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Single-Step, Regioselective Synthesis of Diazadioxacalix[4]arenes and Diazadioxa[1_4]cyclophanes Bearing an Alternating N/O-Bridge Pattern

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Keywords: Calixarenes / Aromatic substitution / Regioselectivity / Chirality / Cyclophanes

Described is a single-step synthesis of diazadioxacalix[4]-arenes and diazadioxa[1_4]cyclophanes bearing an alternating N/O-bridge substitution pattern. The macrocycles are formed regioselectively by condensation of 3- or 4-aminophenols with 1,5-difluoro-2,4-dinitrobenzene. Conformational properties of the macrocyclic products are discussed, as well as mechanistic details of the synthesis leading to the observed bridge-pattern selectivity.

Introduction

The past decade has brought dramatic advances in methodology for the construction of aza- and oxacalixarene macrocycles.[1] Current methods of synthesis permit enhanced control over obtainable functionalization, arene identity, ring size, and bridging-atom patterns, thus facilitating the development of increasingly sophisticated applications.[2] Nucleophilic aromatic substitution (S_NAr) reactions that couple electron-deficient 1,3-dihalides with 1,3-diphenols or 1,3-diaminobenzenes have been used extensively by us[3] and others[4–6] to efficiently generate structurally diverse aza- and oxacalix[4]arenes.

Methods remain limited for the construction of N- and O-bridged heteracalix[4]arenes bearing asymmetrically positioned functional groups, even though the inherently chiral[7] nature of such compounds renders conformational rigid versions desirable as potential chiral ligands and molecular hosts.[8] Use of nonsymmetric monomers in thermodynamically controlled oxacalix[4]arene formation (e.g., from 4-substituted resorcinols or electrophiles) is problematic due to the production of regioisomeric mixtures of products.[3c] Stepwise, fragment-coupling strategies that proceed under kinetic control have proven viable, but these methods require pre-generation and isolation of linear precursors.[9] Only recently has a single-step method for the formation of asymmetrically functionalized azacalix[4]arenes been reported, by regioselective macrocyclization of 4-substituted 1,3-diaminobenzenes with 1,5-difluoro-2,4-dinitrobenzene.[3e]

We have previously disclosed a one-pot procedure for the production of asymmetrically functionalized diazadioxacalix[4]arenes.[3e] The diazadioxacalix[4]arenes were generated by using three different aromatic monomers by initial condensation of a 1,3-diaminobenzene with 2 equiv. of 1,5-difluoro-2,4-dinitrobenzene to form a linear 2:1 adduct (trimer), followed by cyclization through the addition of a 1,3-diphenol. The intermediate linear trimer need not be isolated or purified, as C–N bond formation is nonreversible, and the desired 2:1 linear adduct is formed quantitatively from an ideal stoichiometric ratio of the aromatic monomers. By using this method, a variety of diazadioxacalix[4]arenes bearing N- and O-bridges at adjacent positions (Figure 1a) were produced in good yields (66–72%), and asymmetry was imparted by use of a single 4-substituted diamine or diphenol nucleophile.

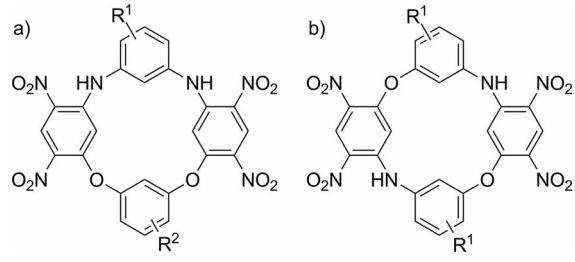

Figure 1. Diazadioxacalix[4]arenes with (a) an adjacent N/O-bridge pattern, (b) an alternating N/O-bridge pattern.

