtained on a 400 MHz Bruker Avance NMR spectrometer at ambient temperature. NMR spectra of tetramethoxycalixarenes **1**, **8a**–**c**, **10a**–**c**, and **12a**–**c** were obtained using a mixture of $CDCl_3/CD_3CN$ (3:1) containing NaI (1 g per 80 mL solution). NMR spectra of other calixarenes were obtained in $CDCl_3$. ^1H NMR shifts are given relative to $SiMe_4$ (0.00 ppm) and ^{13}C NMR shifts are given relative to $CDCl_3$ (77.0 ppm). High resolution time-of-flight or quadrupole mass spectra were obtained using electrospray ionization by the Campus Chemical Instrument Center—Mass Spectrometry & Proteomics Facility at The Ohio State University. Electrospray samples were prepared by dissolving the calixarene in methanol and, in some cases, adding an NaI internal standard. The X-ray structure determination was performed at the University of Kentucky. *cone*-Tetrapropoxy-*p*-*tert*-butylcalix[4]arene,[8] and chloroalkyltetramethoxycalix[4]arenes[12b] were prepared as previously reported.

4.2. General procedure for the synthesis of 2-(ω-chloroalkyl) tetrahydroxy-*p*-*tert*-butylcalix[4]arenes[26] (5a–c)

To a solution of **4** in CH_2Cl_2 (ca. 20 mL per mmol of calixarene) cooled to −78 °C under a nitrogen or argon atmosphere, BBr_3, neat, or as a 1 M solution in CH_2Cl_2 (6.5 equiv) was added by disposable plastic syringe. The resulting mixture was kept at −78 °C for 30–90 min then at ambient temperature for 14–20 h. The mixture was quenched with saturated $NaHCO_3$ (ca. 20 mL per mmol calixarene). The organic phase was washed with saturated $NaHCO_3$ (1×10 mL per mmol calixarene), water (2×15 mL per mmol calixarene), then dried over $MgSO_4$ and concentrated under reduced pressure to obtain **5**, which was recrystallized from methanol as colorless microcrystals.

*4.2.1. 2-(3-Chloropropyl)tetrahydroxy-p-tert-butylcalix[4]arene (**5a**).* Reagents: **4a** (3.15 g, 4.03 mmol); BBr_3 (2.48 mL, 26.2 mmol). Yield: 2.07 g (70.8%); ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 4H), 7.11 (d, J=1.9 Hz, 2H), 7.07 (d, J=2.2 Hz, 2H), 7.05 (d, J=2.1 Hz, 2H), 7.00 (d, J=2.0 Hz, 2H), 4.51 (t, J=7.8 Hz, 1H), 4.25 (d, J=13.9 Hz, 1H), 4.24 (d, J=13.9 Hz, 2H), 3.59 (t, J=6.3 Hz, 2H), 3.48 (d, J=13.9 Hz, 3H), 2.36 ('quartet', J=7.6 Hz, 2H), 1.85–1.76 (m, 2H), 1.22 (s, 18H), 1.20 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.7, 144.6, 144.4, 130.5, 127.7, 127.5, 127.4, 126.0, 125.4, 121.7, 45.0, 35.0, 34.2, 34.0, 32.7, 32.7, 31.4, 31.4, 31.1, 29.4; HRMS calculated for $C_{47}H_{62}ClO_4$ $[M+H]^+$: 725.4337; for $C_{47}H_{61}ClNaO_4$ $[M+Na]^+$: 747.4156, found 725.4344; 747.4141.

*4.2.2. 2-(4-Chlorobutyl)tetrahydroxy-p-tert-butylcalix[4]arene (**5b**).* Reagents: **4b** (1.072 g, 1.348 mmol); 1 M BBr_3 in CH_2Cl_2 (10 mL, 10 mmol). Yield: 0.502 g (50.4%); ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 4H), 7.09 (d, J=2.2 Hz, 2H), 7.07 (d, J=2.4 Hz, 2H), 7.05 (d, J=2.3 Hz, 2H), 7.00 (d, J=2.2 Hz, 2H), 4.49 (t, J=7.8 Hz, 1H), 4.26 (d, J=13.9 Hz, 1H), 4.24 (d, J=13.9 Hz, 2H), 3.52 (t, J=6.7 Hz, 2H), 3.48 (d, J=13.8 Hz, 3H), 2.21 ('quartet', J=7.7 Hz, 2H), 1.85 ('quintet', J=7.1 Hz, 2H), 1.52–1.42 (m, 2H), 1.22 (s, 18H), 1.20 (s, 18H). ^{13}C NMR (100 MHz), CDClC NMR (100 MHz, $CDCl_3$) δ 146.8, 146.7, 144.5, 144.3, 130.8, 127.7, 127.5, 127.4, 125.9, 125.3, 121.7, 44.7, 35.5, 34.2, 34, 32.8, 32.7, 32.5, 31.5, 31.4(2), 25.3; HRMS calculated for $C_{48}H_{63}ClNaO_4$ $[M+Na]^+$: 761.4313, found 761.3788.

