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Resorcinol Condensation Products: a New Class of Colorimetric Sensors for Saccharides.

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RESORCINOL CONDENSATION PRODUCTS: A NEW CLASS OF COLORIMETRIC SENSORS FOR SACCHARIDES

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
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in partial fulfillment of the
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in

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DEDICATION

I dedicate this dissertation to my mother, the late Lois A. Davis, and my wife Kim Conner-Davis. Mama, I know that you are shining down on me from heaven. Thank you for the love, support, and guidance that you gave me while you were here. You instilled great morals and values in me, and you taught me to believe in the power of prayer. I miss you, and I love you. I hope that I have made you proud. Kim, I thank you for your unconditional love, support, understanding, and prayers. I am so lucky to have you in my life, and I thank God for blessing me with you everyday. Thanks for always standing by my side. I LOVE YOU!

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ABSTRACT

Resorcinarenes are a unique class of cyclic aromatic tetramers that have been known for over a century. In our laboratories, we have reported the first synthesis, isolation, and characterization of resorcinarenes with arylboronic acid functionality in their framework. The physical property studies of our new resorcinarene series resulted in covalent and non-covalent binding studies, which revealed the first evidence that chair (c_2h) resorcinarenes can compete effectively with their crown (c_4v) counterparts in the binding of polar guests (i.e. carbohydrates). In addition, the chiral tetraarylboronate octols have demonstrated potential utility as substrates for stereoselective extractions of carbohydrates.

A facile method for detecting and monitoring saccharides is of immense importance to medical diagnostics and industry. Molecular recognition studies in our laboratories have led to the discovery of the most versatile colorimetric sensing test for saccharides to date, which allows for the visual discrimination of 11 different saccharides of biological importance. Our colorimetric test is amenable to carbohydrates, glucose phosphates, amino sugars, carboxylic acid sugars, and oligosaccharides. Importantly, our pioneering efforts utilizing resorcinol-based synthetic receptors affords a simple, rapid, inexpensive, and fully reproducible colorimetric test.

CHAPTER 1

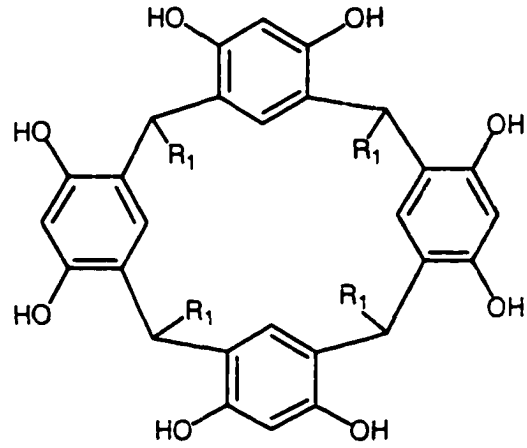
INTRODUCTION

1.1 History of Resorcinarenes

Adolf von Baeyer conducted a study of phenol-based dyes in 1872.[1.1] He reported that the addition of concentrated sulfuric acid to a mixture of resorcinol and benzaldehyde yielded a reddish resin product, which turned violet in basic solution. Upon heating the mixture, Baeyer obtained a crystalline compound in addition to the reddish resin. The crystalline compound was later determined to be an isomer of the red resin. Many years later, the correct elemental composition of this slightly soluble, high melting, crystalline product $(C_{13}H_{10}O_2)_n$ was determined by Michael.[1.2] According to his studies, the product was formed by the combination of an equimolar amount of resorcinol and benzaldehyde followed by loss of an equal number of moles of water. However, there was no estimation of the compound's molecular weight. Nierdel and Vogel conducted extensive studies of condensation products obtained from the reaction of resorcinol and aliphatic aldehydes in 1940.[1.3] As a result, their molecular weight determinations led to the conclusion that the ratio between the resorcinol and aldehyde was 4:4 in the product. Consequently, Nierdel and Vogel proposed the tetrameric structure (**1.1**), which was structurally analogous to porphyrins found in nature. In 1968, Erdtman and coworkers finally proved this structure by X-ray crystal analysis (Figure 1.1).[1.4] Today these compounds are commonly known as resorcinarenes.[1.5]

1.2 Synthesis of Resorcinarenes

The preparation of resorcinarenes involves an acid-catalyzed condensation reaction between resorcinol and an aldehyde. The reactants are usually heated to reflux in a



1.1

Figure 1.1 Nierdel and Vogel's proposed cyclotetrameric structure.

mixture of ethanol and concentrated hydrochloric acid for several hours. However, the optimal reaction conditions vary depending on the aldehyde. Generally, the resorcinarene product crystallizes from the reaction mixture, but in some cases the addition of water is necessary to isolate the product.[1.6] An unsubstituted resorcinol is typically used to carry out these syntheses. In addition, substituted resorcinols such as 2-methylresorcinol and pyrogallol have afforded isolable amounts of product. On the contrary, a resorcinarene product is not generated when resorcinol derivatives contain an electron withdrawing group at the 2-position or when the phenolic hydroxyl groups are partially alkylated.[1.7] A broad range of aliphatic and aromatic aldehydes can be employed to yield product. The only exceptions to this rule are sterically hindered aldehydes such as 2,4,6-trimethylbenzaldehyde or aliphatic aldehydes with functionalities too close to the reaction center (e.g. glucose).[1.6a, 1.8]

The acid-catalyzed condensation reaction mechanism for the formation of resorcinarenes is well known (Figure 1.2).[1,8] In the first step, the aldehyde is protonated

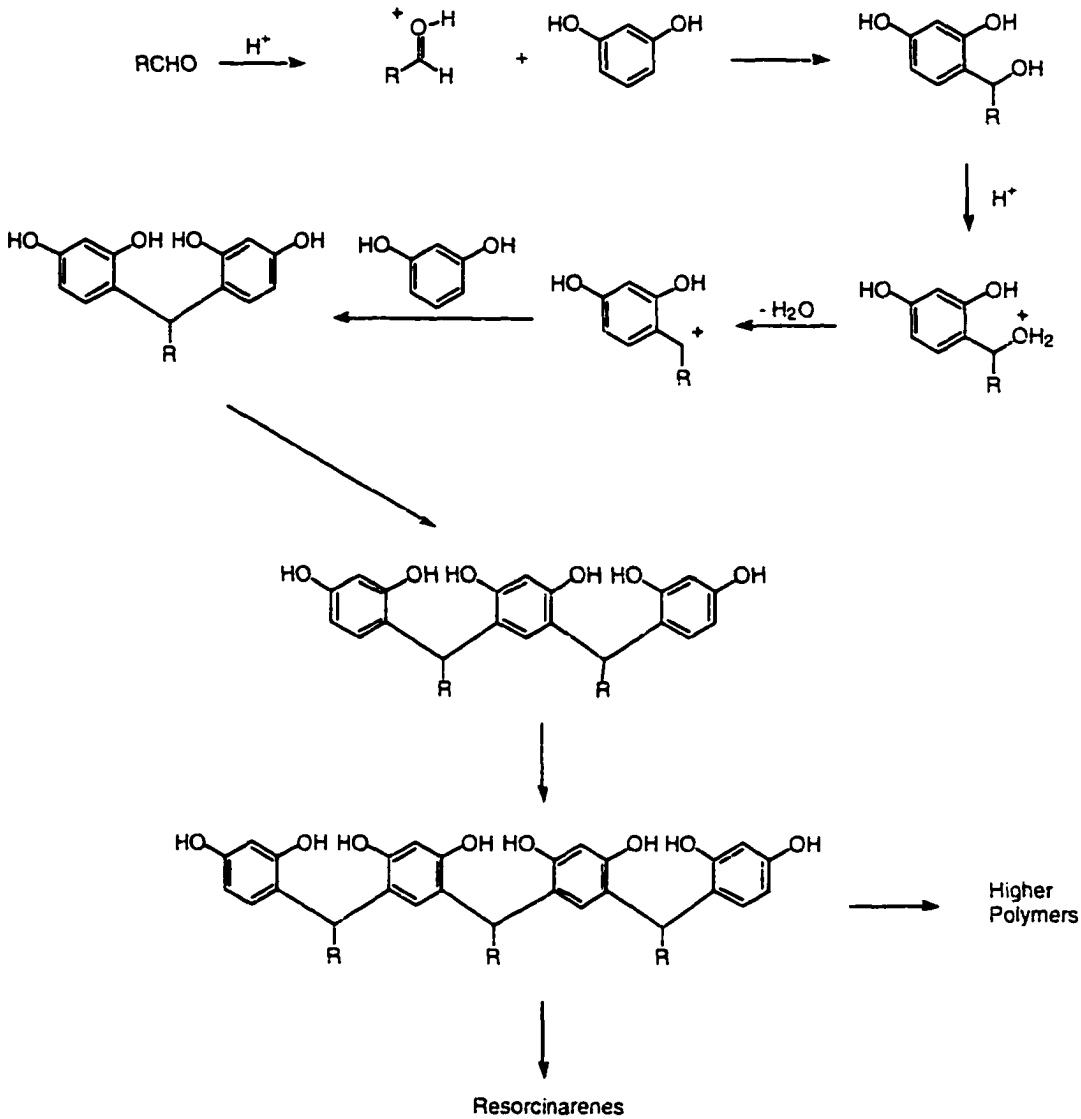


Figure 1.2 The resorcinarene synthesis acid-catalyzed reaction mechanism.

by an acid catalyst. The next step involves an electrophilic addition to a resorcinol unit. Subsequently, the phenolic hydroxyl is protonated generating a mole of water, which is

removed in the next step. This carbocation intermediate undergoes an electrophilic addition with another resorcinol unit for the formation of a dimer. The reaction cycle is repetitive forming trimers, tetramers, and higher polymers in the process. At the tetramer stage, a cyclization usually occurs yielding a resorcinarene product. The rapid cyclization of the resorcinarene is due to its conformation. Resorcinarene conformations are folded rather than linear, which allows for the formation of stronger hydrogen bonds between phenolic hydroxyls on adjacent resorcinol moieties.

