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Enantioselective Tail-to-Head Terpene Cyclizations by Optically Active Hexameric Resorcin[4]arene Capsule Derivatives

*Daria Sokolova, GiovanniMaria Piccini, and Konrad Tiefenbacher**

Abstract: Molecular capsules enable the conversion of substrates inside a closed cavity, mimicking to some extent enzymatic catalysis. Chirality transfer from the molecular capsule onto the encapsulated substrate has been only studied in a few cases. Here we demonstrate that chirality transfer is possible inside a rather large molecular container of approximately 1400 Å^3. Specifically, we present 1) the first examples of optically active hexameric resorcin[4]arene capsules, 2) their ability to enantioselectively catalyze tail-to-head terpene cyclizations, and 3) the surprisingly high sensitivity of enantioselectivity on the structural modifications.

Self-assembled molecular capsules enable the temporary isolation of guest molecules from the bulk solvent inside a closed cavity space.[1] Such host–guest interactions have facilitated the acceleration of reactions, and if product inhibition is overcome, also catalytic turnover.[2] Recent results indicate the growing interest in the field.[3] In a few cases, chirality transfer within a molecular container even enabled enantioselective conversions.[2k,s,4] Examples include photochemical conversions inside cyclodextrins,[5] inspired by the pioneering work of Breslow and others.[6] Moreover, optically active organocatalysts[7] or metal catalysts[8] have been successfully incorporated into molecular containers. Especially relevant for this report are catalytic reactions in which chirality transfer from a synthetic molecular container onto the substrate is purely non-covalent. The groups of Raymond and Bergman reported enantioselective aza-Cope rearrangements[9] and carbonyl-ene cyclizations[10] inside optically active molecular containers of medium size (up to approx. 450 Å^3).[11] Of particular interest for catalysis are capsules with a large inner cavity as they enable a wider reaction and substrate scope. However, as the cavity size increases, the substrate-host interactions naturally decrease as contacts from multiple sides become less likely. This raises the question of whether a chirality transfer from the capsule onto the substrate is still possible with large capsular host systems. Here we answer this question and report that enantioselective tail-to-head terpene cyclizations are indeed possible inside the large 1400 Å^3 volume of a molecular capsule. Tail-to-head terpene cyclizations have been notoriously difficult to catalyze in an enantioselective fashion. The Jacobsen group recently reported modest levels of enantioselectivity of up to 34 % *ee* for limonene, utilizing optimized state-of-the-art chiral urea catalysts.[12] Non-natural modifications, like the installation of an aryl group on the nerol substrate were required to improve substrate catalyst recognition. The results described here (up to 70 % *ee* for limonene), highlight the potential of enantioselective capsule catalysis for non-modified terpene substrates.

The resorcin[4]arene capsule, first reported by the Atwood group,[13] is one of the best-studied examples in the field as it is readily available, and offers an unusually large cavity volume of approximately 1400 Å^3.[13,14] A crystal structure revealed the ability of resorcin[4]arene **1** (Figure 1a) to self-assemble via sixty hydrogen bonds to a hexameric molecular capsule that also incorporates eight water molecules on its surface (Figure 1b). Each of the six resorcin[4]arene units formally lies at a face of a cube, while the water molecules occupy the vertices. However, the symmetry is broken as the building blocks are slightly tilted (see for instance the front resorcin[4]arene units in Figure 1b), producing a D2-symmetry and making the assembly

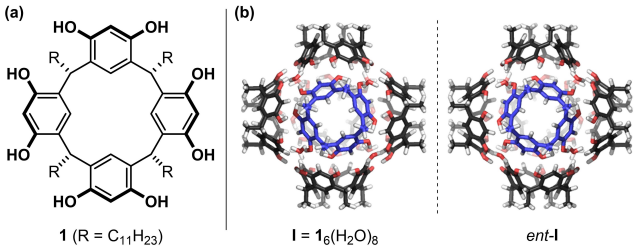

Figure 1. Self-assembly of resorcin[4]arene **1** (a) into the chiral but racemic hexameric capsule **I** (b).

