Tetraarylboronic Acid Resorcinarene Stereoisomers. Versatile New Substrates for Divergent Polyfunctionalization and Molecular Recognition

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The resorcinarenes are unique three-dimensional cyclic aromatic tetramers. Their impact in the disciplines of molecular recognition, supramolecular chemistry, and materials science has been the subject of extensive study and review.[1] Boronic acids have recently achieved great prominence as functional groups. They have been employed in palladium-mediated coupling reactions,[2] carbohydrate recognition and sensing,[3] enzyme inhibition,[4] and molecular transport studies.[5] They readily form strong (and reversible) covalent bonds to diols (the basis of carbohydrate affinity chromatography),[6] and boronate esters are utilized as efficient asymmetric homologation substrates[7] and catalysts.[8] The incorporation of arylboronic acid moieties into resorcinarene frameworks might thus afford access to an array of heterofunctional architectures. Herein we report our preliminary findings concerning the synthesis, derivatization, and properties of a new tetraarylboronic acid resorcinarene stereoisomeric molecular series **1a**−**d** and **2a**−**d** (Figure 1) as well as cavitands **3** and **4** (Figure 2).

It is well-known that the acid-catalyzed condensation of aldehydes with resorcinol affords two major resorcinarene stereoisomers in respective crown (rccc, C_{4v} symmetry) and chair (rctt, C_{2h} symmetry) conformations.[1] Heating (4-formylphenyl)boronic acid (10.0 g, 67.2 mmol) in 75 mL of a 2:2:1 solution of EtOH:H_2O:HCl with resorcinol (7.40 g, 67.2 mmol) for 24 h furnishes a precipitate containing 16.0 g (96%) of a 3:2 mixture of **2a:1a**. Attempts at refining the stereoisomer ratio via prolonged heating of the reaction mixture lead to intractable products; however, **1a** and **2a** can be directly separated (i.e., without prior acylation of the phenolic hydroxyls[1]) via repeated fractional crystallization from hot methanol. Similarly, 2-methylresorcinol condenses with (4-formylphenyl)boronic acid to afford stereoisomeric pairs **2b** and **1b** in a 3:2 ratio, respectively in 61% yield.

The vast majority of resorcinarene chemistry reported to date has involved reactions at the resorcinol moieties of crown stereoisomers;[1] however, the functionalization of substituents proximal to the macrocyclic ring (i.e., at the appendages derived from the aldehyde condensation partner) has begun to attract attention as a means to enhance the properties of the parent macrocycles.[9] Recently, the Botta group reported the synthesis of octamethyl ether resorcinarenes with chiral amide appendages.[10] Others have placed chiral substituents such as amino acids *ortho* to the phenolic hydroxyls via Mannich chemistry.[11] Our syntheses of boronate esters **1c** and **2c** complements these studies, affording the first resorcinarene octols embodying chiral moieties at either (1) the lower rim of a crown (C_{4v}) stereoisomer or (2) as part of a chair (C_{2h}) framework, respectively. The (−)-pinanediol boronate esters **1c**, $[\alpha]^{23}_{589}$ +10.8° (c = 4.1, DMF) and **2c**, $[\alpha]^{23}_{589}$ −12.4° (c = 4.1, DMF) are obtained in 78% and 75% isolated yields, respectively, by heating a solution of **1a** or **2a** and excess (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol (6 equiv) in DMF at 110 °C for 2 days in the presence of Na_2SO_4. In a similar fashion, pinacol esters **1d** and **2d** are both furnished in 72% and 77% yields via reaction of **1a** and **2a** with excess pinacol.

Bridged resorcinarenes (cavitands) have played major roles in the study of molecular recognition via noncovalent interactions and as substrates for advanced architectures such as carceplexes and hemicarceplexes.[1] The chiral tetraboronate cavitand **3**, $[\alpha]^{23}_{589}$ −6.5° (c = 2.74, CH_2Cl_2), is afforded in 22% isolated yield via reaction of **1c** (0.40 g, 0.26 mmol) with 4.6 equiv of $BrCH_2Cl$ in the presence of K_2CO_3 in DMA for 96 h, based on Sherman's recent procedures.[9d] Similarly, **4** derives from **1d** in 13% yield (Figure 2).

We next turned our attention to the molecular recognition properties of the new stereoisomeric octols **1a**−**d** and **2a**−**d**. The crown isomeric (C_{4v}) resorcinarenes have been extensively studied as molecular hosts whereas the chair (C_{2h}) macrocycles have not received attention.[1] Investigations of the related calixarenes, however, revealed that 1,3 alternate conformers could actually bind guests more efficiently than their cone (*all-cis*) counterparts, an unexpected result that was attributed to favorable π-interactions.[12] On the basis of those findings and the fact that the C_{2h} compounds (series **2**) described herein embody divergent π-functionality on each facet of a double molecular cleft, we initiated investigations

