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Tri- and Pentacalix[4]pyrroles: Synthesis, Characterization and Their Use in the Extraction of Halide Salts

Abdullah Aydogan* and Ahmet Akar*[a]

Abstract: Calixpyrrole-based oligomeric compounds were synthesized by "click chemistry" from the corresponding alkyne- and azide-functionalized calix[4]pyrroles. Calix[4]pyrrole **3**, possessing an alkyne functional group, was prepared through a mixed condensation of pyrrole with acetone and but-3-ynyl 4-oxopentanoate. Another alkyne-group-containing calix[4]pyrrole **5** was obtained by treatment of 4′-hydroxyphenyl-functionalized calixpyrrole **4** with propargyl bromide. Tetrakis(azidopentyl)-functionalized calix[4]pyrrole **7** was synthesized by reacting NaN_3 with tetrabromopentyltetraethylcalix[4]pyrrole **6**, which was prepared through a condensation reaction of pyrrole and 7-bromohept-2-one. Oligomeric calixpyrrole compounds were found to be capable of extracting tetrabutylammonium chloride and fluoride salts from aqueous media. Extraction abilities of the oligomeric compounds were monitored by NMR and UV/Vis spectroscopy and thermogravimetric analysis.

Keywords: calix[4]pyrroles · click chemistry · extractants · halides · oligomers

Introduction

The area of anion recognition represents an evolving area of supramolecular chemistry and its impact in such disparate areas as environmental chemistry[1] and biomedicine[2] is becoming increasingly valued. Anions play crucial roles in regulating human health[3] and are ubiquitous in biological systems.[4] In addition, anion receptors can be used as ion-selective receptors,[5] phase-transfer catalysts, and anion-selective optical sensors.[6] Their particular importance in the nuclear fuel cycle is also well recognized.[7] Moreover, chromatographic separation systems have been generated by attaching receptors to an appropriate stationary phase.[8] These and other practical considerations have led to a spectacular growth within the anion-recognition field. However, the weak nature of most anion–receptor interactions, particularly in the case of neutral-anion-receptor systems that reflect the relatively low-charge density of most anions,[9] makes the design of selective and effective receptors an on-going challenge. Thus, while a number of research groups have designed elegant anion receptors, many of which have proven to be quite effective, there still remains a need for simple and easy-to-make anion-binding systems. In this context, calix[4]pyrroles, which are macrocyclic compounds containing four pyrrole units connected to each other through sp^3-hybridized carbon atoms, have emerged as molecules of particular interest,[8] because the core structure can be accessed in one synthetic step and a large number of modifications are readily conceivable. To date, simple *meso*-alkyl-substituted, halogenated,[10] C-rim modified,[11] photoactive and chromophore-modified,[5] strapped,[12] ditopic,[13] expanded,[14] N-confused,[15] siloxane-functionalized,[16] and polyfunctional[17] calixpyrrole derivatives have been reported.

Calix[4]pyrroles have also engendered extensive research effort because of their ability to recognize certain anionic guests (e.g., fluoride, chloride, and dihydrogen phosphate) in organic media.[18] The nature of the binding interactions of these macrocyclic compounds involves hydrogen bonding, which leads to the general expectation that in highly competitive media calixpyrroles would display substantially reduced anion affinities.[19] However, recent reports in which calixpyrroles are either covalently attached to solid supports to produce anion-selective HPLC packings[20] or are embedded in several functional materials, for example, colorimetric sensors[21] and ion-selective electrodes,[22] showed that calix[4]pyrroles and its derivatives can be used as highly effective anion receptors under mixed organic–aqueous interfacial conditions. Particular interest is devoted to calixpyrroles attached to PMMA-based polymeric backbones (PMMA = poly(methyl methacrylate)) with an increased number of receptor sites to enable the extraction of halide salts (e.g., tetrabutylammonium and potassium salts of fluoride and chloride) selectively from aqueous solutions.[23] Although polymeric structures can be used as effective extractants for the specific anions that calixpyrroles can bind selectively, well-defined oligomeric structures, constructed at the *meso*-positions of calix[4]pyrrole cores by taking advantage of click chemistry, can be used as effective linear polymeric analogues. These findings prompted us to consider that soluble oligomeric materials, based on calix[4]pyrrole cores linked

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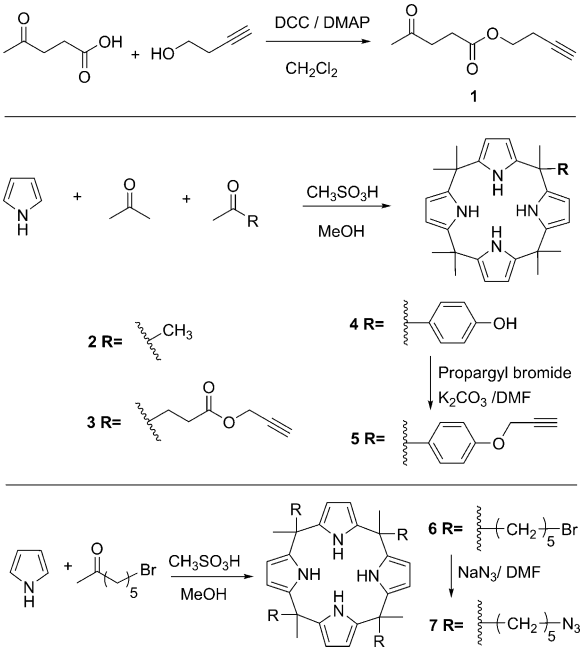
directly to each other through triazole rings, could also be capable of extracting anions from their aqueous solutions. Such materials, based on calix[4]pyrroles, may find utility in addressing a variety of current challenges, including corrosion prevention (e.g., chloride, carbonate, and sulfate control under conditions of combustion[24]) and waste remediation (e.g., sulfate extraction from tank waste[25]).

