One-pot, Gram-Scale Synthesis of Calix[5]- and Calix[6]furan: Derivatization for Polyketone- and Isopyrazole-based Macrocycles with Conformational Analysis

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Dedicated to Professor Atsuhiro Osuka on the occasion of his 70th birthday.

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Abstract: A gram-scale synthesis of calix[5]- and calix[6]furan was achieved by a one-pot condensation of furan and acetone followed by stepwise separation of calix[*n*]furans (*n* = 4–6) using size-selective precipitation procedures. Calix[*n*]furans were converted to cyclic polyketones and then to ethylene-bridged cyclic isopyrazoles. The conformational analysis of the cyclic furan, polyketone, and isopyrazole macrocycles was performed based on their single crystal structures, providing important structural insights for intermolecular interactions. The scalable synthetic procedures for larger calix[*n*]furans and their derivatives would contribute to further coordination and host-guest chemistry using their cavities.

Introduction

Calixarenes and their analogues have attracted the attention of experimental and theoretical chemists for over a century due to their interest in fundamental research in supramolecular, coordination and analytical chemistry.[1] In addition, these macrocyclic compounds have contributed to the development of functional materials such as metal ion detectors, small molecule separators, and photovoltaic devices.[2] Heterocalixarenes, such as calix[*n*]pyrroles[3], calix[*n*]furans,[4] and their hybrid macrocycles[5] have also shown their unique chemistry; as a representative example, Sessler and co-workers demonstrated that calix[4]pyrrole behaves as a good anion receptor,[6] and can therefore be applied to ion exchange resins and sensors.[7] Although calix[*n*]furans have structural similarities to calix[*n*]pyrroles, they have received less attention, presumably because of the poor electron-donating characters of the oxygen atoms, which is not sufficient to form stable metal complexes. Thus, practical synthetic methods for the large-scale preparation of calix[*n*]furans, especially expanded analogues for *n* ≥ 5, have not yet been fully developed.

Recent studies have revealed that calix[*n*]furans are indispensable precursors for important macrocyclic hosts for cation or anion binding (Figure 1). Cyclic polyketones obtained by partial/full hydrolysis of the furan units of calix[*n*]furans using a *m*-chloroperbenzoic acid (*m*-CPBA)/Zn system are useful for the synthesis of calix[*n*]pyrroles and calix[*m*]furan[*n*]pyrroles which show different selectivity and affinity in anion binding.[8] More recently, our group demonstrated that cyclic deca- and dodecaketones exhibit crown ether-like alkaline metal ion binding and catalysis.[9] Despite the utility of calix[*n*]furans and related macrocycles, their continued development has been hindered by limited synthetic access to their ring-expanded analogues.

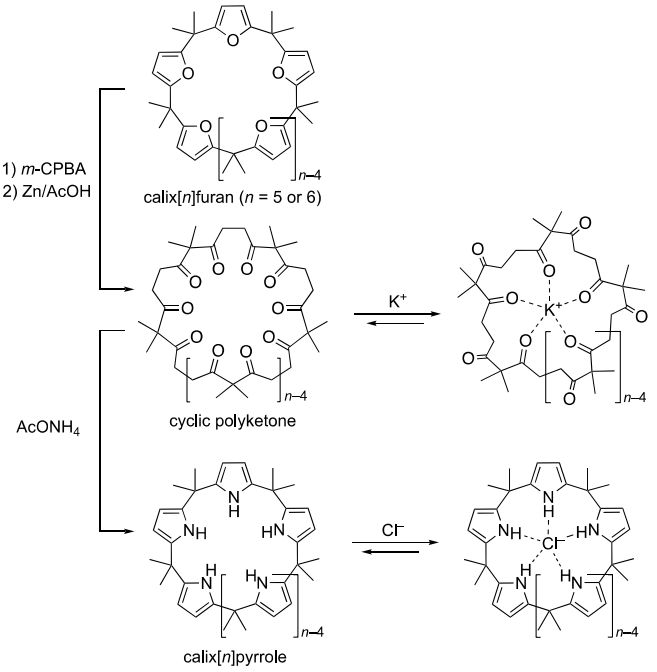


Figure 1. Synthetic derivatization of calix[*n*]furans (*n* = 5, 6) to ion binding macrocyclic hosts.

