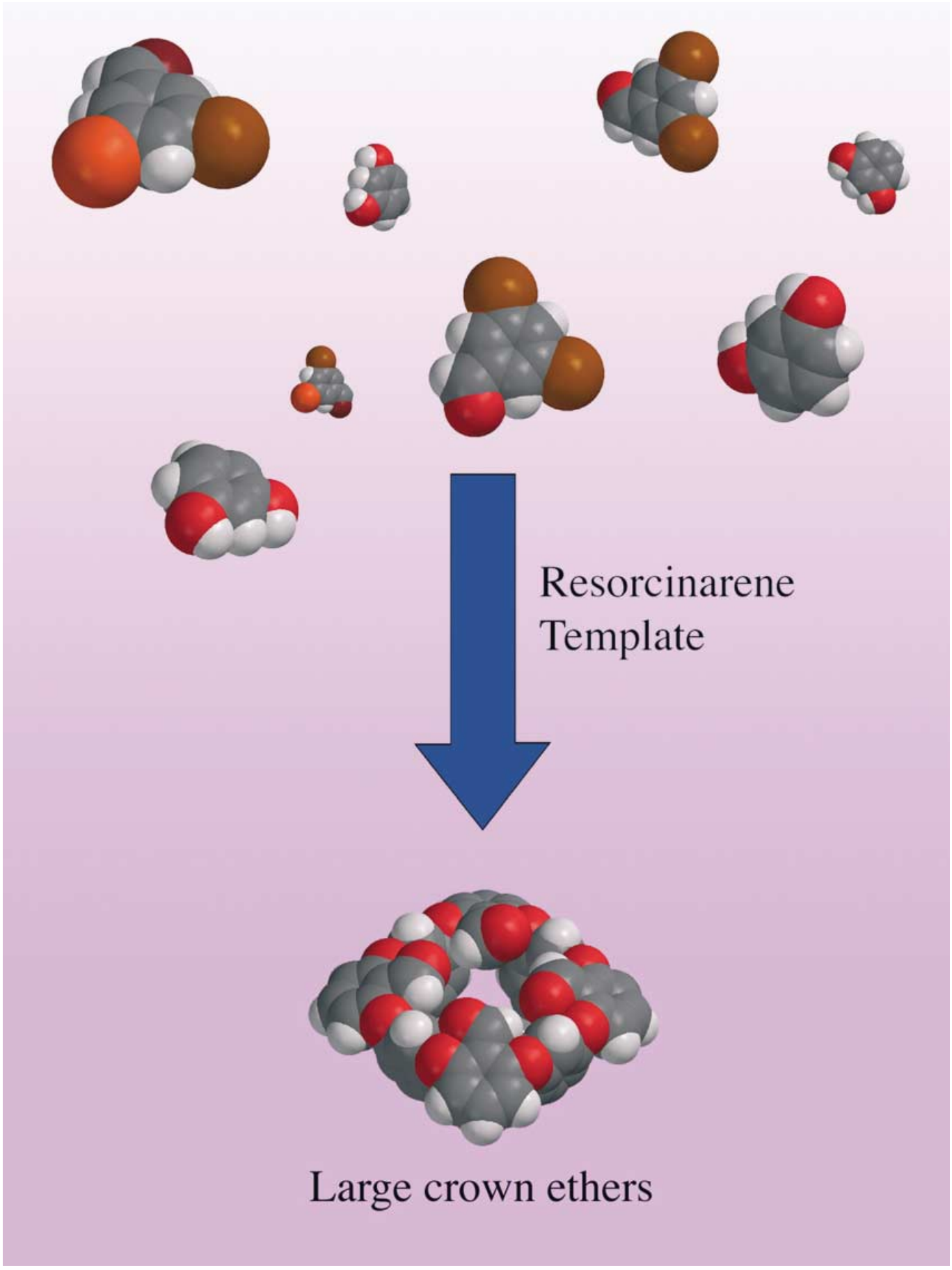

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Resorcinarenes as Templates

Bruce C. Gibb*[a]