Herein, we report the synthesis and characterization of tri- and pentacalix[4]pyrrole precursors, that is, ketone **1** containing an alkyne functional group, calix[4]pyrroles **3** and **5**, compound **7**, with four azide units connected to the *meso*-positions of the calix[4]pyrrole-core structure, and oligomeric calix[4]pyrroles **8**–**11,** synthesized by click chemistry. In addition, we demonstrate that organic solutions of the pentacalix[4]pyrroles are capable of extracting tetrabutylammonium chloride (TBACl) and tetrabutylammonium fluoride (TBAF) from aqueous solutions more effectively than calixpyrrole **2** and tricalix[4]pyrroles **10** and **11** (Schemes 1 and 2). To the best of our knowledge, this is the first example of calixpyrrole receptors constructed to well-defined oligomeric structures and the first report wherein calix[4]pyrrole-receptor-based oligomeric systems of any type have been used to effect anion extraction under interfacial aqueous–organic conditions.

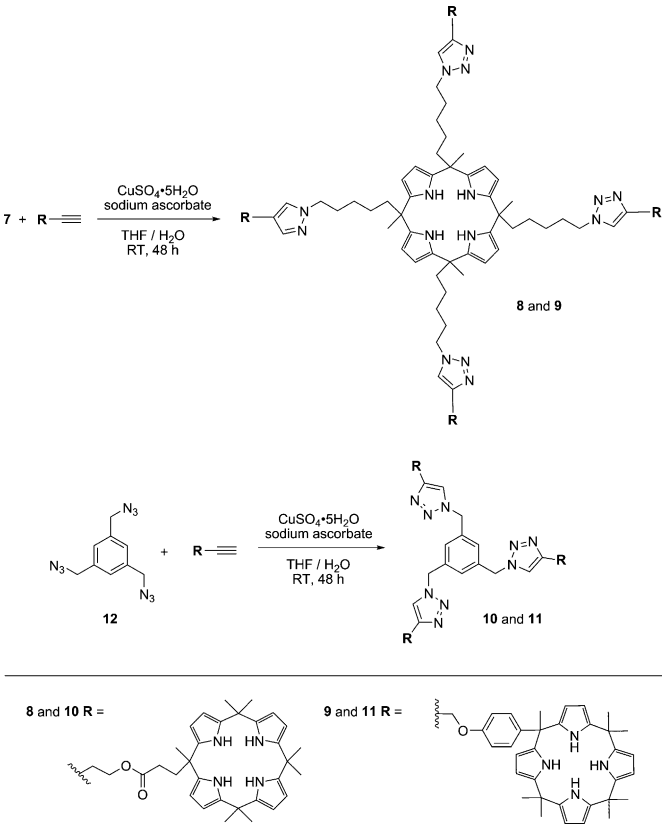
Results and Discussion

The alkyne-functionalized calix[4]pyrrole **3** was prepared in 17% yield through a mixed condensation reaction of pyrrole with **1** and acetone in MeOH using a catalytic amount of methanesulfonic acid (Scheme 1). The second alkyne-functionalized calix[4]pyrrole **5** was synthesized in 90% yield by reacting propargyl bromide with 4-hydroxyphenyl-functionalized calixpyrrole derivative **4**, which was obtained through a mixed condensation reaction of pyrrole with acetone and 4-hydroxyacetophenone. Tetrabromo-functionalized calix[4]pyrrole **6** was synthesized by an acid-catalyzed condensation of pyrrole and 7-bromoheptan-2-one[26] in MeOH. The resulting calix[4]pyrrole **6** was then quantitatively converted to its corresponding tetraazido derivate **7** in the presence of NaN_3 in DMF at room temperature.

Click reactions, named by Sharpless and co-workers, can be characterized as reactions displaying high yields, compatibility with a large scale of functional groups, tolerance to a variety of solvents, and mild reaction conditions.[27] Gale and co-workers reported the synthesis of bis-1,2,3-triazole-strapped calix[4]pyrroles through click chemistry.[28] The synthesis of calix[4]pyrrole-based oligomeric compounds was achieved by click reactions, inspired from Sharpless' and Gale's reports. To obtain the desired oligomeric structures, tetraazido-functionalized calixpyrrole **7** was dissolved in THF and reacted with calixpyrrole **3** or **5** in the presence of an aqueous solution of sodium ascorbate and $CuSO_4 \cdot 5H_2O$ at room temperature (Scheme 2). After 48 h, the crude products were extracted with CH_2Cl_2 and precipitated from hexane after workup. Tricalix[4]pyrroles **10** and **11** were prepared in an analogous manner. In this case, the alkyne-functionalized calixpyrrole compounds **3** and **5** were treated with 1,3,5-tris(azidomethyl)benzene[29] (**12**) to synthesize the desired tripodal oligomeric calix[4]pyrroles.



Scheme 1. Synthesis of alkyne- and azide-functionalized calix[4]pyrroles.



Scheme 2. Synthesis of star-shaped oligomeric calix[4]pyrrole compounds.