Here, we report a facile gram-scale synthesis of calix[5]- and calix[6]furan by one-pot macrocyclization and subsequent ring size-selective precipitation from a reaction mixture. While the total yield of the calix[*n*]furans (*n* = 5 or 6) is 1~3%, the present preparation protocol is inexpensive and scalable, and thus providing an easier access to their polyketone and isopyrazole derivatives. Although several papers have partially and separately

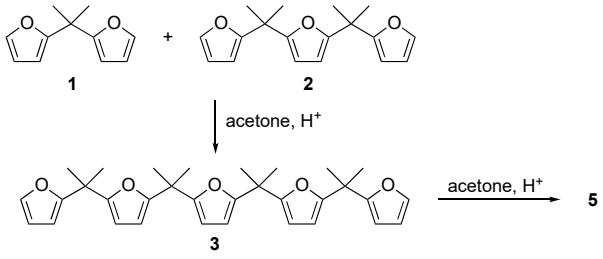
reported on related macrocycles, namely calix[*n*]furans, cyclic polyketones and isopyrazole-based cyclophanes,[10] we conducted head-to-head structural comparison for *n* = 4~12 based on their single crystal X-ray structures to provide fundamental insights for host–guest chemistry.

Results and Discussion

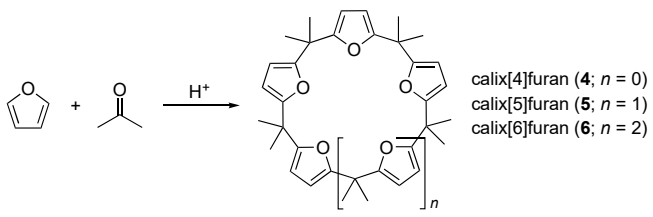
There are two major synthetic routes to access extended calix[*n*]furan macrocycles: (1) ring size-selective synthesis using oligofuran precursors, and (2) one-pot macrocyclization of furan monomer. The first synthesis of calix[5]furan was reported by Kobuke and co-workers in 1976 using method (1).[11] Method (1) has the advantage of ring-size selectivity, which facilitates the isolation of the target calix[*n*]furans, whereas the preparation of the oligofuran precursors requires a multi-step synthesis. Kobuke's group initially synthesized di- and trifuran components **1** and **2** by condensation between furan with acetone, and these components were then coupled to form a linear precursor **3**. While target calix[5]furan (**5**) was obtained in 45% yield from **3**, the total yield of **5** from commercially available furan was only 3.0% after 3 steps, and the entire reaction process took approximately 7 days (Scheme 1a).

Method (2) can be carried out through a one-pot synthesis on a multi-gram scale, although yields and selectivity of expanded analogues are typically lower than those for calix[4]furan. The biggest problem in method (2) is the separation of target expanded macrocycles from a large quantity of calix[4]furan (**4**). Conventional separation techniques, such as repeated silica gel column chromatography or recycling gel permeation chromatography, are time-consuming and ineffective, because **5** and **6** have similar R_f or retention times to those for **4**. We thus investigated a scalable extraction protocol for minor products **5** and **6** using selective precipitation techniques from the reaction mixture of the one-pot synthesis.

a) ***Oligofurane approach***



b) ***One-pot macrocyclization***



Scheme 1. Synthetic approaches to calix[5]furan: a) size-selective synthesize using oligofuran precursors, and b) direct macrocyclization of furan monomer.

When a one-pot condensation reaction (Scheme 1b) was performed between furan and acetone at 1.4 and 8.3 M concentrations using hydrochloric acid, inhomogeneous system appeared; the reaction mixture was composed of viscous dark colored solution and considerable amount of precipitate (Figure S1). ^{1}H NMR analysis (Figure S2) indicated that the reaction mixture contained calix[4]furan (**4**), calix[5]furan (**5**), and calix[6]furan (**6**) in a ratio of approximately 21:1.2:1. Although **4** was always the major macrocyclic product under the various concentrations of substrates we attempted, the above conditions resulted in slightly better selectivity of **5** over **4** and **6**. It was found that the major component **4** can be precipitated directly from the reaction solution by adding water and diethyl ether, resulting in **Mixture 1** as shown in Figure 2. Approximately 19 g of crude **4** was obtained from a one-pot reaction on a 40 g scale reaction for furan. Although **Mixture 1** contained various products, including **5**, **6**, and other polymeric materials, as well as remaining **4**, it was essential to reduce the amount of **4** for further purification.