In theory, there are several different isomeric forms of resorcinarenes that can exist because of their non-planarity. The stereochemistry of resorcinarenes is based on three criteria. One is the conformation of the macrocyclic ring. The macrocyclic ring has five possible highly symmetrical stereoisomers (Figure1.3): the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (D_{2d}) conformation. The boat and chair stereoisomers are the two most prevalent forms of resorcinarenes. Usually, the boat conformation is reported as being a crown conformation. This is due in part to the presence of two boat conformers, which rapidly interconvert yielding a time-averaged crown conformation. Interestingly, only the breaking of at least two covalent bonds affords the rapid interconversion of the diastereomeric boat, chair, and diamond stereoisomers. All three diastereomers are produced in the reaction, however, their ratios are heavily dependent on the conditions employed. When the reaction is performed under homogeneous, acidic conditions; the thermodynamic stability of each stereoisomer determines the product ratio because the reaction is reversible under such conditions. If heterogeneous conditions are used, the product ratio of the stereoisomers is determined by their relative solubilities in the reaction solvent. Consequently, the

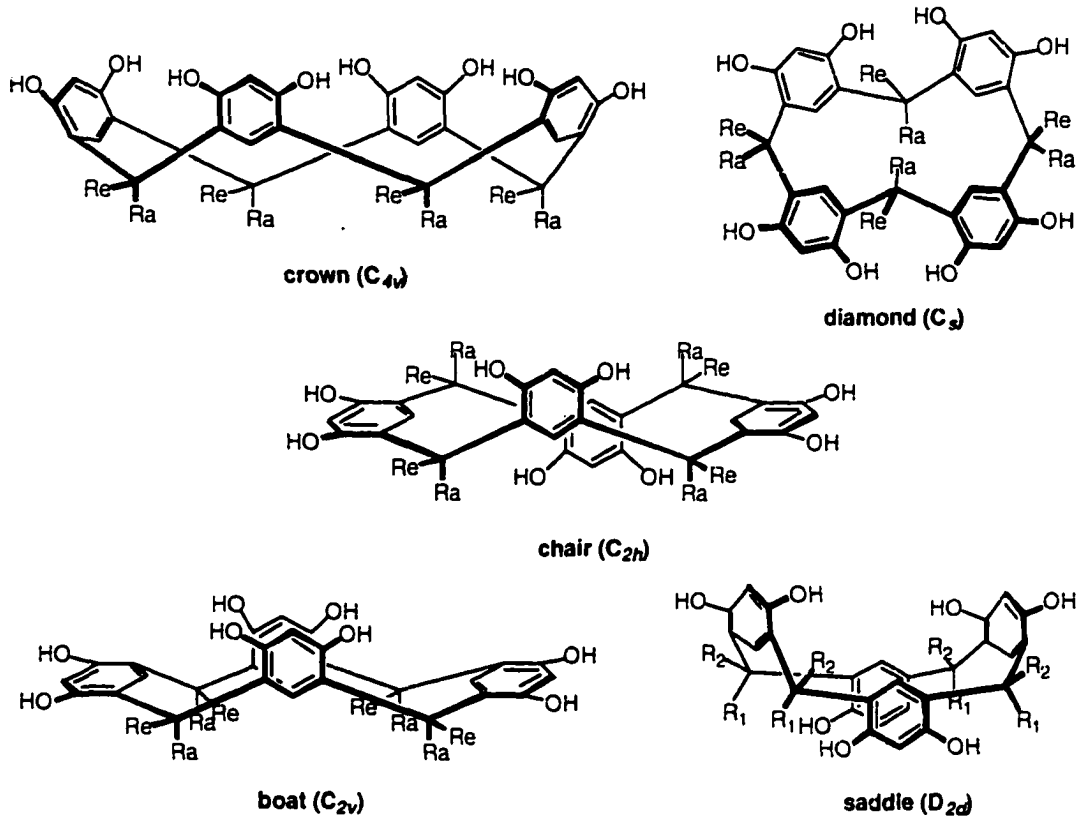


Figure 1.3 The five possible macrocyclic ring conformations.

least soluble stereoisomer precipitates as the sole product. Another criterion for the determination of a resorcinarene's stereochemistry is the relative configuration of the substituents at the methylene bridges (Figure 1.4). The designations are the all-cis (ccc), cis-cis-trans (cct), cis-trans-trans (ctt), and trans-cis-trans (tct) arrangements. The final criterion is the individual configuration of the substituents at the methylene bridge; which may be either axial or equatorial in the macrocyclic conformations with C symmetry. The combination of these three criteria leads to a substantial number of potential stereoisomers, however, only four have been reported experimentally.

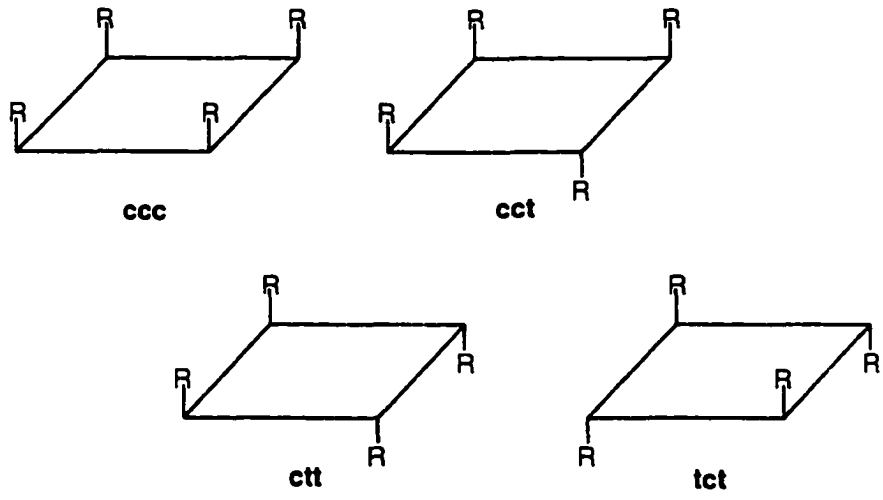


Figure 1.4 Relative configuration of methylene bridge substituents.

1.3 Resorcinarene Complexation of Polar Organic Molecules

Resorcinarenes are suited for binding polar organic molecules, due to the presence of eight phenolic hydroxyl groups at the upper rim. Aoyama and co-workers were the first to exploit this feature of resorcinarenes,[1.9] and the majority of their binding studies have utilized boat stereoisomers as receptors. Aoyama extensively studied the binding of cyclohexanediols to resorcinarenes. He discovered that *cis*-1,4-cyclohexanediol was the most strongly bound isomer compared to its counterparts.[1.10] This can be attributed to the pre-organization of the molecule where one hydroxyl group is axial and the other is equatorial in the *cis* isomer. The cyclic diols compared favorably to their open chain counterparts in resorcinarene binding.[1.11] In addition, the *cis* isomers were eight times stronger at binding than the corresponding *trans* isomers.

Resorcinarenes have shown an ability to bind carbohydrates. In forming complexes with carbohydrates, the 1,4-*cis* hydroxyl selectivity is also observed.[1.12] A

resorcinarene binding study revealed that D-ribose has some degree of solubility in carbon tetrachloride upon complexation with a resorcinarene. The ^{1}H NMR studies have shown that D-ribose is bound exclusively in the α-pyranose form. Moreover, this isomeric form of D-ribose is the only one possessing a 1,4-*cis* hydroxyl orientation. Further extraction studies have provided evidence that the 3,4-*cis* hydroxyl orientation strongly enhances resorcinarene binding. It was also discovered that hydrogen bonding is the key to sugar complexation with resorcinarenes. In addition, the CH-π interaction between the aromatic rings of resorcinarenes and the aliphatic moiety of the guest molecule play a vital role in the binding process.[1.13]

Resorcinarenes have exhibited the ability to complex amino acids in aqueous media.[1.14] Amino acids with polar side chains exhibited a very poor affinity for resorcinarenes. However, the amino acids possessing aromatic or aliphatic side chains displayed a greater affinity for resorcinarenes due to a substantial contribution of CH-π interactions. Resorcinarenes have also shown the ability to complex dicarboxylic acids in chloroform.[1.14] Again, a hydrogen-bonding interaction is the major factor in complexation. Importantly, the binding strength of the dicarboxylic acid is heavily dependent upon the length of the carbon spacer separating the two carboxylic acid end groups. A binding study was conducted comparing glutaric acid, a three-carbon spacer, and pimelic acid, a five-carbon spacer. Aa a result, glutaric acid exhibited a binding affinity over one hundred times stronger than pimelic acid.[1.14a] This result emphasizes the rigidity of the resorcinarene's structure.