[*] D. Sokolova, Prof. Dr. K. Tiefenbacher
Department of Chemistry,
University of Basel
Mattenstrasse 24a, 4058 Basel (Switzerland)
E-mail: konrad.tiefenbacher@unibas.ch

Dr. G. Piccini
Facoltà di Informatica, Istituto Eulero,
Università della Svizzera Italiana (USI)
Lugano (Switzerland)

Prof. Dr. K. Tiefenbacher
Department of Biosystems Science and Engineering,
ETH Zurich
Mattenstrasse 26, 4058 Basel (Switzerland)

chiral. As building block **1** is achiral, a racemic capsule mixture is formed. Moreover, the two capsule enantiomers should rapidly interconvert (racemize) as only a slight rotation of each building block is required.[15] Although enantioenriched resorcin[4]arene derivatives have been described,[16] to our knowledge, there are no reports of such derivatives forming enantioenriched self-assembled capsules. This is most likely due to the steric bulk installed at the resorcin[4]arene rim in most literature examples that prevents self-assembly. Our group reported that the encapsulation of chiral, optically active amines induces some handedness onto the capsular system.[17] However, the uptake and protonation of the chiral amine prevent reactions from taking place inside the cavity. Hence, there are no reports about enantioselective catalysis inside the resorcin[4]arene container that involve a chirality transfer from the capsule onto the product. The few examples reported for enantioselective catalysis inside **I**, utilize a chiral co-catalyst (L-proline) that covalently transfers its chirality onto the product via iminium intermediates.[7a,c,18] While there are no reports of enantioenriched capsule **I** derivatives, other enantioenriched molecular capsules that are catalytically active are known.[2k] The tetrahedral gallium-phenolate capsule, developed by the Raymond group,[19] was utilized for enantioselective aza-Cope[9] and Prins[10] cyclizations. A reasonable transfer of chirality (with *ee*s in the 60s) was achieved inside the relatively small capsular host that features a volume of up to approximately 450 Å^3.[11]

At the outset of this project, we envisioned two alternative strategies to turn the achiral resorcin[4]arene moiety **1** into a chiral derivative still able to assemble to a hexameric capsule. First, the installation of chiral residues at the R-"feet" of **1** was explored (Figure 2a). Interestingly, chiral feet derivatives of **1** have been reported by the groups of Mattay and Rebek,[16i,20] however, their self-assembling properties to hexameric capsules remained unexplored. Derivatives **2a**–**b** were prepared according to the literature procedure from the respective chiral aldehydes ((*S*)-citronellal or vitamin D2) and resorcinol.[20] In addition, we prepared a third derivative, **2c**, via a similar strategy in three steps starting from (*S*)-3-phenyl butyric acid (see Supporting Information chapter 2). The second strategy involved breaking the symmetry of **1** via mono-phenol alkylation to produce derivatives **3a**–**c** (Figure 2b). A monobenzylation of **1** has been reported by Konishi,[21] however, neither chiral resolution nor its self-assembling properties have been studied. While the monoalkylation strategy produced the desired chiral derivatives **3a**–**c** directly in one step from **1**, the separation of the enantiomers proved difficult. After extensive screening, separation via preparative HPLC using the Chiralpak IB N-5 column was successful. One enantiomer of each derivative (**3a**–**c**) was obtained in pure form and fully characterized (see Supporting Information chapter 2).

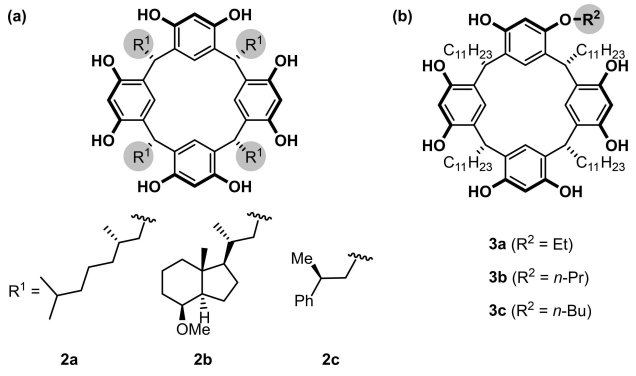

Figure 2. Chiral derivatives of resorcin[4]arene investigated. They either carry the chiral information at the feet (a), or the rim of the macrocycle(b).