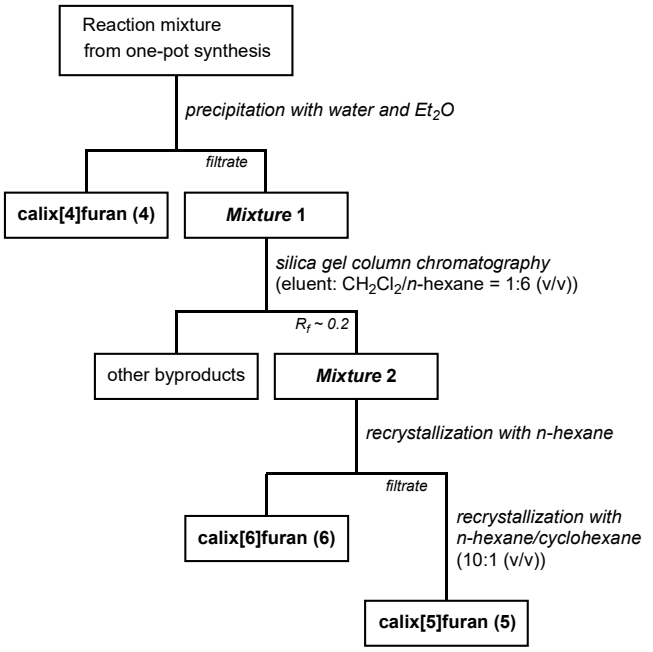
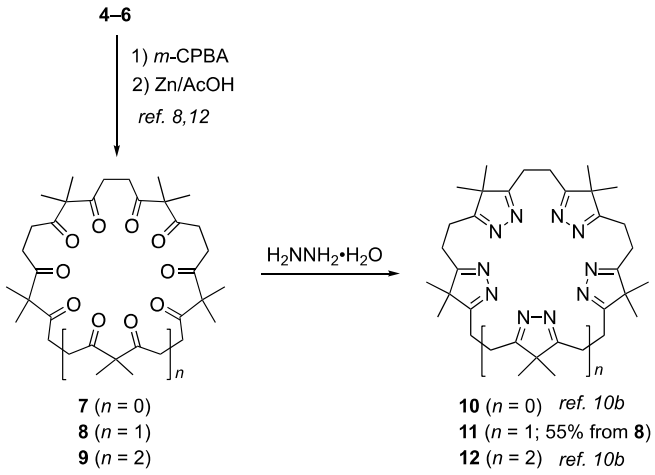


Figure 2. Purification procedure of Calix[*n*]furans (*n* = 4, 5, and 6) from one-pot synthesis.

Mixture 1 (*ca.* 40 g) was further chromatographed twice on silica gel using a CH_2Cl_2/*n*-hexane (1:3 and 1:6 (v/v)) mixture as eluent to obtain **Mixture 2** with an R_f of ~0.2 (CH_2Cl_2/hexane =1:6 (v/v)) , which contained **5** and **6**. Recrystallization with **Mixture 2** from *n*-hexane resulted in the precipitation of **6** (1.8 g, 2.8% yield) as a colorless crystalline solid, while **5** (1.7 g) remained in the filtrate was collected by recrystallization with cyclohexane. Analytically pure **5** was also obtained by further recrystallization using a *n*-hexane/cyclohexane (10:1 (v/v)) mixture in 1.4% yield. Although the total yields for **5** and **6** were slightly less than those obtained with the oligofuran method (1), our procedure can produce gram scale quantities of expanded calix[*n*]furans **5** and **6** within one or two days from furan.