1.4 Background on Boronic Acid Binding to Saccharides

Boron containing compounds have played a significant role in organic synthesis for many years.[1.15] There has been great current interest in the synthesis of aromatic boronic acid compounds that can serve as receptors for molecules such as saccharides.[1.16] Michaelis and Becker carried out the first synthesis of phenylboronic acid in 1880.[1.17] In 1954, Kuivila and co-workers published the first binding studies of boronic acids to diols; where they discovered that boronic acids solubilized saccharides and polyols, and they proposed the formation of a cyclic ester product.[1.18] This result was in accord with the well known ability of borates to form complexes with polyhydroxyl compounds.[1.19] In 1959, Lorand and Edwards published the first quantitative interactions between boronic acids and saccharides.[1.20]

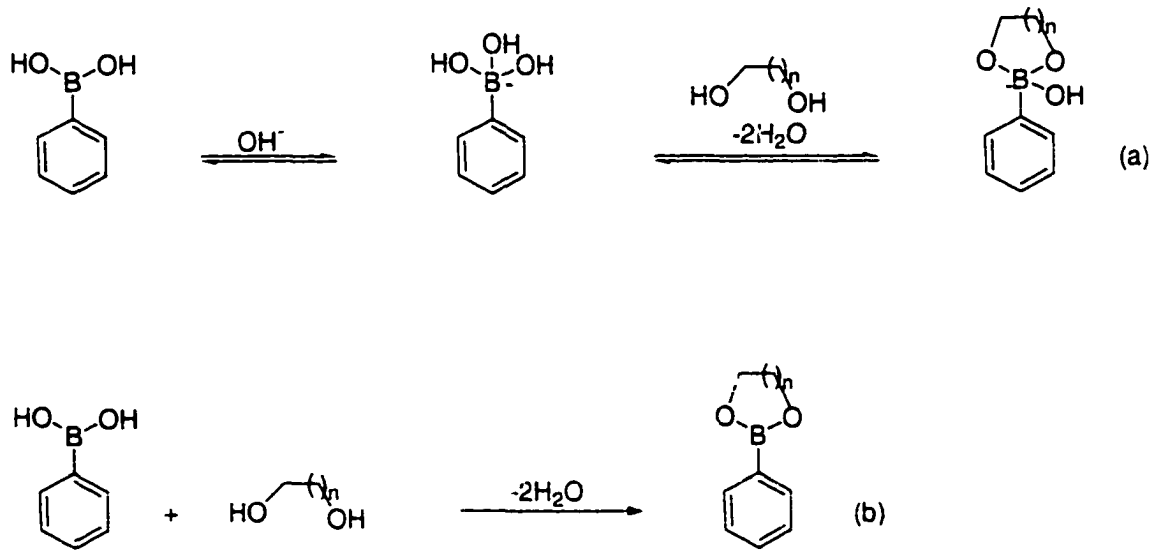


Figure 1.5 Formation of boronate esters with phenylboronic acid. (a) Reaction with aqueous base and (b) Reaction in aprotic media.

In the reaction of boronic acids with diols, a covalent bond is formed with 1,2- or 1,3-diols for the formation of a five or six membered cyclic ester in both basic and nonaqueous media (Figure 1.5). Saccharides containing rigid, *cis* diols form more stable cyclic esters than their simple acyclic diol counterparts. The structure of the cyclic ester formed with saccharides is often complex due to the potential isomerization of the saccharide from the pyranose to furanose form. Lorand and Edwards found that phenylboronic acid had the following binding affinity for saccharides: D-fructose > D-galactose > D-mannose > D-glucose.[1.20]

1.5 Saccharide Sensing via pH Studies

Dyes containing boronic acid moieties have been known for years,[1.21] but it was not until recently that investigations were made into the effect of saccharides on the coloration of these compounds. For example, the molecular internal-charge-transfer

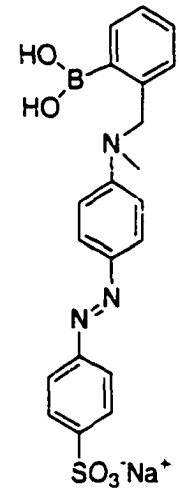


Figure 1.6 Internal-charge-transfer sensor.

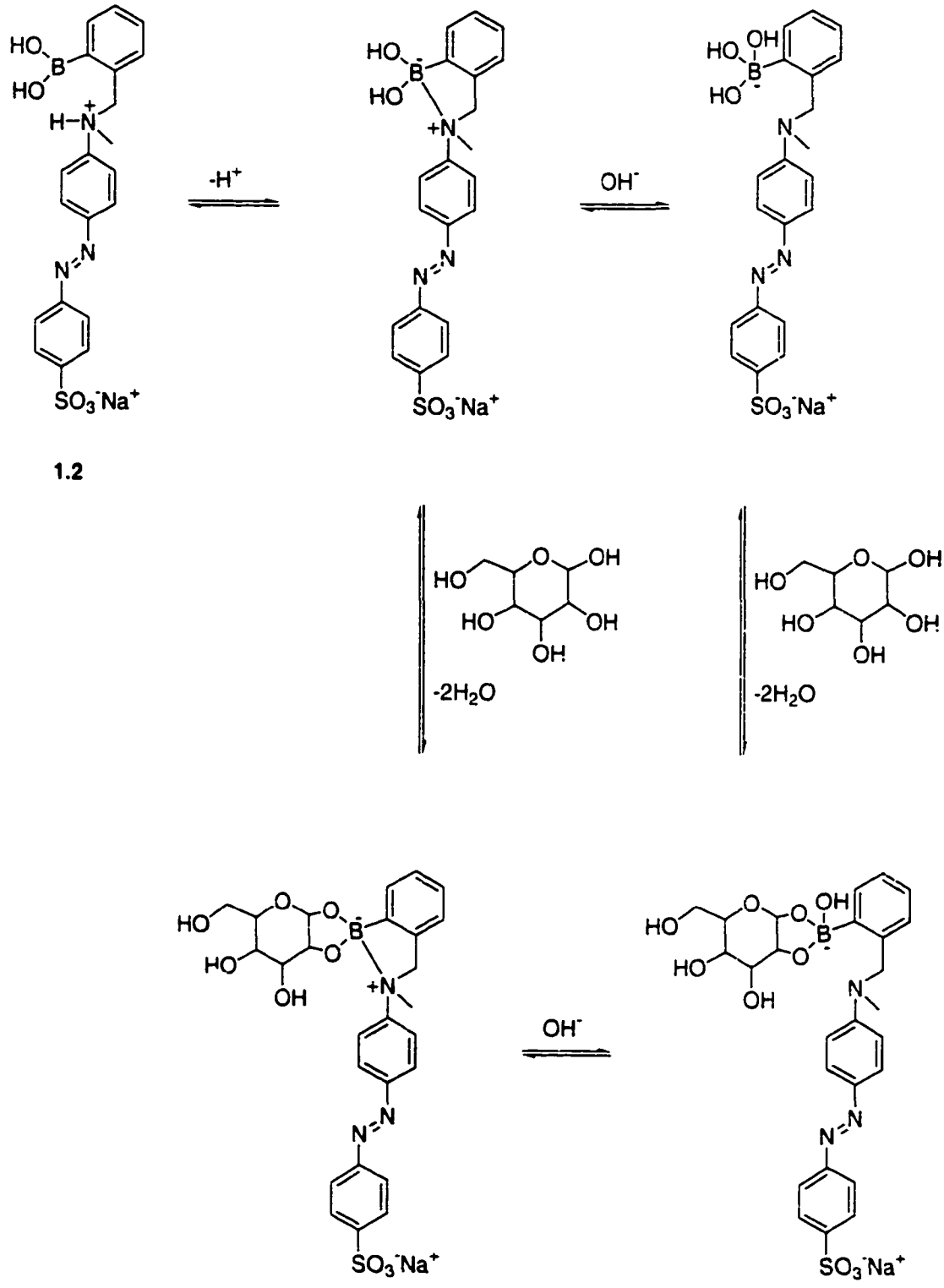


Figure 1.7 Formation of the boronic acid-saccharide complex at different pH values.

sensor (**1.2**)[1.22] functions based on an intramolecular interaction between the boronic acid moiety and the tertiary amine (Figure1.6).[1.23] The tertiary amine creates an alkaline environment adjacent to the boronic acid, which can facilitate the sugar/boronic acid interaction and lowers the working pH of sensor **1.2**.[1.24] As the pk_a of the boronic acid moiety changes, an electronic change occurs due to the formation of a boronic acid-saccharide complex.[1.20] Consequently, the amine facilitates the electronic change, and a blue shift is observed in the chromophore's visible spectrum. The pk_a value of the complex is contingent upon the boron-nitrogen interaction in **1.2**, and a shift occurs upon the addition of saccharides (Figure 1.7). The formation of boronic acid-saccharide complexes has achieved very limited success in producing a color change upon binding. This can be ameliorated with the development of either more suitable chromophores or improved receptors that are selective and sensitive color sensors. The synthesis of such a sensor could potentially lead to the development of inexpensive and stable "test strips" for the detection of blood glucose.

