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Ketocalixarenes: Versatile yet still Unexplored Macrocycles

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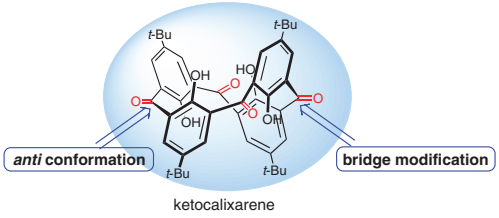
This paper is dedicated to the memory of our collaborator and friend Dr. Norbert Itzhak



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Abstract Ketocalix[*n*]arenes can be prepared via oxidation of the methylene groups of protected calix[*n*]arenes. The presence of carbonyl groups at the bridges alters the preferred conformation and reactivity of the macrocycle and provides an entry point (via nucleophilic additions reactions) to a wide array of methylene-substituted derivatives as well as calix[*n*]radialenes.

Key words macrocycles, calixarenes, cyclophanes, nucleophilic substitution, stereochemistry

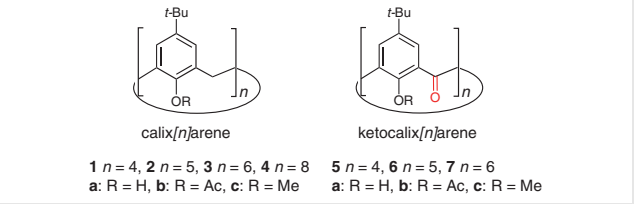


Figure 1 Structures **1**–**7**

nate, and *1,3-alternate* (Figure 2).[1f] These conformations arise from the possible different relative orientations of the rings ('up' or 'down') relative to the mean macrocyclic plane.

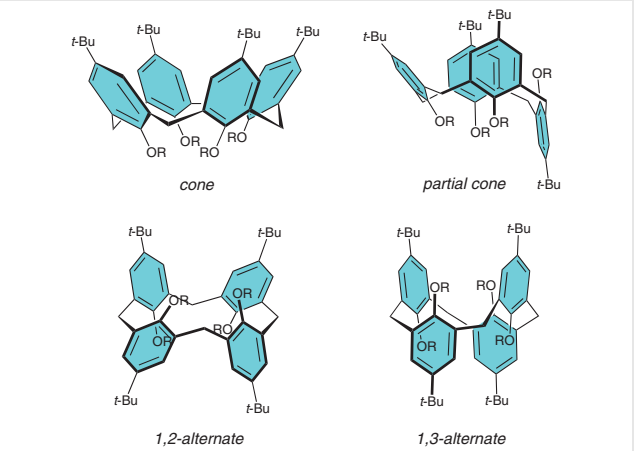


Figure 2 The four conformations of the calix[4]arene scaffold

1 Introduction

The 'classical' calix[*n*]arenes are synthetic macrocycles consisting of a cyclic array of *n* phenolic rings interconnected by bridging methylene groups (e.g.,**1a**–**4a**, Figure 1).[1]

The conformation of the parent *p-tert*-butylcalix[4]arene **1a** and its derivatives is usually discussed in terms of four conformations: *cone*, *partial-cone*, *1,2-alter-*

The parent system (i.e., with unprotected OH bonds, **1a**) adopts a *cone* conformation stabilized by a circular array of hydrogen bonds. In this arrangement, each hydroxyl serves both as donor and acceptor of hydrogen bonds.[2] The sense of direction of the hydrogen bonds ('clockwise' or 'counterclockwise') renders the macrocycle chiral. Reversal of the sense of direction results in enantiomerization of the molecule (Figure 3). This barrier was determined in **1a** by mea-

surement of the transverse ^{13}C nuclear spin relaxation[3] and by a dynamic NMR experiment[4] affording values of $\Delta G^{\ddagger}$ = 10.7 kcal mol^{-1} (at 221 K) and $\Delta G^{\ddagger}$ = 10.5 kcal mol^{-1} (at 204 K), respectively.

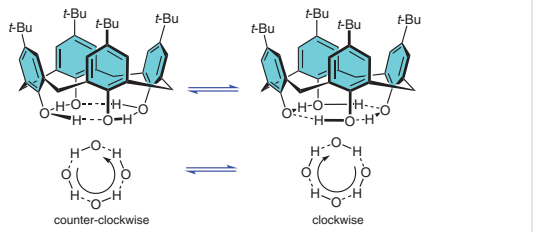


Figure 3 Reversal of the sense of direction of the circular array of hydrogen bonds in **1a**

An additional dynamic process involves rotation around the CH_2–aryl bonds and passage of the OH groups through the central cavity of the macrocycle (sometimes referred as 'rotation through the annulus' or 'ring inversion', Figure 4). This process can be followed by dynamic NMR since the ring inversion mutually exchanges the equatorial and axial methylene protons. For the parent **1a**, the barrier in $CDCl_3$ is 15.7 kcal mol^{-1}.[5]

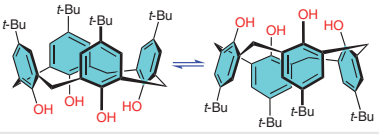


Figure 4 Ring inversion (*cone*-to-*cone*) of *p*-*tert*-butylcalix[4]arene **1a**; the OH groups pass through the macrocyclic cavity

Calixarene derivatives where the bridging methylene groups have been replaced by carbonyl groups can be dubbed 'ketocalixarenes'.[6,7] In contrast to the parent systems, the chemistry of the ketocalixarenes has been relatively unexplored. The ketocalixarenes differ in several significant ways from the parent compounds: (i) in contrast to a methylene bridging group, a carbonyl group may be conjugated to the geminal aryl rings. This feature can be recognized by naked eye: whereas the classical calixarenes are colorless, ketocalixarenes **5a**–**7a** possess a faint yellow color, which intensifies upon deprotonation of the OH groups. (ii) The carbonyl groups are hydrogen-bond-accepting groups and in principle may disrupt the circular array of hydrogen bonds. (iii) The Ar–CO–Ar bond angle is larger than in the parent systems due to the sp^2 hybridization of the carbonyl carbon, and this feature may affect the conformational preferences. (iv) The electron-withdrawing properties of the conjugated carbonyl groups may modify the reactivity of the aromatic rings and allow aromatic nucleophilic substitution reactions which are not observed in the phenolic rings of the parent system. (v) The carbonyl groups may undergo nucleophilic addition reaction, thus providing an entry into a wide range of methylene-substituted calixarenes and expanding the chemical diversity of the calix scaffold.[8] In this article we will review the synthesis, conformation, and reactions of the ketocalixarenes.[9]