Following the success of the synthetic method described above, we sought to develop a complementary strategy for the synthesis of inherently chiral[10] diazadioxacalix[4]-arenes. It was envisaged, by taking advantage of nucleophilicity differences between arylamines and phenols and the potential for reversible C–O bond formation, that 3-aminophenols could be induced to react with 1,5-difluoro-2,4-dinitrobenzene (**1**) and regioselectively form diazadioxaca-

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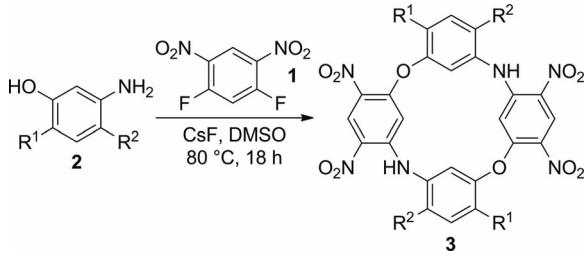
lix[4]arenes bearing an alternating pattern of N- and O-linkages (Figure 1b). This approach would allow for the selective formation of asymmetrically substituted macrocycles by use of functionalized aminophenols enforced through bridge-pattern control. 3- and 4-aminophenols were first investigated as nucleophiles in S_NAr-based heteracalix[4]arene formation in 1974.[4b] However, the described method produced mixtures of regioisomeric macrocycles that were not separated nor fully characterized. No subsequent reports of diazadioxacalix[4]arenes bearing an alternating N/O-bridge pattern have appeared in the literature. We now report that 3-aminophenols and 4-aminophenols will regioselectively condense with 1,5-difluoro-2,4-dinitrobenzene (**1**) in a single step to yield only the corresponding diazadioxacalix[4]arenes and diazadioxa[1$_4$]cyclophanes bearing alternating N/O-bridge connectivity, and we describe details of the synthetic method, our initial mechanistic investigations, and the scope of accessible macrocycles.

Table 1. Synthetic scope of diazadioxacalix[4]arenes **3**.[a]



Entry	Aminophenol	Product	Yield[b]
1	**2a** (R^1 = CH_3, R^2 = H)	**3a**	37%
2	**2b** (R^1 = H, R^2 = H)	**3b**	86%
3	**2c** (R^1 = Cl, R^2 = H)	**3c**	56%
4	**2d** (R^1 = Cl, R^2 = Cl)	**3d**	77%
5	**2e** (R^1 = OCH_3, R^2 = H)	**3e**	59%
6	**2f** (R^1 = CO_2CH_3, R^2 = H)	**3f**	53%

[a] 1.0 equiv. of aminophenol **2**, 1.0 equiv. of **1**, 10 equiv. of CsF. [b] Isolated yield after chromatographic purification.

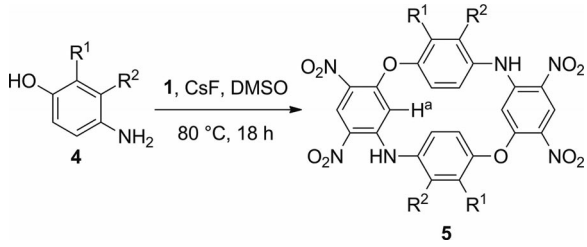
Results and Discussion

Condensation of 5-amino-2-methylphenol (**2a**) with **1** by using CsF as base in DMSO at temperatures below 60 °C led to the formation of linear species, with only small amounts of macrocycle formation evident. Extended reaction times at 80 °C slowly yielded the heteracalix[4]arene, and it was evident from ^{1}H NMR analysis that diazadioxacalix[4]arene **3a** was being selectively generated as the major product. Under optimized conditions (CsF, DMSO, 80 °C, 18 h), **3a** was formed as >80% of the unpurified reaction mixture without detectable amounts of the alternative bridge-pattern regioisomer. The formation of **3a** was most efficient when the reaction was carried out at relatively high concentration (0.25 M with respect to **2a**), which is consistent with related ring formations.[3e,5b]