With six chiral, optically active resorcin[4]arene derivatives in hand, their ability to self-assemble to hexametric capsules was explored. Diffusion ordered spectroscopy (DOSY) NMR has been established as a reliable tool to interrogate assembly sizes in solution as demonstrated conclusively by the Cohen group.[22] Accordingly, all derivatives (**2a**–**c**, **3a**–**c**) were studied under conditions typically utilized for catalysis inside capsule **I** (20 mM, $CDCl_3$, 30 °C). The translational diffusion coefficients (D) obtained ($0.23–0.27 \times 10^{-9}$ m^2 s^{-1}, Supporting Information chapter 5.1) are in good agreement with the hexameric parent capsule **I** (0.23×10^{-9} m^2 s^{-1}). Smaller assemblies would have substantially larger diffusion coefficients.[23] Furthermore, encapsulation studies with tetrabutylammonium bromide (TBAB) were performed for all novel capsules. Encapsulation and a slow guest exchange on the ^{1}H NMR scale were observed in all cases (Supporting Information chapter 5.2); similarly to the parent capsule formed from resorcin[4]arene **1**. Accordingly, we concluded that all derivatives likely self-assemble to hexameric capsules in chloroform solution. This result is not surprising for derivatives **2a**–**c**, as they feature the same hydrogen bonding motifs as the parent compound **1**. However, the results for **3a**–**c** are not obvious, as one hydrogen bond donor on each resorcin[4]arene is blocked and the formed alkyl ether moiety presents a steric disturbance to the elaborate hydrogen bond network of capsule **I**. However, we recently demonstrated in another context that the self-assembly process of **I** tolerates some covalent modifications close to the hydrogen bonding motifs.[24] The optically active capsules were characterized by optical rotation measurements, and ECD spectroscopy (Supporting Information chapter 3). These characterization methods along with TD-DFT calculations enabled us to assign the axial chirality and optical activity for **3a**–**c** (Supporting Information chapter 3).[25]

Our group has demonstrated that tail-to-head monoterpene cyclizations performed inside capsule **I** display distinct product selectivities that differ from regular bulk solution reactivity.[26] For the study of enantioselective catalysis, the cyclization of nerol is best suited as it produces a chiral main product, α-terpineol (Figure 3). Besides the achiral main products eucalyptol and α-terpinene, also chiral limonene is formed.

Hence, nerol cyclization studies were performed with the chiral, optically active resorcin[4]arene derivatives **2a**–**c** and **3a**–**c** under the standard reaction conditions established for

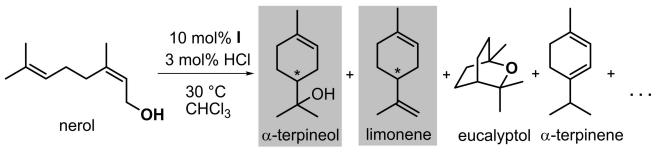

Figure 3. The capsule **I**-catalyzed cyclization of nerol produces two chiral products, α-terpineol and limonene, and was chosen to explore the potential for enantioselective catalysis inside the capsules formed from derivatives **2a–c** and **3a–c**.