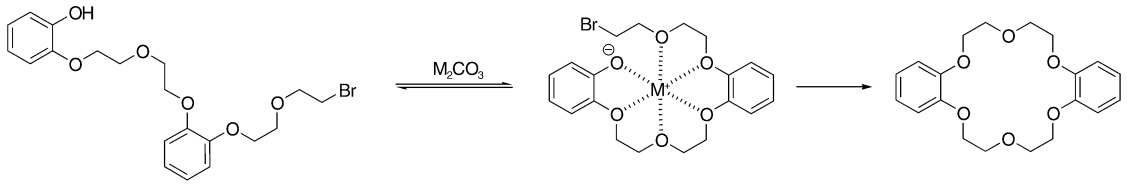
Abstract: Metal ions are superb at templating the synthesis of small macrocycles that are decorated with Lewis basic sites. However, for the synthesis of larger macrocycles, or the synthesis of macrocycles devoid of an array of Lewis basic sites, metal ions are less useful. Here we demonstrate that resorcinarenes can be used as templates to engender the efficient formation of large crown ethers. A three step process of 1) tethering moieties to the template, 2) linking those moieties, and 3) then cleaving off the template leads to the efficient formation of a family of aromatic crown ethers. If adaptable, this approach will prove useful for the construction of macrocycles that are hard to obtain from a step-wise synthesis.

Keywords: crown compounds · macrocycles · resorcinarenes · templation synthesis

Introduction

Availability is everything. Consequently, any protocol that represents a more efficient alternative to a long and tedious process is always welcome. Templation is one such protocol that engenders, among other things, mass production and the construction of countless architectural designs. In chemical terms, templation involves the use of a molecule or ion to promote the formation of one compound from a reaction that would otherwise form a complex mixture.[1] Using a molecular or ionic scaffold in this manner opens up new areas of research, by providing efficient access to compounds that are otherwise hard to synthesize using step-wise syntheses.

At the most rudimentary of levels, there are two types of chemical template. Thermodynamic templates cause shifts in the equilibria that relate the various constituents of a reaction. Thus they form the basis of dynamic combinatorial libraries.[2, 3] Kinetic templates on the other hand promote the irreversible formation of one product by lowering the free energy of activation of only its rate-determining step. Transcription and translation, that is, the DNA-templated formation of messenger RNA and the RNA-templated synthesis of proteins, respectively, are examples of kinetic templation. Also coming under the heading of kinetic templation is arguably the most familiar example of a synthetic templation process, the synthesis of crown ethers (Scheme 1).[4, 5] In these reactions, the rate of formation of the macrocycles is intimately tied to the nature of the cation that is present.[6] If it can fit snugly in the incipient crown, the reaction rate and yield will be much greater than in the parallel experiment in which an ill-fitting cation is present. The best-case scenarios of such reactions lead to the efficient synthesis of the smaller crown ethers; the [12]crown-4, [15]crown-5, and [18]crown-6 systems. As a result countless variations on these systems have been synthesized,[7–9] including aza and thio derivatives, and their cryptands[10] and calix-crown[11–13] conjugates. These syntheses have been instrumental in the development of chemical templation[1] and in our understanding of noncovalent forces involving cations.[14, 15] Furthermore, the ease of these syntheses has resulted in crown ethers increasingly finding application as phase-transfer reagents[16, 17] catalysts,[16–18] membrane transporters,[19, 20] sensors,[21, 22] and in separation technologies,[23] such as the removal of cesium from alkaline nuclear waste.[24, 25] It is evident from a perusal of the Chemical Abstracts that the focus of this swath of research has been on relatively small macrocycles. Figure 1 shows the



Scheme 1. The templated synthesis of dibenzo[18]crown-6.