With enough calix[*n*]furans in hand, we conducted the derivatization of **4**–**6** to produce polyketone and isopyrazole macrocycles **7**–**9** and **10**–**12** (Scheme 2), respectively, for analysis of their size dependence on the conformations. Polyketone macrocycles **7**–**9** were synthesized via oxidative furan ring cleavage using *m*-CPBA and subsequent reduction with zinc according to the reported procedure.[8,12] Although pentameric isopyrazole macrocycle **11** has not been previously reported, it was obtained in 55% yield using the synthetic procedure for **10** and **12** reported by Williams and co-workers.[10b] For the conformational analysis, single crystal X-ray structures of **7** and **11** [13] were newly measured, while crystallographic data for other macrocycles were obtained from Cambridge Crystallographic Data Center (Figure 3).[14]



Scheme 2. Derivatization of calix[*n*]furans **4**–**6** to cyclic polyketone **7**–**9** and isopyrazole-containing macrocycles **10**–**12**.

In the crystalline state, calix[4]furan **4** adopted a 1,3-alternate conformation, which is known as the most stable conformation for the corresponding calix[4]pyrrole.[15] Macrocycle **4** consisted of two pairs of furan rings arranged almost parallel, forming a square cavity with an O(1)–O(3) distance of 4.81 Å. Furan units in calix[5]furan **5** were oriented in disparate directions, forming a non-symmetric conformation. The inner cavity of **5** was almost occupied by a furan ring which was placed parallel to the macrocyclic plane. In the case of calix[6]furan **6**, four of the six furan rings were perpendicular to the macrocyclic plane, while the other two are in parallel. The inner cavity of **6** was also mostly occupied by a furan unit, similar to **5**. Although the solid-state conformations of calix[*n*]furans **4**–**6** were observed to be less symmetrical, aromatic protons for each macrocycle were observed as singlets in the ^{1}H NMR spectra, indicating rapid conformational changes on the NMR time scale.

Polyketone macrocycles **7**–**9** are structurally more flexible than **4**–**6**, and have polar carbonyl groups that can change solid state conformations through inter/intramolecular hydrogen bonding. Octaketone **7** exhibited an S_4-symmetric conformation, with four of the eight carbonyl oxygen atoms facing inward and the others facing outward. All the ethylene units in **7** adopted a gauche conformation. Decaketone **8** exhibited a crumpled conformation in which four of the five ethylene bridges adopted gauche conformations, while the other one was observed as anti-periplanar. Presumably due to the internal hydrogen bonds, macrocycles **7** and **8** did not show any obvious cavity in the solid state. Single crystals of **9**, obtained by recrystallization from dichloromethane, showed a roughly hexagonal conformation with all the ethylene units in gauche conformations. Two dichloromethane molecules were trapped inside the cavity by CH•••O hydrogen bonding interactions. As previously discussed for **8** and **8**•K$^+$ complex,[9] polyketone macrocycles change their conformations upon guest inclusion in an adaptive manner, switching favourable conformations of the ethylene bridges.

Isopyrazole macrocycles **10**–**12** showed polygonal-shaped conformations in which flexible ethylene and rigid isopyrazole units behaved as the bending and planar subunits, respectively. Macrocycle **10** adopted a 1,3-alternate-like conformation, resulting in a square cavity, similar to **4**. The ethylene units in **10** took gauche conformations with dihedral angles of 64–70°. A water molecule was bounded to an isopyrazole unit through an OH•••N hydrogen bond. Macrocycle **11** showed a pentagonal structure with all ethylene units in gauche conformations (dihedral angles: 70-86°). Ethyl acetate was trapped in the cavity by CH•••π interactions, while it was disordered with dichloromethane with occupancies of 61% and 39%, respectively. Macrocycle **12** had a rectangular structure in which four of the six ethylene units were in gauche conformations (dihedral angles: 66–86°) and the other two were in antiperiplanar conformations (torsion angles: 166°). A toluene molecule was trapped in the cavity of **12** through CH(toluene)•••π(isopyrazole) interactions. Two water molecules were also found around the macrocycle **12**, indicating hydrogen-bonding interactions at the nitrogen atoms in a similar fashion to **10**.