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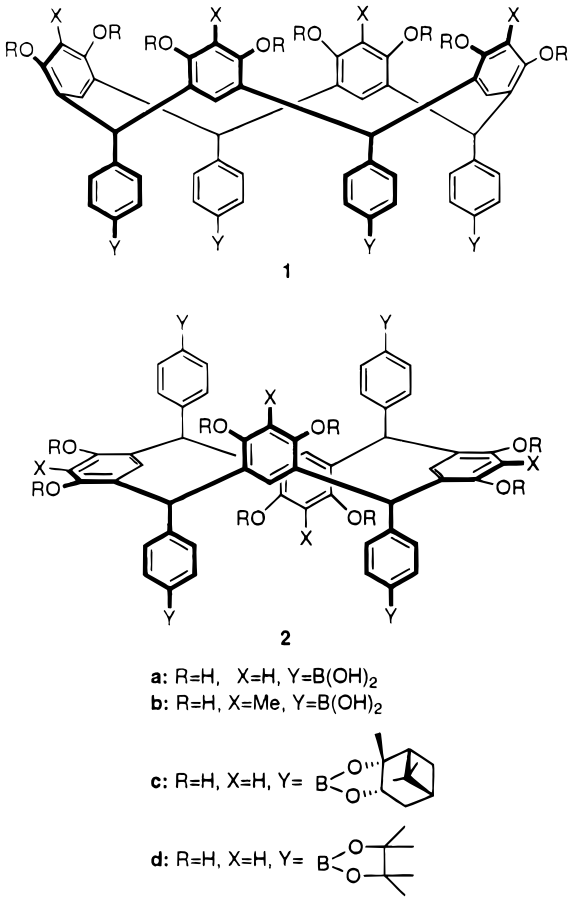

Figure 1. Structures of **1a**−**d** (C_{4v}, rccc) and **2a**−**d** (C_{2h}, rctt) stereoisomeric resorcinarenes.

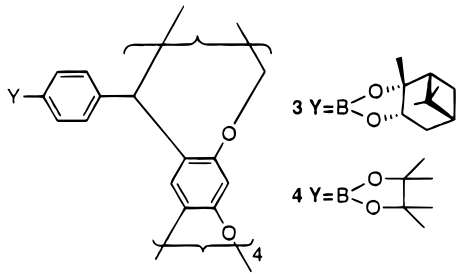

Figure 2.

aimed at contrasting the binding properties of the series **1** and **2** resorcinarenes.

We first compared the covalent binding of **1a** vs **2a** to D-glucose. Solutions of **1a** or **2a** at fixed concentrations (1.03×10^{-5} M in DMSO-d_6, 5 mg in 1 mL) were stirred at room temperature with varying amounts of D-glucose for 24 h without rigorous removal of water. Successive disappearance of the boronic acid proton resonances (**1a**, δ 7.68 ppm, 8H; **2a**, δ 7.53 ppm, 8H) was monitored upon increased glucose concentration by comparison of the integral areas of the boronic acid proton resonances (which exhibited significant broadening upon glucose addition) and the aromatic proton resonances ortho to boron (**1a**, δ 7.40 ppm, 8H; **2a**, δ 7.30 ppm, 8H). For **1a**, the boronic acid proton integral areas decreased in amounts of 64%, 61%, 73%, and 74% and for **2a** in amounts of 76%, 78%, 84%, and 83% in the presence of 0.5, 1.0, 1.5, and 2.0 equiv of D-glucose, respectively. Apparently, C_{2h} **2a** exhibited a greater degree (12−28% greater decrease in boronic acid proton integral) of covalent interaction in DMSO-d_6 with glucose than did C_{4v} **1a**.

In order to contrast the noncovalent binding properties of the stereoisomers, we explored the solid−liquid extraction of D- and L-fucose. Importantly, **1c** and **2c** are soluble in CCl_4; previously, Aoyama utilized resorcinarenes with long chain alkyl substituents in order to confer solubility in organic solvents and perform extractions of polar molecules.[13] We dissolved **1c** or **2c** (81.2 mg, 0.0540 mmol) in 6 mL of CCl_4 over 24 h and then added (400 mg, 2.44 mmol) of either D- or L-fucose (insoluble in CCl_4). Vigorous stirring at ambient temperature was continued for 3 days, at which time the solutions were centrifuged and filtered. The filtrates containing extracted fucose and macrocycle were then evaporated to dryness and the resultant solids stirred with 2 mL of a 0.012 M stock solution of NaOAc in D_2O for 24 h to effect complete dissolution of fucose. The ^{1}H NMR spectra of aliquots of the D_2O solutions revealed the amount of extracted fucose via comparison of the integral areas of the fucose methyl protons with those of the NaOAc standard methyl protons. The molar extractability (moles fucose extracted/moles macrocycle) of D- and L-fucose by **1c** was determined to be 0.4 and 0.07, respectively. The extractabilities were 2.4 for D- and 0.7 for L-fucose by **2c**. Thus, both **1c** and **2c** exhibited greater stereoselectivity for D- over L-fucose and, in both the covalent and noncovalent binding experiments, the C_{2h} (rctt) stereoisomers exhibited stronger affinity for the carbohydrates studied.

In conclusion, we have (1) performed a gram scale synthesis and direct isolation of boronic acid-functionalized stereoisomeric resorcinarenes; (2) polyfunctionalized at divergent macrocyclic sites, affording unique chiral and achiral resorcinarene octols and cavitands; (3) presented preliminary evidence that the relatively little-explored C_{2h} resorcinarene octols can compete effectively with their C_{4v} counterparts in both covalent and noncovalent binding of polar guests; and (4) demonstrated the potential utility of the chiral tetraarylboronate octols as substrates for stereoselective extractions. The continued exploration of the chemical and physical properties of the boronic acid-derived resorcinarenes is ongoing in our laboratory.

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Supporting Information Available: Experimental procedures for the synthesis of **1**−**4** and characterization data (5 pages).

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