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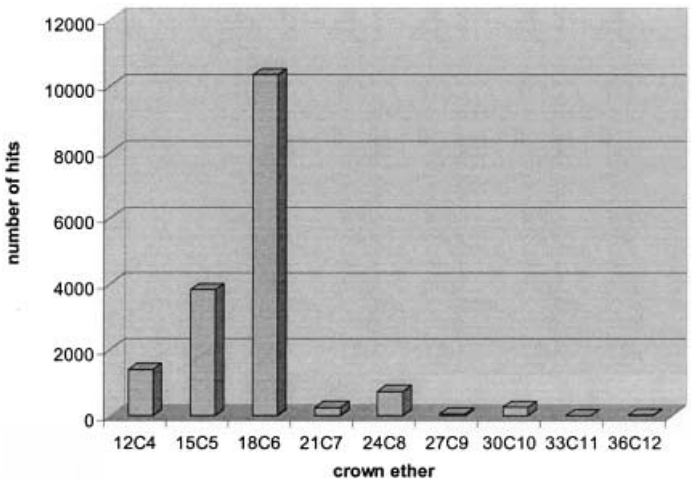


Figure 1. Number of "hits" in a Chemical Abstract search of different crown ethers ([*n*]crown-*m*).

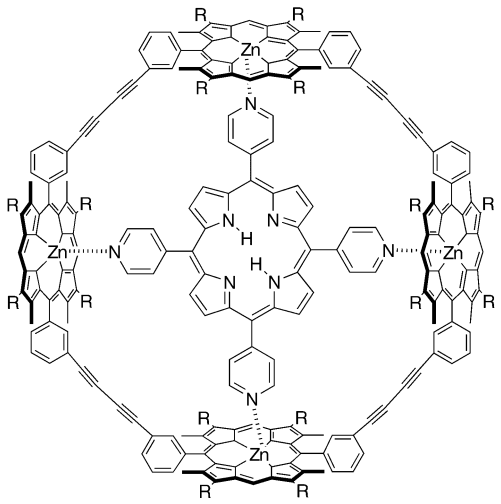
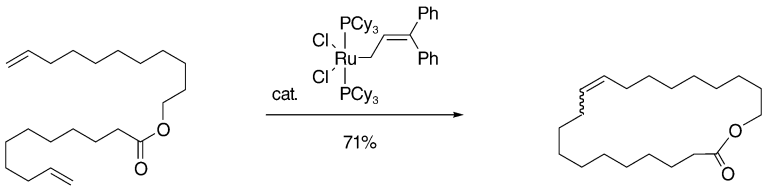


Figure 2. A cyclic porphyrin tetramer containing the tetrapyridylporphyrin template used to synthesize it.

results from a search of titles and abstracts containing the term, "[*n*]crown-*m*" (whereby *m* is an integer between 4 and 12, and $n = 3 \times$ m). It is evident from this data that over 92% of crown ether research has focused only(!) on the readily templated crowns possessing macrocyclic chains of 18 atoms or less.[26] Availability is everything!

What of larger crown ethers, or indeed larger macrocycles in general? For crowns with more than roughly 24 atoms in their macrocyclic chain, metal ions are just too small to be effective templates. Generally it has therefore been necessary to revert to step-wise syntheses, whereby the combination of the multi-step processes, slow rates of the final cyclization steps, and purification difficulties often leads to poor yields. Alternatives are, however, constantly being devised. For example, with macrocycles that are not conveniently decorated with ligating atoms, one alternative is to change strategy entirely and move the metal out of a central templation role into a peripheral one. By this approach, ring-closing metathesis allows the formation of large, relatively unfunctionalized macrocycles (Scheme 2).[27] Returning to templates that literally play a central role in the efficient formation of a target, if larger macrocycles are desired, then, simply put, larger templates must be utilized. Figure 2 shows one such example from the Sanders group.[28]



Scheme 2. A ring closing metathesis. The ruthenium carbene catalyst acts as a template.

In the search for other sizable molecular templates that may function in a similar fashion to the porphyrin in Figure 2, the primary considerations must be availability and adaptability. Any molecular template that is perceived by the chemical community to fit these two criteria has exciting prospects. Here we discuss the concept of using resorcinarenes[29–31] as templates.[32] These unique macrocycles undoubtedly fit the first criteria of availability, although more research is necessary to determine if they can also fulfill the criteria of adaptability. If they can, they may be able to extend the envelope of readily available macrocycles "beyond" [18]crown-6.

Resorcinarenes as Templates

As is so often the case in science, the idea that resorcinarenes can be used as templates came about in a rather serendipitous manner. As the importance of serendipity in research can never be over emphasized, we have embellished the description of the research leading to the concept with our thoughts at that time.