*4.2.3. 2-(5-Chloropentyl)tetrahydroxy-p-tert-butylcalix[4]arene (**5c**).* Reagents: **4c** (3.66 g, 4.52 mmol); BBr_3 (2.8 mL, 30 mmol). Yield: 2.96 g (86.9%); ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 4H), 7.09 (d, J=2.2 Hz, 2H), 7.07 (d, J=2.4 Hz, 2H), 7.05 (d, J=2.4 Hz, 2H), 6.99 (d, J=2.2 Hz, 2H), 4.48 (t, J=7.8 Hz, 1H), 4.26 (d, J=13.9 Hz, 1H), 4.24 (d, J=13.9 Hz, 2H), 3.51 (t, J=6.7 Hz, 2H), 3.47 (d, J=13.8 Hz, 3H), 2.19 ('quartet', J=7.7 Hz, 2H), 1.77 ('quintet', J=7.1 Hz, 2H), 1.56–1.46 (m, 2H,), 1.39–1.30 (m, 2H), 1.22 (s, 18H), 1.20 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.7, 144.4, 144.3, 131.1, 127.8, 127.5, 127.3, 126.0, 125.9, 125.2, 121.7, 45.0, 35.5, 34.2, 34.0, 32.8, 32.7, 32.4, 32.1, 31.4, 27.3, 26.8; HRMS calculated for $C_{49}H_{65}ClNaO_4$ $[M+Na]^+$: 775.4469, found 775.4442.

4.3. General procedure for the synthesis of 2-(ω-chloroalkyl) tetrapropoxy-*p*-*tert*-butylcalix[4]arenes (6a–c)[8]

A Schlenk vessel (typically 125 mL size to accommodate foaming) was charged with **5** and a 60% dispersion of NaH in mineral oil (10.4 equiv) under an inert atmosphere. To remove the mineral oil, the NaH was washed with three portions of hexanes. To the vessel was added DMF (ca. 4 mL per mmol calixarene) and NaCl (2 equiv). After the resulting slurry was cooled to 0 °C, 1-iodopropane was added (10.3 equiv) to the mixture, followed by additional DMF (ca. 4 mL per mmol calixarene). After at least 14 h stirring at ambient temperature the reaction mixture was vented and the excess NaH was quenched by the slow addition of 2 M HCl (ca. 16 mL per mmol calixarene). The crude product precipitated from the reaction mixture, was collected by filtration, and washed with water (ca. 15 mL per mmol calixarene). Pure **6** was obtained after trituration with methanol and filtration.

*4.3.1. 2-(3-Chloropropyl)tetrapropoxy-p-tert-butylcalix[4]arene (**6a**).* Reagents: **5a** (1.30 g, 1.79 mmol), NaH, 60% in oil (0.806 g, 33.6 mmol), NaCl (0.211 g, 3.61 mmol), 16 mL DMF total, 1-iodopropane (1.8 mL, 18 mmol). Yield: 1.313 g (82.0%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.780 (d, J=2.4 Hz, 2H), 6.777 (s, 4H), 6.76 (d, J=2.4 Hz, 2H), 4.78 (t, J=8.1 Hz, 1H), 4.39 (d, J=12.4 Hz, 3H), 3.9–3.7 (m, 8H), 3.63 (t, J=6.4 Hz, 2H), 3.12 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 1H), 2.16–2.08 (m, 2H), 2.08–1.98 (m, 8H), 1.98–1.88 (m, 2H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (t, J=7.4 Hz, 6H), 0.99 (t, J=7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.72, 153.67, 144.26, 144.19, 136.3, 133.9, 133.73, 133.70, 124.9, 124.82, 124.75, 121.7, 77.2, 76.9, 45.4, 35.6, 34.0, 33.8, 31.71, 31.66, 31.51, 31.47, 31.17, 31.09, 23.5, 23.3, 10.4, 10.3; HRMS calculated for $C_{59}H_{85}ClNaO_4$ $[M+Na]^+$: 915.6034, found 915.6041.

*4.3.2. 2-(4-Chlorobutyl)tetrapropoxy-p-tert-butylcalix[4]arene (**6b**).* Reagents: **5b** (0.750 g, 1.02 mmol), NaH, 60% in oil (0.80 g, 33 mmol), NaCl (0.142 g, 2.43 mmol), 9 mL DMF total, 1-iodopropane (1.0 mL, 10 mmol). Yield: 0.601 g (65%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J=2.8 Hz, 2H), 6.77 (d, J=2.8 Hz, 2H), 6.76 (d, J=2.4 Hz, 2H), 6.75 (d, J=2.4 Hz, 2H), 4.76 (t, J=8.1 Hz, 1H), 4.39 (d, J=12.4 Hz, 3H), 3.9–3.7 (m, 8H), 3.56 (t, J=6.8 Hz, 2H), 3.11 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.4 Hz, 1H), 2.11–1.94 (m, 10H), 1.88 ('quintet', 2H), 1.64–1.56 (m, 2H), 1.08 (s, 18H), 1.06 (s, 18H), 1.03 (t, J=7.6 Hz, 6H), 1.00 (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.71, 153.66, 144.2(2), 136.6, 133.9, 133.8, 133.7, 124.9, 124.8, 124.6, 121.7, 77.2, 77.0, 44.9, 36.2, 33.9, 33.8, 33.6, 33.0, 31.51, 31.47,

31.1, 31.0, 25.8, 23.5, 23.3, 10.4, 10.3; HRMS calculated for $C_{60}H_{87}ClNaO_4$ $[M+Na]^+$: 929.6191, found 929.6183.

