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A perspective to resorcinarene crowns

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1. Introduction

In supramolecular chemistry crown ethers are one of the oldest and most explored but still today a very intriguing class of compounds. They have a remarkable ability to act as receptors or ionophores for a variety of guest species depending on their chemical and structural properties, which can be modified just by changing the number of oxygen donors, i.e., altering the size of the crown ether, or replacing them with nitrogen or sulfur atoms or by adding additional functional groups, such as aromatic rings as part of the scaffold. These alterations change the geometry of the host and thus binding affinity and selectivity toward guests, such as alkali,[1] alkaline earth[2] and transition metal cations,[3] and ammonium ions[4] making crown ethers very useful compounds in

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designing artificial sensory systems.[5] The cyclic structure and hydrogen bond donors of crown ethers make them also very useful in the construction of rotaxane and pseudorotaxane-type assemblies and therefore as components for molecular machines and devices.[6] The crown ether moieties have subsequently been employed as a part of a structure of other supramolecular hosts, such as calix[4]arenes to form a group of calix[*n*]crowns, which have shown to exhibit remarkable ionophoric properties as hosts for alkali and alkali earth metals as well as tertiary amines.[7]

The subclass of calixarene family, namely calix[4]resorcinarenes, or simply resorcinarenes share lot of common features with their close relatives, calix[4]arenes.[8] Therefore resorcinarenes provide a good but relatively little explored alternative for crown ether functionalization with sufficiently different properties to calix crowns in respect to binding properties and structural features. For example, in case of calixarenes the bridging is limited to the narrow side of the cavity[9] or alternatively 1,2- or 1,3-alternate conformations (Fig. 1),[10] which in double bridging orient the bridges to the opposite sides of the calixarene core. Both approaches somewhat limit the utilization of the interactions to calixarene core in complexations. With resorcin[4]arenes, on the other hand, the hydroxyl groups are situated at the open end of the cavity, which enables the resorcinarene core to take part in the cation binding with cation–π interactions (Fig. 1). Alternatively the conformation of resorcinarenes can be rigidified into a crown by linking the hydroxyl groups of the upper rim to a cavitand structure, which provides a higher degree of preorganization and enables crown ether modification to a position between the upper rim oxygens creating an extended cavity for guest binding.[11]

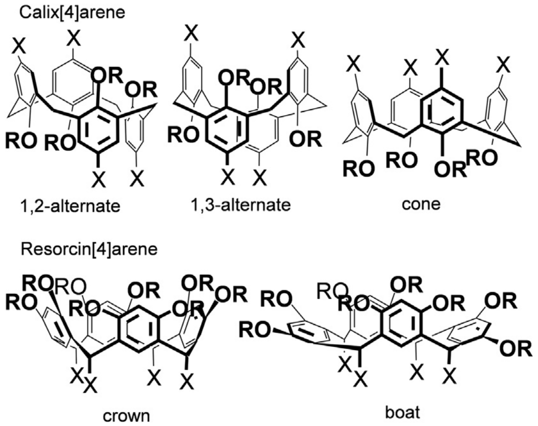

Fig. 1. Some examples of typical conformations adopted by calix[4]arenes and resorcin[4]arenes.

This review focuses on the crown ether functionalization of the resorcinarene scaffold and discusses the structural and complexation properties of these compounds. The potential applications of resorcinarene crowns in construction of supramolecular assemblies, such as pseudorotaxanes, and solid lipid nanoparticles, as well as their potential as transporter mimics and in antibacterial coatings are reviewed.

2. Synthesis of resorcinarene crowns

The skeleton of resorcinarenes differs from calixarenes as it is built from resorcinol units instead of phenols, which enables multiple sites for functionalizations on the upper rim, either to hydroxyl groups or to carbon atoms between them (so called 2-position).[8] Also the lower rim is accessible for functionalization, either directly during the acid-catalyzed condensation reaction by choosing the suitable functionalized aldehyde as a starting compound, or via post-synthetic modification of the lower rim. All functionalization possibilities have been exploited when designing resorcinarene crown ethers.