The compounds were characterized and the occurrence of the click reactions was monitored by using FTIR and NMR spectroscopy and corroborated by mass spectrometry. For example, in the case of the ^{1}H NMR analysis of compound **11**, the extent of conversion of azido moieties to triazole rings was monitored by observing the disappearance of the N_3–CH_2 signal of compound **12** at $\delta = 4.39$ ppm and the appearance of the C*H* protons of compound **11** belonging to the triazole ring at $\delta = 7.56$ ppm. Additionally, CH_2–C≡C protons of the calix[4]pyrrole **5** showed an upfield shift from $\delta = 4.65$ to 5.15 ppm after the formation of the triazole ring (Figure 1). Although all the oligomeric compounds have

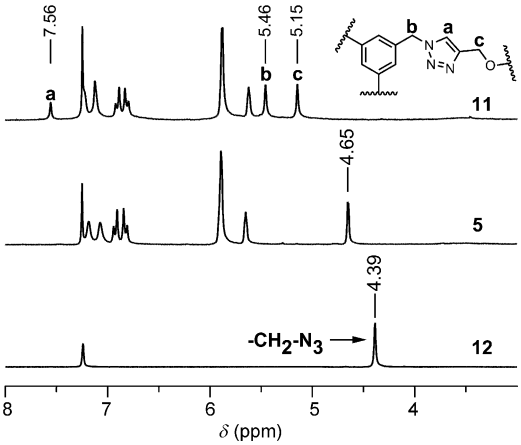


Figure 1. Partial ^{1}H NMR spectra of the compounds **5**, **11**, and **12**, recorded in $CDCl_3$.

good solubility in common organic solvents, ^{1}H NMR spectra of some oligomers revealed relatively broadened peaks (see the Supporting Information), reflecting the asymmetric nature and high molecular weight of the oligomers.

The structures of both starting materials and oligomers were also monitored by FTIR spectroscopy. Figure 2 shows the results of the FTIR spectroscopic analysis of alkyne-functionalized calix[4]pyrrole **3**, tetraazide-functionalized calix[4]pyrrole **7**, and tri-calix[4]pyrrole **10**. The presence of

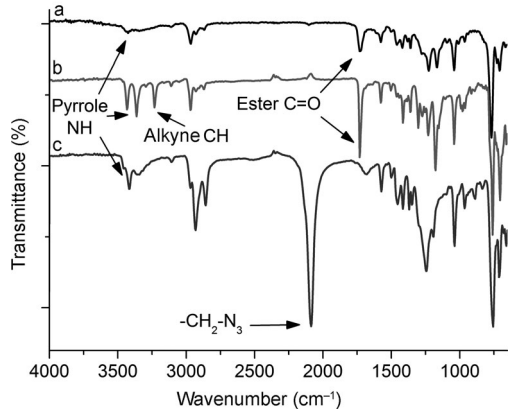


Figure 2. FTIR spectra of the compounds a) **10**, b) **3**, and c) **7**.

alkyne groups was evidenced by characteristic bands of H–C≡C at $\tilde{\nu} = 3234$ cm^{-1} for compound **3**. Pyrrole N–H stretching bands of compound **3** were observed at $\tilde{\nu} = 3433$ and 3367 cm^{-1}, while the same stretching band belonging to compound **10** was observed at $\tilde{\nu} = 3421$ cm^{-1}. Compounds **6** and **7** were also subjected to FTIR spectroscopic analysis. Figure 2 shows the actual conversion of tetrabromo-substituted calix[4]pyrrole **6** into its corresponding tetraazido-substituted derivative **7**, based on the presence of a N_3 stretching band at $\tilde{\nu} = 2082$ cm^{-1}. These spectral characterizations clearly support that the desired alkyne- and azide-functionalized calix[4]pyrroles have been synthesized successfully.

The disappearance of the azide stretching band of compound **10** at $\tilde{\nu} = 2082$ cm^{-1} after click reaction supports the expected triazole-ring formation of the obtained oligomeric calix[4]pyrrole compound **10**. Similar results that indicate the successful synthesis of oligomeric compounds were also observed in the case of the compounds **8**, **9**, and **11** (see the Supporting Information).

Once the star-shaped oligomeric calix[4]pyrrole compounds were fully characterized, efforts were directed towards exploring their ability to bind anions under interfacial conditions. Initial qualitative evidence that **8** and **9** could extract chloride salts into organic media came from a visual test involving compound **13**, a water-soluble dye that contains a chloride counterion. Treatment of an aqueous solution of **13** (25.5 μM) with a solution of **8** (0.90 mM) and **9** (0.89 mM) in CH_2Cl_2 resulted in green organic phases (Figure 3, see the Experimental Section for a detailed explanation of the extraction process).

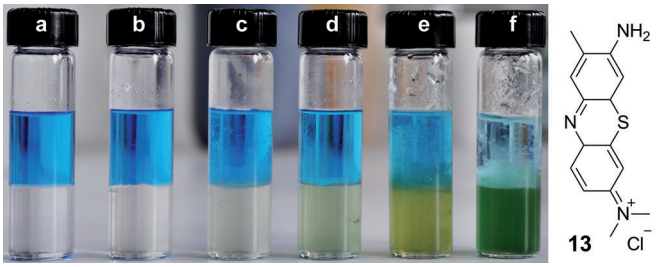


Figure 3. Aqueous solutions of **13** (top layers): a) After treatment with CH_2Cl_2 and after treatment with solutions of b) **2**, c) **10**, d) **11**, e) **8**, and f) **9** in CH_2Cl_2 (bottom layers).

As control experiments, solutions of the dye were also exposed to CH_2Cl_2 and solutions of **2** (6.23 mM), **10** (1.43 mM), and **11** (1.42 mM) in CH_2Cl_2; however, the observed transfer of color was not as intense as for **8** and **9**. These results were quantified by using UV/Vis spectroscopy (Figure 4). Analysis of the aqueous phases of these extraction experiments confirmed that **9** was able to extract **13** into the organic phase more effectively than **2**, **10**, and **11** (greater than 56–79%, see the Supporting Information for detailed extraction data).