Much of our recent research efforts have been directed towards building large host molecules based on resorcinarenes such as **1**. The first step towards this goal, the stereoselective bridging with benzal bromides, yields a family of deep-cavity cavitands of general structure **2** (Scheme 3).[33–35] Although eight new bonds and four new stereogenic centers are formed in this process, yields as high as 70% are obtained. This corresponds to an average diastereoselectivity of $>91\%$ for each of the stereogenic centers, and an average of $>95\%$ efficiency for the formation of each of the new bonds. The overall result of this process can be expressed in a number of ways. From a host–guest chemistry point of view, the effect is to deepen the cavity of the resorcinarene. However, an alternative viewpoint is that benzal bridging of the resorcinarene positions the four new aromatic rings at set distances from each other. In other words, it preorganizes them in a positional or spatial sense. With the former viewpoint still very much taking up our thoughts, we went

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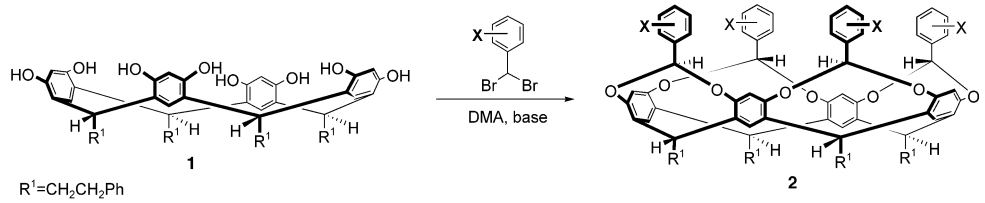
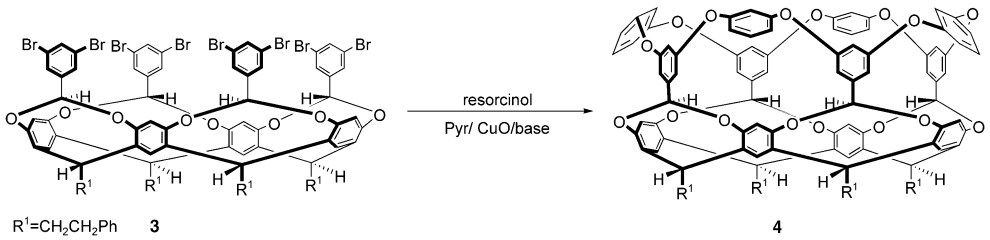


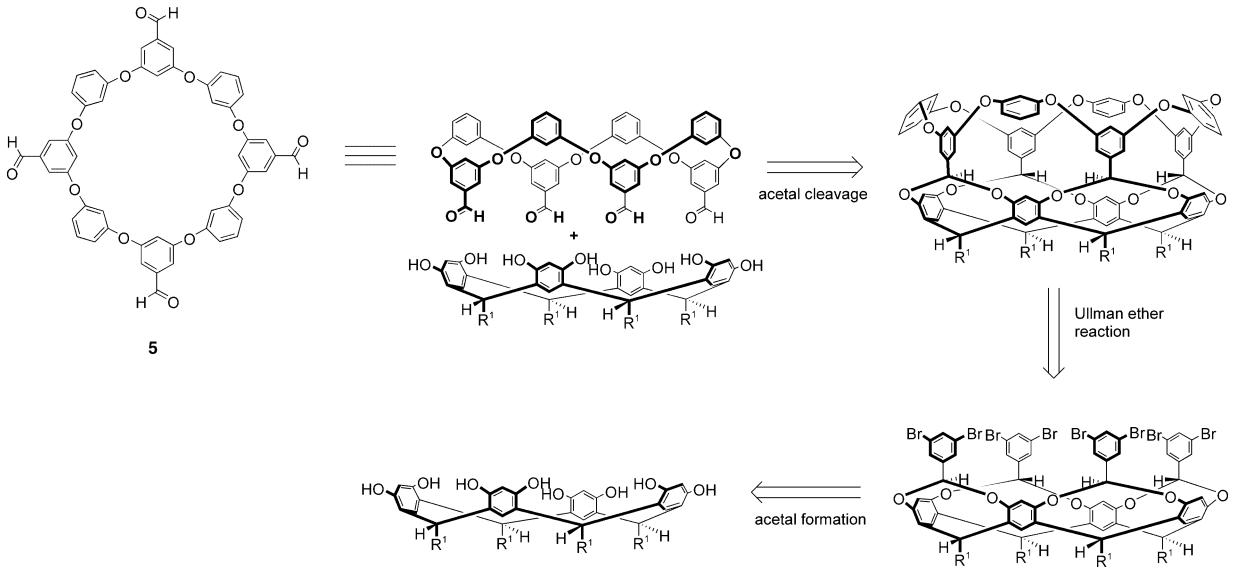
Scheme 3. The synthesis of deep-cavity cavitands ($R^1 = -CH_3$, $-(CH_2)_3CH_3$, $-CH_2CH_2Ph$, $-(CH_2)_{10}CH_3$, X = various).