*4.3.3. 2-(5-Chloropentyl)tetrapropoxy-p-tert-butylcalix[4]arene (**6c**).* Reagents: **5c** (3.753 g, 4.988 mmol), NaH, 60% in oil (2.564 g, 107 mmol), NaCl (0.705 g, 12.1 mmol), 42 mL DMF total, 1-iodopropane (4.9 mL, 50 mmol). Yield: 3.455 g (75.2%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J=2.7 Hz, 2H), 6.773 (d, J=2.7 Hz, 2H), 6.770 (d, J=2.3 Hz, 2H), 6.75 (d, J=2.3 Hz, 2H), 4.75 (t, J=8.1 Hz, 1H), 4.40 (d, J=12.4 Hz, 3H), 3.90–3.64 (m, 8H), 3.53 (t, J=6.7 Hz, 2H), 3.11 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.4 Hz, 1H), 2.11–1.94 (m, 10H), 1.85–1.75 (m, 2H), 1.64–1.50 (m, 4H), 1.08 (s, 18H), 1.06 (s, 18H), 1.03 (t, J=7.4 Hz, 6H), 1.00 (t, J=7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.74, 153.67, 144.15, 144.12, 136.8, 133.9, 133.8, 133.6, 124.9, 124.8, 124.5, 121.7, 77.1, 76.9, 45.1, 36.1, 34.2, 33.9, 33.8, 32.6, 31.5, 31.2, 31.0, 27.8, 27.3, 23.5, 23.3, 10.4, 10.3; HRMS calculated for $C_{61}H_{89}ClNaO_4$ $[M+Na]^+$: 943.6347, found 943.6364.

4.4. *cone*-2-(5-Iodopentyl)tetrapropoxy-*p*-*tert*-butylcalix[4]arene (7)

Sodium iodide (0.692 g, 4.616 mmol) and **6c** (2.128 g, 2.308 mmol) were combined in 2-butanone (75 mL) in a round-bottom flask. The resulting mixture was heated under reflux for 7 days after which the volatiles were removed under reduced pressure and the reaction mixture was partitioned between water and dichloromethane. The organic phase was washed with water (2×), dried over $MgSO_4$, and evaporated to dryness under reduced pressure. Recrystallization from methanol afforded a colorless microcrystalline powder, dried in vacuo to recover 1.438 g of **7** (61.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J=2.7 Hz, 2H), 6.773 (d, J=2.7 Hz, 2H), 6.766 (d, J=2.7 Hz, 2H), 6.75 (d, J=2.3 Hz, 2H), 4.74 (t, J=8.1 Hz, 1H), 4.40 (d, J=12.4 Hz, 3H), 3.90–3.70 (m, 8H), 3.19 (t, J=7.0 Hz, 2H), 3.11 (d, J=12.4 Hz, 2H), 3.10 (d, J=12.5 Hz, 1H), 2.11–1.92 (m, 10H), 1.85 ('quintet', J=7.0, 2H), 1.53–1.43 (m, 4H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (t, J=7.5 Hz, 6H), 0.99 (t, J=7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.75, 153.68, 144.15, 144.13, 136.8, 133.9, 133.8, 133.6, 124.9, 124.8, 124.6, 121.7, 77.14, 76.9, 36.2, 34.2, 33.9, 33.8, 33.5, 31.55, 31.47, 31.2, 31.1, 31.0, 27.5, 23.5, 23.3, 10.5, 10.3, 7.0; HRMS calculated for $C_{61}H_{89}INaO_4$ $[M+Na]^+$: 1035.5703, found 1035.5699.

4.5. General procedure for the synthesis of 2-(ω-azidoalkyl) tetraalkoxy-*p*-*tert*-butylcalix[4]arenes (8a–c and 9a–c)

A reaction mixture of **4** or **6** (1 equiv), NaI (2 equiv), and NaN_3 (2 equiv) was prepared in DMF (ca. 20–65 mL per mmol calixarene) and heated at ca. 90–120 °C for 24 h in a round-bottom flask. After completion of the reaction, as judged by ^{1}H NMR spectrometry, the reaction mixture was cooled to room temperature, diluted with diethyl ether (ca. 10 mL per mmol calixarene), and washed with saturated ammonium chloride (3×; ca. 10 mL per mmol calixarene). The aqueous extracts were back-extracted with diethyl ether (2×; ca. 10 mL per mmol calixarene) after which all organic fractions were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product. Recrystallization from methanol yielded colorless, microcrystalline **8** or **9**.

*4.5.1. 2-(3-Azidopropyl)tetramethoxy-p-tert-butylcalix[4]arene (**8a**).* Reagents: **4a** (2.373 g, 3.036 mmol), NaI (0.910 g, 6.07 mmol), NaN_3 (0.397 g, 6.11 mmol), 50 mL DMF. Yield: 1.68 g (70.1%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.25 (d, J=2.3 Hz, 2H), 7.24 (s, 4H), 7.23 (d, J=2.3 Hz, 2H), 4.67 (t, J=8.4 Hz, 1H), 4.27 (d, J=12.4 Hz, 3H), 4.15 (s, 6H), 4.14 (s, 6H), 3.48 (d, J=12.5 Hz, 2H), 3.47 (d, J=12.4 Hz, 1H), 3.38 (t, J=6.6 Hz, 2H), 2.28–2.19 (m, 2H), 1.68–1.59 (m, 2H), 1.21 (s, 18H), 1.20 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.1, 147.9, 136.9, 133.91, 133.86, 133.8, 125.4, 125.3, 125.2, 124.5, 121.5, 64.2, 63.9, 50.5, 34.5, 33.6, 33.5, 30.19, 30.18, 30.1, 29.1, 28.9, 27.4; HRMS calculated for $C_{51}H_{69}N_3NaO_4$ $[M+Na]^+$: 810.5186, found 810.5186.