1.6 Significance of Boronic Acid Binding to Saccharides

There is great current interest in the recognition of biologically important compounds by synthetic receptors. Since saccharides play a significant role in the metabolic pathway of living organisms, the ability to detect the presence and concentration of biologically important sugars such as glucose, fructose, and galactose in aqueous solution is of interest to the fields of medicine and industry. Recognition of D-glucose is of specific interest, because the breakdown of glucose transport in humans has been linked to diseases such as renal glycosuria,[1.25, 1.26] cystic fibrosis,[1.27] diabetes[1.28, 1.29] and cancer.[1.30] The industrial applications range from monitoring the

process of fermentation to the determination of the enantiomeric purity of synthetic drugs. The current enzymatic detection methods for saccharides are quite limited in specificity. Moreover, enzymatic sugar sensors are very unstable under harsh conditions. Thus the development of a stable boronic acid derived receptor could lead to saccharide sensors, which are sugar specific.

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CHAPTER 2

TETRAARYLBORONIC ACID RESORCINARENE STEREOISOMERS: VERSATILE NEW SUBSTRATES FOR DIVERGENT POLYFUNCTIONALIZATION AND MOLECULAR RECOGNITION*

2.1 Introduction

Resorcinarenes are a unique class of three-dimensional cyclic aromatic tetramers. They have been the subject of extensive study and review in the disciplines of molecular recognition, supramolecular chemistry, and materials science .[2.1] Boronic acids have achieved great prominence as functional groups. Resorcinarenes have been employed in palladium-mediated coupling reactions,[2.2] carbohydrate recognition and sensing,[2.3] enzyme inhibition[2.4] and molecular transport studies.[2.5] They readily form reversible covalent bonds to diols, which is the basis of carbohydrate affinity chromatography,[2.6] and their respective boronate esters are utilized as efficient asymmetric homologation substrates[2.7] and catalysts.[2.8] Thus, the incorporation of arylboronic acid moieties into resorcinarene frameworks might lead to a range of heterofunctional architectures. We have synthesized and conducted property studies of the new stereoisomeric molecular series **2.1a-c** and **2.2a-c**. Herein, we report the results of our studies.

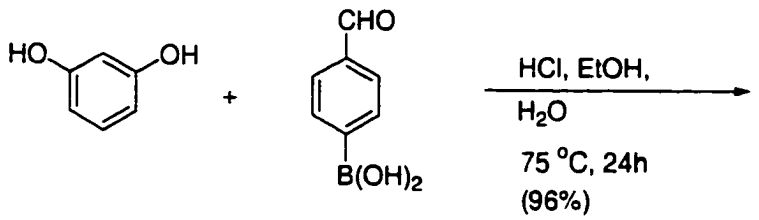
2.2 Results and Discussion

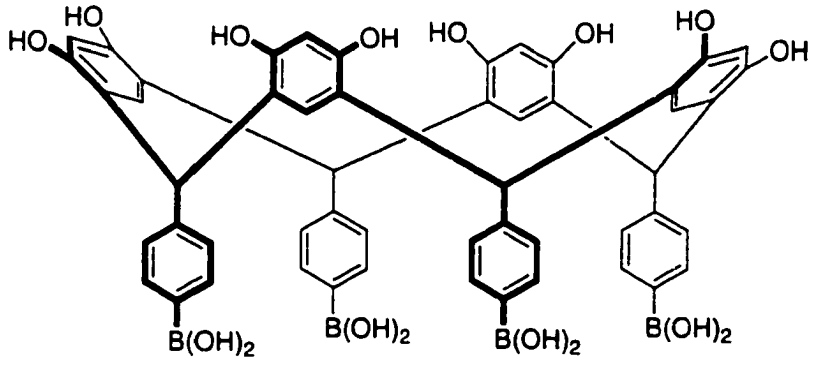
It is well known that the acid-catalyzed condensation of aldehydes with resorcinol affords two major resorcinarene stereoisomers in respective crown (rccc,

*Reprinted in part with permission from *Journal of Organic Chemistry*, 1997, *Volume 62*, pages 6110-6111; Patrick T. Lewis, Claude J. Davis, Mareclo C. Saraiva, W. Dale Treleaven, Tracy D. McCarley, and Robert M. Strongin; Tetraarylboronic Acid Resorcinarene Stereoisomers. Versatile New Substrates For Divergent Polyfunctionalization And Molecular Recognition.

C_{4v} symmetry) and chair (rctt, C_{2h} symmetry) conformations.[2.1] Patrick Lewis found that heating 4-formylphenylboronic acid in 75 mL of a 2:2:1 solution of EtOH:H_2O:HCl with resorcinol yields a precipitate containing 96% of a 3:2 mixture of **2.2a**:**2.1a**. The stereoisomers 2.1a and 2.2a can be directly separated (i.e., without prior acetylation of the phenolic hydroxyls[2.1]) via repeated fractional crystallization from hot methanol. Similarly, 2-methylresorcinol condenses with 4-formylphenylboronic acid to afford stereoisomeric pairs **2.2b** and **2.1b** in a 3:2 ratio, respectively in 61% yield.

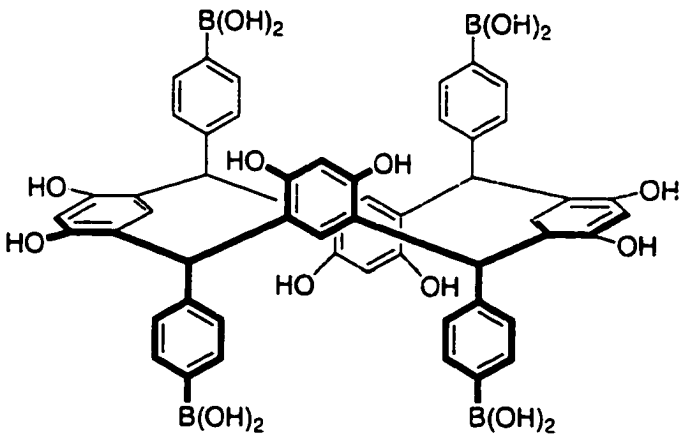
The majority of resorcinarene chemistry reported to date has involved reactions occurring at the resorcinol moieties of crown stereoisomers.[2.1] However, the functionalization of substituents proximal to the macrocyclic ring (i.e., at the appendages derived from the aldehyde condensation partner) has begun to attract attention as a means to embellish the properties of the parent macrocycles.[2.9] Botta and coworkers have reported the synthesis of octamethylether resorcinarenes with chiral amide appendages.[2.10] Other groups have placed chiral substituents, such as amino acids, *ortho* to the phenolic hydroxyls via Mannich chemistry.[2.11] Lewis' synthesis of boronate esters 2.1c and 2.2c complements these studies, affording the first resorcinarene octols embodying chiral moieties at either the lower rim of a crown (C_{4v}) stereoisomer or as part of a chair (C_{2h}) framework, respectively. The (-)-pinanediol boronate esters **2.1c** and **2.2c** are prepared by heating a solution of **2.1a** or **2.2a** with an excess of 1R, 2R, 3S, 5R-(-)-pinanediol in DMF at 110 °C for two days in the presence of Na_2SO_4.





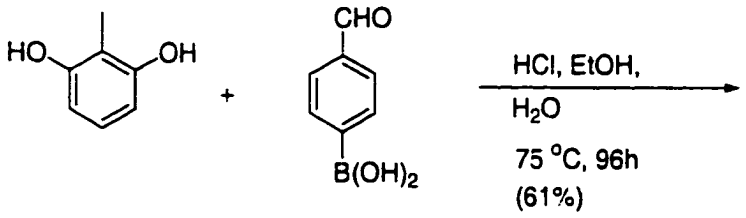
2.1a

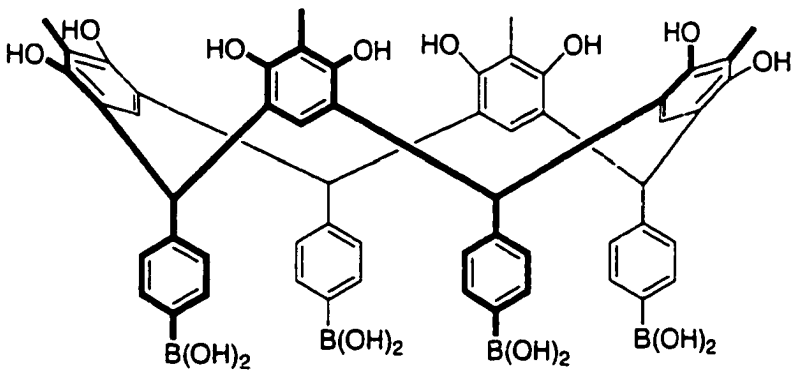
+



2.2a

Figure 2.1 Synthesis of tetraarylboronic acid resorcinarenes.





