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Synthesis of Electron-Deficient Oxacalix[2]arene[2]triazines and Their Isomeric Analogs from a One-Pot Reaction of Perfluorinated Dihydroxybenzenes with Dichlorotriazines

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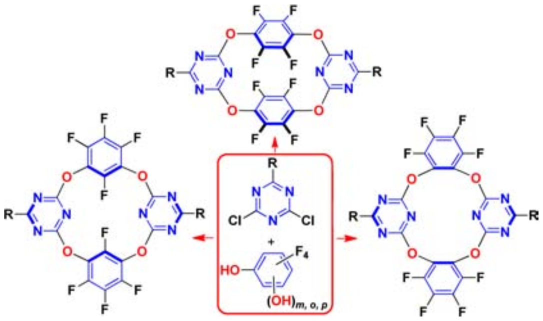
ABSTRACT



Efficient synthesis of tetraoxacalix[2]perfluoroarene[2]triazines and their isomeric analogs from a one-pot macrocyclic condensation reaction of methoxy- and amino-substituted dichlorotriazines with tetrafluorobenzene-1,3-, -1,4-, and -1,2-diols was developed. X-ray analysis demonstrates that they adopt drastically different 1,3-alternate conformations in the crystalline state while in solution they undergo very fast conformational changes relative to the NMR time scale.

Heteracalixaromatics, or heteroatom-bridged calix(het)arenes, are a new generation of macrocyclic host molecules in supramolecular chemistry.[1] By means of the fragment coupling approach (FCA)[1,2] and one-pot macrocyclic condensation reaction,[1,3] a wide variety of heteracalixaromatics, including functionalized and both symmetrically and unsymmetrically substituted ones, have been successfully synthesized from simple and easily available starting materials.[4–6] Because of the easy chemical manipulations on both aromatic units and bridging heteroatoms, heteracalixaromatics provide versatile platforms for the

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construction of sophisticated macrocycles[7] and high-level molecular architectures.[8] Due to the electronic and steric effects of heteroatoms in the linking positions, heteracalixaromatics adopt interesting conformational structures in which various conjugational systems between heteroatoms and aromatic rings are formed.[2,9,5b] The interplay between heteroatoms and their adjacent aromatic rings also plays a very important role not only in fine-tuning the structure and size of the macrocyclic cavity but also in regulating the electronic features and therefore the molecular recognition properties of the resulting macrocyclic hosts. It is particularly worth addressing that various heteracalixaromatics have found diverse applications ranging from recognition of metal ions,[11] anions,[12] neutral organic molecules[13] including fullerenes[2,9,14] and chiral molecules,[15] fabrications of HPLC stationary phases for analysis of complex samples[16] and of Langmuir–Blodgett films for voltammetric analysis,[17] discrete coordination cages,[18] organometallic clusters,[19] and infinite metal–organic frameworks.[20] Azacalixarenes have also been shown as promising CO_2 absorbents[21] and spin-electronic materials.[22]

As a member of heteracalixaromatics, oxacalix[2]arene[2]triazine[2a] shows powerful capability to selectively complex various anions of different geometries and shapes.[12] As revealed by the X-ray crystallography, two triazine rings embedded in a macrocycle form a tunable electron-deficient cleft, chelating an anion through typical anion–π interaction and lone-pair electron–π interaction. It has also been demonstrated theoretically and experimentally that the presence of electron-withdrawing groups enhances triazine's power to complex an anion species.[12a] Our interest in the supramolecular chemistry of heteracalixaromatics[1] and anion–π interactions[12] led us to undertake the current study. We envisioned that the replacement of benzene units in oxacalix[2]arene[2]triazine by perfluorobenzene moieties would result in a more electron-deficient macrocycle. To understand the bridging pattern on the conformational structures, macrocycles that are composed of triazine and tetrafluorobenzene-1,2- or -1,4-diols were also included in our study. We disclose herein the efficient synthesis of oxacalix[2]perfluoroarene[2]triazines and their isomeric analogs from a one-pot macrocyclic condensation reaction of methoxy- and amino-substituted dichlorotriazines with tetrafluorobenzene-1,3-, -1,4-, and -1,2-diols. Conformational structures of the resulting macrocycles in the solid state and in solution phase are also reported.