2.1. Bridged resorcinarene crowns

The most common sites for the crown ether functionalization are the hydroxyl groups of the upper rim of the resorcinarene, which can be bridged to form extended and multifunctional cavities, or substituted by a podand arms having a crown ether part and thus creating a separate binding site outside the resorcinarene cavity. When designing the bridging an important factor to consider is the effect of the bridging on the conformational properties, i.e., how the bridging alters the dimensions and shape of the binding cavity. The other significant factor is the requirement for optimized synthesis of desired products instead a vast number of inseparable isomers, when altogether eight hydroxyl groups are available for attaching the bridges. Therefore, most of the bridged resorcinarene crowns have been made for resorcinarene platforms with inherently limited bridging possibilities, i.e., cavitands or tetramethoxyresorcinarenes.[11,12]

Reinhoudt et al.[13] were the first to study the crown ether bridging with resorcinarenes. Instead of using resorcinarenes with free hydroxyl groups more rigid platform, tetrahydroxy resorcinarene cavitand ($R=C_5H_{11}$), with four hydroxyl groups at the 2-position available for bridging, was chosen. Alkylation of the tetrahydroxycavitand[14] with polyethylene glycol ditosylates afforded two different regioisomers of mono-bridged products: 1,2-bridged crown[*n*]cavitand (**1a**–**c**, n=5–7) and 1,3-bridged crown[6]cavitand (**2**, Fig. 2). The results clearly showed that the alkylation favors the bridging of two hydroxyl groups at the adjacent aromatic rings over the bridging of the opposite aromatic rings as the best yield obtained for 1,2-crown[*n*]cavitand is 33% (**1b**) and only 3% for 1,3-crown[6]cavitand **2**. The best yields of 1,2-crown[*n*]cavitand synthesis were obtained for 1,2-crown[6]cavitand **1b** (20–33%) in the reaction of tetrahydroxy cavitand and 1 equiv of pentaethylene glycol in the presence of a sodium salt (NaH or Na_2CO_3) in DMF. With shorter tetraethylene glycol ditosylate the yield of 1,2-crown[5]cavitand **1a** was only 8%, whereas a longer hexaethylene glycol ditosylate as a bridging agent gave mono-crown cavitand **1c** with a reasonable yield of 20%. These results suggest that the shortness and inflexibility of the tetraethylene glycol ditosylate compared to the longer pentaethylene and hexaethylene glycol ditosylates, makes the bridging reaction more difficult.

The synthesis of 1,3-crown[6]cavitand **2** was done in acetonitrile using Na_2CO_3 as a base and also in DMF using K_2CO_3 or Cs_2CO_3 as a base. The latter conditions also produced a bis-crown derivative **3a** in a modest yield of 8–10% (Fig. 2). Few years later Kang et al.[15] succeeded in synthesizing a bis-crown[4]cavitand **3b** ($R=C_2H_4Ph$) with an improved yield of 25% (Fig. 2). The difference in their synthetic methodology was to use 3 equiv of triethylene glycol ditosylate per 1 equiv of tetrahydroxycavitand[14] and K_2CO_3 or Cs_2CO_3 as a base in DMA.

Another alternative for more restricted approach for bridging was to choose tetramethoxy resorcinarene[12] as a platform for resorcinarene crowns.[16,17] Tetramethoxy resorcinarene, first synthesized by McIldowie et al.,[12] has only four hydroxyl groups for intramolecular bridging thus reducing the number of possible isomers during the bridging. Tetramethoxy resorcinarene bis-crown-4 **4** ($R=C_2H_5$) and bis-crown-5 **5a**–**h** ($R=C_mH_{2m+1}$, m=2–5, 7, 9–11) were accomplished by a reaction of tetramethoxy resorcinarene with 2 equiv of tri- or tetraethylene glycol ditosylates, respectively, in the presence of Cs_2CO_3 in DMF with 15–30% yields (Fig. 3). The same reaction conditions also produced a mono-bridged tetramethoxy resorcinarene **6a** as a side product and the