Encouraged by these initial results, we next sought to address the question if the oligomers **9** and **10** (as model com-

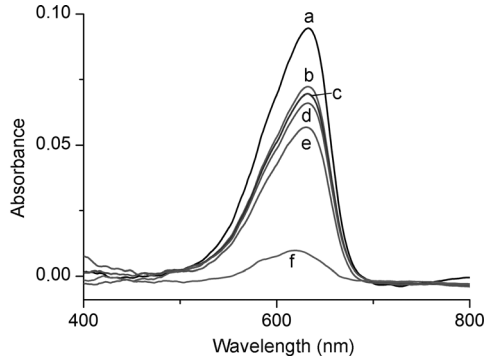


Figure 4. UV/Vis spectra of aqueous solutions of **13** (initial concentration = 25.5 μm) after exposure to an equal volume of a) a CH_2Cl_2 solution and solutions of b) **2**, c) **10**, d) **11**, e) **8**, and f) **9** in CH_2Cl_2.

pounds) could extract TBA^+ salts (for a detailed explanation of the extraction process see the Experimental Section). As shown in Figure 5, the addition of a solution of tetrabutylammonium fluoride (TBAF, 90 mM) in D_2O to a solution of oligomer **9** (0.5 mM) in CD_2Cl_2 resulted in a substantial downfield shift of the pyrrole NH protons (as typically seen upon anion binding[18a]). In addition, peaks ascribable to the methylene units in the TBA^+ counter ion (at $\delta = 3.2$ ppm) were visible, supporting the notion that both the anion (F^-) and the cation were present in the organic phase. In contrast, no shifts in the NH resonances and no peaks ascribable to TBA^+ were observed when a 29 mM solution of octamethylcalix[4]pyrrole (**2**) in CD_2Cl_2 was exposed to aqueous solutions of TBAF.

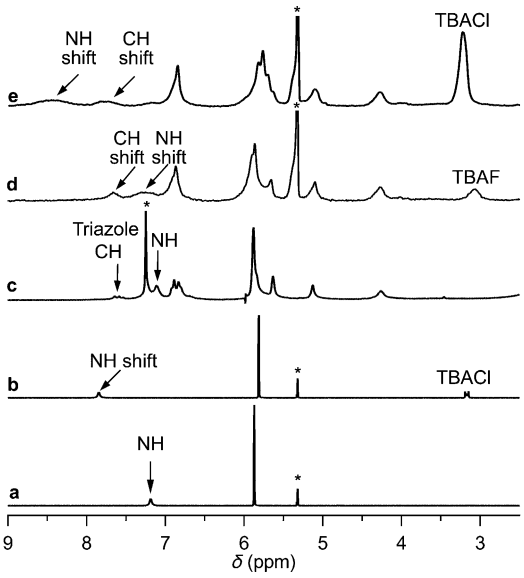


Figure 5. ^1H NMR spectra of solutions of a/b) oligomer **2** (29 mM) and d/e) oligomer **9** (0.5 mM) in CD_2Cl_2 after i) adding a solution of TBAX in D_2O (90 mM, 0.5 mL), ii) shaking the tube vigorously, and iii) allowing the phases to separate. c) Oligomer **9** in $CDCl_3$. * = residual solvent.

A solution of the tripodal oligomer **10** (0.8 mM) in CH_2Cl_2 was also subjected to extraction of TBAF and TBACl under the same conditions that were used for the compound **9**. As show in Figure 6, no TBAF extraction was observed when compound **10** was used as the extractant. Figure 6b indicates the absence of peaks referable to the methylene units of the TBA^+ counterion, as well as no shift of the pyrrole NH resonances. However, in the case of TBACl, both the TBA^+ ascribable peaks and the downfield shift of the pyrrole NH resonances were observed. These results led us to conclude that tripodal oligomer **10** can extract Cl^- ions into organic media better than control compound **2**. Another result that can be concluded from Figures 5 and 6 is that the pentacalix[4]pyrrole **9** extracts F^- and Cl^- ions better than the tricalix[4]pyrrole **10** and the control compound **2**, as judged from the integration of the peaks referring to the methylene units of the TBA^+ counterions and the resonances of the β-pyrrolic CH protons. The enhanced extraction ability of pentacalix[4]pyrrole **9** compared to tricalix[4]pyrrole **10** points out a possible cooperative effect of the number of individual calixpyrrole units present in the structure of **9**.

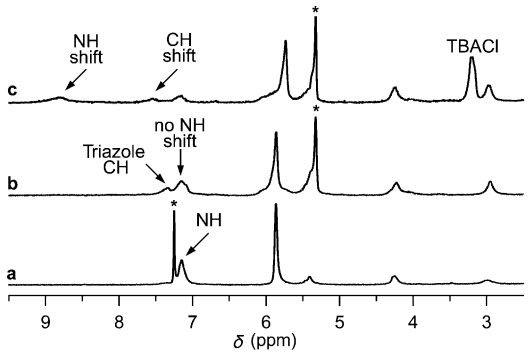


Figure 6. ^1H NMR spectra of a) oligomer **10** in $CDCl_3$; b) after i) adding a solution of TBAF in D_2O (90 mM, 0.5 mL) to a solution of **10** in CD_2Cl_2 (0.8 mM), ii) shaking the tube vigorously, and iii) allowing the phases to separate; and c) solution of **10** after being subjected to the same treatment with TBACl, as applied in (b). * = residual solvent.