*4.5.2. 2-(4-Azidobutyl)tetramethoxy-p-tert-butylcalix[4]arene (**8b**).* Reagents: **4b** (3.825 g, 4.808 mmol), NaI (1.436 g, 9.580 mmol), NaN_3 (0.627 g, 9.64 mmol), 60 mL DMF. Yield: 2.88 g (74.7%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.24 (d, J=2.4 Hz, 2H), 7.23 (s, 4H), 7.22 (d, J=2.2 Hz, 2H), 4.66 (t, J=8.3 Hz, 1H), 4.27 (d, J=12.4 Hz, 3H), 4.15 (s, 6H), 4.14 (s, 6H), 3.47 (d, J=12.4 Hz, 2H), 3.46 (d, J=12.4 Hz, 1H), 3.31 (t, J=6.8 Hz, 2H), 2.21–2.14 (m, 2H), 1.70 ('quintet', J=7.2, 2H), 1.44–1.39 (m, 2H), 1.208 (s, 18H), 1.206 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.1, 148.0, 137.2, 133.9, 133.8, 125.4, 125.0, 121.6, 64.1, 63.9, 50.2, 34.9, 33.6, 33.5, 32.6, 30.23, 30.19, 29.1, 29.0, 28.1, 25.2; HRMS calculated for $C_{52}H_{71}N_3NaO_4$ $[M+Na]^+$: 824.5342, found 824.5275.

*4.5.3. 2-(5-Azidopentyl)tetramethoxy-p-tert-butylcalix[4]arene (**8c**).* Reagents: **4c** (2.026 g, 2.502 mmol), NaI (0.504 g, 3.36 mmol), NaN_3 (0.325 g, 5.00 mmol), 100 mL DMF. Yield: 0.935 g (45.8%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.24 (d, J=2.2 Hz, 2H), 7.23 (s, 4H), 7.21 (d, J=2.2 Hz, 2H), 4.65 (t, J=8.2 Hz, 1H), 4.27 (d, J=12.4 Hz, 3H), 4.15 (s, 6H), 4.13 (s, 6H), 3.47 (d, J=12.4 Hz, 2H), 3.46 (d, J=12.5 Hz, 1H), 3.27 (t, J=6.8 Hz, 2H), 2.29–2.10 (m, 2H), 1.61 ('quintet', J=7.1, 2H), 1.53–1.43 (m, 2H), 1.42–1.33 (m, 2H), 1.206 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.0, 147.9, 137.3, 133.9, 133.8, 125.4, 125.0, 121.6, 64.1, 63.9, 50.4, 34.8, 33.0, 29.1, 29.0, 27.7, 27.6, 26.0; HRMS calculated for $C_{53}H_{73}N_3NaO_4$ $[M+Na]^+$: 838.5499, found 838.5480.

*4.5.4. 2-(3-Azidopropyl)tetrapropoxy-p-tert-butylcalix[4]arene (**9a**).* Reagents: **6a** (3.005 g, 3.36 mmol), NaI (1.007 g, 6.718 mmol), NaN_3 (0.434 g, 6.68 mmol), 60 mL DMF. Yield: 1.485 g (49.1%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 4H), 6.77 (s, 4H), 4.77 (t, J=8.2 Hz, 1H), 4.39 (d, J=12.4 Hz, 3H), 3.80 (m, 8H), 3.36 (t, J=6.7 Hz, 2H), 3.12 (d, J=12.6 Hz, 2H), 3.10 (d, J=12.5 Hz, 1H), 2.10–1.98 (m, 10H), 1.79–1.72 (m, 2H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (t, J=7.6 Hz, 6H), 0.99 (t, J=7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.70, 153.65, 144.26, 144.18, 136.3, 133.9, 133.7, 124.9, 124.8, 124.8, 121.6, 51.74, 35.89, 33.95, 33.81, 31.49, 31.46, 31.41, 31.1, 31.0, 28.0, 23.5, 23.3, 10.4, 10.3. Mp 179–184 °C. HRMS calculated for $C_{59}H_{85}N_3NaO_4$ $[M+Na]^+$: 922.6438, found 922.6396.

*4.5.5. 2-(4-Azidobutyl)tetrapropoxy-p-tert-butylcalix[4]arene (**9b**).* Reagents: **6b** (0.139 g, 0.153 mmol), NaI (0.0615 g, 0.410 mmol), NaN_3 (0.0321 g, 0.494 mmol), 10 mL DMF. Yield: 0.067 g (47.9%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (br, 4H), 6.76 (s, 4H), 4.76 (t, J=7.8 Hz, 1H), 4.39 (d, J=12.5 Hz, 3H), 3.90–3.70 (m, 8H), 3.28 (t, J=7.1 Hz, 2H), 3.11 (d, J=12.4 Hz, 2H), 3.10 (d, J=12.6 Hz, 1H), 2.10–1.96 (m, 10H), 1.75–1.68 (m, 2H), 1.52 (br s, 2H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (t, J=7.5 Hz, 6H), 0.99 (t, J=7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.6, 144.2, 136.6, 133.9, 133.73, 133.66, 124.9, 124.8, 124.6, 121.6, 77.2, 76.9, 51.3, 36.1, 33.9, 33.8, 31.49, 31.46, 31.1, 31.0, 29.1, 25.7, 23.5, 23.3, 10.4, 10.3; HRMS calculated for $C_{60}H_{87}N_3NaO_4$ $[M+Na]^+$: 936.6594, found 936.6525.