2 Synthesis of Ketocalix[*n*]arenes

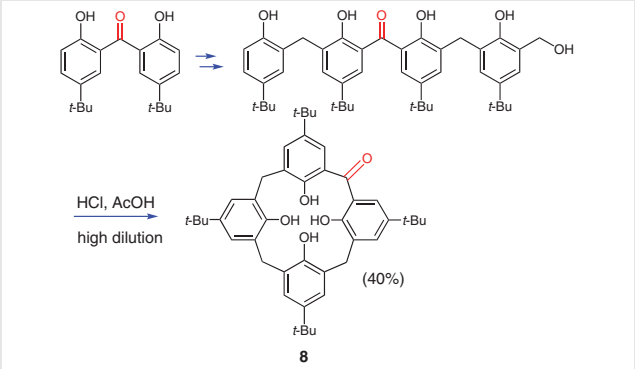
2.1 Ketocalix[4]arene Derivatives

In principle, ketocalix[*n*]arenes may be obtained by direct oxidation of the methylene groups of the calix[*n*]arene scaffold. However, this approach requires protecting the phenolic groups (usually as their acetate or methyl ether derivatives) since reaction of unprotected calixarenes with oxidation reagents results in the oxidation of the phenolic rings (e.g., yielding calixspirodienone,[10] 5,5′-bicalix[*n*]arenes,[11] or calixquinone[12] derivatives). In a pioneering study, Ninagawa and co-workers reported in 1985 the first calixarenes possessing a carbonyl bridge using a reaction sequence involving protection of the phenolic rings by acetylation, CrO_3 oxidation of the methylene groups at 45 °C, and basic hydrolysis of the acetate groups. Calix[4]- and calix[6]arenes yielded their monooxo derivative while calix[8]arene yielded a trioxo derivative.[13] Monooxoketocalix[4]arene **8** was later prepared by Sone and co-workers by a multistep route involving synthesis of a linear oligomer possessing a single carbonyl followed by macrocyclization using high dilution conditions (Scheme 1).[14] The same route was successfully applied also for the synthesis of the monooxoketocalix[5]arene and monooxoketocalix[6]arene.[14]

Biographical Sketches

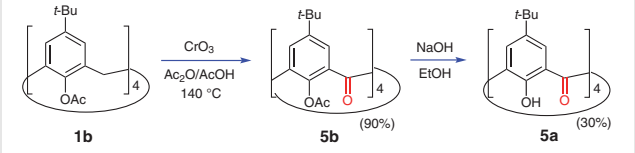
Ori Shalev completed his PhD studies at the Hebrew University under the supervision of Prof. Silvio Biali. After postdoctoral work with Prof. Yoram Cohen at Tel-Aviv University, he joined the core facility at the Faculty of Medicine, where he is currently the head of the Metabolomics Center.

Silvio Biali completed his PhD thesis under the supervision of Prof. Zvi Rappoport at The Hebrew University and spent two years of postdoctoral work in the group of Prof. Kurt Mislow (Princeton University). He joined the faculty of The Hebrew University in 1987.



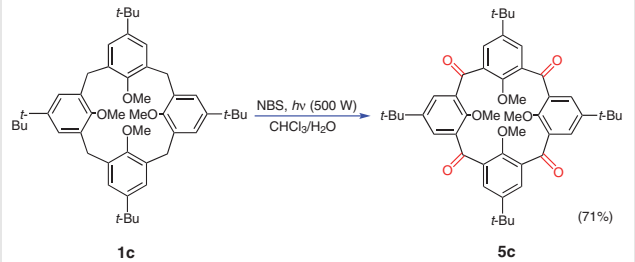
Scheme 1 Preparation of the monooxoketocalix[4]arene **8** by a stepwise procedure[14]

Tetraoxoketocalix[4]arene **5a** was first reported by Görmar and co-workers in 1990.[15] The preparation utilized the same three-step strategy introduced by Ninagawa and coworkers but utilized a higher temperature (140 °C) in the crucial CrO_3 oxidation step, resulting in the oxidation of all the methylene bridges (Scheme 2). In 1995 Iwamura and co-workers reported the oxidation ($Na_2Cr_2O_7$/AcOH) of a dehydroxylated calix[6]arene to yield the corresponding OH-depleted hexaoxoketocalix[6]arene.[16]



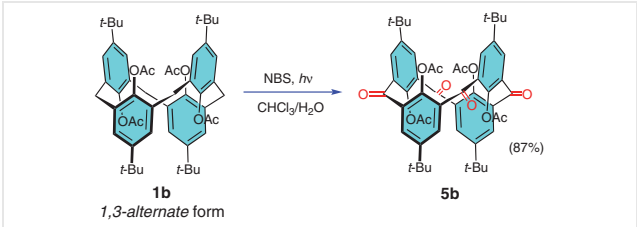
Scheme 2 Preparation of tetraoxoketocalixarene **5a**[15]

A photochemical one-step oxidation of all the methylene groups of the *p-tert*-butylcalix[4]arene derivative **1c** was reported by Fischer et al.[17] The reaction involved the use of excess NBS, UV irradiation (500 W lamp), and a mixture of $CHCl_3$ and water as solvent (Scheme 3). Presumably, the reaction involves radical bromination of the methylene bridges followed by hydrolysis at their dibromomethylene stage.