2.1b

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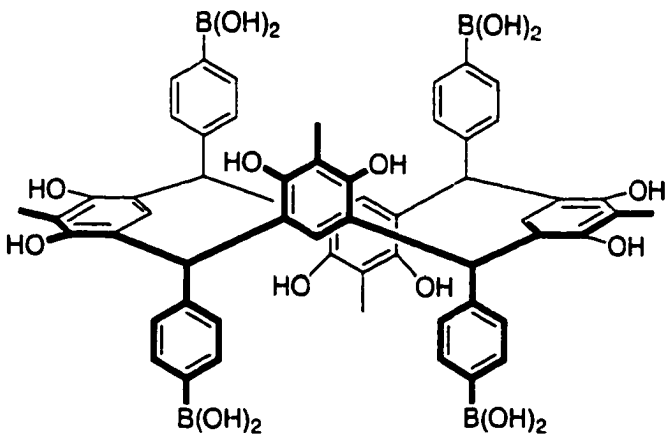
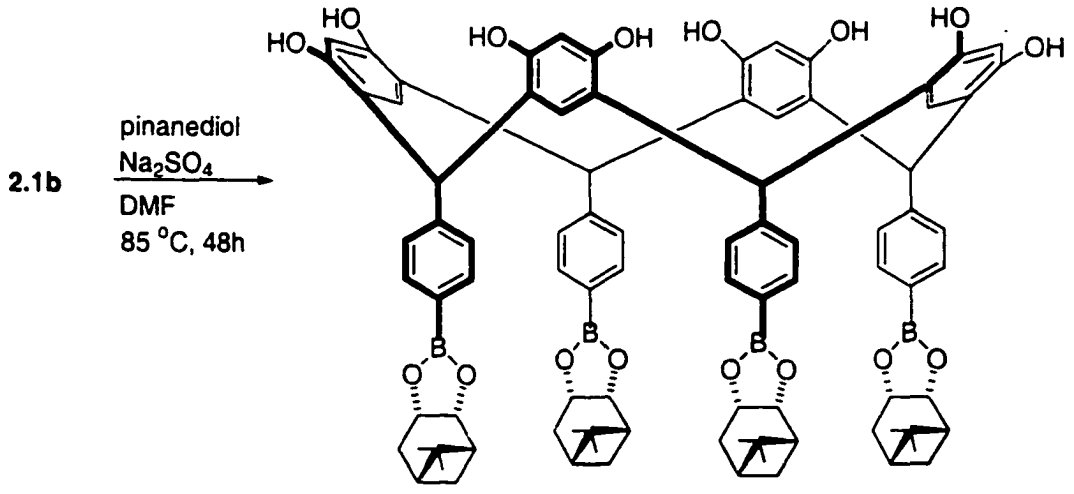
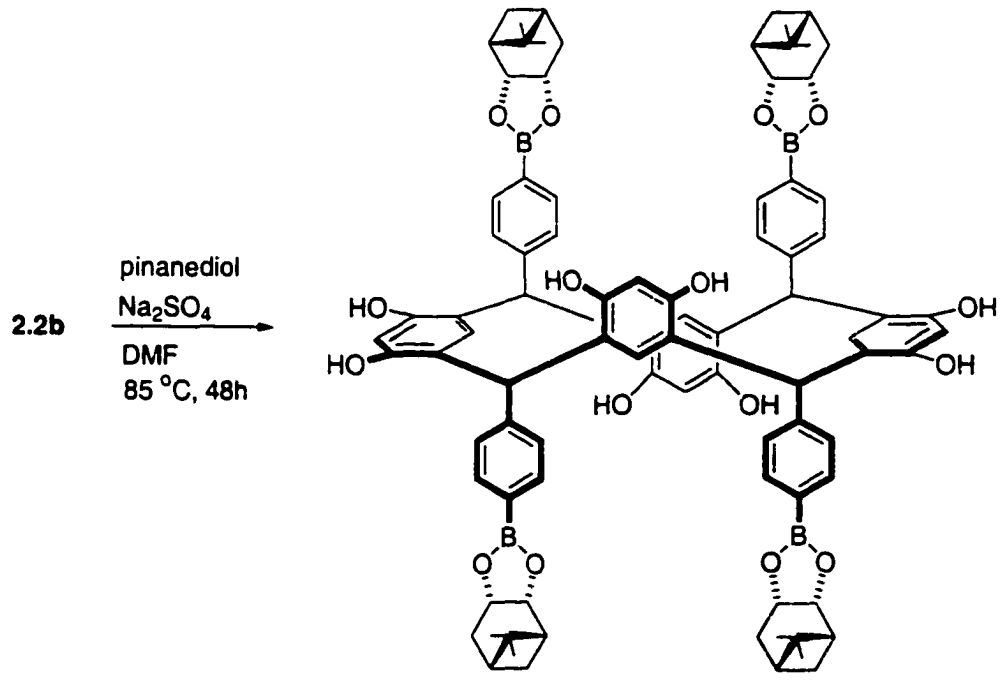


2.2b

Figure 2.2 Synthesis of tetraarylboronic acid macrocycles with 2-methylresorcinol.



2.1c



2.2c

Figure 2.3 Synthesis of the chiral pinane boronate esters.

We next turned our attention to the molecular recognition properties of the new stereoisomeric octols **2.1a**, **2.2a**, **2.1c**, and **2.2c**. The crown isomeric (C_{4v}) resorcinarenes have been extensively studied as molecular hosts whereas the chair (C_{2h})

macrocycles have not received attention.[2.1] 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.[2.12] On the basis of those findings and the fact that the C_{2h} compounds (series **2.2**) described herein embody divergent π-functionality on each facet of a double molecular cleft, we initiated investigations aimed at contrasting the binding properties of **2.1a**, **2.1c**, **2.2a**, and **2.2c** resorcinarenes.

We first compared the covalent binding of **2.1a** vs. **2.2a** to D-glucose. Solutions of **2.1a** or **2.2a** 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 (**2.1a**: δ 7.68 ppm, 8H; **2.2a**: 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 (**2.1a**: δ 7.40 ppm, 8H; **2.2a**: δ 7.30 ppm, 8H). For **2.1a**, the boronic acid proton integral areas decreased in amounts of 64%, 61%, 73%, and 74% and for **2.2a** in amounts of 76%, 78%, 84%, and 83% in the presence of 0.5, 1.0,1.5 and 2.0 equivalents of D -glucose, respectively. Apparently, C_{2h} **2.2a** exhibited a greater (12-28% greater decrease in boronic acid proton integral) degree of covalent interaction in DMSO-d_6 with glucose than did C_{4v} **2.1a**.

In order to contrast the non-covalent binding properties of the stereoisomers, we explored the solid-liquid extraction of D- and L-fucose. Importantly, **2.1c** and **2.2c** are

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

Table 2.1 Covalent binding study of the tetraarylboronic acid resorcinarenes.

Equivalents of Glucose	**2.1a** % Disappearance of $B(OH)_2$ Protons	**2.2a** % Disappearance of $B(OH)_2$ Protons
0.5	64	76
1.0	61	78
1.5	73	84
2.0	74	83

polar molecules.[1.13] We dissolved **2.1c** or **2.2c** (81.2 mg, 0.0540 mmol) in 6 mL of CCl_4 over 24 h and then added (400 mg, 2.44 mmol) 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 ^1H 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 **2.1c** was determined to be 0.4 and 0.07, respectively. The extractabilities were 2.4 for D- and 0.7 for L-fucose by **2.2c**. Thus, both **2.1c** and **2.2c** exhibited greater stereoselectivity for D- over L-fucose and, in both the covalent and non-covalent binding experiments, the C_{2h} (rctt) stereoisomers exhibited stronger affinity for the carbohydrates studied.

Table 2.2 Noncovalent binding study of the chiral pinane boronate ester resorcinarenes.

Solid-Liquid Phase Transfer Agent	Molar Extractability In D-Fucose	Molar Extractability in L-Fucose
2.1c	0.4	0.07
2.2c	2.4	0.7

2.3 Conclusions

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 non-covalent 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.

2.4 Experimental Procedures

General. All chemicals were purchased from the Aldrich Chemical Company and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were acquired With Bruker AC-200, Bruker AC-250, or Bruker AM-400 spectrometers. Residual ^{1}H signals from deuterated solvents were used as a reference unless TMS (δ 0.00) was present. FAB mass spectra were acquired with a Finnigan MAT 900 double focusing mass spectrometer or a Finnjgan TSQ-70 triple quadropole mass spectrometer equipped with a liquid SIMS ionization source. IR spectra were obtained using a Perkin Elmer

FT-IR Spectrometer 1760 X. A Beckman DU-7 spectrophotometer was used to obtain UV spectra.