*4.5.6. 2-(5-Azidopentyl)tetrapropoxy-p-tert-butylcalix[4]arene (**9c**).* Reagents: **6c** (2.415 g, 2.623 mmol), NaI (0.783 g, 5.22 mmol), NaN_3 (0.348 g, 5.35 mmol), 120 mL DMF. Yield: 1.804 g (74.1%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J=2.5 Hz, 2H), 6.77 (d, J=2.5 Hz, 2H), 6.76 (d, J=2.4 Hz, 2H), 6.75 (d, J=2.4 Hz, 2H), 4.75 (t, J=8.1 Hz, 1H), 4.40 (d, J=12.4 Hz, 3H), 3.89–3.71 (m, 8H), 3.26 (t, J=6.9 Hz, 2H), 3.11 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 1H), 2.11–1.96 (m,

10H), 1.66–1.60 (m, 2H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (t, *J*=7.6 Hz, 6H), 0.99 (t, *J*=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.74, 153.67, 144.15, 144.13, 136.8, 133.9, 133.8, 133.6, 124.9, 124.8, 124.6, 121.7, 77.1, 76.9, 51.5, 36.2, 34.3, 33.9, 33.8, 31.52, 31.47, 31.2, 31.1, 28.9, 28.1, 27.1, 23.5, 23.3, 10.4, 10.3; HRMS calculated for $C_{61}H_{89}N_3NaO_4$ $[M+Na]^+$: 950.6751, found 950.6720.

4.6. General procedure for the cycloaddition of 8 and 9 with ethynyltoluene or 1-hexyne. (10–13)

A reaction mixture of **8** or **9** (1 equiv), Cu powder (4 equiv), $CuSO_4$ (1 equiv) was prepared in a 4:1 *tert*-butanol/water mixture (20–40 mL per mmol calixarene). The alkyne (ethynyltoluene or 1-hexyne; 1 equiv) was added by syringe, and the reaction mixture was heated at ca. 75 °C for 16–24 h. After completion of the reaction, as judged from ^{1}H NMR spectra, the reaction mixture was filtered through Celite and the volatiles were removed under reduced pressure. The residue was partitioned between water (ca. 25 mL per mmol calixarene) and dichloromethane (ca. 25 mL per mmol calixarene), and the organic layer was washed with water (2×; ca. 20 mL per mmol calixarene). The aqueous portions were combined and washed with CH_2Cl_2 (ca. 20 mL per mmol calixarene) then all organic portions were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a glass or oil. Solid product was obtained from trituration with methanol (**10c** and **11a** crystallized from 50:50 methanol/acetonitrile).

*4.6.1. 2-(3-((4-p-Tolyl)-1H-1,2,3-triazolyl)propyl)tetramethoxy-p-tert-butylcalix[4]arene (**10a**).* Reagents: **8a** (0.700 g, 0.888 mmol), 4-ethynyltoluene (0.10 g, 0.11 mL, 0.89 mmol), Cu (0.226 g, 3.55 mmol), $CuSO_4$ (0.222 g, 0.888 mmol), 35 mL solvent. Yield: 0.566 g (70.5%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.98 (s, 1H), 7.70 (d, *J*=8.1 Hz, 2H), 7.26–7.20 (m, 8H), 7.17 (d, *J*=2.3 Hz, 2H), 4.70 (t, *J*=8.2 Hz, 1H), 4.51 (t, *J*=6.8 Hz, 2H), 4.26 (d, *J*=12.4 Hz, 3H), 4.14 (s, 6H), 4.13 (s, 6H), 3.47 (d, *J*=12.4 Hz, 2H), 3.46 (d, *J*=12.4 Hz, 1H), 2.38 (s, 3H), 2.27–2.17 (m, 2H), 2.04–1.95 (m, 2H), 1.20 (s, 18H), 1.17 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.2, 148.0, 146.7, 136.9, 136.7, 133.89, 133.85, 133.83, 128.6, 128.2, 125.4, 125.3, 125.2, 124.7, 121.4, 119.1, 64.2, 63.9, 49.3, 34.3, 33.6, 33.4, 30.2, 29.8, 29.1, 28.9, 28.8, 20.1; HRMS calculated for $C_{60}H_{77}N_3NaO_4$ $[M+Na]^+$: 926.5812, found 926.5728.

*4.6.2. 2-(4-((4-p-Tolyl)-1H-1,2,3-triazolyl)butyl)tetramethoxy-p-tert-butylcalix[4]arene (**10b**).* Reagents: **8b** (1.25 g, 1.56 mmol), 4-ethynyltoluene (0.18 g, 0.20 mL, 1.56 mmol), Cu (0.396 g, 6.24 mmol), $CuSO_4$ (0.390 g, 1.56 mmol), 35 mL solvent. Yield: 0.691 g (48.5%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.91 (s, 1H), 7.68 (d, *J*=8.0 Hz, 2H), 7.27–7.18 (m, 10H), 4.64 (t, *J*=8.2 Hz, 1H), 4.42 (t, *J*=7.1 Hz, 2H), 4.26 (d, *J*=12.4 Hz, 1H), 4.25 (d, *J*=12.4 Hz, 2H), 4.14 (s, 6H), 4.10 (s, 6H), 3.46 (d, *J*=12.4 Hz, 3H), 2.38 (s, 3H), 2.25–2.16 (m, 2H), 2.11–1.97 (m, 2H), 1.48–1.36 (m, 2H), 1.20 (s, 18H), 1.19 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.1, 148.0, 146.6, 137.1, 137.0, 133.91, 133.89, 133.78, 128.7, 127.2, 125.4, 124.7, 121.6, 119.0, 64.1, 63.9, 49.2, 34.9, 33.6, 33.5, 32.4, 30.23, 30.20, 29.6, 29.1, 29.0, 25.1, 20.2; HRMS calculated for $C_{61}H_{79}N_3NaO_4$ $[M+Na]^+$: 940.5968, found 940.5991.

