Synthesis of resorcin[4]arene cavitands by ring-closing metathesis†

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The synthesis and X-ray crystal structures of the first resorcin[4]arene cavitands by ring-closing metathesis reaction are described.

The calix- and resorcin[4]arene cavitands, with enforced cavities large enough to complex complementary organic compounds or ions, have been established as fruitful platforms for the attachment of different ligating sites giving rise to ionophores for anions, cations and neutral molecules.[1] These cavitands have the ability to encapsulate and stabilize guest molecules, and to catalyze chemical transformations within their "microreactor" cage like structure.[2] Conformationally rigid, bowl-shaped resorcin[4]arene cavitands are widespread building blocks also in supramolecular chemistry[3] and are of particular interest due to their robust cavity bearing framework, upon which covalent modifications to either the upper or lower rims can be achieved, without compromising the structural integrity of the inner cavity.

Covalent linkage of the neighboring phenolic groups on the adjacent phenyl rings upon condensation with a suitable linker has been the key synthetic procedure leading to conformationally locked "bowl shaped" resorcin[4]arene cavitands.[4] The synthesis of ethylene-, propylene-, dialkylsilicon-, phosphoryl- and heterophenylene-bridged cavitands has been reported (Fig. 1).[3b,5]

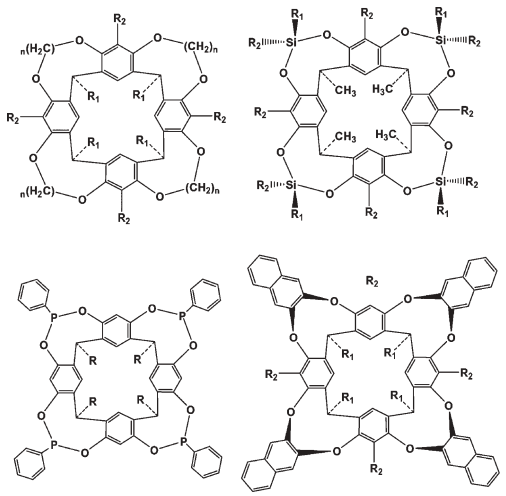

Fig. 1 Bridged-resorcin[4]arenes.

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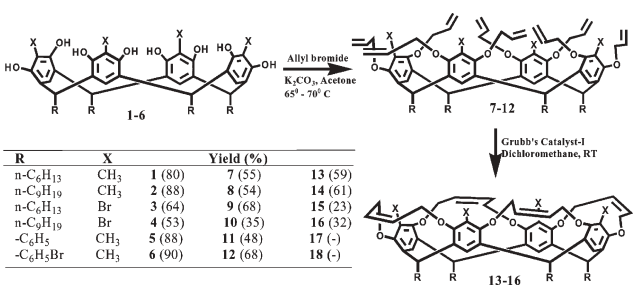
In recent years, ring-closing metathesis (RCM) has been rapidly established as an efficient approach to synthesis of medium to large ring systems. The ring-closing metathesis reaction provides interesting possibilities for manipulation of the cavity size in resorcin[4]arene cavitands; novel cavitands with unusual properties can thus be prepared.[6] Although, RCM reactions of alkenyl substituents have been reported in calix- and resorcin[4]arenes by the groups of McKervey,[7a,b] Chen[7c] and Balasubramanian,[7d] to the best of our knowledge, there has been no report describing the utility of RCM reaction in synthesis of the resorcin[4]arene cavitands.

In this communication, the synthesis and X-ray crystal structures of first resorcin[4]arene cavitands by ring-closing metathesis reaction are described. The ring-closing metathesis reaction on perallylated resorcin[4]arenes, where allyl groups on adjacent phenyl rings serve as acyclic diene precursors for RCM, led to the formation of bridged resorcin[4]arene cavitands (Scheme 1). The process allows manipulation of the cavity size as demonstrated by the enlarged diameter of the upper rim. The cavity can be further manipulated/ functionalized.

