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Synthesis and Functionalization of Inherently Chiral Tetraoxacalix[2]-arene[2]pyridines

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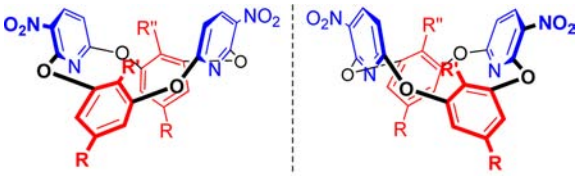
ABSTRACT



Inherently chiral tetraoxacalix[2]arene[2]pyridines containing C_2 symmetry were synthesized efficiently from a macrocyclic condensation reaction of resorcinol derivatives with 2,6-dichloro-3-nitropyridine in a one-pot reaction manner, while tetraoxacalix[2]arene[2]pyridine with an ABCD-substitution pattern was prepared in a good yield by means of a stepwise fragment coupling approach. Postmacrocyclization chemical manipulations led to functionalized tetraoxacalix[2]arene[2]pyridines. A racemic sample was resolved into enantiopure (+)- and (−)-inherently chiral compounds.

Heteracalixaromatics are a new generation of macrocyclic host molecules in supramolecular chemistry.[1] Being different from the methylene linkages in conventional calixarenes, heteroatoms such as nitrogen can adopt different electronic configurations and, more remarkably, form various conjugation systems with their adjacent aromatic rings. As a consequence, bond lengths and bond angles of bridging elements are varied, resulting in a wide array of conformation and cavity self-tunable macrocycles.[2] The interplay between heteroatoms and (hetero)aromatic rings also engenders synthetic macrocyclic receptors' tunable electronic features that are essential in molecular recognition toward electron-neutral or charged guest species.[3−8]

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Inherently chiral calixarenes are chiral calixarenes not based on a chiral subunit but on the absence of a plane of symmetry or an inversion center in the molecule.[9−11] A large number of racemic inherently chiral calixarenes have been synthesized, and some of them have been resolved into enantiomerically pure form.[9−11] Applications of inherently chiral calixarene derivatives in molecular recognition[12] and asymmetric catalysis[13] have been demonstrated.

Owing to the intrinsic structural features,[1] we envisioned that heteracalixaromatics would provide a unique platform for the construction of inherently chiral macrocycles. The combination of different heteroatoms in the bridging positions with various (hetero)aromatic rings can foreseeably lead to an unlimited amount of inherently chiral heteracalixaromatics. Inherently chiral heteracalixaromatics can be roughly cataloged into three subtypes based on their aromatic building units and bridging elements. For example, differing only the aromatic rings or the bridging heteroatoms would result in *type*-1 or *type*-2 inherently chiral heteracalixaromatics, respectively, while *type*-3 inherently chiral heteracalixaromatics are constructed by varying both aromatic rings and heteroatom linkages.

We reported in 2004 the synthesis of azatrioxa- and triazaoxacalix[2]arene[2]triazines, *type*-3 inherently chiral macrocyclic compounds, based on the fragment coupling protocol.[1] A number of *type*-3 and *type*-1 inherently chiral hetaracalixaromatics have been synthesized by us,[14] Katz,[15] and Siri[16] since then using a similar stepwise synthetic strategy with or without isolation of linear "trimeric" intermediates. It is interesting to note that whereas the reaction between 1,3-dihydroxybenzene and 2,4-dichloroquinazoline gives a regioisomeric mixture of tetraoxacalix[2]arene[2]quinazolines,[17] the simple one-pot condensation reaction between 3-aminophenols or 4-substituted 1,3-phenylenediamine and 1,5-difluoro-2,4-dinitrobenzene regioselectively affords *type*-3 inherently chiral diazadioxa or tetraazacalix[4]arene products in moderate to good yields.[15] The *type*-1 inherently chiral azacalix[2]arene[2]pyridines have also been obtained from a desymmetrical *m*-bromination reaction of the pyridine moiety of the parent symmetric macrocycle.[18] Few *type*-2 inherently chiral heteracalixaromatics are known in literature,[3c,19] and among them 1,3-alternate azacalix[4]pyridines bearing two different substituents on the alternating nitrogen bridges are the representative examples.[3c] Our interest in the supramolecular chemistry of heteracalixaromatics has led us to undertake the current study. We report herein the efficient synthesis of inherently chiral tetraoxacalix[2]arene[2]pyridines with C_2 symmetry from the one-pot reaction between 1,3-dihydroxybenzene derivatives and 2,6-dichloro-3-nitropyridine. Employing the fragment coupling approach, we have also prepared an inherently chiral tetraoxacalix[2]arene[2]pyridine with an ABCD-substitution pattern. Facile postmacrocyclization chemical manipulations allowed us to conveniently construct the functionalized inherently chiral macrocycles and calix-crown molecule. Resolution of a racemic sample by means of HPLC with a chiral stationary-phase-coated column will also be presented.