Scheme 3 One-step oxidation of all the methylene groups of the *p-tert*-butylcalix[4]arene derivative **1c**[17]

In a related development, in 2014 Xiong and co-workers reported the NBS-mediated oxidation of the methylene groups of diarylmethane derivatives to the corresponding benzophenones using in a $CHCl_3$/water mixture and natural light as the irradiation source.[18] The optimized reaction conditions utilized 1 mmol of substrate and 5 mmol of water. Labeling experiments indicated that the oxygen atoms at the carbonyl functionalities originated from the water molecules and not from the atmospheric oxygen gas. The photochemical approach was also applied for the oxidation of *p-tert*-butylcalixarene tetraacetate **1b**. Oxidation of the *1,3-alternate* form of **1b** (see below) was conducted with NBS in a $CHCl_3$/water mixture (Scheme 4) while irradiating with a common 100 W spot lamp, yielding the ketocalixarene **5b**. Although HBr is formed during the reaction, no cleavage of the acetate groups took place under the reaction conditions.[19]



Scheme 4 Oxidation of the *1,3-alternate* form of **1b**

In contrast to **1a** and **1c**, in the tetraacetate derivative **1b** the four forms depicted in Figure 2 possess a substantial barrier to mutual interconversion[20] (since an acetate is bulkier than a hydroxy or methoxy group) and can be separated by fractional crystallization.[21] The product of the acid-catalyzed acetylation of **1a** is a mixture of isomers of **1b**.[21] A reinvestigation of the CrO_3 oxidation of **1b** revealed an unexpected feature: methylene groups located between pairs of rings in an '*anti*' disposition were found to be oxidized faster than those between rings in a *syn* arrangement (Figure 5).

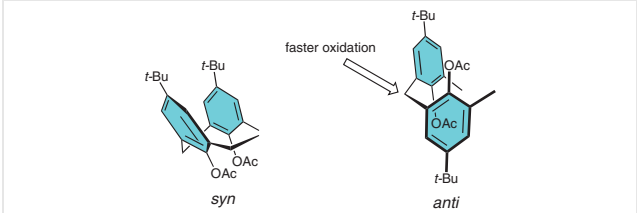
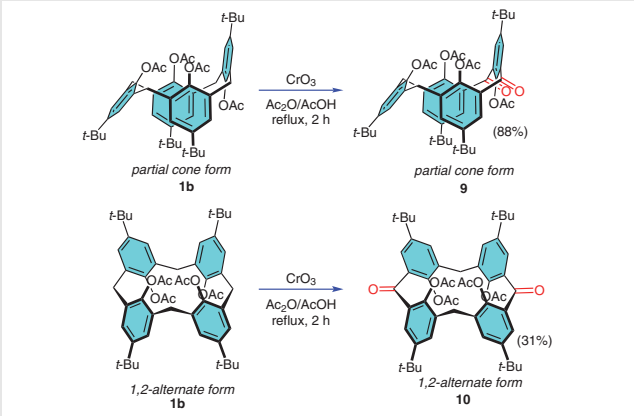


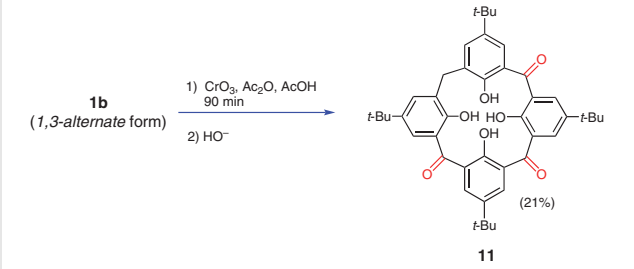
Figure 5 *Syn* and *anti* arrangements of a pair of geminal rings. Methylene groups in-between a pair of rings oriented *anti* are oxidized faster.

Thus, whereas oxidation of the *1,3-alternate* isomer of **1b** afforded the tetraoxo derivative **5b**, oxidation of the *partial cone* and *1,2-alternate* forms of **1b** afforded dioxo derivatives with the pair of carbonyls at adjacent or opposite bridges, respectively (Scheme 5).[22]



Scheme 5 CrO_3 oxidation of different forms of tetraacetoxycalix[4]arene **1b** proceeds with different regioselectivity. Under the reaction conditions, only methylene groups located between a pair of rings oriented *anti* are oxidized.

The *1,3-alternate* form of **1b** is the atropisomer where all methylenes can be readily oxidized since all groups are located between pairs of *anti*-geminal rings. Optimizing the reaction time and the amount of CrO_3 afforded a 3:1 mixture of trioxo- and tetraoxoketocalixarene derivatives. After hydrolysis of the acetate groups, the two ketocalixarenes were separated by trituration with EtOH. Basic hydrolysis of the acetate groups yielded the tetrahydroxy trioxocalix[4]arene **11** (Scheme 6).[23]



Scheme 6 Preparation of tetrahydroxytrioxocalix[4]arene **11**

2.2 Systems Possessing both Carbonyl and Bromomethane Bridges

Bromination of **1c** with 6.3 equivalents of NBS yielded two derivatives possessing dibromomethylene and bromomethylene groups located at either distal or proximal positions. Hydrolysis of the dibromomethylene groups afforded calix[4]arenes **12a** and **13a** having two carbonyls and two bromomethylene bridges (Figure 6).[24] The bromomethylene groups undergo reactions with nucleophiles (e.g., alcohols, N_3^-, acetic acid) under S_N1 conditions affording ketocalixarenes functionalized at two methylene bridges. Calix[4]arene **13a** was also used as an alkylating agent of aromatic rings in solvolytic Friedel–Crafts reactions to afford dioxocalixarene derivatives substituted at two methylene bridges by aryl groups (**13c** and **13d**).[24]