We initiated our study with the synthesis of oxygen-bridged calix[2]perfluoroarene[2]triazine **4a** by means of a stepwise fragment coupling approach[2] (Scheme 1). In the presence of K_2CO_3 as a base, tetrafluorobenzene-1,3-diol **1** reacted efficiently with 2 equiv of 2,4-dichloro-6-methoxy-1,3,5-triazine **2a** at ambient temperature in dry acetone to afford intermediate **3a**. The intermediate **3a** was very reactive and underwent decomposition upon purification. To our delight, however, without isolation and purification, intermediate **3a**, formed in situ, reacted with another equivalent of **1** in refluxing acetone in 1.5 h to produce desired macrocycle **4a** as the sole product in an excellent yield. Replacement of methoxy-substituted dichlorotriazine **2a** with 2-dimethylamino-4,6-dichloro-1,3,5-triazine **2b** led to a sluggish reaction because of the lower electrophilicity of the latter. For example, in the presence of a stronger base such as Cs_2CO_3 at 30 °C, the formation of **3b** from the reaction between **1** and **2b** required 8 h. It took another 38 h to convert **3b** into a macrocyclic product. The one-pot synthesis furnished, nevertheless, oxacalix[2]perfluoroarene[2]triazine **4b** in 54% yield.

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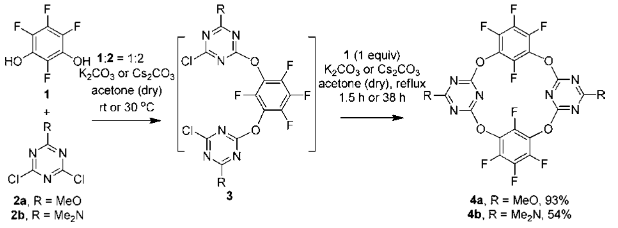
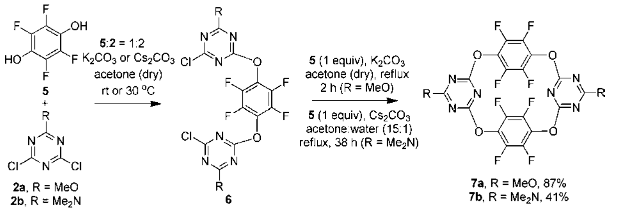
Scheme 1. Synthesis of **4**



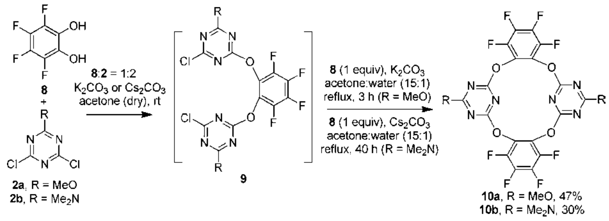
Scheme 2. Synthesis of **7**



Encouraged by the facile synthesis of oxacalixaromatics from simple operations in a one-pot reaction manner, we then attempted the preparation of macrocyclic compounds **7** and **10** that have conceivably varied conformational and cavity structures. Illustrated in Scheme 2 are the syntheses of oxygen-bridged cyclophanes from perfluorinated hydroquinone **5** and dichlorotriazines **2**. Similar to the synthesis of **4a**, a one-pot reaction between **2a** and **5** took place efficiently to give product **7a** in a high yield. Under the conditions for the preparation of **4b**, only 30% of product **7b** was obtained from the reaction of **5** with **2b**. Interestingly, the use of a small amount of water (acetone/water = 15:1) in the second step macrocyclization reaction led to the increase of chemical yield of **7b** to a 41% yield. When isolated linear trimer **6b** was employed to react with **5**, macrocycle **7b** was obtained in 65% yield. It should be noted that further optimization of the reaction conditions using other bases, solvents, and the ratio of acetone over water unfortunately did not improve the formation of macrocyclic product **7b** (see Supporting Information Table S2).