The comparison of the solid-state structure of **4**–**12** provided important insights into the host-guest interactions of these macrocycles. While calix[*n*]furans **4**–**6** did not show any significant intermolecular interactions, carbonyl groups in **7**–**9** and iminic nitrogen atoms in **10**–**12** were found to be effective interaction sites for binding guest molecules. Furthermore, isopyrazole-based macrocycles **10**–**12**, which are structurally less flexible than polyketones **7**–**9**, were advantageous in forming well-defined cavities that might be suitable for size-selective binding of guest molecules and metal coordination.[10b]

Conclusion

In conclusion, we achieved a gram-scale synthesis of calix[*n*]furans (*n* = 5, 6) by improving the product isolation process in the one-pot macrocyclization method using ring-size selective precipitation techniques. Although the total yields of the ring-expanded analogues **5** and **6** were low, the present one-pot method enables quicker access to them than previous synthetic methods using oligofuran precursors. Sufficient amount of calix[5]furan **5** allowed derivatization into novel isopyrazole macrocycle **11** via cyclic decaketone **8**. Extensive conformational analysis was conducted using crystal structures of macrocycles **4**–**12**, providing important insights into the host–guest chemistry using them. Although calix[5]- and calix[6]furans have not received much attention, their easy preparation method and synthetic utility suggest potential for further research on the host-guest chemistry using related macrocycles.