on to investigate the hosting properties of compounds of general structure **2**. Unfortunately these molecules are not good hosts, a point of fact that we attributed to the poor preorganization (in a rotational sense) of the second row of aromatic rings. The logical step was therefore to inhibit this rotation by linking together each of the rings in the second row. Our first approach to this task has proven to be our most successful to date. Thus, when the second row rings of **3** are linked in an eightfold Ullmann ether reaction with resorcinol (Scheme 4), the molecular host **4** is isolated in 88 % yield.[36] In this process, the average C–O bond is being formed with an efficiency of greater than 98 %. What is the root of this efficiency? Undoubtedly the positional preorganization of the second row of aromatic rings is important. However, experiments also reveal that the nature of the base used in the reaction is also crucial. Sodium carbonate does not work, potassium carbonate is ideal, while cesium carbonate lies somewhere between these two extremes.[37] Perhaps metal-ion templation is also important.

We have gone on to examine some of the hosting properties of **4** and related deep-cavity cavitands.[38–40] Our long-term goals for these compounds include the development of shape-selective reagents and catalysts, and in this regard it was a concern for us that the four acetals of **4** might be susceptible to acid-catalyzed cleavage. To a host–guest chemist this would not be good news. However, as we just then realized, for a chemist interested in templation, quite the opposite is true. Thus, as the (retrospective) retrosynthesis shown in Scheme 5 demonstrates, an efficient formation of aromatic crown **5** can be brought about by the cleavage of the four acetals of **4**. As it transpired, our worries of instability in acidic media were unfounded. Host **4** was returned unscathed after dissolution in 1:1 $EtOH/H_2SO_4$, and heating to reflux for one week. Presumably, if one acetal group is cleaved, it can reform before any other of the remaining acetals can be broken. Considering now not just a host–guest perspective, but also a templation chemist's point of view, some of our efforts turned towards the destruction of our newly formed host; a notion



Scheme 4. The synthesis of molecular host **4** ($R^1 = CH_2CH_2Ph$).



Scheme 5. A (retrospective) retrosynthesis of macrocycle **5**.

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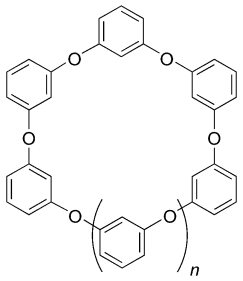
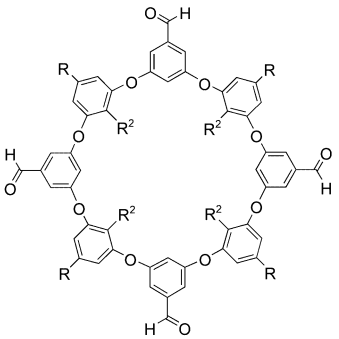
that was initially met with some resistance to those who had just synthesized it! For cleaving the acetals, an irreversible approach proved effective; the removal of the resorcinarene template of **4** was affected by treatment with BBr_3. After hydrolysis of the crude reaction mixture, which consisted of a mixture of isomers possessing aldehyde and/or benzal bromide groups, the fully aromatic crown ether **5** was isolated in 87% yield. This corresponds to a 50% yield starting from the readily available resorcinarene **1** ($R = CH_2CH_2Ph$) and commercially available 3,5-dibromobenzaldehyde. The [32]crown-8 **5** has not been previously reported, and so a precise measure of the efficiency of this templation protocol cannot be determined. As a gauge however, we can note that the smaller, unfunctionalized analogues **6** and **7** were prepared by means of step-wise protocols that gave overall yields in the sub 0.1% range.[41]