Tetraarylboronic acid resorcinarene stereoisomers 2.1b and 2.2b. To a solution of 2-methylresorcinol (2.00g,16.2 mmol) and 4-formylphenylboronic acid (2.41g, 16.2 mmol) in 30mL of EtOH and 30mL of H_20 was added 15 mL of concentrated HCI dropwise. The reaction mixture was heated at 75 °C for 96 hours under N_2. The precipitate was washed with water and dried affording 2.53g (61%) of a 3:2 mixture of **2.2b:2.1b**. The stereoisomers were separated by heating in methanol (as in the separation of **2.1a** and **2.2a**) affording 1.22 g of pure **2.2b** and 0.207 g of **2.1b** after drying. (**2.1b**) m.p.>300 C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 1.91 (s, 9H, CH_3 ortho to OH) 5.81 (s, 4H, CH), 6.29 (s, 4H, ArH meta to OH), 6.76 (d, J = 8 Hz,8H, ArH meta to $B(OH)_2$), 7.42 (d, J = 8 Hz, 8H, ArH ortho to $B(OH)_2$), 7.51 (s, 8H, OH), 7.67 (s, 8H, $B(OH)_2$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 74.5, 85.4, 90.5, 91.1, 96.5, 110.2, 113.8, IR (KBr) 3421, 3402, 1609, 1477, 1406, 1340, 1193, 1092, 1015, 751, 640, 569 cm^{-1}; UV (MeOH) λ_{max} 291.5 nm, 484.5 nm; FAB-MS 1248.0 m/z [M + 4 glycerol -8H_2O]$^+$; (**2.2b**) m.p;> 300 C; ^{1}H NMR 400 Mhz $(CD_3)2SO$) δ 1.91 (s, 6H, CH_3 ortho to OH), 2.10 (s, 6H, CH_3 ortho to OH), 5.65 (s, 4H, CH), 5.90 and 6.29 (s, 4H, ArH meta to OH), 6.68 (d, J = 8 Hz, 8H, ArH meta to $B(OH)_2$), 7.37 (d, J = 8 Hz, 8H, ArH ortho to $B(OH)_2$), 7.36 and 7.52(s, 4H, OH), 7.59 (s, 8H, $B(OH)_2$); ^{13}C NMR (100 Mhz, $(CD_3)_2SO$) δ 6.79, 73.8, 74.0, 84.5, 86.0, 91.3, 91.6, 92.6, 96.3, 108.5, 113.55, 113.61 ; IR (Kbr) 3426, 3391, 1645, 1609, 1477, 1406, 1345, 1198, 1092, 1015, 645; UV (MeOH) λ_{max} 287.5 nm; FAB-MS 1248.0 m/z [M + 4 glycerol -8H_2O]$^+$.

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CHAPTER 3

SIMPLE AND RAPID VISUAL SENSING OF SACCHARIDES*

3.1 Introduction

Facile methods for detecting and monitoring saccharides are of immense importance to medical diagnostics and industry. A current challenge in this area is the fabrication of readily accessible, stable artificial receptors that promote fast, sensitive and selective detection.[3.1] Such materials could lead to improved sensors relative to degradable enzyme-based systems or to those requiring complex and expensive syntheses or instrumentation. We have found that a tetraarylboronic acid resorcinarene macrocycle **3.1**, obtained on large scale in one step and easily purified,[3.2] promotes the most versatile visible detection of sugars observed to date (Figure 3.1). Characteristic and dramatic solution color changes are attained for carbohydrates, glucose phosphates, amino sugars and sialic and uronic acids.

The visual determination of saccharides has been of great interest for more than a century. In 1887, Seliwanoff reported a resorcinol color test that was specific for ketoses.[3.3] Other resorcinol-based color tests for sugars were later developed.[3.4,3.5] In this decade great progress has been made towards the enhanced selective visible detection of saccharides via the pioneering studies of Shinkai and coworkers, based mainly on chromophore-functionalized arylboronic acids[3.1] or the affinity of nitrogen-containing chromophores for arylboronic acids.[3.6] A recent review underscored the lack of sugar receptors that promote dramatic color changes

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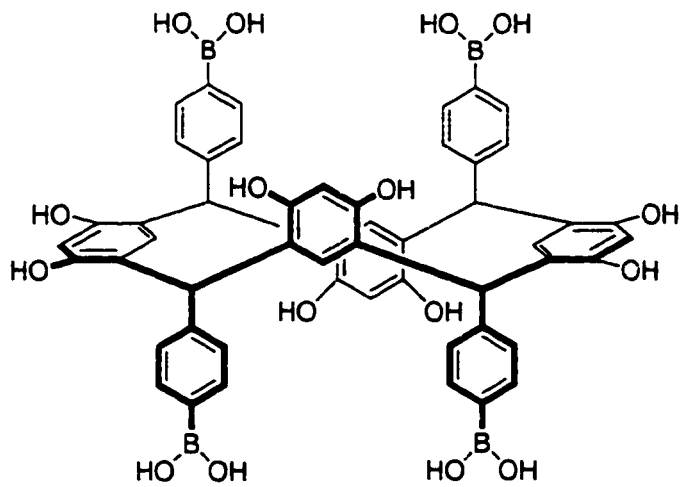
in the presence of individual analytes.[3.1] Powerful color receptors could be of practical utility for monitoring disease states or the products of fermentation processes.

3.2 Results and Discussion

We have reported a facile synthesis of macrocycles which embody both arylboronic acid and resorcinol moieties.[3.2] One of these, compound **3.1**, is obtained as a white solid which forms a colorless solution when dissolved in DMSO at room temperature. After standing in solution for several hours or upon heating at 90 °C for 1 min the solution develops a pinkish-purple color. These color changes can be monitored in the UV-vis spectrum of **3.1** via the appearance of a new absorption at 536 nm. The fluorescence spectrum of colorless solutions of **3.1** exhibits only short-wavelength excitation and emission bands at 350 and 410 nm, respectively. The colored solutions additionally display long-wavelength excitation at 525 nm and emission at 570 nm. When stored as a white solid over a period of several months, no change in the UV-vis or fluorescence spectrum of **3.1** is observed.



3.1

Figure 3.1. Resorcinarene colorimetric sensor for saccharides.

Heating colorless solutions of **3.1** (5.2 mM, 10:1 DMSO:H_2O, 1 mL) and 3.0 equiv of either D-(-)-fructose, α-D-glucose or sucrose at 90 °C for 1 min results in selective coloration. The fructose solution is deep yellow and the glucose solution pink-yellow. The solution containing sucrose, which exhibits the weakest binding to boronic acids in this series,[3.7,3.8] is purple and easily distinguished from glucose and fructose. It is similar in appearance to the solution of **3.1** heated by itself. Upon heating in the presence of excess (16 mg) Na_2SO_4, which we previously employed to promote boronate ester formation of **3.1** with diols,[3.2] the colors of the glucose and fructose/**3.1** solutions become more distinct, turning peach-colored and yellow, respectively.[3.9] Reheating the colored solutions of **3.1** alone in the presence of 3 equiv of each of the three saccharides produces the same solution colors observed when heating initially colorless solutions of **3.1** containing the sugars. The decrease in relative absorbances for the sugars, measured at 536 nm, qualitatively mirrors the known relative binding affinity of fructose (A=0.057) > glucose (A=0.067) > sucrose (A=0.10) for arylboronic acids.[3.7,3.8] This trend is confirmed by ^{1}H NMR via the successive decrease of the integral areas of the boronic acid protons of solutions of **3.1** containing these added carbohydrates.

D-Glucose-6-phosphate and α-D-glucose-1-phosphate are two intermediates in glycogen biosynthesis.[3.10] Heating colorless solutions of these sugars (3 equiv) in the presence of **3.1** (5.2 mM) in 10:1 DMSO: H_2O at 100 °C for 1.5 min results in a very bright crimson color for α-D-glucose-1-phosphate disodium salt monohydrate (λ_{max}=495 nm, A=1.1 and 536 nm, A=0.49) and a dark reddish brown for the D-glucose-6-phosphate monosodium salt solution (λ_{max}=471 nm, A=1.8). The same

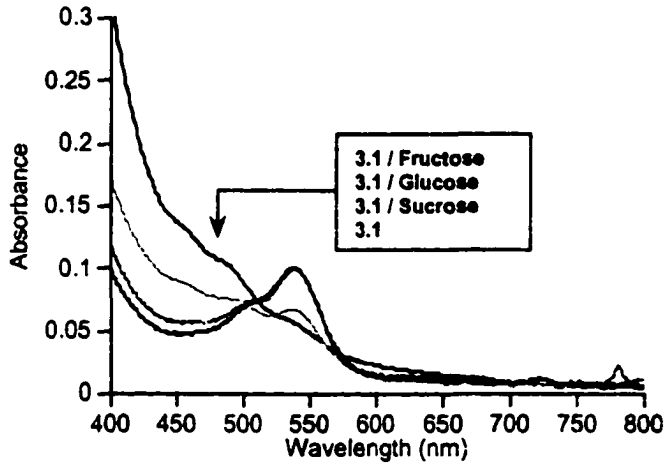


Figure 3.2. Absorption spectrum of macrocycle **3.1** upon heating at 90 °C for 1 minute in the presence of D-(-)-fructose, sucrose, or α-D-glucose. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1), 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

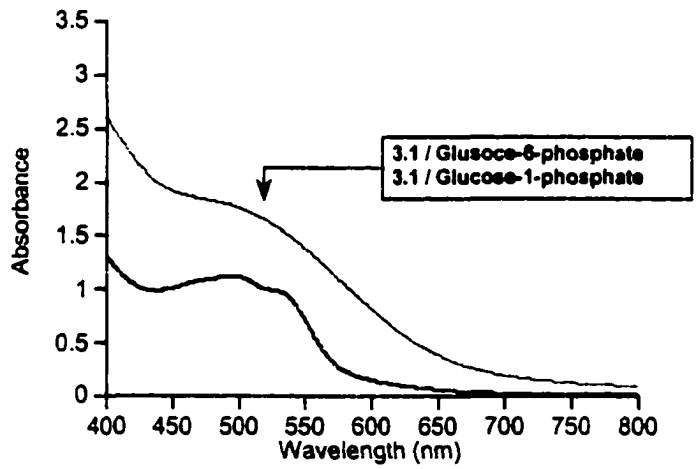


Figure 3.3. Absorption spectrum of macrocycle **3.1** upon heating at 100 °C for 1.5 minutes in the presence of D-glucose-6-phosphate monosodium salt or α-D-glucose-1-phosphate disodium salt. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1) and 3 equiv. carbohydrate).

respective colors are observed for G-1-P monosodium salt and G-6-P disodium salt. The results of the sugar/**3.1** color experiments are reproducible as evidenced by visual inspection and spectrophotometric measurements. The average relative error in the absorbance measurements of three separate thermolyses of the five sugar/**3.1** complexes is 4.6%.