We initiated our study with the examination of the reaction between resorcinol **1a** and 2,6-dichloro-3-nitropyridine **2** in a 1:1 stoichiometry (Table 1). The reaction proceeded effectively at 60 °C in DMSO in the presence of 2 equiv of Cs_2CO_3 as an acid scavenger. Remarkably, the inherently chiral tetraoxacalix[2]arene[2]pyridine **3a** was isolated as the sole product in 56% yield. The macrocyclic condensation reaction was then found to be very efficient for the synthesis of functionalized inherently chiral macrocyclic products. For example, the employment of resorcinol analogs **1b**−**f** that bear an alkoxy group at the 5-position, which were prepared readily from monoalkylation of 1,3,5-trihydroxybenzene (see Supporting Information (SI)), under identical conditions afforded the corresponding inherently chiral compounds **3b**−**f** in good yields (entries 2−6, Table 1). A high yield of the upper-rim bishydroxylated inherently chiral tetraoxacalix[2]arene-[2]pyridine **3g** was obtained from the reaction of **2** with 1,3,5-trihydroxybenzene **1g** (entry 7, Table 1). In this case, the free phenolic hydroxyl groups on the upper-rim position remained intact. Inherently chiral tetraoxacalix-[2]arene[2]pyridines functionalized on the lower-rim position were also successfully synthesized by means of the same one-pot reaction approach. This has been exemplified by the preparation of the bisformyl-substituted tetraoxacalix[2]arene[2]pyridine **3h** using 2,6-dihydroxybenzaldehyde **1h** as a starting bisnucleophilic component (entry 8, Table 1). It was also noteworthy that the one-pot reaction worked equally well with 2,5-disubstituted resorcinol derivatives such as 5-*tert*-butybenzene-1,2,3-triol. The reaction produced inherently chiral tetraozacalix[2]arene-[2]pyridine **3i** that contains substituents at both lower and upper rims. It should be addressed that all reactions tested in the study afforded inherently chiral tetraoxacalixaromatics

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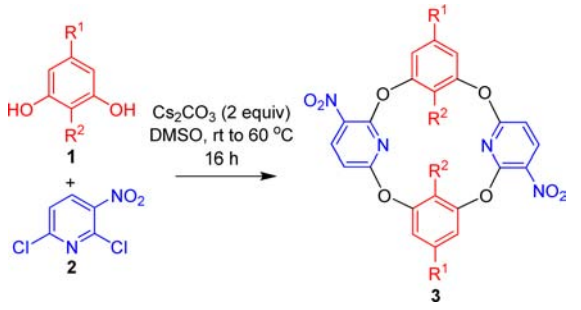
exclusively. In other words, two nitro groups are dissymmetrically positioned on the opposing benzene rings, generating C_2 symmetry within the macrocyclic scaffold. No symmetric products were observed in the reaction.

Table 1. Synthesis of **3** from One-Pot Reaction of **1** with **2**[a]

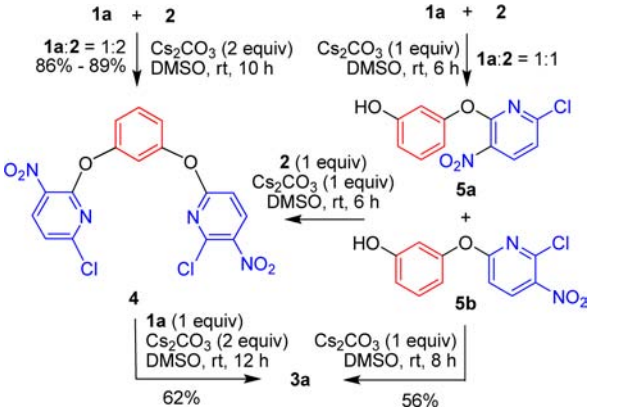


entry	1	R^1	R^2	3	yield (%)[b]
1	**1a**	H	H	**3a**	56
2	**1b**	CH_2=$CHCH_2O$-	H	**3b**	78
3	**1c**	$CH_3CH_2CH_2O$-	H	**3c**	75
4	**1d**	CH_2=$CHCH_2CH_2O$-	H	**3d**	80
5	**1e**	$CH_3CH_2CH_2CH_2O$-	H	**3e**	73
6	**1f**	$MeOCH_2CH_2OCH_2O$-	H	**3f**	84
7	**1g**	OH	H	**3g**	82
8	**1h**	H	CHO	**3h**	50
9	**1i**	$(CH_3)_3C$	OH	**3i**	56