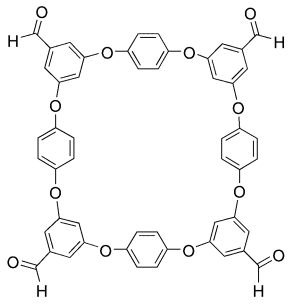


6 (*n*=1)
7 (*n*=2)

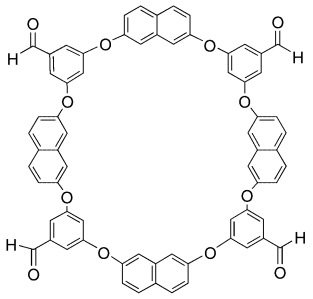
Within the confines of Ullman ether reactions on **3**, this templation process turns out to be quite general. Hence, reactions on **3** can be expanded to include: 2- and 5-methyl resorcinol, 3,5-dihydroxybenzyl alcohol, hydroquinone, and 2,7-dihydroxy naphthalene. The resorcinarene moiety of each product can then be removed to yield the respective crowns **8**–**12**. The benzyl chloride groups of **10** arise through the chlorination of the benzyl alcohol moieties of the corresponding tetrabenzyl alcohol "host" **13**. Because this compound has low solubility in many solvents, the normal template removal process could not be used, and a combination of $SOCl_2$ and BCl_3 was necessary to affect removal. In general, the synthesis of these larger or more elaborate macrocycles is as efficient as the formation of **5**. For example, the yield for the two steps involved in transforming **3** to **12** is 63%. Taken together, these results demonstrate that a range of bis-phenols of different widths can be inserted between the benzal bridges of **3**. The starting cavitand is evidently preorganized, but not so rigid as to preclude some variability. This resorcinarene template protocol can also be extended to the synthesis of lower symmetry macrocycles that do not possess a C_4 axis. Thus, by a two-step Ullman ether process it is possible to form **14**, which possesses one methyl group at the rim of its cavity. Treating this compound to the usual template removal process yields macrocycle **15** (Scheme 6).



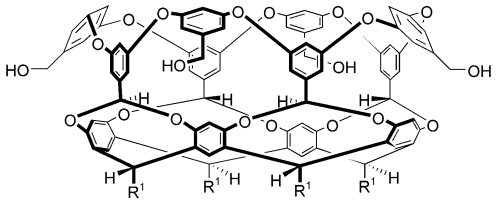
8 (R=H, R^2=Me)
9 (R=Me, R^2=H)
10 (R=CH_2Cl, R^2=H)



11



12



13
R^1=CH_2CH_2Ph

To sum up, resorcinarenes can be used in a three-step templation process. The first step involves tethering four molecules to the template. The second then links the newly tethered molecules together. The third step involves the removal of the resorcinarene template to yield the new macrocycle.[42]

We are just beginning to explore the physicochemical properties of these new macrocycles; their very nature suggests some interesting discoveries may lie ahead. Additionally, there is the possibility of using these compounds as starting points for further manipulations. Their relatively high degree of functionality suggests that they may open the way up to a range of fascinating compounds. In short, these compounds open up some interesting possibilities. However, the latent power of resorcinarene templation will only be realized by expanding beyond the synthesis of the aromatic crown ethers described here. For this to occur, and the synthesis of a disparate range of macrocycles to be realized, each variable in the protocol must prove adaptable. There are three such variables: 1) the template, 2) how and what type of moieties are tethered to the template, 3) how and what type of moieties are added during the second stage linking. We will examine each of these in turn.