Room temperature fluorescence anisotropy measurements of colored solutions of **3.1** revealed that the species associated with the long-wavelength fluorescence has a much slower rotational correlation time (r=0.189) than that associated with the short-wavelength fluorescence (r=0.010). Saccharides appear to perturb an aggregation-deaggregation equilibrium; added analytes change the relative intensities of the long- and short-wavelength fluorescence. Importantly, this property is sugar-specific. In addition, each heated saccharide/**3.1** solution exhibits a characteristic rotational correlation time (Table 3.1).

Table 3.1. Fluorescence properties of **3.1** (5.2 mM in DMSO) heated alone and in the presence of 3 equiv of various saccharides showing the maximum excitation and emission of the long-wavelength fluorescence, the fluorescence anisotropy (r) of the long-wavelength species and the intensity of the long-wavelength fluorescence relative to the short-wavelength fluorescence (I_{long}/I_{short}).

Added Sugar	λ_{ex}(nm)	λ_{em}(nm)	Anisotropy(r)	I_{long}/I_{short}
None	543	575	0.189	3.2
α-D-glucose	535	573	0.255	3.3
glucose-1-phosphate	550	585	0.155	5.2
glucose-6-phosphate	490	580	0.161	5.7
Fructose	492	572	0.100	1.6
Sucrose	540	578	0.129	4.4

A significant blue shift in λ_{ex} of 60 nm is observed for D-glucose-6-phosphate compared to α-D-glucose-1-phosphate. This complements recent efforts involving the fluorescent sensing of these molecules. In the prior studies, glucose-1- and -6-phosphate were differentiated by observed changes in ^{31}P NMR and CD spectra[3.11] or variations in fluorescence emission intensities upon receptor binding.[3.12]

It is intriguing that **3.1** does not have extended π-conjugation and yet heated solutions of **3.1** display spectrophotometric absorption as well as fluorescence excitation and emission in the visible region. The ^{1}H and ^{13}C NMR spectra of DMSO-d_6 solutions of **3.1**, heated for 3 min as above, exhibit no change in chemical shifts or peak area integrals compared to colorless samples. After prolonged (12-24 h) heating of air saturated solutions of **3.1** in DMSO at 180 °C no evidence of carbonyl formation by ^{13}C NMR or FT-IR spectroscopy is observed; moreover, the ^{11}B NMR spectra reveal no evidence of boronate ester formation or boronic acid hydrolysis. This does not, however, allow us to rule out the presence of trace amounts of highly colored oxidized material appearing at levels too low to detect.

If trace amounts of oxidized products are responsible for the coloration, then altering the concentrations of the oxidized materials should afford variable color schemes. To test this hypothesis we heated solutions of **3.1** alone (183 °C) and in the presence of 3 equiv of the five saccharides for 3 min (control set, affording the same visible color schemes as noted above but with increased absorbance intensities due to greater heating), in the dark, and with N_2 or air saturation. Upon N_2 saturation every solution is observably fainter in color than in the control case, with absorbance decreases of 39-82%. Importantly, the solution of **3.1** alone exhibits a significant absorbance decrease of 61% (536 nm). Upon air saturation the two glucose phosphate solutions begin to change color within seconds and are the most

darkened, with glucose-6-phosphate showing a >7.5-fold increase and glucose-1-phosphate exhibiting a >2-fold increase in absorbance intensity. Upon heating in the dark the glucose and sucrose solutions are the faintest in color, displaying respective absorbance decreases of 33% and 26% compared to the control case. Light and oxygen[3.13] are therefore clearly factors in the coloration process. We ascribe the coloration of solutions of **3.1** as due to the production of trace amounts of highly absorbing, oxidized (quinone) derivatives of **3.1**.

Oxidation of either an arylboronic acid or resorcinol moiety must result in sp^2 hybridization of a macrocycle methine carbon. This would place the resultant quinone in π-conjugation with two aromatic rings. Only partial oxidation of **3.1** at

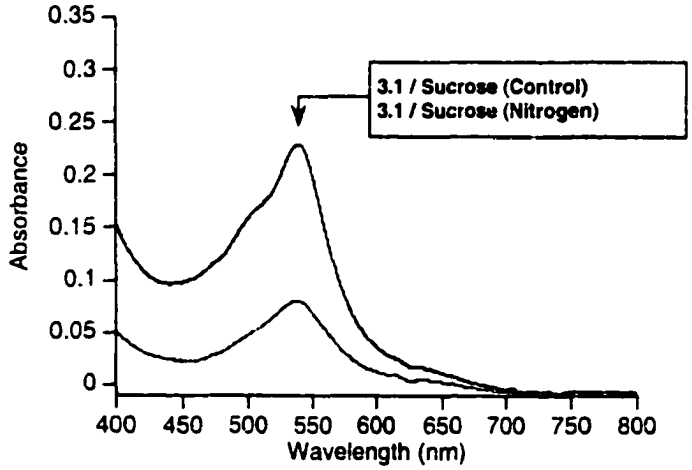


Figure 3.4. Absorption spectrum of macrocycle **3.1** upon heating at 189 °C for 3 minutes in the presence of sucrose. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1), 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

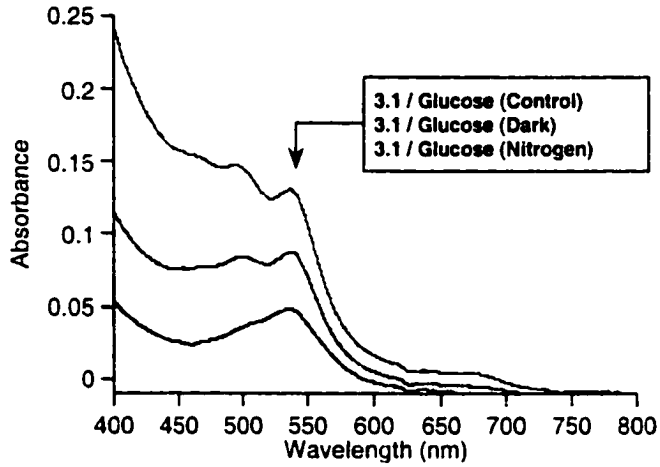


Figure 3.5. Absorption spectrum of macrocycle **3.1** upon heating at 189 °C for 3 minutes in the presence of α-D-glucose. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1), 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

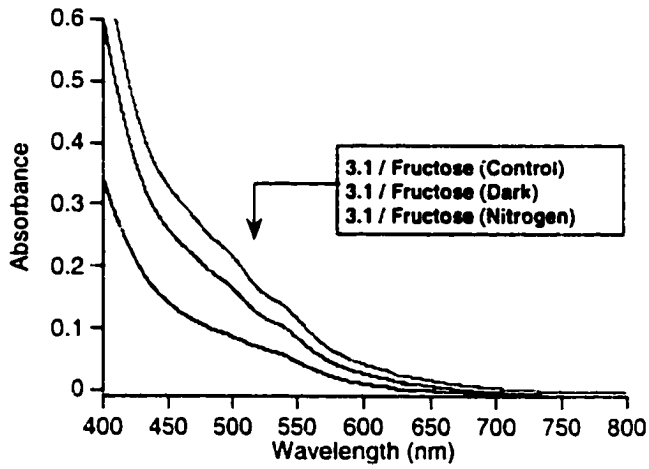


Figure 3.6. Absorption spectrum of macrocycle **3.1** upon heating at 189 °C for 3 minutes in the presence of D-(-)-fructose. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1), 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

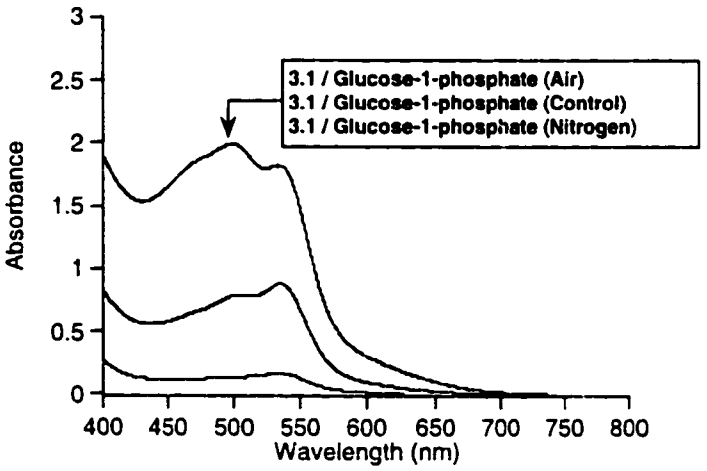


Figure 3.7. Absorption spectrum of macrocycle **3.1** upon heating at 189 °C for 3 minutes in the presence of α-D-glucose-1-phosphate disodium salt. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1) and 3 equiv. carbohydrate).