[a] A 1:1 stoichiometric ratio between two reactants was employed. [b] Isolated yield.

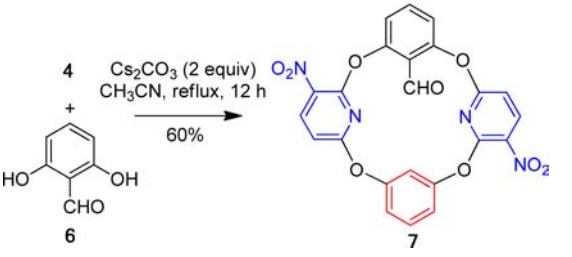
The pronounced regioselectivity of the macrocyclic condensation reaction between resorcinol derivatives **1** and 2,6-dichloro-3-nitropyridine **2** was highly intriguing. To shed light on the origin of the highly regioselective macrocyclization, the following experiments were conducted (Scheme 1). The interaction of resorcinol **1a** with 2 equiv of **2** at rt in DMSO exclusively gave a linear trimeric product **4** in 10 h. Acetonitrile as solvent gave an analogous result while other nonpolar solvents had a detrimental effect on the reaction. On the basis of ^{1}H and ^{13}C NMR spectroscopic data, the resulting compound **4** is dissymmetrically substituted. Further treatment of the trimer **4** with an equimolar amount of **1a** furnished the formation of the inherently chiral macrocyclic product **3a** in 62% yield. We also tested the reaction of an equimolar mixture of **1a** and **2** at rt in the presence of 1 equiv of Cs_2CO_3. After 6 h, an isomeric mixture of products **5a** and **5b**, which was not separable by chromatography, was observed. The ratio of two isomers was roughly 1:1 based on integration of the intensity of resonance signals in the ^{1}H NMR spectrum. Interestingly, two isomers in the mixture were converted into a single inherently chiral tetraoxacalix[2]arene[2]-pyridine product **3a** after a prolonged period of time after addition of another equivalent of base. Finally, treatment of the mixture of the two isomers with another equivalent of **2** gave rise to the formation of trimer **4**. The outcomes convincingly indicated that a stepwise approach to inherently chiral tetraoxacalix[2]arene[2]pyridine proceeds through dissymmetrical linear trimer intermediate **4**, whereas the direct one-pot condensation reaction between resorcinol **1a** and 2,6-dichloro-3-nitropyridine **2** produces first dimeric isomers **5a** and **5b**, which then undergo respectively *self* rather than *crossover* condensation. The convergent formation of either the final macrocyclic product **2** or the linear trimer **4** implied the most likely thermodynamically controlled nature of the reactions.

Scheme 1. Reactions between **1a** and **2**



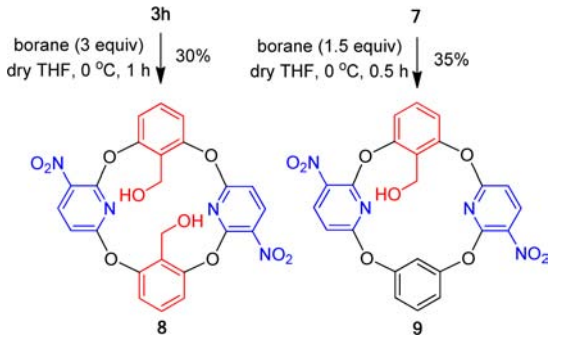
Taking advantage of the easy formation of a dissymmetric linear trimer **4** and its reactivity toward 1,3-dihydroxybenzene, the synthesis of inherently chiral tetraoxacalixaromatics with an ABCD-substitution pattern was attempted. Thus, the reaction between **4** and 2,6-dihydroxybenzaldehyde **6** in refluxing acetonitrile afforded the desired product **7** in 60% yield (Scheme 2). Neither **3a** nor **3h** was formed, indicating the stability of the diaryl ether bond which did not undergo a scrambling reaction.