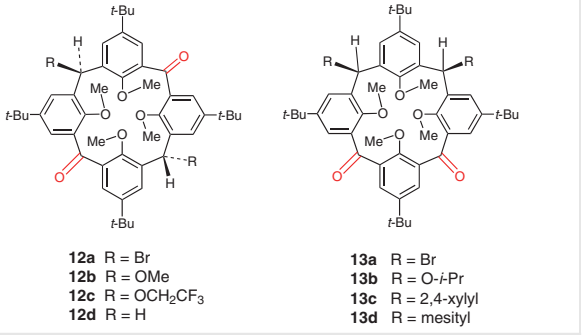
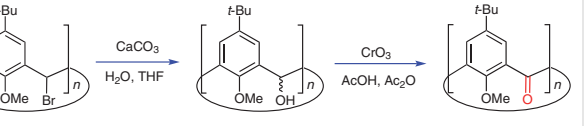


Figure 6 Structures **12** and **13**

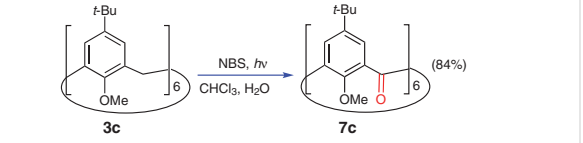
2.3 Pentaoxoketocalix[5]arene and Hexaoxoketocalix[6]arene Derivatives

The pentamethylether of ketocalix[5]arene (**6c**) was synthesized from **2c** by a reaction sequence involving photochemical monobromination of all the bridges (yielding the pentabromo derivative **14a**) followed by hydrolysis (H_2O, $CaCO_3$/THF) of the bromomethylene groups. The last step yielded an isomeric mixture of the pentahydroxycalix[5]arene derivative **15a**. This mixture of isomers was used as starting material for the oxidation reaction with CrO_3 yielding the pentaoxoketocalix[5]arene **6c**.[25] An analogous reaction sequence was utilized for the preparation of the larger analogue **7c** (Scheme 7).



Scheme 7 Preparation of polyoxoketocalix[*n*]arenes (*n* = 5,6) via hydrolysis of bromocalixarenes followed by CrO_3 oxidation of the hydroxyl groups[25]

Later on, hexaoxoketocalix[6]arene **7c** was prepared by reaction of **3c** with NBS in a $CHCl_3$/water mixture (Scheme 8). Since **7c** undergoes O–Me cleavage under the reaction conditions (presumably by the nascent HBr generated in the reaction), prolonged reaction times were avoided.[26]

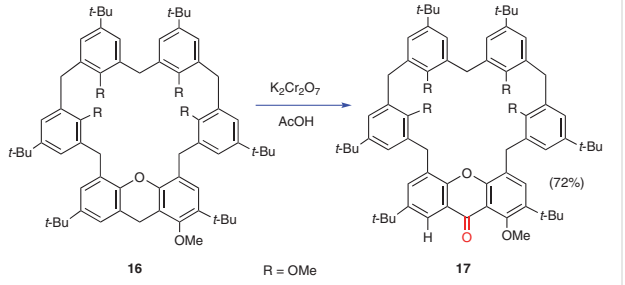


Scheme 8 Preparation of hexaoxoketocalix[6]arene **7c**

Hexahydroxy hexaoxoketocalix[6]arene (**7a**) was prepared by CrO_3 oxidation of the methylene bridges of the hexaacetate derivative of *p-tert*-butylcalix[6]arene **3b**, followed by basic hydrolysis of the acetoxy groups.[27]

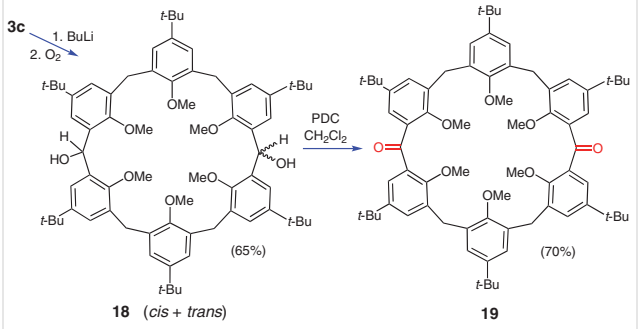
2.4 Monooxo- and Dioxoketocalix[6]arenes

A monoxoketocalix[6]arene derivative was obtained by oxidation of the xanthenocalix[6]arene with $K_2Cr_2O_7$/AcOH. Only the xanthene methylene group was selectively oxidized to a carbonyl group under the reaction conditions (Scheme 9).[28]



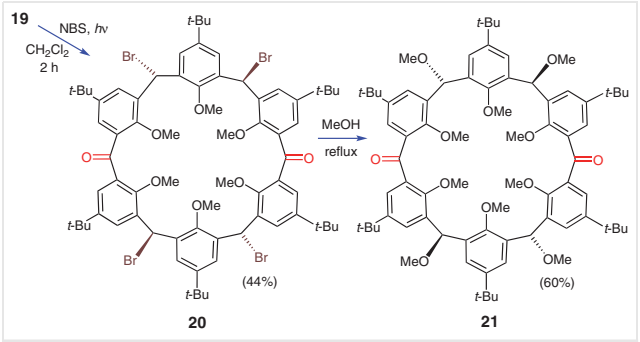
Scheme 9 Oxidation of a xanthenocalix[6]arene

Reaction of the calix[6]arene **3c** with ten equivalents of *n*-BuLi at rt, followed by reaction with oxygen gas, resulted in a 2:1 mixture of the *trans* and *cis* isomers of a derivative with a pair of opposite bridges hydroxylated (**18**).[29] Oxidation of the mixture with PDC afforded the dioxoketocalix[6]arene **19** (Scheme 10).[30]



Scheme 10 Preparation of dioxoketocalix[6]arene **19** via lithiation/oxygenation of **3c** followed by oxidation of the ensuing hydroxyl groups[29,30]