*4.6.3. 2-(5-((4-p-Tolyl)-1H-1,2,3-triazolyl)pentyl)tetramethoxy-p-tert-butylcalix[4]arene (**10c**).* Reagents: **8c** (1.00 g, 1.23 mmol), 4-ethynyltoluene (0.15 g, 0.16 mL, 1.2 mmol), Cu (0.313 g, 4.92 mmol), $CuSO_4$ (0.307 g, 1.23 mmol), 35 mL solvent. Yield: 0.691 g (48.5%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.88 (s, 1H), 7.70 (d, *J*=8.2 Hz, 2H), 7.26–7.17 (m, 10H), 4.63 (t, *J*=8.2 Hz, 1H), 4.38 (t, *J*=7.0 Hz, 2H), 4.26 (d, *J*=12.3 Hz, 1H), 4.25 (d, *J*=12.4 Hz, 2H), 4.13 (s, 6H), 4.10 (s, 6H), 3.46 (d, *J*=12.5 Hz, 1H), 3.45 (d, *J*=12.5 Hz, 2H), 2.38 (s, 3H), 2.20–2.07 (m, 2H), 2.05–1.88 (m, 2H), 1.52–1.32 (m, 4H), 1.20 (s, 18H), 1.19 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.2, 148.1, 146.6, 137.4, 137.1, 134.0, 133.8, 128.8, 127.4, 125.5, 125.1, 124.7, 121.8, 120.2, 119.1, 64.0, 63.8, 49.5, 35.0, 33.7, 33.6, 33.0, 30.33, 30.28, 29.9, 29.3, 29.2, 29.0, 27.7, 25.9, 20.3; HRMS calculated for $C_{62}H_{81}N_3NaO_4$ $[M+Na]^+$: 954.6125, found 954.6109.

*4.6.4. 2-(3-((4-p-Tolyl)-1H-1,2,3-triazolyl)propyl)tetrapropoxy-p-tert-butylcalix[4]arene (**11a**).* Reagents: **9a** (0.746 g, 0.830 mmol), 4-ethynyltoluene (0.10 g, 0.11 mL, 0.89 mmol), Cu (0.211 g, 3.32 mmol), $CuSO_4$ (0.202 g, 0.830 mmol), 45 mL solvent. Yield: 0.079 g (9.4%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.694 (d, *J*=8.0 Hz, 2H), 7.690 (s, 1H), 7.22 (d, *J*=7.8 Hz, 2H), 6.80–6.69 (m, 8H), 4.80 (t, *J*=7.3 Hz, 1H), 4.48 (t, *J*=6.6 Hz, 2H), 4.38 (d, *J*=12.5 Hz, 1H), 4.37 (d, *J*=12.4 Hz, 2H), 3.92–3.59 (m, 8H), 3.11 (d, *J*=12.4 Hz, 2H), 3.10 (d, *J*=12.4 Hz, 1H), 2.34 (s, 3H), 2.13–1.95 (m, 12H), 1.07 (s, 18H), 1.05 (s, 18H), 1.00 (t, *J*=7.4 Hz, 6H), 0.98 (t, *J*=7.4 Hz, 6H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.6, 147.9, 144.3, 144.2, 137.9, 136.0, 133.9, 133.8, 133.6, 129.4, 125.6, 124.9, 124.8, 123.1, 121.3, 118.8, 77.2, 76.9, 50.7, 35.9, 33.9, 33.8, 31.7, 31.5, 31.4, 31.3, 31.1, 31.0, 29.7, 23.4, 23.2, 21.2, 10.4, 10.2; HRMS calculated for $C_{68}H_{93}N_3NaO_4$ $[M+Na]^+$: 1038.7064, found 1038.7097.