Octahydroxy resorcin[4]arenes, **1–6** were synthesized, following a standard synthetic protocol (Scheme 1).[8] Compounds **1–6** were characterized from their NMR and mass spectral analysis, which was identical to the data reported.[4b,8] Although, the resorcin[4]-arenes can have four different conformations, namely, crown (C_{4v}), boat (C_{2v}), chair (C_{2h}) and saddle (D_{2d}) only two, crown and chair, are predominantly formed. Compounds **1–4** were isolated as the C_{4v} symmetric crown conformers while compounds **5** and **6**, were isolated as the chair conformer. The perallylation of the hydroxyl resorcin[4]arenes **1–6**, in acetone or DMF with allyl bromide using potassium carbonate as a base, under standard reflux condition did not always gave the best yield. The allylation reaction was therefore performed in a pressure tube at increased reaction temperature and pressure, which gave improved yields (35–68%) for compounds **7–12**.

The perallylated compounds **7–12** are being reported for the first time and were characterized from their ^{1}H and ^{13}C NMR,



R	X	Yield (%)		
n-C_6H_{13}	CH_3	**1** (80)	**7** (55)	**13** (59)
n-C_9H_{19}	CH_3	**2** (88)	**8** (54)	**14** (61)
n-C_6H_{13}	Br	**3** (64)	**9** (68)	**15** (23)
n-C_9H_{19}	Br	**4** (53)	**10** (35)	**16** (32)
-C_6H_5	CH_3	**5** (88)	**11** (48)	**17** (-)
-C_6H_5Br	CH_3	**6** (90)	**12** (68)	**18** (-)

Scheme 1 Allylation and ring-closing metathesis.

HRMS spectral analysis and, when possible, by single-crystal X-ray diffraction data‡ (see ESI†). The ^{1}H NMR spectra proved to be of limited utility because of the observed line broadening. Nonetheless the allyl group ^{1}H resonances were observed, for example in compound **7**, at 4.0 (4H, OCH_2), 5.1 (1H, =CH_2), 5.2 (1H, =CH_2) and 5.9 (1H, =C*H*) ppm (Fig. 2). ^{1}H NMR integrals confirmed perallylation. The ^{13}C NMR spectrum was better resolved and therefore used for unambiguous assignment of carbon resonances using correlation from an HMQC experiment. The allyl group carbon resonances in **7** were observed at 73.2 (O*C*H$_2$), 116.0 (=*C*H$_2$) and 134.4 (=*C*H) ppm (Fig. 2). A single carbon resonance for a set of four equivalent carbons suggested a four-fold axis of symmetry in the molecule.

Structures of compounds **8**, **9** and **10** were similarly confirmed from their ^{1}H, ^{13}C and HRMS spectral analysis (see ESI†). The NMR analysis is supported by 2D NMR correlation experiments. Even though synthesized from **2** (crown, C_{4v}), conformational dynamics in compound **8** were quite interesting and suggested a preferred boat (C_{2v}) conformation in solution. The conformational dynamics of such molecules have been previously described by Cram *et al.*[3a] In resorcin[4]arenes the intramolecular hydrogen bond formed by the eight hydroxyl groups rigidifies the crown conformer but when the –OH hydrogens are substituted, the flexibility of the skeleton increases. The molecule exists in equilibrium between the C_{4v} (crown) and C_{2v} (boat) symmetries; the barrier to interconversion is typically 17–19 kcal mol^{-1}.[3a] Perallylated resorcin[4]arenes, **7**, **9** and **10**, are likely to be interconverting rapidly between the two isomers, preferring the crown (C_{4v}) conformer in solution, and their ^{1}H NMR possess, in particular, a single aromatic resonance. In contrast, compound **8**, was the boat (C_{2v}) conformer in solution, and its ^{1}H NMR spectrum possess two sets of aromatic resonances at 6.5 and 7.6 ppm. Crystallization of compound **10** from ethyl acetate–hexane (7 : 3) gave light yellow colored crystals suitable for X-ray analysis. The single-crystal X-ray analysis showed that resorcin[4]arene **10** exists, in the solid state, in a C_{2v} 'boat' conformation.