The reaction scope is summarized in Table 1. In all cases, the corresponding diazadioxacalix[4]arenes **3** constituted >80% of the unpurified reaction mixtures as analyzed by ^{1}H NMR spectroscopy in [D$_6$]DMSO. Isolated yields were variable, reflecting the extent of material loss during chromatographic purification.[4b] The sparingly soluble macrocycle **3a** was obtained in modest yield following purification (37%, Entry 1), while the increased solubility observed for **3b** and **3d** led to much higher isolated yields (86% and 77%, respectively for **3b** and **3d**, Entries 2, 4). Both reactivity and regioselectivity were maintained for 3-aminophenols bearing strong electron-donating (**3e**, Entry 5) or electron-withdrawing substituents (**3f**, Entry 6). Halogen substitution was also readily accommodated at the 2-position (**3c**, Entry 3) and at the 2- and 4-positions (**3d**, Entry 4), with the higher yield of **3d** reflecting the markedly improved solubility of **3d** over **3c**.

The ability of both 2- and 4-aminophenols to regioselectively form diazadioxa[1$_4$]cyclophanes with an alternating bridge pattern was also investigated. Reaction of 2-aminophenol with **1** did not produce macrocyclic products; hetera[1$_4$]cyclophane formation is likely complicated by base-catalyzed self-condensation of the 2-aminophenol.[11] In contrast, 4-aminophenols reacted analogously to 3-aminophenols, both with respect to the high selectivity for the desired diazadioxa[1$_4$]cyclophanes **5** and the variable isolated yields due to low solubility for some systems (Table 2). Reaction efficiency was similar for 4-aminophenols substituted at the 3-position (**4b**, Entry 2) or at the 2-position (**4c**, **4d**, Entries 3, 4). In addition, the 4-aminophenol could be substituted with either electron-donating (**4c**, Entry 3) or electron-withdrawing groups (**4d**, Entry 4), producing macrocycles **5c** and **5d** in 57% and 51% isolated yields, respectively.

Table 2. Synthetic scope of diazadioxa[1$_4$]cyclophanes **5**.[a]



Entry	Aminophenol	Product	Yield[b]
1	**4a** (R^1 = H, R^2 = H)	**5a**	60%
2	**4b** (R^1 = H, R^2 = Cl)	**5b**	66%
3	**4c** (R^1 = OCH_3, R^2 = H)	**5c**	57%
4	**4d** (R^1 = CO_2CH_3, R^2 = H)	**5d**	51%

[a] 1.0 equiv. of aminophenol **4**, 1.0 equiv. of **1**, 10 equiv. of CsF. [b] Isolated yield after chromatographic purification.

^{1}H and ^{13}C NMR spectral analysis of macrocycles **5c** and **5d** indicate that these compounds exist as mixtures of atropisomers that are slow to interconvert on the NMR timescale.[12] This is evident by two distinct ^{1}H signals observed for the hydrogen atoms on the electrophile-derived

aromatic rings that are oriented towards the inner cavity of cyclophanes **5c** and **5d** (labeled as H^a in Table 2). The observed diastereomeric ratios in [D$_6$]DMSO at 25 °C are 1:1 for **5c** and 2:1 for **5d**. Chemically distinct ^{1}H NMR signals in the same ratios are also present for hydrogen atoms on the methoxy group of **5c** and the methoxycarbonyl group of **5d**. It is assumed that compound **5b** also exists as a mixture of atropisomers, but the conformers could not be differentiated by ^{1}H or ^{13}C NMR spectroscopy. NMR investigations of **5b**–**5d** in alternative solvents, as well as measurement of the atropisomeric preferences and rotational barriers to interconversion of these systems, are ongoing and will be reported in a subsequent publication.