By far, the most common resorcinarenes are those composed of four resorcinol rings.[29–31] These tetramers represent the global thermodynamic minimum in the acid-catalyzed Friedel–Crafts alkylation of resorcinol with aldehydes or acetals. These reactions produce a myriad of linear and cyclic oligomers; the trick is to choose a solvent combination that persuades the poorly soluble cyclic tetramer to precipitate out of solution. Le Chatelier's principle then takes care of the rest. Access to other resorcinarenes could open the way to the templation of larger macrocycles, and in this regard, the determination of processes that allows the isolation of

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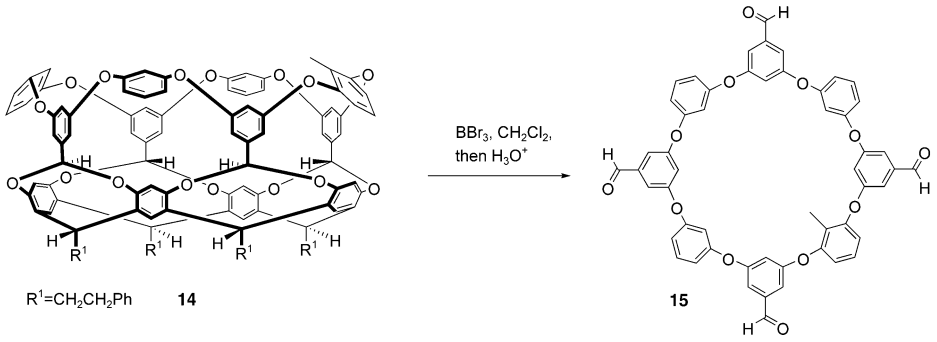
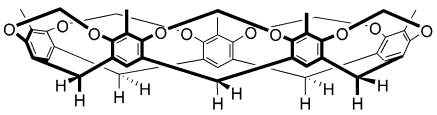


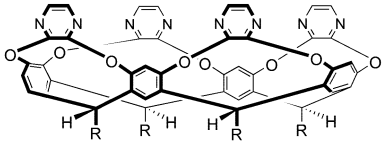
Scheme 6. Synthesis of macrocycle **15**.

resorcinarenes that contain five, six, and seven resorcinol rings is of considerable interest.[43, 44] Most recently, these resorcinarenes have also been converted to their corresponding methylene bridged cavitands, for example, **16**.[45] Unfortunately, "wide-bodied" resorcinarenes are kinetic products of the normal reactions used to make the cyclic tetramers, and can only be isolated in low yield. In addition, a 2-methyl group on the resorcinol ring is necessary to avoid alkylation reactions at this point from competing with the pathways leading to the desired products. This structural requirement is unfortunate as it may prevent moieties that are tethered to a calix[5]resorcinarene template from adopting a suitable conformation for the second-stage linking. Taken together, these points suggest that for the moment we are currently restricted to using calix[4]resorcinarenes as templates. Hopefully this will change in the future.

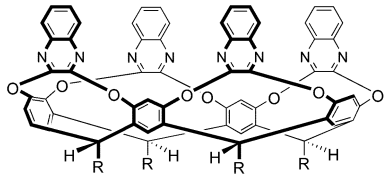


16

In terms of tethering moieties to the template, doing this while linking together the phenolic pairs is perhaps the obvious choice, as the resulting cavitand is much more preorganized than the starting resorcinarene. This is not to say that other connection points cannot be envisioned, but they do not benefit from this increase in preorganization. Concentrating therefore just on phenol bridging, we can also note that there is not much space at the base of the cavity where the benzal hydrogen atoms in structure **2** are located. Hence, a bridging process must be utilized that either places nothing larger than a methyl group at this position, or does not result in any such inward pointing groups. Although the stereoselective bridging of resorcinarenes with benzal bromides was the first documented example of inserting stereogenic carbon bridges,[34] it was by no means the first case of stereoselective bridging of resorcinarenes. There have been, for example, many reported cases of stereoselective bridging with phosphorus species.[46] Thus, at least in terms of stereochemistry, stereoselective bridging does not appear to be a problem, and, in theory, many different moieties could be attached to the resorcinarene template in this manner. There are also a number of non-stereoselective bridging processes that may be ripe with possibilities. Reactions analogous to those used in the synthesis of pyrazine- or quinoxaline-bridged resorcinarenes **17** and **18** may prove fruitful in this regard,[47] even though these cavitands are less rigid than benzal bridged cavitands such as **3**.