capsule **I**: 10 mol % capsule, 3 mol % HCl, 20 mM in $CDCl_3$, 30 °C. The reactions were monitored by achiral GC with a focus on the two chiral products of the cyclization, α-terpineol and limonene. The enantiomeric ratio of the products was determined by chiral GC measurement, utilizing commercially available samples of racemic and enantioenriched α-terpineol and limonene as reference compounds. The results of these studies are summarized in Table 1 and provide additional strong evidence for the self-assembly of hexameric capsules for all derivatives **2a–c** and **3a–c**. In all cases, significant amounts of α-terpineol are produced, in analogy to the parent system **I**, indicating that the conversion takes place inside a capsular host closely related to the parent hexameric host. Similarly to **I**, catalytic turnover was observed (TON = 10). The results concerning the optical activity of the products formed demonstrate that the chiral feet derivatives **2a–c** are not suitable for transferring chirality onto the cyclization products. In all three cases (entries 1–3), no significant enantioselectivities were observed. Interestingly, the rim-functionalized derivatives **3a–c** displayed a different behavior. Ethyl derivative **3a** produced α-terpineol with some enantioselectivity (e.r. 59:41 (±1)), entry 4), favoring the (*S*)-enantiomer. The other chiral product, limonene, however, was produced in racemic form. Most interestingly, the monopropyl derivative **3b** performed best in catalysis, producing (*S*)-(−)-limonene (e.r. 81:19 (±1)) and (*S*)-(−)-α-terpineol (e.r. 74:26 (±1)) after 24 h of reaction time. The enantioselectivity was also monitored during the reaction, and no significant changes in *ee* were observed (Figure S24). Furthermore, by performing the reaction at 4 °C, the enantioselectivity was further increased to 70 % *ee* (e.r. 85:15 (±1)) for limonene and 60 % *ee* (e.r. 80:20 (±1)) for α-terpineol (Supporting Information chapter 4.5)). Such levels of enantioselectivity are noteworthy, as it is comparable to that achieved for other reactions by the significantly smaller (approximately 400 $Å^3$) state-of-the-art capsule system.[9,10] Moreover, the Jacobsen group demonstrated how challenging the enantioselective catalysis of tail-to-head terpene cyclizations is.[12] State-of-the-art chiral urea catalysts enabled only modest levels of enantioselectivity of up to 34 % *ee* for limonene. Non-natural modifications, like the installation of an aryl group, on the nerol substrate were required to improve substrate catalyst recognition, highlighting the potential of enantioselective capsule catalysis for non-modified terpene substrates presented herein. To our knowledge, only chiral leaving groups were successful in performing such cyclizations on unmodified terpenes previous to this report.[27] Intriguingly, the slightly larger butyl derivative **3c** produced only racemic material (entry 6). To support this surprising finding by excluding potential signal overlap in the chiral GC, the other enantiomer of the best performing catalyst building block **3b** was isolated. When submitted to the standard reaction conditions, it indeed delivered the same high levels of enantioselectivity for the two main products, limonene and α-terpineol, however, as expected, favoring the other product enantiomer (entry 7). In previous work, we demonstrated that the water content can have a substantial impact on conversion and yield.[26b,28] Higher water content generally reduced conversion for terpene cyclizations. Interestingly, Reek and co-workers recently presented evidence that a Diels–Alder reaction is accelerated by capsule **I** at higher water concentration, and proposed a water-expanded capsule as the catalytically active species..[3d] Moreover, recent studies by the Thompson group highlighted the different interaction modes of water and capsule **I**.[29] Therefore, the effects of different water content were examined (Supporting Information chapter 4.4). As observed in our previous studies, a low water content (6.3 equiv/capsule) leads to the fastest conversions. The influence on the enantioselectivity, however, was very modest. The standard conditions (8.0 equiv water/capsule) are superior, especially concerning the yield of the chiral products, limonene and α-terpineol.

The high sensitivity of product enantioselectivity on the structural modifications of the capsule building blocks was surprising to us. While the ethyl- and butyl-derivatives **3a**

Table 1: Results of the nerol cyclization reaction inside capsules based on resorcin[4]arenes **2a–3c**. Reaction conditions: 10 capsule, 3 mol % HCl, 20 mM in $CDCl_3$, 30 °C, 24 h. Yields and enantiomeric ratios were determined by GC measurements. Reactions were performed in triplicate and standard deviations were determined.

Entry	Capsule	α-Terpineol Yield [%]	e.r. (*S*/*R*)	Limonene Yield [%]	e.r. (*S*/*R*)	Conversion [%]	Yield of Chiral Products [%]	Yield of Achiral Products [%]
1	**2a**	13 ± 3	49:51 (±0)	5 ± 1	49:51 (±1)	98 ± 1	18 ± 4	24 ± 5
2	**2b**	34 ± 1	53:47 (±0)	10 ± 1	53:47 (±2)	95 ± 1	44 ± 1	20 ± 1
3	**2c**	34 ± 3[a]	50:50 (±1)	9 ± 1[a]	50:50 (±2)	80 ± 3[a]	43 ± 3[a]	15 ± 1[a]
4	(−)-**3a**	16 ± 4[b]	59:41 (±1)	8 ± 2[b]	52:48 (±1)	65 ± 7[b]	24 ± 4[b]	10 ± 2[b]
5	(−)-**3b**	43 ± 2	74:26 (±1)	30 ± 3	81:19 (±1)	99 ± 1	73 ± 3	25 ± 2
6	(−)-**3c**	20 ± 1[b]	53:47 (±1)	10 ± 1[b]	52:48 (±1)	62 ± 1[b]	30 ± 2[b]	15 ± 1[b]
7	(+)-**3b**	41 ± 1	27:73 (±1)	26 ± 1	20:80 (±2)	98 ± 1	67 ± 2	21 ± 2