The regioselective formation of the alternating N/O-bridge connectivity pattern is perhaps the most intriguing aspect of these macrocyclization reactions. To probe the reaction mechanism, 1,5-difluoro-2,4-dinitrobenzene (**1**) was condensed with 3-aminophenol **2d**, and samples of the reaction mixture were removed periodically, precipitated by addition of aqueous acid, and the unpurified solid residue was analyzed by ^{1}H NMR spectroscopy. Aliquots removed at short reaction times (5 min at 25 °C; 5 min at 80 °C) revealed that only two compounds are initially formed: O-linked dimer **A**, and O,O′-linked trimer **B** (Figure 2).[13] At extended reaction times (1–18 h at 80 °C), increasing amounts of **3d** are formed concomitantly with the disappearance of intermediates **A** and **B**. There is no evidence for the buildup of significant quantities of any other discrete linear precursor to **3d**. Furthermore, the sharp resonances and lack of baseline broadening suggest that long linear oligomers are not formed, and subsequently equilibrated, under the reaction conditions.

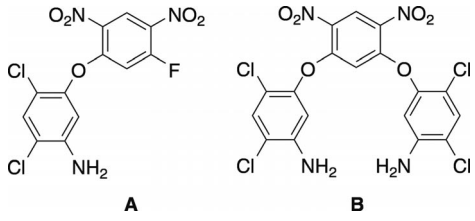


Figure 2. Intermediates formed in the production of diazadioxacalix[4]arene **3d**.

Tentatively, we suggest that formation of diazadioxacalix[4]arene **3d** proceeds as follows: Rapid and reversible formation of both O-linked dimer **A** and O,O′-linked trimer **B**, followed by self-condensation of two dimers **A**[14] by rate-determining intermolecular C–N bond formation. Rapid intramolecular cyclization of the resultant linear (tetrameric) precursor leads to diazadioxacalix[4]arene **3d**. Reversible C–O bond formation permits the recycling of O,O′-linked trimer "errors" in chain growth, while the low nucleophilicity of arylamines likely precludes the formation of N,N′-linkages in the growing oligomer chain.

Several experiments were conducted to probe the reversibility of C–O and C–N bond formation during the synthesis of macrocycles **3**. First, when a 1:1 mixture of diazadioxacalix[4]arenes **3b/3c** was subjected to the cyclization conditions (CsF, DMSO, 80 °C, 18 h), no products resulting from exchange of nucleophilic monomers were formed, and no linear species were observed. Second, macrocycle **3b** was combined with 2 equiv. of either 3-aminophenol **2e**, or 4-ethylresorcinol under the cyclization conditions (CsF, DMSO, 80 °C, 18 h). In both cases, compound **3b** remained intact, and no exchange of nucleophilic monomers was observed. These experiments suggest that macrocycles **3** are formed in a kinetically controlled cyclization step, and that C–O and C–N bond cleavage is not observed on intact macrocycles **3**.

The structures of **3a** and **5b** were confirmed by X-ray crystallographic analysis.[15] Diazadioxacalix[4]arene **3a** adopts an expected 1,3-alternate conformation, and unlike a relatively similar *anti*-azacalix[4]arene,[3e] exhibits almost no gearing in the solid state from the asymmetrically disposed substituents (Figure 3a). Diazadioxa[1$_4$]cyclophane **5b** crystallized as a single atropisomer, with the chlorine atoms pointing to the same side of the macrocycle (Figure 3b). The chlorine-substituted rings were found to tilt the chlorine atoms significantly toward each other, with a distance of 4.42 Å between chlorine atoms and an angle between ring planes (deviation from coplanarity) of 30.5°.