The one-pot reaction strategy was extended to the construction of another type of isomeric analogs, viz. vicinal oxygen linked cyclophanes **10** using perfluorinated catechol **8** as a building block (Scheme 3).[10] We found that the purity of reactant **8**, which was prepared from the reaction of perfluorobenzene and ethylene glycol followed by $AlCl_3$-mediated dealkylation,[23] was critical to the synthesis of **10**. Since catechol **8** also undergoes a spontaneous auto-oxidation reaction under atmospheric conditions, it was beneficial to conduct the synthesis under an inert atmosphere. By applying the optimized conditions for the synthesis of **7b**, the reaction of **8** and **2a** proceeded rapidly to yield expected product **10a** in 47% yield, whereas the same reaction between **8** and **2b** took a much longer time to go to completion giving the corresponding macrocyclic product **10b** in a slightly diminished chemical yield. Isolation of trimeric intermediates **9** was not successful in these cases due to probably their instability.

Scheme 3. Synthesis of **10**



All macrocyclic products synthesized are crystalline compounds, and their structures are established on the basis of their spectroscopic data and microanalysis results. To understand the conformation structures of oxacalix[2]perfluoroarene[2]triazines **4** and their isomeric analogs **7** and **10**, single crystals of **4a**, **4b**, **7a**, and **10a** were cultivated and their X-ray molecular structures were determined.

As depicted in Figure 1, dimethoxy-substituted oxacalix[2]perfluoroarene[2]triazine **4a** adopts a slightly twisted 1,3-alternate conformation, which is similar to its nonfluorinated counterpart.[25] The averaged bond lengths (see captions of Figure S1) of the bridging oxygen to the carbon of triazine ($d_{\mathrm{O-C(triazine)}}$) and to the carbon of tetrafluorobenzene ($d_{\mathrm{O-C(tetrafluorobenzene)}}$) are 1.36 and 1.38 Å, respectively. The smaller bond length difference indicates the formation of conjugation of bridging oxygen atoms with both triazine and tetrafluorobenzene rings, with the former being slightly stronger. The variation of a substituent on the triazine ring does not affect the conformational structure. This has been exemplified by the X-ray molecular structure of amino-substituted oxacalix[2]perfluoroarene[2]triazine **4b** which shows a highly symmetric 1,3-alternate conformation with C_{2v} symmetry (Figure S2).

The interaction of macrocycles with CH_2Cl_2 molecules in the crystalline state was worth noting. As illustrated in Figure 1B, two CH_2Cl_2 molecules are included in between two electron-deficient tetrafluorobenzene rings of **4a**. One of the chloride atoms of each CH_2Cl_2 interacts with tetrafluorobenzene rings through σ-type Cl−C ($d_{\mathrm{Cl1-C9}}$ = 3.36 Å) interactions. Interestingly, the other chloride atom of CH_2Cl_2 locates above the triazine ring of another **4a** molecule. The short contact distance between chloride and the plane of triazine is 3.42 Å ($d_{\mathrm{Cl2\text{-}plane}}$), indicating weak lone-pair electron−π interaction.

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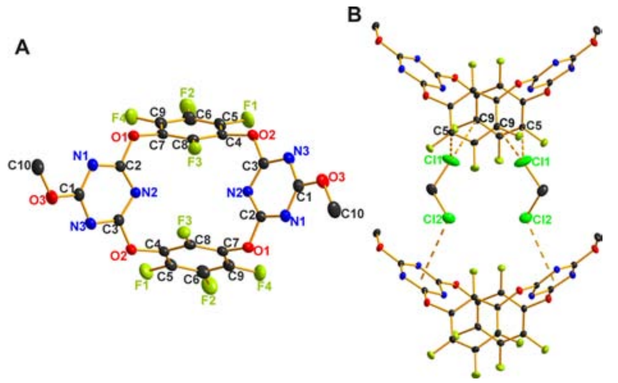

Figure 1. Crystal structure of **4a**. Top view (A) of the macrocycle and side view (B) of the complex of **4a** with dichloromethane.