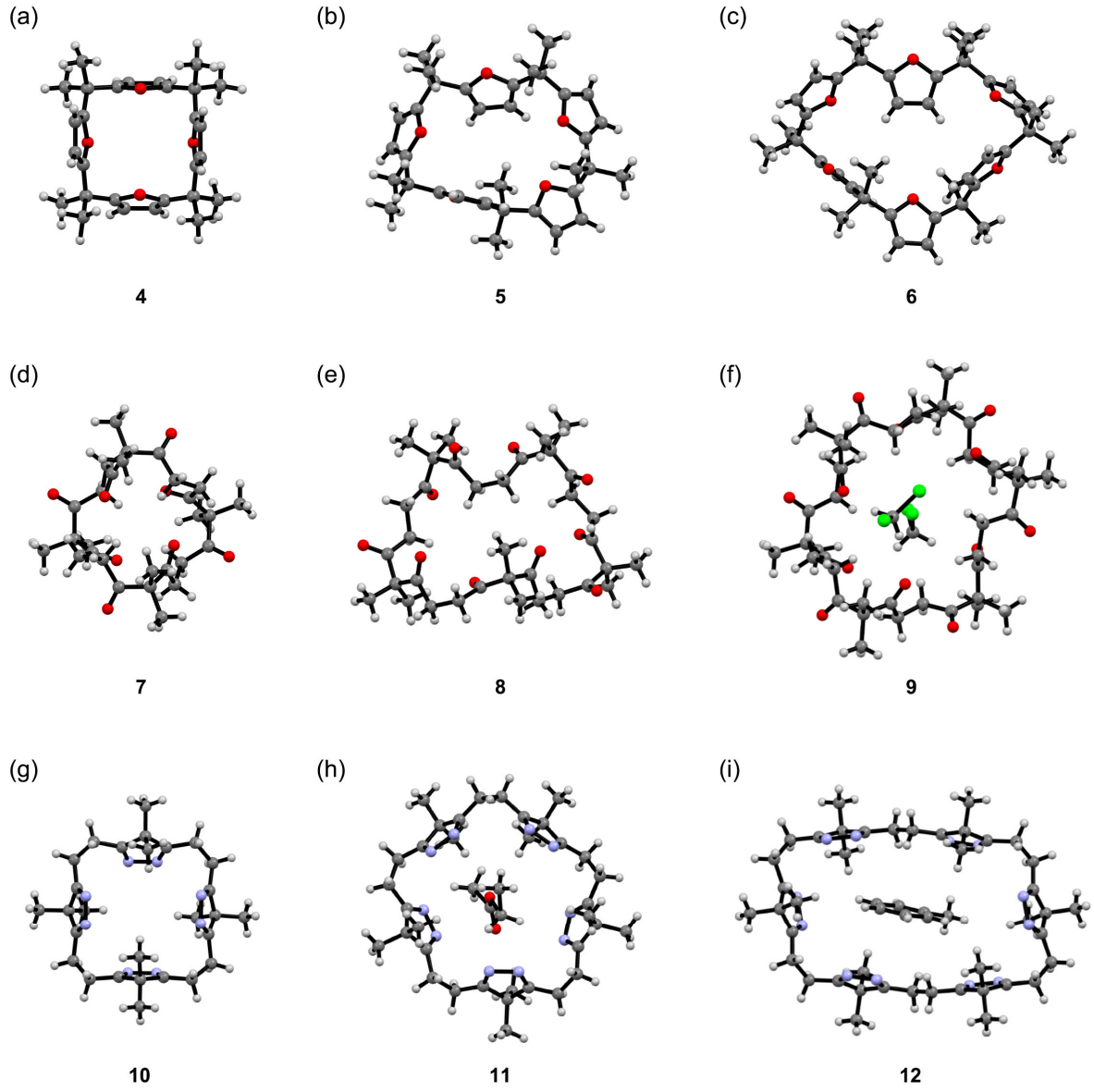


Figure 3. Crystal structures of (a) **4**, (b) **5**, (c) **6**, (d) **7**, (e) **8**, (f) **9**, (g) **10**, (h) **11**, and (i) **12**. Solvent molecules found in the macrocyclic cavity are also shown (In case the guests are disordered, only the major part is shown).

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

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Keywords: Calix[5]furan• Cyclic dekaketone• Isopyrazole• one-step synthesis• Fractional recrystallization

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[13] Crystal data for **7**: Single crystals for X-ray analysis were grown by vapor diffusion of hexane into dichloromethane solution. $C_{28}H_{40}O_8$, M = 504.60, crystal size: 0.36 × 0.19 × 0.17 mm^3, Tetragonal, space group $P4_2/n$, a = b = 12.5770(5) Å, c = 8.4417(5) Å, V = 1335.32(13) Å^3, Z = 2, T = 123(2) K, μ = 0.091 mm^{-1}, D_{calc} = 1.255 g/cm^3, 2.290º ≤ θ ≤ 25.989º, 1084 unique reflections out of 1315 with $I > 2\sigma(I)$, GOF = 1.066, R_1 = 0.0510 and wR_2 = 0.1481 for all data.

Crystal data for **11**: Single crystals for X-ray analysis were grown by vapor diffusion of ethyl acetate into dichloromethane solution. [$(C_{35}H_{50}N_{10})$•0.613$(C_4H_8O_2)$•0.387$(C_2H_2Cl_2)$], M = 697.72, crystal size: 0.30 × 0.25 × 0.05 mm^3, Monoclinic, space group $P2_1/n$, a = 14.82750(10) Å, b = 15.18790(10) Å, c = 18.23030(10) Å, β = 108.7650(10)º, V = 3887.22(5) Å^3, Z = 4, T = 123(2) K, μ = 1.067 mm^{-1}, D_{calc} = 1.192 g/cm^3, 3.359º ≤ θ ≤ 76.365º, 7902 unique reflections out of 7318 with $I > 2\sigma(I)$, GOF = 1.024, R_1 = 0.0631 and wR_2 = 0.1713 for all data. Deposition numbers <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/ajoc.202400023">2325244 (for **7**) and 2311447 (for **11**) </url> contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

[14] Crystal data numbers used in Figure 3: CCDC-1192062 (for **4**), -2080609 (for **5**), -1270031 (for **6**), -2141342 (for **8**), -2141344 (for **9**), -214699 (for **10**), and -214700 (for **12**).

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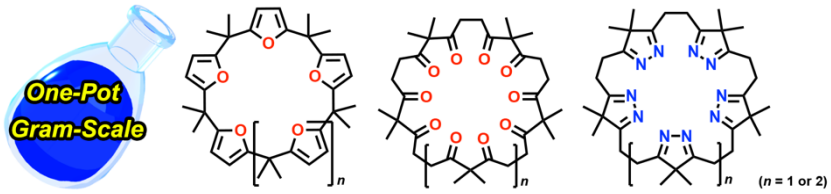

Gram-scale synthesis of calix[5]- and calix[6]furan was achieved through a one-pot process by improving the isolation process of the reaction mixture using size-selective precipitation techniques. The obtained calix[*n*]furans were transformed into cyclic polyketones and isopyrazole-containing macrocycles. Insights into host-guest interactions were obtained through systematic conformational analysis using single crystal structures.