The ability of the oligomers **9** and **10** to extract several other TBA^+ salts was also tested. While no extraction was observed in the case of aqueous solutions of tetrabutylammonium dihydrogen phosphate, upon addition of TBACl downfield shifts of the NH proton signals greater than those observed with TBAF for analogous anion concentrations were visible. Such findings, which are consistent with an enhanced ability to extract chloride relative to fluoride or dihydrogen phosphate, are in contrast to the relative anion affinities observed in CH_2Cl_2.[18a] However, they are in accordance with the expectations based on the so-called Hofmeister bias,[30] namely, that a more hydrophobic anion, such as chloride ($\Delta G_h = -340$ kJ mol^{-1}), is extracted more easily than a highly hydrophilic species, such as dihydrogen phosphate ($\Delta G_h = -465$ kJ mol^{-1}) or fluoride ($\Delta G_h = -465$ kJ mol^{-1}).[31] Consistent with this rationale is the finding that the control calixpyrrole **2** was able to extract

TBACl under the aforementioned interfacial conditions, albeit with efficiencies of less than 50% relative to oligomer **9** (as calculated from NMR integrations of the β-pyrrolic and TBA^+ signals). On the other hand, the fact that efficient extraction of TBAF was only seen in the case of oligomer **9** (and not for compounds **2** and **10**) underscores the notion that the calixpyrrole receptors constructed to an oligomeric backbone and the number of calix[4]pyrrole units in the oligomers play a critical role, as judged from our previous studies.[23]

Further support for the suggestion that oligomers **9** and **10** could extract fluoride and chloride ions was based on thermal analyses. As shown in Figure 7, after independently

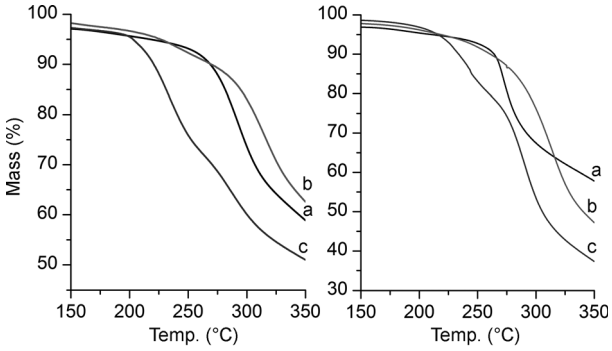


Figure 7. Partial thermogravigrams of oligomers **9** (left) and **10** (right) a) before and after treatment with b) TBAF or c) TBACl.

exposing TBAF or TBACl to a solution of **9** in CH_2Cl_2, as described above, organic layers of these samples were subjected to thermogravimetric analysis. For this purpose CH_2Cl_2 was removed after the extraction experiment and the remaining solid was dried for 24 h under reduced pressure.

As can be judged from Table 1, for the sample of **9** exposed to TBAF an 8% mass loss was observed upon heating to 290°C. This is low in comparison to the theoretical mass loss of 34.5%, assuming that the TBAF became completely volatile over the aforementioned temperature range and was present in less than a 1:1 stoichiometry relative to each calix[4]pyrrole unit in the oligomer. In contrast, the sample of **9** exposed to TBACl exhibited a 32% mass loss (theoretical: 31.7%) upon heating to 290°C. For comparison, tricalix[4]pyrrole **10** was also subjected to thermogravimetric analysis after exposure to TBACl and TBAF under the same conditions applied for **9**. In the case of TBAF no reasonable mass loss was observed upon heating to 290°C, whereas a 30% mass loss (theoretical: 31%) was observed in the case of TBACl. Considering the relative extraction abilities of **9** and **10** towards TBACl and TBAF (see above), the observed mass losses were considered reasonable.

Table 1. Mass losses of the dried organic layers after extraction.[a]

Compound	TBAF [%][b]	TBACl [%][b]
9	8	32
10	<1	30

[a] Obtained from TGA (TGA = thermogravimetric analysis). [b] Percentages were calculated after subtracting the mass losses of the pure compounds upon heating to 290°C.

Conclusion

In conclusion, we have demonstrated the synthesis of four different oligomeric calix[4]pyrrole compounds in excellent yields. The process involves the synthesis of azide-functional core structures and subsequent click reaction of these compounds with alkyne-functionalized calix[4]pyrroles. The strategy that was used in this study is entirely satisfactory in terms of efficiency and simplicity. This method is the first example of click chemistry directly applied for the construction of star-shaped oligomeric calix[4]pyrrole compounds. Furthermore, these oligomeric calix[4]pyrrole compounds were used in the extraction of F^- and Cl^- salts of tetrabutylammonium cations. Extraction experiments revealed that, while pentacalix[4]pyrrole derivatives **8** and **9** were extracting fluoride and chloride ions into the organic phase, tricalix[4]pyrrole derivatives **10** and **11** were just able to extract chloride ions. Another major conclusion is that these oligomeric calixpyrrole compounds are as effective and selective as polymeric analogues of this class of macrocycles. Detailed investigations of binding stoichiometries, affinity constants of the compounds, and of exploring the possible cooperative effects of calix[4]pyrrole units in the extraction of specific anions are underway.

Experimental Section

General considerations: All solvents were dried before use according to standard literature procedures. Unless specifically indicated, all other chemicals and reagents used in this study were purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra used for the characterization of products were recorded on Varian Unity 300 or 400 MHz and Bruker 250 MHz AC-3000 spectrometers using a residual solvent as the reference. Low-resolution FAB and CI mass spectra were obtained on a Finningan MAT TSQ 70 mass spectrometer. High-resolution FAB and CI mass spectra were obtained on a VG ZAB2-E mass spectrometer. UV/Vis measurements were studied on a Bio HITACHI U-0080D spectrometer. Thermogravimetric analyses were carried out by using a TA, TGA Q50 instrument in a flowing nitrogen atmosphere at a heating rate of 20°C min^{-1}.