*4.6.5. 2-(3-((4-Butyl)-1H-1,2,3-triazolyl)propyl)tetramethoxy-p-tert-butylcalix[4]arene (**12a**).* Reagents: **8a** (0.700 g, 0.888 mmol), 1-hexyne (0.073 g, 0.10 mL, 0.89 mmol), Cu° (0.226 g, 3.55 mmol), $CuSO_4$ (0.222 g, 0.888 mmol), 35 mL solvent. Yield: 0.488 g (63.1%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.42 (s, 1H), 7.23 (s, 4H), 7.22 (d, *J*=2.3 Hz, 2H), 7.15 (d, *J*=2.3 Hz, 2H), 4.68 (t, *J*=8.3 Hz, 1H), 4.41 (t, *J*=6.8 Hz, 2H), 4.26 (d, *J*=12.4 Hz, 3H), 4.14 (s, 6H), 4.13 (s, 6H), 3.47 (d, *J*=12.4 Hz, 2H), 3.46 (d, *J*=12.4 Hz, 1H), 2.68 ('t', *J*=7.7 Hz, 2H), 2.20–2.11 (m, 2H), 2.00–1.85 (m, 2H), 1.64 ('quintet', *J*=7.6, 2H), 1.43–1.30 (m, 2H), 1.20 (s, 18H), 1.19 (s, 18H), 0.93 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.2, 148.0, 147.4, 136.7, 134.0, 133.93, 133.89, 125.42, 125.40, 125.3, 121.5, 120.2, 64.3, 63.9, 49.1, 34.4, 33.7, 33.5, 30.8, 30.4, 30.2, 29.9, 29.1, 29.0, 28.8, 24.5, 21.4, 12.9; HRMS calculated for $C_{57}H_{80}N_3O_4$ $[M+H]^+$: 870.6149, found 870.6097.

*4.6.6. 2-(4-((4-Butyl)-1H-1,2,3-triazolyl)butyl)tetramethoxy-p-tert-butylcalix[4]arene (**12b**).* Reagents: **8b** (1.25 g, 1.56 mmol), 1-hexyne (0.10 g, 0.18 mL, 1.6 mmol), Cu (0.396 g, 6.24 mmol), $CuSO_4$ (0.390 g, 1.56 mmol), 35 mL solvent. Yield: 0.684 g (49.7%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.37 (s, 1H), 7.23 (s, 4H), 7.22 (d, *J*=2.3 Hz, 2H), 7.21 (d, *J*=2.3 Hz, 2H), 4.62 (t, *J*=8.2 Hz, 1H), 4.33 (t, *J*=7.1 Hz, 2H), 4.26 (d, *J*=12.4 Hz, 3H), 4.14 (s, 6H), 4.10 (s, 6H), 3.47 (d, *J*=12.4 Hz, 3H), 2.65 ('t', *J*=7.7 Hz, 2H), 2.22–2.12 (m, 2H), 2.02–1.96 (m, 2H), 1.60 ('quintet', *J*=7.6, 2H), 1.41–1.30 (m, 4H), 1.20 (s, 36H), 0.93 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.1, 148.1, 147.3, 137.1, 133.91, 133.89, 133.8, 125.4, 125.1, 121.6, 120.1, 64.1, 63.9, 49.0, 34.8, 33.6, 33.5, 32.5, 30.7, 30.25, 30.20, 29.7, 29.1, 29.0, 25.1, 24.4, 21.4, 12.9; HRMS calculated for $C_{58}H_{81}N_3NaO_4$ $[M+Na]^+$: 906.6125, found 906.6122.

*4.6.7. 2-(5-((4-Butyl)-1H-1,2,3-triazolyl)pentyl)tetramethoxy-p-tert-butylcalix[4]arene (**12c**).* Reagents: **8c** (1.00 g, 1.23 mmol), 1-hexyne (0.10 g, 0.14 mL, 1.2 mmol), Cu (0.313 g, 4.92 mmol), $CuSO_4$ (0.307 g, 1.23 mmol), 35 mL solvent. Yield: 0.462 g (41.8%); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3CN/NaI) δ 7.40 (s, 1H), 7.23 (s, 4H), 7.22 (d, *J*=2.3 Hz, 2H), 7.21 (d, *J*=2.3 Hz, 2H), 4.63 (t, *J*=8.2 Hz, 1H), 4.30 (t, *J*=7.1 Hz, 2H), 4.27 (d, *J*=12.3 Hz, 3H), 4.15 (s, 6H), 4.12 (s, 6H), 3.47 (d, *J*=12.4 Hz, 3H), 2.67 ('t', *J*=7.7 Hz, 2H), 2.17–2.09 (m, 2H), 1.88 ('quintet', *J*=6.9, 2H), 1.68–1.58 (m, 2H), 1.48–1.31 (m, 6H), 1.203 (s, 18H), 1.198 (s, 18H), 0.93 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3CN/NaI) δ 150.0, 148.0, 147.9, 147.2, 137.3, 133.9, 133.7, 125.3, 125.0, 121.6, 120.2, 64.1, 63.9, 49.1, 34.8, 33.6, 33.4, 32.9, 30.7,

30.23, 30.17, 29.2, 29.1, 28.9, 27.6, 25.8, 24.4, 21.3, 12.8; HRMS calculated for $C_{59}H_{83}N_3NaO_4$ $[M+Na]^+$: 920.6281, found 920.6256.