Scheme 2. Synthesis of **7** with a ABCD-Substitution Pattern



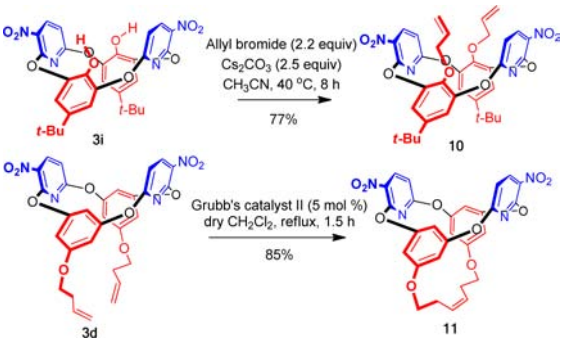
The resulting tetraoxacalixaromatics serve as versatile platforms for the fabrication of sophisticated macrocyclic host molecules because of the preinstallation of transformable functional groups such aldehyde, hydroxy, nitro, and olefin. As illustrated in Scheme 3, for example, reduction of aldehyde in compounds **3h** and **7** using borane at 0 °C gave hydroxymethylated inherently chiral molecules **8** and **9**, respectively. These molecules and compounds **3g** and **3i** that contain phenolic units may act as hydrogen

Scheme 3. Preparation of **8** and **9**



bond donors in molecular recognition and self-assembly. *O*-Alkylation of **3i** with allyl bromide with the aid of Cs_2CO_3 led to product **10** in which the rotation of benzene rings around the macrocyclic annulus is prohibited because of the steric hindrance of bulky substituents (Scheme 4). An inherently chiral tetraoxacalix[2]arene[2]pyridine-crown type molecule **11** was also readily prepared in high yield from the ring closure metathesis of but-3-enyloxy-substituted oxacalixaromatics **3d** catalyzed by the second generation Grubbs catalyst[20] (Scheme 4).

Scheme 4. Synthesis of **10** and **11**



To resolve samples of prepared inherently chiral tetraoxacalix[2]arene[2]pyridines, high efficiency liquid chromatography (HPLC) was employed using columns that are coated with chiral stationary phases. While most of the racemic inherently chiral teraoxacalix[2]arene[2]-pyridines were not resolved, separation of a pair of enantiomers of compound **10** was successfully achieved on a DAICEL Chiralcel ADH column. Circular dichroism (CD) spectra of (+)- and (−)-enantiomers, which were depicted in Figure 1, showed perfect mirror images. The absolute stereochemistry of enantiomers was assigned based on DFT calculations of electronic circular dichroism spectra (see SI).

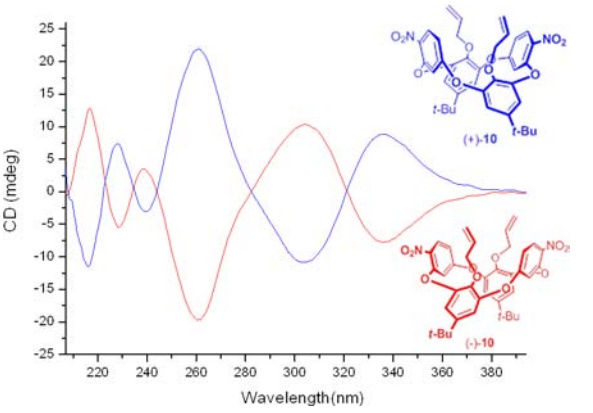


Figure 1. CD of (+)- and (−)-**10**.

In summary, we have developed an efficient one-pot reaction protocol for the preparation of various inherently chiral tetraoxacalix[2]arene[2]pyridine compounds that contain C_2 symmetry starting from readily available resorcinol derivatives and 2,6-dichloro-3-nitropyridine. We have also synthesized an inherently chiral tetraoxacalix-[2]arene[2]pyridine with an ABCD-substitution pattern using a stepwise fragment coupling approach. Postmacrocyclization chemical manipulations through the transformation of preinstalled functional groups have provided useful methods for the construction of functionalized macrocyclic products. Resolution of a racemic sample on an HPLC column coated with a chiral stationary phase gave, for the first time, enantiomerically pure (+)- and (−)-inherently chiral heteracalixaromatics.

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Supporting Information Available. Experimental details, ^1H and ^{13}C spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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