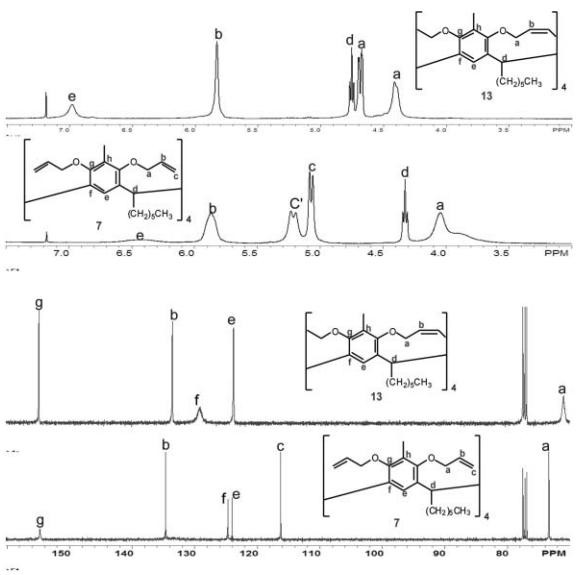


Fig. 2 ^{1}H and ^{13}C NMR of compound **13** and its precursor **7**.

Compounds **5** and **6** are known to prefer the chair conformation (C_{2h}); in which two adjacent phenyl rings have equatorial orientation and while the other two phenyl rings have axial orientation. Perallylation of **5** and **6** was performed to synthesize compounds **11** and **12**, respectively, which were analyzed from their NMR and mass spectral data. The chair conformation of **11** and **12** were evident in their ^{1}H NMR where two resonances for benzylic protons were observed in accordance with C_{2h} symmetry. Compound **11** was crystallized from ethyl acetate–hexane (3 : 7) for X-ray analysis.‡ The X-ray crystal structure of compound **11** confirmed its chair conformation (C_{2h}).

RCM reactions on perallylated resorcin[4]arenes **7–12** were carried out employing 5–10 mol% of Grubb's generation I catalyst, under nitrogen atmosphere, in dry dichloromethane and at room temperature. Perallylated resorcin[4]arenes **7**, **8**, **9** and **10** led to formation of ring-closed products **13**, **14**, **15** and **16**, respectively, in 58–60% yield. Progress of the reaction was monitored by TLC in ethyl acetate–hexane (1 : 4). The products were isolated upon column chromatography using an ethyl acetate–hexane gradient system with increasing ethyl acetate in the eluent (6–10%). RCM reactions on perallylated resorcin[4]arenes **11** and **12**, led to a complex mixture of products.

The alkenyl regions of the ^{1}H NMR spectra of the perallylated compound **7** and the product **13** are shown in Fig. 2. A comparison of the two spectra revealed that the resonances (5.1–5.3 ppm) for the terminal alkenyl methylenes (=CH_2, Hc and Hc' in Fig. 2) were absent in the spectrum of the product **13**. In the ^{13}C NMR spectrum of **13**, also, the alkenyl methylene resonance ($\sim$116 ppm) was not observed. Additionally, the ^{1}H spectrum of the product **13** showed resonances attributed to the methylene (–CH_2–) and the methine (=CH–) groups which were deshielded ($\Delta\delta$ = 0.5 ppm), possibly due to the rigidity of the structure. The presence of one resonance for a set four carbons in its ^{13}C NMR spectrum suggested a C_{4v} symmetric crown conformation for compound **13**. A high-resolution ESI mass spectral analysis [calc. 1089.7178 (M + H$^+$); found 1089.7182 (M + H$^+$)] confirmed the molecular integrity of the product **13**.