*4.6.8. 2-(3-((4-Butyl)-1H-1,2,3-triazolyl)propyl)tetrapropoxy-p-tert-butylcalix[4]arene (**13a**).* Reagents: **9a** (0.661 g, 0.734 mmol), 1-hexyne (0.06 g, 0.08 mL, 0.7 mmol), Cu (0.186 g, 2.94 mmol), $CuSO_4$ (0.183 g, 0.734 mmol), 40 mL solvent. Yield: 0.392 g (54.4%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.77 (s, 4H), 6.76 (d, J=2.4 Hz, 2H), 6.69 (d, J=2.3 Hz, 2H), 4.78 (t, J=7.6 Hz, 1H), 4.41 (t, J=7.0 Hz, 2H), 4.38 (d, J=12.4 Hz, 1H), 4.37 (d, J=12.5 Hz, 2H), 3.90–3.75 (m, 6H), 3.72–3.63 (m, 2H), 3.11 (d, J=12.6 Hz, 2H), 3.10 (d, J=12.5 Hz, 1H), 2.70 ('t', J=7.7 Hz, 2H), 2.10–1.94 (m, 12H), 1.68–1.58 (m, 2H), 1.43–1.32 (m, 6H), 1.07 (s, 18H), 1.05 (s, 18H), 1.01 (t, J=7.5 Hz, 6H), 0.98 (t, J=7.3 Hz, 6H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.6, 144.3, 144.2, 136.0, 133.9, 133.8, 133.6, 125.7, 124.9, 124.8, 121.3, 120.1, 77.2, 76.9, 50.5, 35.9, 33.9, 33.8, 31.6, 31.5, 31.43, 31.37, 31.1, 31.0, 29.7, 25.4, 23.5, 23.2, 22.3, 13.8, 10.4, 10.2; HRMS calculated for $C_{65}H_{96}N_3O_4$ $[M+H]^+$: 982.7401, found 982.7421.

4.7. X-ray crystal structure of *cone*-2-(4-chlorobutyl) tetrapropoxy-*p-tert*-butylcalix[4]arene (6b)

X-ray data were collected on a Nonius Kappa-CCD diffractometer using Mo Kα radiation. The structures were solved using Shelxs and refined using Shelxl from the Shelx-97 program package.[31] Molecular fragment editing, including the construction of suitable disorder models was performed using the XP program of Shelxtl.[31] With the exception of a few minor component atoms of some disordered groups, non-hydrogen atoms were refined with anisotropic displacement parameters. The majority of hydrogen atoms were found in difference-Fourier maps, but some belonging to disordered groups were indistinct. All hydrogens were subsequently placed at calculated positions and refined using an appropriate riding model. Absorption corrections were applied during scaling and merging using Scalepack, which models absorption using spherical harmonics.[32] Further details of the structure analyses are given in the Supplementary data. The high R-value for this refinement is largely a consequence of poor crystal quality. This is a perennial problem for compounds of calixarenes, especially those that contain occluded solvent, where extensive disorder is common. In such cases the spatial quality of the fit, as obtained by the R-tensor,[33] can be invaluable in distinguishing between poor counting statistics and an inadequate model as the source of high R-values. For the structure presented here, the lack of severe anisotropy of the fit implies poor counting statistics, which are a direct consequence of crystal quality.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 827754. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Drs. Thomas A. Evans and Joseph J. Reczek for helpful comments. Support for this research by the Denison University and the Denison University Research Foundation is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.022.

References and notes

1. Gutsche, C. D. *Calixarenes: An Introduction*, 2nd ed.; RSC Publishing: Cambridge, 2008.
2. Gutsche, C. D. Calixarenes Revisited In. *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998; Vol. 6.
3. Lang, J.; Deckerová, V.; Czernek, J.; Lhoták, P. *J. Chem. Phys.* **2005**, *122*, 044506.
4. Harada, T.; Rudzinski, J. M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2109–2116.
5. (a) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385–2392; (b) Soi, A.; Bauer, W.; Mauser, H.; Moll, C.; Hampel, F.; Hirsch, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1471–1478; (c) Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1994**, *116*, 11957–11960.
6. Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325–4342.
7. Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J. *Calixarenes 2001*; Kluwer Academic: Dordrecht, 2001.
8. Arduini, A.; Casnati, A. In *Macrocycle Synthesis. A Practical Approach*; Parker, D., Ed.; Oxford University: New York, NY, 1996; pp 145–173.
9. Lalor, R.; DiGesso, J. L.; Mueller, A.; Matthews, S. E. *Chem. Commun.* **2007**, 4907–4909.
10. Bohmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745.
11. (a) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657–1658; (b) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037–13052; (c) Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267–6270.
12. (a) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741–2744; (b) Hertel, M. P.; Behrle, A. C.; Williams, S. A.; Schmidt, J. A. R.; Fantini, J. L. *Tetrahedron* **2009**, *65*, 8657–8667.
13. Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667–675.
14. (a) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495–12503; (b) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136–6142.
15. (a) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967–8968; (b) Kumar, S.; Chalwa, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073–7075.
16. (a) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927–2929; (b) Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598–2606.
17. Görmar, G.; Seiffarth, K. *Makromol. Chem.* **1990**, *191*, 81–87.
18. Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577–1580.
19. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598; (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633–645.
20. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
21. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
22. Bew, S. P.; Brimage, R. A.; L'Hermit, N.; Sharma, S. V. *Org. Lett.* **2007**, *9*, 3713–3716.
23. Morales-Sanfrutos, J.; Ortega-Muñoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7768–7771.
24. Gruner, M.; Fischer, C.; Gruber, T.; Weber, E. *Supramol. Chem.* **2010**, *22*, 256–266.
25. Compound **3** was identified by comparison with NMR spectra described in Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955–4962.
26. McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289–2292.
27. Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938–12949.
28. Kelderman, E.; Derhaeg, L.; Heesink, G. J. T.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1075–1077.
29. Shinkai, S. *Tetrahedron* **1993**, *49*, 8933–8968.
30. Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.
31. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
32. Otwinowski, Z.; Minor, W. *International Tables for Crystallography*; 2006; Vol. F, 1st online ed., ch. 11.4, pp. 226–235. Chester: International Union of Crystallography.
33. Parkin, S. *Acta Crystallogr., Sect. A* **2000**, *56*, 157–162.