Dioxoketocalix[6]arene **19** was functionalized at the methylene bridges. A tetrabromo dioxoketocalix[6]arene was prepared by reaction of **19** with 4.1 equivalents of NBS. The main product was the chiral isomer **20** with an *all-trans* disposition of the bromomethylene bridges. Reaction of **20** with methanol proceeded in stereoselective fashion affording the *all-trans* substitution product **21** (Scheme 11).[31]



Scheme 11 Functionalization of the methylene bridges of dioxocalix[6]arene **19**[31]

3 Conformation of Ketocalixarenes

The determination of the preferred conformation and the barrier of the rotation through the annulus was more challenging for **5a** than for the parent **1a**, due to the absence of methylene protons and the high symmetry of the preferred conformation. The low-temperature NMR data indicated a highly symmetric conformation consistent with either a *cone* or a *1,3-alternate* conformation. A distinction between the two alternatives was achieved by ^{13}C NMR spectroscopy in the presence of the chiral solvating agent. In the *cone* conformation the four carbonyl groups are homotopic (Figure 7). These carbonyl groups should be undistinguishable in both achiral and chiral environments. On the other hand, in a *1,3-alternate* conformation, pairs of carbonyl groups attached to a given ring are enantiotopic and may display separate signals in a chiral nonracemic media (Figure 7). The low-temperature ^{13}C NMR spectrum of **5a** in the presence of a chiral solvating agent (*R*)-(–)-α-(trifluoromethyl)benzyl alcohol displayed two carbonyl signals, in agreement with the presence of the *1,3-alternate* conformation. Dynamic NMR study of the mutual exchange between the two carbonyl signals afforded a rotational barrier of 15.2 kcal mol^{-1} for the ring-inversion process. [32]

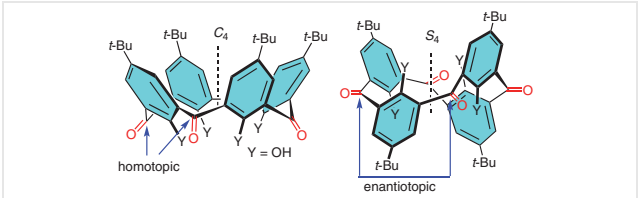


Figure 7 Left: the four carbonyl groups in the *cone* conformation of **5a** are homotopic since they are related by the C_4-symmetry axis. Right: pairs of carbonyls attached to the same ring are enantiotopic in the *1,3-alternate* conformation and are distinguishable in the presence of a chiral solvating agent.

A crystal-structure analysis of **5a** that crystalized with the chiral solvating agent indicated that the macrocycle adopts a *1,3-alternate* conformation (Figure 8).[32,33] The four

carbonyls are nearly coplanar to the mean macrocyclic plane and are pointing outside the cavity. No intramolecular hydrogen bonding was observed between the OH and carbonyl groups.

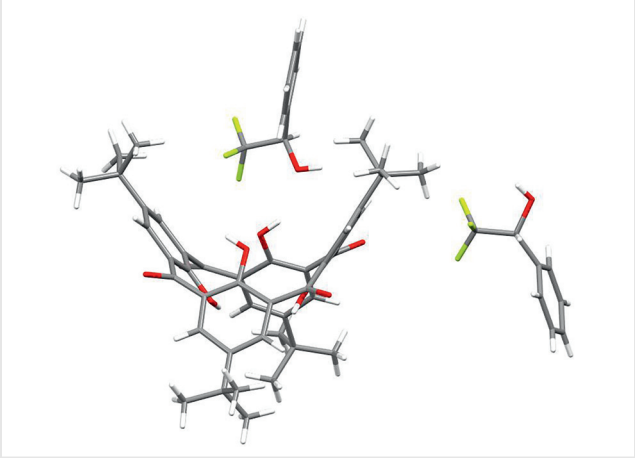


Figure 8 Crystal structure of **5a**. In contrast to the parent **1a** that exists in a *cone* conformation, **5a** assumes a *1,3-alternate* conformation.

X-ray analysis indicated that the trioxocalix[4]arene **11** adopts in the crystal a *1,2-alternate* conformation. Similarly to **5a**, no intermolecular hydrogen bond was observed between the hydroxyls and the carbonyls group.[23]

The tetramethoxy ether **5c** adopts a *1,3-alternate* conformation to the crystal, and MMFF94 calculations indicated that this conformation is 17.3 kcal mol^{-1} lower in energy than the *cone* conformation.[17] In the crystal structures of the methyl ethers of the dioxoketocalix[4]arenes **12a–d**, and **13b–d** it was found that pairs of geminal rings connected to a given carbonyl adopt an *anti* conformation.[24]

4 Reactions of Ketocalixarenes

4.1 Alkylation of the OH Groups

Alkylation of the OH groups of ketocalix[4]arene **5a** can be readily performed by reaction with the alkylating agent in the presence of K_2CO_3 as base. By modifying the reaction conditions, mono-, di-, tri-, and tetramethyl ether derivatives were obtained.[34] Although methylation of **1a** with excess MeI and K_2CO_3 as base does not proceed beyond the dialkylation step, all phenol rings of **5a** are methylated under these conditions. This is probably the result of the increased acidity of the phenolic OH groups of **5a** at the bis- and trialkylated stage due to the electron-withdrawing properties of the carbonyl groups.

Notably, the preferred dialkylation product (MeI/K_2CO_3 or benzylbromide/K_2CO_3) of **5a** is the proximal dialkylated isomer (two geminal rings are alkylated)[34] while alkylation of **1a** using this base yields the distal (i.e., '1,3') isomer.[35] This difference in reactivity can be rationalized by inspection of the two possible anions obtained after deprotonation of the monoalkylated form. In the *cone* conformation of **1a**, the negative charge on the distal phenolate can be stabilized by two hydrogen bonds while only a single bond is possible for a proximal phenolate (Figure 9).