Extraction of TBA^+ salts: In a tube an aqueous solution of the desired TBA^+ salt was added to a solution of the sample in CD_2Cl_2 (in the case of UV/Vis analysis the solvent was CH_2Cl_2). The resulting mixture was shaken vigorously until an emulsion was obtained. The organic and aqueous layers were separated clearly within 5 min with the aid of centrifugation at 4000 rpm. These two layers were subjected individually to UV/Vis, NMR, or thermogravimetric analyses.

But-3-ynyl 4-oxopentanoate (1): Levulinic acid (3 g, 25.8 mmol), 3-butyn-1-ol (1.75 mL, 23.48 mmol), and DMAP (32 mg, 0.26 mmol) were dissolved in CH_2Cl_2 (30 mL) and DCC (5.32 g, 25.8 mmol) was added. The reaction mixture was stirred for 24 h at room temperature and the insoluble matter was filtrated off. The resulting filtrate was collected and washed with first 0.5 N HCl (30 mL), followed by saturated $NaHCO_3$ (30 mL), and then finally water (30 mL). The organic layer was then

dried over Na_2SO_4 and the solvent was removed under vacuum. Flash column chromatography (silica gel, CH_2Cl_2) afforded the compound **1** as a light yellow liquid (3.8 g, 96%). FTIR (ATR): $\tilde{\nu}$ = 3281, 2964, 2916, 1715, 1408, 1356, 1154, 1068, 1031, 1001 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.99 (t, J = 2.4 Hz, 1H; CH), 2.18 (s, 3H; CH_3), 2.51 (td, J = 2.4, 6.8 Hz, 2H; CH_2), 2.59 (t, J = 6.6 Hz,2H; CH_2), 2.75 (t, J = 6.3 Hz, 2H; CH_2), 4.17 ppm (t, J = 6.8 Hz, 2H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 27.9, 29.7, 37.9, 62.2, 69.9, 80.0, 172.4, 206.3 ppm; LRMS (EI): m/z (%): 169.0 (100) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865; found: 168.1236.

***meso*-Alkyne-functionalized calix[4]pyrrole (3)**: Pyrrole (3 mL, 43.2 mmol) and **1** (1.82 g, 10.8 mmol) were dissolved in MeOH (50 mL) at 0°C and bubbled with argon for 10 min. Acetone (2.38 mL, 32.4 mmol) was then added to the mixture. Following this addition, methanesulfonic acid (1.97 mL) was added dropwise over the course of 10 min, while shielding the reaction vessel from light. The mixture was then stirred at 0°C for 3 h and subsequently at room temperature overnight. The yellow precipitate that formed during this time was collected by filtration. Chromatographic purification (silica gel, CH_2Cl_2/hexanes: 80/20) yielded the calixpyrrole **3** as a yellow solid (1 g, 17%). M.p. >200°C (decomp); FTIR (ATR): $\tilde{\nu}$ = 3421, 3363, 3231, 2968, 1730, 1576, 1414, 1303, 1273, 1177, 1040, 759, 705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.41–1.54 (brm, 21H; *meso*-CH_3), 1.98 (t, J = 2.5 Hz, 1H; CH), 2.15–2.19 (brm, 4H; CH_2), 2.46 (td, J = 6.7, 2.5 Hz, 2H; CH_2), 4.10 (t, J = 6.7 Hz, 2H; CH_2), 5.88 (brs, 8H; pyrrole CH), 7.03 ppm (brs, 4H; pyrrole NH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.1, 172.4, 137.8, 137.8, 137.5, 137.3, 135.2, 135.1, 103.2, 101.9, 101.9, 101.8, 79.1, 68.8, 61.0, 50.5, 50.5, 37.4, 34.2, 34.2, 34.2, 28.0, 24.9, 17.9 ppm; LRMS (ESI): m/z (%): 537.29 (100) $[M]^-$; HRMS (ESI): m/z calcd for $C_{34}H_{41}N_4O_2$ $[M]^-$: 537.3235; found: 537.4601.

***meso*-4′-Hydroxyphenyl-functionalized calix[4]pyrrole (4)**: Pyrrole (6 mL, 86.7 mmol) and 4-hydroxyacetophenone (2.95 g, 21.7 mmol) were dissolved in MeOH (250 mL) at 0°C and bubbled with argon for 10 min. Acetone (4.78 mL, 65.1 mmol) was then added to the mixture. Following this addition, methanesulfonic acid (4.22 mL) was added dropwise over the course of 10 min, while shielding the reaction vessel from light. The mixture was then stirred at 0°C for 3 h and subsequently at room temperature overnight. The white precipitate that formed during this time was collected by filtration. Chromatographic purification (silica gel, CH_2Cl_2/hexanes: 80/20, CH_2Cl_2/MeOH: 99/1) yielded the calixpyrrole **4** as a white solid (1,83 g, 16.6%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 2H; NH), 7.07 (s, 2H; NH), 6.86 (d, J = 6.85 Hz, 2H; ArH), 6.66 (d, J = 6.85 Hz, 2H; ArH), 5.89 (s, 6H; pyrrole CH), 5.65 (s, 2H; pyrrole CH), 4.74 (s, 1H; OH), 1.83 (s, 3H; CH_3), 1.54–1.49 ppm (m, 18H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.2, 139.0, 138.8, 138.7, 137.2, 128.8, 114.8, 105.9, 103.3, 103.0, 44.3, 35.5, 29.9, 28.9 ppm; LRMS (ESI): m/z (%): 507 (100) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{33}H_{38}N_4O$ $[M]^+$: 506.3046; found: 506.2641.