17
R=alkyl



18
R=alkyl

Irrespective of the approach, bridging the phenolic groups of a resorcinarene results in a truncated, cone-shaped cavitand. The tapered sides of the cavitand mean that the distance between the remote ends of the molecules tethered to the template increases as the tethered molecules themselves increase in length. Put another way, the longer the molecules tethered to the template, the larger the subsequent molecules used to link them can be. We will come back to this point.

A note of caution regarding the method by which molecules are tethered to the template is warranted. At some point the template must be removed. Hence, the tethers between the molecules and the template must be broken by using chemistry that does not destroy the nascent macrocycle. In the example we have described, the orthogonality between (fairly resistant) acetals and aryl ethers is good. Along similar lines, care will be required in designing alternative tethering protocols to ensure that the template can be readily cleaved from the target macrocycle. This point not withstanding, it is apparent that a broad range of molecules may be tethered to the phenolic pairs of resorcinarenes.

With the second stage of the templation process in mind, it seems reasonable to assume that reactions other than Ullman ether reactions could be used to link the preorganized subunits on the template. How successful such reactions ultimately are will depend on the source of the high yields observed when, for example, **3** is converted to **4**. If these high yields are solely the result of templation by the resorcinarene, rather than templation by metal ions, then it should be possible to efficiently link many different resorcinarene-

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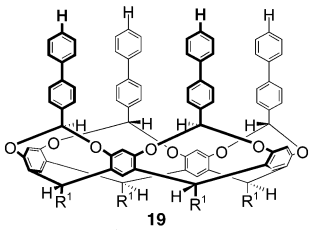
templated moieties. Presumably, a general rule that will be identified is that the efficiency of this step will be dependant on the rigidity of the four moieties on the template, and the four being introduced. The linking reactions should not of course cause the deleterious decomposition of the templation intermediate. For example, deep-cavity cavitands of general structure **2** are acetals and can decompose under acidic conditions. For this family of molecules the substituent on the benzal moiety is crucial. Cavitand **2** (X = 4-OH) rapidly decomposes in the presence of catalytic amounts of acid.[48] However, other members of the family decompose much more slowly and could, in theory, be amenable to a fast linking step under acidic conditions. Hence, a safe guiding principle would be to focus on linking strategies under basic or neutral conditions. Barring these provisos, and the point that it must be possible to cleave the macrocycle from the template without damaging the target, it would seem that almost any suitably sized moiety could be introduced. Precisely how big the suitably sized linking moiety can be depends on the distance between the remote ends of the tethered moieties. Cavitands such as **3**, **17**, or **18** approximate to truncated cones. Hence, extending the length of the set of moieties tethered to the resorcinarene creates more space between those tethered moieties, and allows longer linking molecules to be introduced between them. Presumably, there is a trade-off here. The longer the moieties attached to the template, the less preorganized the distal ends and the less effective the template will be. Thus, the "upper" hydrogen atoms of cavitand **19**[33] are less preorganized than the equivalent



19
$R^1 = Ch_2CH_2Ph$

hydrogen atoms in unsubstituted cavitand **2** (X = H). Determining how remote the templated functional groups can be, whilst still being capable of undergoing efficient linking, will have to wait for further research. Indeed, we look forward to seeing how this variable, and the questions of template and tethering technique, evolve in the future.

Conclusion

The concept that resorcinarenes can be used as templates for the efficient synthesis of large macrocycles has been discussed. For any template to prove valuable, it must prove itself to be both available and adaptable. Resorcinarenes are certainly available. The rich and wealthy can purchase them if they so desire, the rest of us can easily synthesize them on the kilogram scale. On the other hand, the question of adaptability has yet to be addressed. They have proven themselves useful for the efficient synthesis of larger, aromatic crown ethers, but whether or not they can be creatively utilized to synthesize other new macrocycles remains to be seen. Hopefully this will turn out to be the case.

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