Crystallization of product **13**, from methanol–ethyl acetate (7 : 3) gave crystals of the hemi-ethyl acetate solvate suitable for X-ray analysis.‡ Single-crystal X-ray diffraction results (Fig. 3) confirmed its structure as a completely four-bridged resorcin[4]-arene cavitand in which the adjacent phenyl rings are connected covalently through an ethenylenedioxy bridge. The *cis*-geometry of the double bond is also visible in the structure (Fig. 3). This is the first report of such resorcin[4]arene cavitands. The diagonal distance at the upper (*a*) and lower rim (*b*) and the height (distance from the substituent on the upper rim to the lower carbon of the four aryls, *h*) are a good measure of the cavity size in cavitands. Measurement of the cavity size in cavitand **13** revealed a substantially enlarged cavity (*a* = 13.7 (C30–C32), 13.2 (C39–C47), 9.1 (C29–C31) Å; *b* = 4.9 (C3–C20), 5.2 (C13–C27) Å; *h* = 4.3 (C20–C31) Å).[5a]

Similar structural analysis of the products **14**, **15** and **16** was undertaken; ^{1}H and ^{13}C NMR of **14**, **15** and **16** were in agreement with the four-bridged structure. HRMS measurements confirmed their molecular integrity. For compound **14**, HRMS-ESI: calc. *m*/*z* 1274.9321 (M + NH_4^+); obs. *m*/*z* 1274.9280 (M + NH_4^+); **15,** HRMS-APCI: calc. *m*/*z* 1345.2978 (M + H$^+$); obs. *m*/*z* 1345.2918

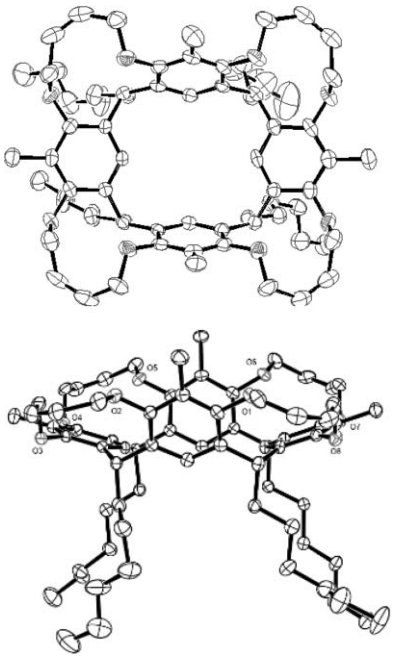


Fig. 3 X-Ray crystal structure of one of the two independent molecules (top and sideview) of compound **13**, with 50% ellipsoids. H atoms are not shown.

($M + H^+$); **16**, HRMS-APCI: calc. *m*/*z* 1513.4856 ($M + H^+$); obs. *m*/*z* 1513.4900 ($M + H^+$).

Ring-closing metathesis reaction on substrates **11** and **12** under various reactions conditions and catalyst concentration always led to a complex mixture of products. It was not possible to isolate and characterize the partly bridged intermediates for this report. The results can be attributed to the different conformations of the perallylated resorcin[4]arenes **7–10** and **11–12**. Resorcin[4]arenes **7–10** exist in equilibrium between the crown (C_{4v}) and the boat (C_{2v}) conformers enabling the crown conformer to be trapped by RCM resulting in formation of the four-bridged cavitands **13–16**. The resorcin[4]arenes **11** and **12**, on the other hand, exist in the chair (C_{2h}) conformation; the crown conformers being energetically less favored because of the repulsion between equatorial aryl ring and the allyloxy groups.

It is important to mention that bridging of the *chair*-methylresorcin[4]arenes **5** and **6** with bromochloromethane has been reported to yield methylenedioxy bridged cavitands, most probably a result of ring-inversion to the corresponding cone conformation which is stabilized by the intramolecular hydrogen bonds.[4b] However, such ring inversion in **11** and **12** is not possible due the size of the allyloxy group.

In summary, we have synthesized the first resorcin[4]arene cavitands in which the adjacent phenyl rings are connected covalently through an ethenylenedioxy bridge by tandem ring-closing metathesis reaction. This type of cavitands present interesting opportunities for various applications, for example, the encapsulation of much larger molecules may now be possible in the enlarged cavity and the modification of the alkenylene bridge could lead to functionalization/deepening of the upper rim/cavity. Efforts are currently underway in our laboratories to exploit the alkenylene bridge functionalization.

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‡ CCDC 654498–654500. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712981e

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