***meso*-4′-(Ethynyloxy)phenylcalix[4]pyrrole (5)**: A mixture of compound **4** (0.669 g, 1.32 mmol), propargyl bromide (0,294 g, 1,98 mmol), and potassium carbonate (0,365 g, 2.64 mmol) in DMF (50 mL) was reacted at 50°C for 24 h. After the reaction was complete, DMF was removed under vacuum and the resulting crude solid was dissolved in CH_2Cl_2. The solution in CH_2Cl_2 was washed with water and dried over Na_2SO_4. Chromatographic purification (silica gel, CH_2Cl_2) yielded the compound **5** as a white solid (0,650 g, 90%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.50–1.54 (brm, 18H; *meso*-CH_3), 1.84 (s, 3H; *meso*-CH_3), 2.50 (t, J = 2.5 Hz, 1H; C≡CH), 4.65 (d, J = 4.6 Hz, 2H; CH_2), 5.65 (s, 2H; pyrrole CH), 5.89 (s, 6H; pyrrole CH), 6.81 (d, J = 8.5 Hz, 2H; ArH), 6.91 (d, J = 8.5 Hz, 2H; ArH), 7.07 (brs, 2H; NH), 7.19 ppm (brs, 2H; NH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.0, 139.8, 137.6, 137.4, 137.3, 135.7, 112.9, 104.8, 101.8, 101.8, 77.7, 74.4, 74.3, 54.8, 43.0, 34.2, 28.7, 27.5 ppm; LRMS (ESI): m/z (%): 543.58 (100) $[M]^-$; HRMS (ESI): m/z calcd for $C_{36}H_{39}N_4O$ $[M]^-$: 543.3129; found: 543.5832.

Tetra-1-bromopentyltetramethylcalix[4]pyrrole (6): Pyrrole (1.74 g, 25.9 mmol) and 7-bromoheptane-2-one (5 g, 25.9 mmol) were dissolved in dry MeOH (100 mL) at 0°C and bubbled with argon for 10 min. Following this bubbling, methanesulfonic acid (1.18 mL, 18.1 mmol) was added dropwise over the course of 10 min, while shielding the reaction vessel from light. The mixture was then stirred at 0°C for 3 h and subsequently at room temperature overnight. The white precipitate was collected by filtration and washed with MeOH, yielding the calixpyrrole **6** as a white solid (4.9 g, 78.1%). FTIR (ATR): $\tilde{\nu}$ = 3420, 2932, 2857, 1574, 1501, 1414, 1247, 1193, 1037, 756, 711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.01–1.14 (brm, 8H; CH_2), 1.39–1.41 (brm, 20H; *meso*-CH_3 CH_2), 1.71–1.83 (brm, 16H; CH_2), 3.35 (brt, J = 6.75 Hz, 8H; CH_2), 5.87–5.88 (m, 8H; pyrrole CH), 6.96 ppm (brs, 4H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.0, 103.8, 40.5, 38.8, 33.7, 32.7, 28.7, 26.6, 23.6 ppm; LRMS (ESI): m/z (%): 963.05(100) $[M]^-$; HRMS (ESI): m/z calcd for $C_{44}H_{63}N_4$ $[M]^-$: 963.1792; found: 963.1583.

Tetra-1-azido-tetramethylcalix[4]pyrrole (7): **6** (200 mg, 0.2 mmol) and sodium azide (134.2 mg, 2 mmol) were dissolved in dry DMF (25 mL) at room temperature and stirred for two days. After the reaction was complete, DMF was removed under vacuum at 60°C. The resulting crude material was dissolved in CH_2Cl_2 and washed with water three times. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum, yielding the calixpyrrole **7** as a light yellow solid (166 mg, 98.4%). FTIR (ATR): $\tilde{\nu}$ = 3415, 3358, 2968, 2858, 2086, 1680, 1572, 1453, 1415, 1396, 1244, 1038, 756, 711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.09–1.53 (brm, 36H; CH_2, CH_3), 1.76–1.83 (brm, 8H; CH_2), 3.20 (t, J = 6.68 Hz, 8H CH_2), 5.86–5.87 (m, 8H; pyrrole CH), 6.98 ppm (brs, 4H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 103.8, 51.4, 40.6, 38.8, 28.9, 27.3, 26.4, 24.0 ppm; LRMS (FAB): m/z (%): 817 (100) $[M+H]^+$; HRMS (FAB): m/z calcd for $C_{44}H_{65}N_{16}$ $[M+H]^+$: 817.5573; found: 817.9816.

Pentacalix[4]pyrrole (8): In a flask, **7** (50 mg, 61 μmol) and **3** (145.05 mg, 269.25 μmol) were dissolved in THF (50 mL). A freshly prepared aqueous solution of sodium ascorbate (106.7 mg, 0.54 mmol; 0.5 mL) was added, followed by an aqueous solution of copper(II) sulfate pentahydrate (64.8 mg, 0.27 mmol; 0.5 mL). The ratio of the azide and alkyne groups was 1:4. The mixture was stirred for two days at ambient temperature. THF was removed under vacuum and the remaining crude mixture was dissolved in CH_2Cl_2 and washed with water three times. The organic layer was then dried over Na_2SO_4 and the excess of solvent was removed under vacuum. Precipitation from hexane afforded the compound **8** as a white solid (181 mg, 95%). FTIR (ATR): $\tilde{\nu}$ = 3423, 2965, 1730, 1575, 1417, 1224, 1165, 1039, 764 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39–7.03 (m, 24H; NH, CH), 5.87 (s, 40H; pyrrole-CH), 4.24 (m, 16H; N–CH_2, O–CH_2), 2.96 (t, J = 2.9 Hz, 8H; CH_2), 2.15–1.40 ppm (m, 144H; CH_3, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.8, 137.9, 137.6, 137.4, 135.2, 103.1, 101.9, 101.8, 62.2, 49.2, 37.7, 37.4, 34.2, 34.2, 28.7, 28.2, 28.1, 25.9, 25.0, 24.4, 13.1 ppm; LRMS (ESI): m/z (%): 3002 (100) $[M+H+MeOH]^+$; HRMS (ESI): m/z calcd for $C_{181}H_{237}N_{32}O_9$ $[M+H+MeOH]^+$: 3002.9066; found: 3002.7298;. elemental analysis calcd (%) for $C_{181}H_{237}N_{32}O_9$: C 72.74, H 7.87, N 15.08, O 4.31; found: C 72.13, H 8.09, N 14.71, O 4.87.