[a] The values are given after 10 h of the reaction time. [b] The values are given after 8 h of the reaction time.

and **3c** failed to significantly transfer optical activity onto the products, the propyl-derivative **3b** did so rather efficiently, especially when compared to the state-of-the-art results obtained in much smaller capsules. The relatively efficient transfer of chirality in such a large capsule was certainly not obvious a priori and might be related to the activation of the substrate close to the capsule surface.[30] However, as the superior performance of **3b** remained puzzling, we decided to compare the experimental characterization data of the three assemblies. Interestingly, the ^{1}H NMR spectra of the assemblies formed feature entrapped alkyl signals with a slow exchange at the NMR time scale (Supporting Information Figure S51–S53). However, the integral of the encapsulated signal decreases from **3a** to **3c**, and therefore does not correlate with the level of enantioselectivity obtained. The only preliminary correlation we observed concerns the ECD spectra (Figure 4). The $\Delta\varepsilon$ maximum observed between 300–310 nm correlates with the enantioselectivity observed in the nerol cyclization. The $\Delta\varepsilon$ maximum, as well as the e.r. of the product α-terpineol decreases in the following order **3b** > **3a** > **3c**. However, as there are only three data points available, and the enantioselectivities obtained for **3a** and **3c** are quite similar, it remains to be seen whether this preliminary correlation is confirmed by additional derivatives.

In conclusion, we presented the synthesis of four novel enantioenriched resorcin[4]arene building blocks, and demonstrated that these derivatives are able to self-assemble to hexameric capsules. To our knowledge, these are the first reports on enantioenriched hexameric resorcin[4]arene capsules. All capsules formed showed catalytic activity in the tail-to-head terpene cyclization of nerol. The derivatives that feature the chiral information outside of the capsule's surface failed to induce enantioselective terpene cyclizations. Apparently, the distance between the chiral information and the encapsulated substrate that is additionally shielded by the capsule walls prevents a transfer of chirality. However, two of the monoalkylated derivatives that carry the chiral information at the surface of the capsule, induced significant enantiomeric excesses of up to 70 % *ee*. The enantioselectivities obtained are comparable to state-of-the-art results in smaller capsules for other reactions. As the resorcinarene hexamer capsule is quite large, which prevents efficient contact between multiple capsule walls and the substrate, such enantioselectivities were not expected a priori. The results obtained certainly augur well for performing enantioselective catalysis inside large molecular capsules. Future research will deal with optimizing chirality transfer and expanding the reaction scope.

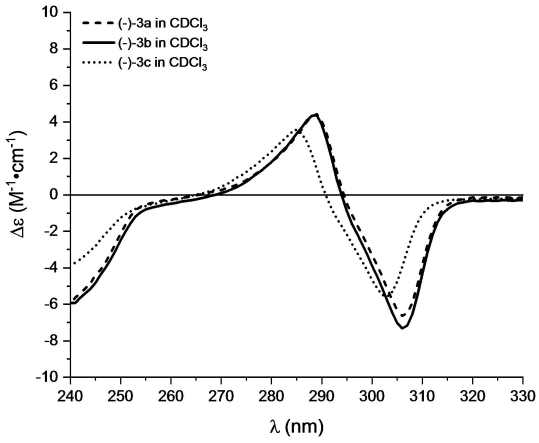

Figure 4. Comparison of the ECD spectra of (−)-**3a–3c** in chloroform.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Chiral Self-Assemblies · Enantioselective Catalysis · Resorcinarene Capsules · Supramolecular Catalysis · Terpene Cyclization

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