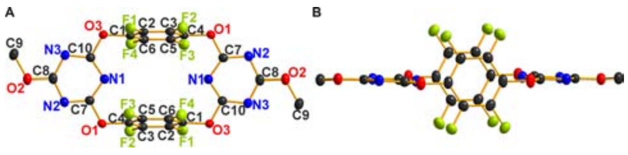

Figure 2. Crystal structure of **7a**. Top (A) and side (B) views.

As we expected, when fluorinated phenylene units are *para*- or *ortho*-linked to triazines by the bridging oxygen atoms, the resulting macrocycles adopt different conformational structures. For example, **7a** adopts a macrocyclic structure in which the two fluorinated benzene rings are face-to-face paralleled whereas the two triazine rings are edge-to-edge aligned (Figure 2). In the case of compound **10a**, macrocycle gives another type of 1,3-alternate conformation. It is worth addressing that the cavity formed by two triazine rings in **10a** is narrower (Figure 3) than that in **4a** and **4b**. The upper rim distance between two triazine rings in **10a** (Figure S4) is, for instance, 5.56 Å ($d_{C(33)-C(29)}$), while, in **4a** and **4b**, distances of 8.87 and 9.15 Å are observed, respectively in the solid state (Figures S1 and S2).

Different macrocyclic conformations derived from perfluorinated *meta*-, *para*-, and *ortho*-benzene diols indicate the effect of linkage of or the substitution pattern of benzene units on the structures. The general 1,3-alternate alignment of four aromatic rings in each macrocycle is most probably attributable to the dipole–dipole repulsion between neighboring aromatic rings.[24]

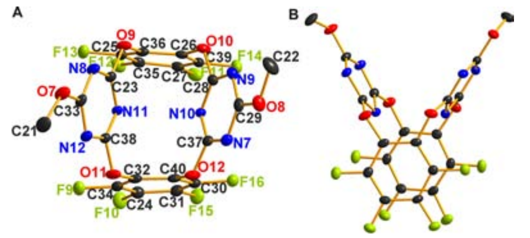

Figure 3. Crystal structure of **10a**. Top (A) and side (B) views.

It was noteworthy that all macrocyclic compounds obtained exhibit one set of proton, fluorine, and carbon resonance signals in their ^{1}H, ^{19}F, and ^{13}C NMR spectra (Figures S5–S25), respectively. For instance, only one sharp singlet signal corresponding to a methoxy or dimethylamino group was observed in their ^{1}H NMR spectra, while fluorine signals in accordance to 1,3,4,5-, 1,2,4,5-, and 1,2,3,4-tetraflurinated benzene moieties were evidenced in the ^{19}F NMR spectra of **4**, **7**, and **10**, respectively. The NMR spectroscopic features suggest that oxacalix[2]perfluoroarene[2]triazines **4** and their isomeric macrocycles **7** and **10** in solution may not retain their solid state conformation structures. It is most likely that all macrocycles are fluxional and they undergo very fast conformational changes in solution relative to the NMR time scale.

In summary, we have provided an effective and practical one-pot reaction method for the synthesis of perfluorinated oxacalix[2]arene[2]triazines and their isomeric macrocyclic analogs starting from readily available materials. Synthesized macrocycles adopt drastically different 1,3-alternate conformations in the crystalline state while in solution they undergo very fast conformational changes at rt relative to the NMR time scale. The highly electron-deficient nature of the macrocycles would render them intertesting hosts for the recognition of anion species, which is being actively investigated in this laboratory.

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Supporting Information Available. Experimental details; ^{1}H, ^{13}C, and ^{19}F NMR spectra of products; X-ray structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.