Pentacalix[4]pyrrole (9): This compound was prepared by click reaction of **7** (50 mg, 61.19 μmol) and **5** (146.7 mg, 269.25 μmol), using the same procedure used to prepare **8**. The product **9** was obtained as a white solid (169 mg, 92%). FTIR (ATR): $\tilde{\nu}$ = 3428, 2967, 2931, 1693, 1575, 1506, 1460, 1416, 1223, 1038, 766 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.64–7.54 (brm, 4H; CH), 7.24 (brs, 12H; NH), 7.11 (brs, 8H; NH), 6.89 (brd, J = 6.9 Hz, 8H; ArH), 6.83 (brt, J = 6.9 Hz, 8H; ArH), 5.88 (brs, 32H; pyrrole CH), 5.63 (brs, 8H; pyrrole CH), 5.13 (brs, 8H; CH_2), 4.26 (brt, J = 7.8 Hz, 8H; CH_2), 1.83–1.23 ppm (brm, 128H; CH_3, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.9, 138.7, 138.5, 137.5, 137.0, 128.7, 114.0, 106.0, 103.3, 103.0, 62.3, 50.5, 44.2, 35.5, 35.4, 30.2, 29.9, 28.7 ppm; LRMS (ESI): m/z (%): 3026 (100) $[M+H+MeOH]^+$; HRMS (ESI): m/z calcd for $C_{189}H_{229}N_{32}O_5$ $[M+H+MeOH]^+$: 3029.8643; found: 3029.9435; elemental analysis calcd (%) for $C_{189}H_{229}N_{32}O_5$: C 75.37, H 7.54, N 14.96, O 2.14; found: C 74.56, H 8.72, N 14.02, O 1.86.

Tricalix[4]pyrrole (10): This compound was prepared by click reaction of **3** (219.27 mg, 407 μmol) and 1,3,5-tris(azidomethyl)benzene (30 mg, 123.34 μmol), using the same procedure used to prepare **7**. The product **10** was obtained as a white solid (215 mg, 94%). FTIR (ATR): $\tilde{\nu}$ = 3424, 2967, 1729, 1577, 1419, 1226, 1166, 1040, 767 cm^{-1}; ^1H NMR (250 MHz,

$CDCl_3$): $\delta = 7.25$ (brs, 6H; CH, ArH), 7.15 (brs, 12H; NH), 5.87 (brs, 24H; pyrrole CH), 5.41 (brs, 6H; CH_2), 4.20–4.29 (brm, 6H; CH_2), 2.91–3.06 (brm, 6H; CH_2), 2.13–1.73 (brm, 12H; CH_2), 1.48–1.39 ppm (brm, 63H; CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 181.5$, 172.5, 138.0, 137.6, 137.4, 135.2, 103.1, 101.8, 101.7, 61.9, 52.1, 37.4, 34.2, 28.2, 28.0, 24.5 ppm; LRMS (ESI): *m/z* (%): 1857 (100) $[M]^-$; HRMS (ESI): *m/z* calcd for $C_{111}H_{135}N_{21}O_6$ $[M]^-$: 1857.0904; found: 1857.8914; elemental analysis calcd (%) for $C_{111}H_{135}N_{21}O_6$: C 71.70, H 7.32, N 15.82, O 5.16; found: C 71.98, H 7.04, N 16.12, O 5.48.

Tricalix[4]pyrrole (11): This compound was prepared by click reaction of **5** (221.72 mg, 407 μmol) and 1,3,5-tris(azidomethyl)benzene (30 mg, 123.34 μmol), which was prepared from 1,3,5-tris(bromomethyl)benzene, using the same procedure used to prepare **7**. The dendrimer **11** was obtained as a white solid (215 mg, 93%). FTIR (ATR): $\tilde{\nu} = 3419$, 2968, 1605, 1578, 1416, 1223, 1039, 768 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta =$ 7.56 (brs, 3H; CH), 7.25 (brs, 9H; NH, ArH), 7.13 (brs, 6H; NH), 6.92 (d, $J = 6.8$ Hz, 6H; ArH), 6.83 (d, $J = 6.8$ Hz, 6H; ArH), 5.88 (d, $J =$ 5.8 Hz, 18H; pyrrole CH), 5.62 (s, 6H; pyrrole CH), 5.46 (s, 6H; N–CH_2), 5.15 (s, 6H; O–CH_2), 1.83 (s, 9H; CH_3), 1.54–1.49 (brm, 54H; CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 137.6$, 137.5, 137.3, 135.9, 135.7, 127.5, 112.8, 104.8, 101.8, 61.1, 52.3, 43.0, 34.2, 28.7, 27.5 ppm; LRMS (ESI): *m/z* (%): 1906.95 (100) $[M + MeOH]^-$; HRMS (ESI): *m/z* calcd for $C_{118}H_{133}N_{21}O_4$ $[M + MeOH]^-$: 1907.0849; found: 1906.9502; elemental analysis calcd (%) for $C_{118}H_{133}N_{21}O_4$: C 74.85, H 6.93, N 15.67, O 2.56; found: C 74.11, H 7.28, N 15.21, O 2.98.

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