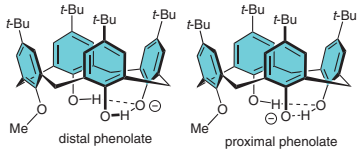
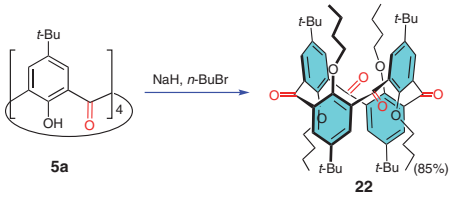


Figure 9 Hydrogen-bonding stabilization in a distal and proximal phenolate derived from the monomethyl ether of **1a**. A distal phenolate can be stabilized by two hydrogen bonds, whereas only a single hydrogen bond can stabilize the proximal phenolate.

Assuming a *1,3-alternate* arrangement in the monoalkylated phenolates of **5a**, neither the proximal nor distal phenolates can be stabilized by intramolecular hydrogen bonds. The proximal pathway is likely favored by statistical factors (an alkylated ring is flanked by two proximal rings but only a single ring is positioned at a distal position) and steric effects.

Alkylation of **5a** with 1-bromobutane using NaH as base proceeds with high stereoselectivity and affords the *1,3-alternate* tetrabutylated derivative **22** as the sole product (Scheme 12).[19]

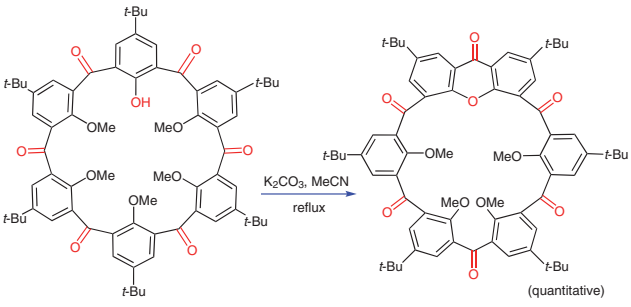


Scheme 12 Alkylation of tetrahydroxyketocalix[4]arene **5a** with 1-bromobutane

4.2 Intramolecular Aromatic Nucleophilic Substitution

Unexpectedly, methylation of the ketocalix[6]arene **7a** under standard conditions (e.g., MeI, K_2CO_3) yielded ketocalix[6]arene derivatives incorporating one or two xanthone subunits. Presumably, a methylated ring undergoes an intramolecular S_NAr reaction where a geminal phenolate serves as the nucleophile and a methoxy group as the leaving group. Although nucleophilic substitution reaction of the lower rim OR groups is not observed in classical calix[*n*]arenes, the reaction is probably feasible in a ketocalixarene due to the electron-withdrawing properties of the carbonyl groups which activate the ring towards S_NAr reactions. This hypothesis was corroborated by the reaction of pentamethoxycalixarene **23** with K_2CO_3 which yielded the

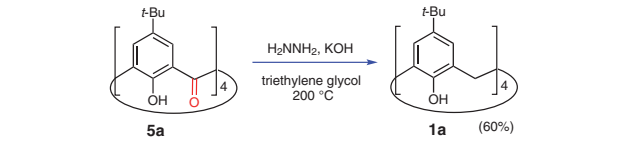
monoxanthone derivative **24** (Scheme 13).[36] In contrast to **7a**, intramolecular S_NAr reactions were not observed in the methylation of ketocalix[4]arene **5a**. It seems likely that the smaller macrocycle is less able to cushion the angular strain resulting from the incorporation of a planar xanthone in the macrocyclic ring.



Scheme 13 Intramolecular S_NAr reaction of **23**

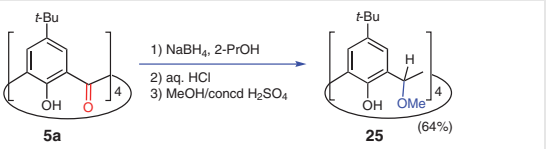
4.3 Reduction of the Carbonyl Groups

Görmar and co-workers showed that the carbonyl groups of **5a** can be reduced to methylene groups under Wolff–Kishner conditions. Thus, heating at 200 °C a mixture of **5a**, hydrazine/KOH in triethyleneglycol regenerated the 'classic' tetrahydroxycalix[4]arene **1a** (Scheme 14).[15]



Scheme 14 Wolff–Kishner reduction of the carbonyl groups of ketocalixarene **5a**

Reduction of the carbonyl groups of tetrahydroxyketocalix[4]arene with $NaBH_4$ in 2-propanol presumably affords a derivative with carbonyls reduced to alcohols, but its insolubility precluded its spectroscopic characterization. Heating this product to reflux in $MeOH/H_2SO_4$ yielded a mixture of stereoisomers of the tetrahydroxycalix[4]arene derivative with all bridges monosubstituted by a methoxy group (**25**, Scheme 15).[37] The last step probably involved a S_N1-type reaction involving protonation of an OH group at a bridge, detachment of a water molecule, and reaction of the resulting carbocation with the alcohol.



Scheme 15 Preparation of a tetrahydroxycalix[4]arene derivative with all bridges monosubstituted by a methoxy group

The xanthone calix[6]arene **17** was reductively dimerized by treatment with Zn/HCl, yielding a dixanthylenecalix[6]arene[28]

4.4 Reaction of 5c with PhLi

Addition of a nucleophile (e.g., an organolithium reagent) to the carbonyl groups of a tetraoxoketocalix[4]arene creates four stereocenters. Four isomeric forms are possible for such systems (Figure 10), and the number increases if the addition is conducted on a hexaoxoketocalix[6]arene scaffold.