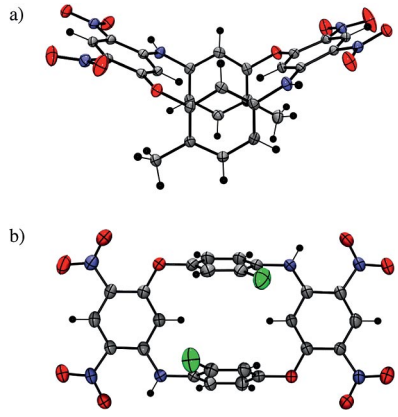


Figure 3. X-ray crystal structures of (a) **3a** and (b) **5b**. Thermal ellipsoids are drawn at the 30% probability level; oxygen = red, nitrogen = blue, carbon = gray, chlorine = green, hydrogen = black. Solvent molecules have been removed for clarity.

Conclusions

We have described a single-step, regioselective method for the synthesis of diazadioxacalix[4]arenes and diazadioxacalix[1$_4$]cyclophanes from 3- and 4-aminophenol nucleophiles. The selectivity for alternating N/O-bridge connectivity greatly facilitates the selective synthesis of asymmetrically substituted hetera[1$_4$]cyclophanes. Investigations into the rates of conformational interconversion of the described macrocycles, further mechanistic details of their synthesis, and resolution of enantiomers, are ongoing and will be reported in due course.

Experimental Section

General Reaction Conditions for the Synthesis of Diazadioxacalix[4]arenes 3 and Diazadioxa[1$_4$]cyclophanes 5: Under ambient atmosphere, an air-dried flask was charged with aminophenol **2** or **4** (0.245 mmol, 1 equiv.) and 1,5-difluoro-2,4-dinitrobenze (50.0 mg, 0.245 mmol, 1 equiv.). DMSO (1.0 mL) was added, followed by CsF (369 mg, 2.45 mmol, 10 equiv.). The reaction mixture was heated to 80 °C under a positive pressure of argon and stirred for 18 h. After cooling to room temperature, the product was precipitated by the addition of water (10 mL) and 1 M HCl (1 mL). Unpurified **3** or **5** was isolated by vacuum filtration, washed with water (10 mL), and dried in vacuo. Macrocycle **3** or **5** was then dissolved in 7 mL of CH_2Cl_2, and stirred vigorously for 30 min. The solution consisting of dissolved product was filtered, and the filtrate subjected to flash column chromatography.

Supporting Information (see footnote on the first page of this article): Compound characterization for **3a**–**f** and **5a**–**d**, X-ray crystallographic experimental data for **3a** and **5b**, and ^{1}H NMR spectra from mechanistic investigations.

Acknowledgments

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[10] Inherently chiral macrocycles described in this Communication lack internal planes of symmetry due to asymmetrically disposed substituents and are formed as racemic mixtures that may undergo conformational enantiomerization at ambient temperature. Measurements of enantiomerization rates, conformational rigidification of the macrocycles, and resolution of enantiomers will be addressed in a future manuscript.

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[12] An atropisomeric mixture was also reported for a related tetraaza[1$_4$]cyclophane (ref.[5h]).

[13] Unreacted **1** was not detected by ^{1}H NMR spectroscopy and was presumably hydrolyzed and removed during the aqueous workup of the unpurified reaction mixtures.

[14] Alternately, nucleophilic attack of dimer **A** on O,O′-linked trimer **B** followed by C–O bond cleavage will lead to the same tetrameric precursor.

[15] Crystallographic data: **3a**: M = 574.46, orthorhombic, space group $P2(1)2(1)2(1)$, a = 9.1641(9) Å, b = 12.1597(13) Å, c = 21.919(2) Å, V = 2442.5(4) Å^3, Z = 4, R_1 = 0.0503, R_w = 0.1108, GOF = 1.053. **5b**: M = 698.21, triclinic, space group $P\bar{1}$, a = 8.9497(7) Å, b = 9.5830(8) Å, c = 18.4492(15) Å, α = 80.564(2)°, β = 86.242(2)°, γ = 66.7940(10)°, V = 1434.6(2) Å^3, Z = 2, R_1 = 0.0741, R_w = 0.1830, GOF = 0.898. CCDC-866173 (for **3a**) and CCDC-866172 (for **5b**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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