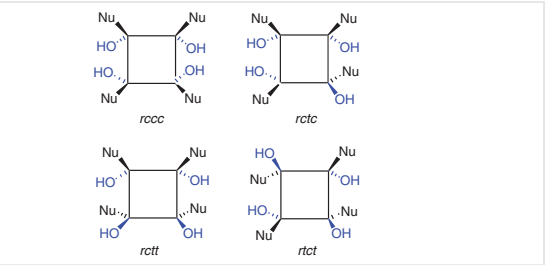
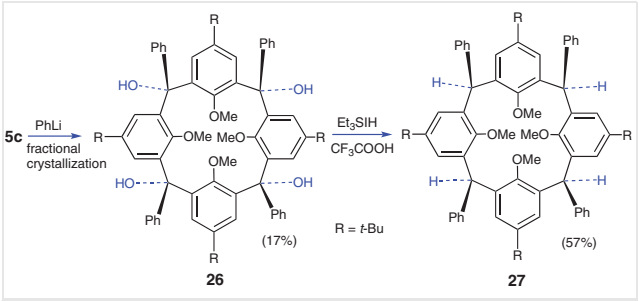


Figure 10 The four possible isomers of a calix[4]arene resulting from fourfold nucleophilic addition of a given nucleophile to the carbonyl groups of a tetraoxoketocalix[4]arene. The macrocyclic ring is schematically depicted as a square. The letters '*c*' and '*t*' denote a *cis* or *trans* disposition relative to the reference ('*r*') substituent.

Reaction of the tetramethoxy ketocalixarene derivative **5c** with excess PhLi proceeded in nonstereoselective fashion affording a mixture of the four possible configurational stereoisomers of the tetraaddition product. The *rccc* form (i.e., *all-cis*, **26**) was separated by crystallization. The alcohol functionalities of **26** were reduced by ionic hydrogenation (Et_3SiH/CF_3COOH) affording **27** (Scheme 16).[38]

The tetraaddition product **26** is a rare example of a calixarene derivative where each methylene bridge is disubstituted by two different substituents (Ph and OH).

Unexpectedly, in the ^1H NMR spectrum of *all-cis* **26** in acetone-d_6, the low-field methoxy signal resembled the familiar shape of a quintet instead of the expected singlet (Figure 11).[39]



Scheme 16 The tetraaddition of PhLi to tetraoxoketocalixarene **5c** proceeds in nonstereoselective fashion. The hydroxyls were reduced by ionic hydrogenation yielding the *all-cis* isomer of the product **27**[38]

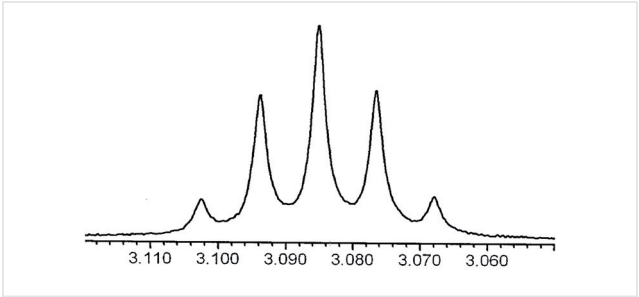


Figure 11 ^{1}H NMR spectrum of the low-field methoxy signals of **26** in acetone-d_6. The apparent multiplet is the result of a single and double isotopic perturbation of the 'in–out' equilibrium.[39]

Calixarene **26** adopts in the crystal a *1,3-alternate* conformation. In this conformation a single methoxy group is pointing 'in' (directed towards the cavity) and is hydrogen bonded to the two neighboring hydroxyl groups. Upon dissolution in acetone-d_6, the OH protons exchange with the deuterium atoms present in the residual water of the solvent. In some species, the 'in–out'/'out–in' conformational equilibrium of a pair of methoxy groups becomes nondegenerate (Figure 12). The four external lines of the apparent multiplet were ascribed to a single and double isotopic perturbation[40] of this 'in–out' conformational equilibrium.[39]

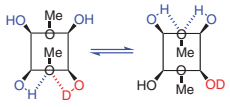
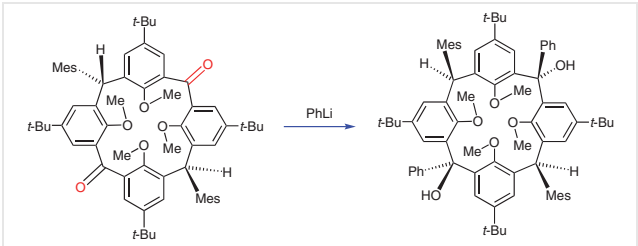


Figure 12 The 'in–out'–'out–in' conformational equilibrium in the monodeuterated **26**. In the unlabeled **26**, the two conformations are equivalent. The presence of a single OD group perturbs the conformational equilibrium. Right: the methoxy group pointing 'in' is hydrogen bonded to two OH groups. Left: the methoxy group pointing 'in' is hydrogen bonded to one OH and one OD.

Reaction of **5c** with 2.2 equivalents of PhLi in THF at 0 °C afforded the *trans* diaddition product in 42% yield. The reaction is both regio- and stereoselective. Two opposite carbonyl bridges react affording the *cis* isomer as the major product. Addition of PhLi to the carbonyls of the dimesityl dioxo derivative **28** proceeds in stereoselective (*trans*) fashion yielding **29** (Scheme 17).[24]



Scheme 17 Stereoselective addition of PhLi to the carbonyl groups of **28**

4.5 Reaction with *tert*-Butyllithium

The reaction of **5c** with excess *t*-BuLi was studied to test the steric limitations of the synthetic route involving nucleophilic addition to the carbonyl groups. The reaction afforded a mixture of addition products from which a di-*tert*-butylated trimethoxy derivative **30** and a tri-*tert*-butylated derivative **31** were isolated (Figure 13). Surprisingly, the formation of **30** indicated that one of the four methyl ether groups of **5c** was cleaved under the reaction conditions. Both systems displayed appreciable barriers for the tripod rotation of the *t*-Bu at the bridges (in the 12.7–14.5 kcal mol^{-1} range), and at low temperature separate signals were observed for each methyl of a given *t*-Bu group of **31** (Figure 14).[41]

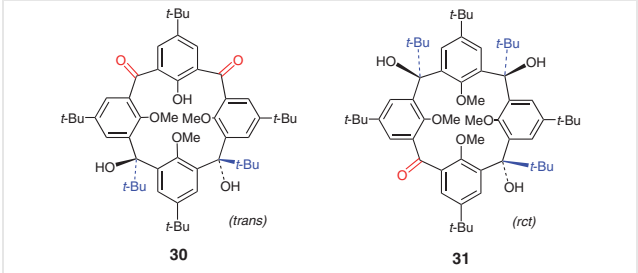


Figure 13 Structures **30** and **31**

5 From Ketocalix[*n*]arenes to Calix[*n*]radialenes and Calix[*n*]rotanes

Reaction of MeLi with **5c**, **6c**, **7c**, **12a**, **13a**, and **19** proceeded in a nonstereoselective fashion, yielding a mixture of stereoisomeric alcohols. Notably, in the reactions of **12a** and **13a**, both addition to the carbonyl groups and C–Me bond formation at the brominated bridges took place.[42] The mixtures were dehydrated by treatment with acid to afford calixarenes with exocyclic double bonds at the bridges ('calixradialenes') as shown for **12a** in Scheme 18.

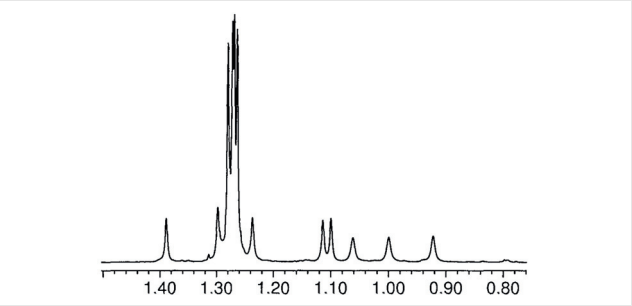
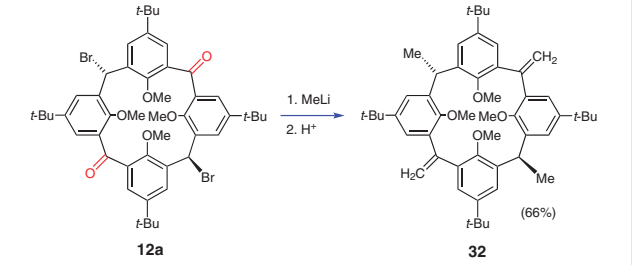
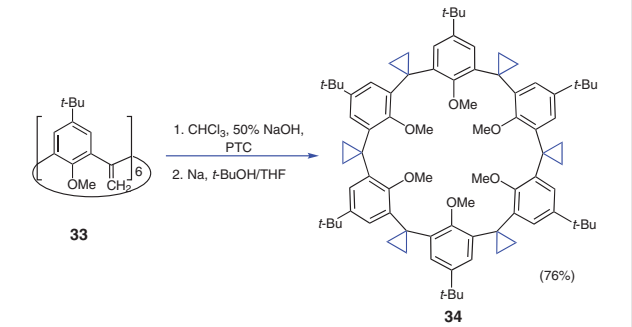


Figure 14 500 MHz ^{1}H NMR spectrum of the *t*-Bu region of **31** at 249 K. The four signals at 1.26–1.28 ppm correspond to the *p-tert*-butyl groups. Each methyl signal of the *t*-Bu groups at the bridges displays a separate signal (one signal is hidden by the *p*-*t*-Bu signals) indicating 'frozen' tripod rotations.[41]



Scheme 18 Reaction of ketocalixarene **12a** with MeLi followed by dehydration yields a derivative with two methylated bridges and two exocyclic double bonds

The exocyclic double bonds of the **32** could be transformed into spirocyclopropyl groups by reaction of dichlorocarbene (generated from chloroform/50% aq. NaOH and phase-transfer catalysis) followed by reductive perdechlorination (Na in *t*-BuOH/THF). The sequence was conducted also with calix[6]radialene **33**, which after sixfold cyclopropanation afforded calix[6]rotane **34** with six spirocyclopropyl bridges (Scheme 19).[30]



Scheme 19 Preparation of calix[6]rotane **34**

Notably, **34** adopts both in solution and in the crystal a *1,3,5-alternate* conformation where all pairs of geminal rings are oriented in an *anti* fashion (Figure 15). As observed for the cyclohexane ring,[43] the incorporation of spirocyclopropyl groups increases the rigidity of the macrocyclic ring as reflected in the barrier for the *1,3,5-alternate* to *1,3,5-alternate* inversion process (14.6 kcal mol^{-1}).[42]

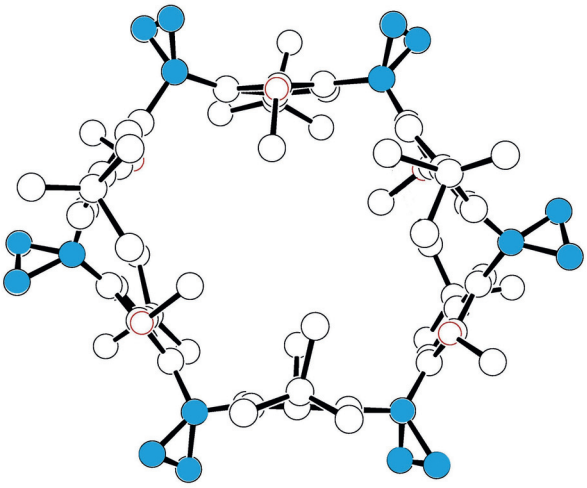


Figure 15 Top view of the crystal structure of calixrotane **34** with the spirocyclopropyl groups highlighted in blue

6 Summary and Outlook

Ketocalixarenes are readily available by oxidation of protected calixarenes. The presence of carbonyl bridges in the ketocalix[*n*]arenes alters the preferred conformation and reactivity of the calix scaffold, enables otherwise unfeasible reactions, and provides an entry point into a wide array of systems modified at the bridges (such as calix[*n*]radialenes and calix[*n*]rotanes)

Conflict of Interest

The authors declare no conflict of interest.

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