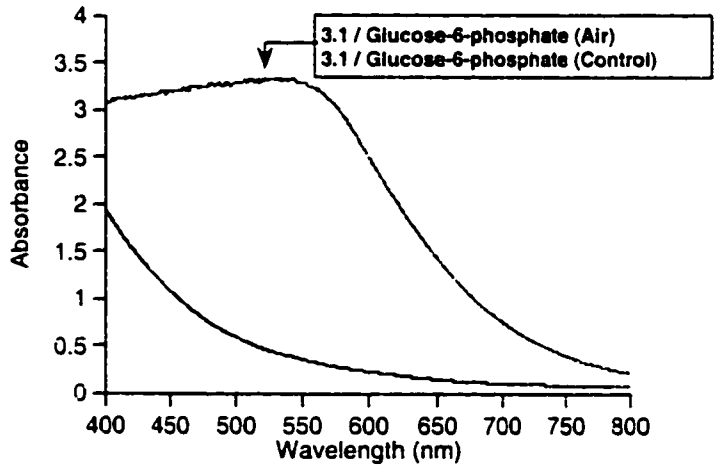


Figure 3.8. Absorption spectrum of macrocycle **3.1** upon heating at 189 °C for 3 minutes in the presence of D-glucose-6-phosphate monosodium salt. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO / H_2O (10:1) and 3 equiv. carbohydrate).

low levels would occur due to the strain imparted to the macrocyclic ring upon introduction of sp^2 hybridization. We propose that binding with the respective analytes could then afford selective coloration via sugar-specific perturbations in torsion angles and/or aggregation-deaggregation equilibrium (as evidenced by fluorescence anisotropy, *vide supra*).[3.14] The presence of strongly π-accepting, oxidized aromatics enhances intermolecular π -donor/ π -acceptor interactions, thereby contributing to the order of magnitude change in rotational correlation time observed for the colored solutions of **3.1**.

The visual detection of saccharides promoted by **3.1** is versatile, not limited to the carbohydrates and glucose phosphates described above. D-Glucuronic acid and D-galacturonic acid promote monosaccharide oxidation and vitamin C biosynthesis.[3.15] Sialic acid is an important antigenic cell-surface residue.[3.16] Colorless DMSO solutions of **3.1** (5.2 mM) and 3.0 equiv each of these three structurally related carboxylic acid sugars, upon heating in the presence of excess Na_2SO_4 for 2 min until reflux, are bright gold (λ_{max}=450 nm, A=0.20) faint yellow (λ_{max}=456 nm, A=0.10) and reddish-orange (λ_{max}=440 nm, A=0.80), respectively.

D-Glucosamine and *N*-acetyl-D-glucosamine (NAG) are the major constituents of chitin, one of the most abundant polysaccharides on earth.[3.17] (+)-*N*-Acetylmuramic acid (NAM) is a component of bacterial cell walls.[3.18] Colorless solutions of **3.1** (5.2 mM) containing 3 equiv of these amino sugars, upon heating in the presence of excess Na_2SO_4 for 2 min until reflux, are pale pink (λ_{max}=540 nm, A=0.13), pale yellow (λ_{max}=460 nm, A=0.43), and very dark orange (λ_{max}=425 nm, A=3.1) for NAG, NAM, and D-glucosamine hydrochloride, respectively.

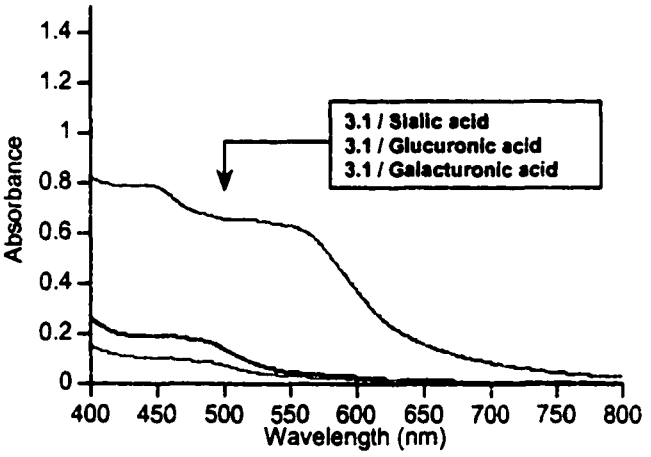


Figure 3.9. Absorption spectrum of macrocycle **3.1** upon heating at 90 °C for 1 minute in the presence of D-glucuronic acid, D-galacturonic acid, or *N*-acetylneuramic acid. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO, 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

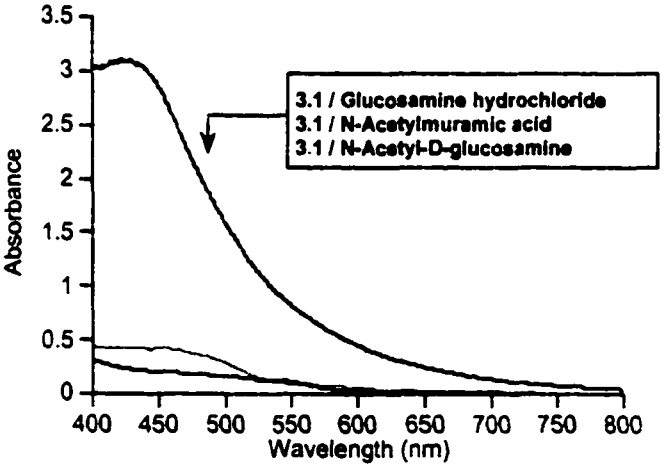


Figure 3.10. Absorption spectrum of macrocycle **3.1** upon heating at 90 °C for 1 minute in the presence of D-glucosamine hydrochloride, (+)-*N*-acetylmuramic acid, or *N*-acety-D-glucosamine. (Conditions: Macrocycle **3.1** (5.2 mM) in DMSO, 22 equiv. sodium sulfate, and 3 equiv. carbohydrate).

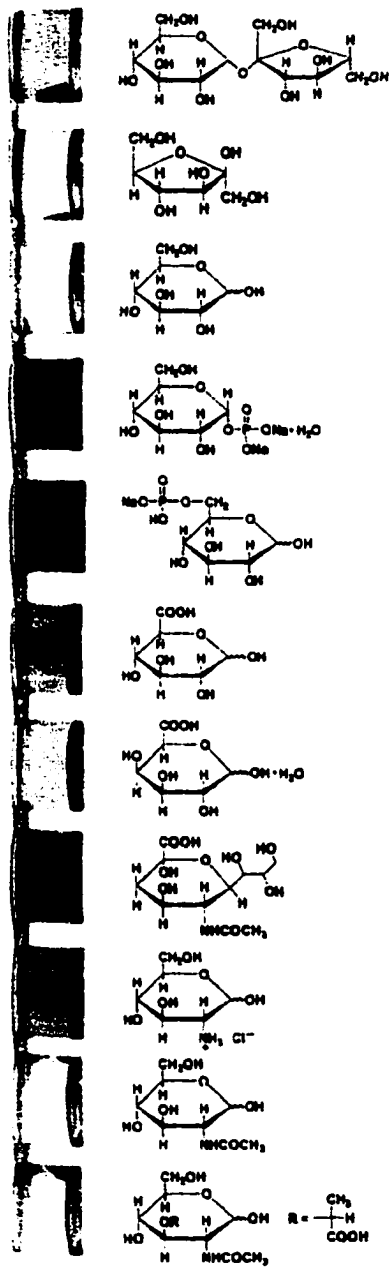


Figure 3.11 Heated 5.2 mM DMSO solutions of **3.1** and 3 equiv of (from top to bottom) (i) carbohydrates, sucrose, D-(-)-fructose, α-D-glucose; (ii) glucose phosphates, α-D-glucose-1-phosphate, disodium salt hydrate, D-glucose-6-phosphate monosodium salt; (iii) carboxylic acid and amino sugars, D-glucuronic acid, D-galacturonic acid monohydrate, sialic acid, D-glucosamine hydrochloride, *N*-acetyl-D-glucosamine, (+)-*N*-acetylmuramic acid.

3.3 Conclusions

In conclusion, solutions of receptor **3.1** containing added saccharides exhibit dramatic, characteristic solution color changes that are readily distinguished by visual inspection. The color selectivities can be tuned by altering simple parameters such as added water or a drying agent. This unique methodology is rapid and reproducible, with the solution colors remaining stable by visual inspection for periods lasting typically up to several days. Since tetraarylboronic acid resorcinarenes are amenable to a variety of synthetic modifications,[3.2,3.19] this research should lead to the fabrication of new classes of color sensing materials. Our current efforts include the synthesis and study of **3.1** and congeners and related oxidized model resorcinol- and/or boronic acid-derived compounds. We are also investigating the possibility of sugar (e.g., furfural or other sugar-derived aldehyde condensation) reactions with **3.1** or oxidized, ring-opened (as a result of the strain induced upon sp^2 hybridization) **3.1**. In addition, comparative studies of the coloration process employing **3.1** and simple aliphatic and aromatic diols vs. other hydroxy compounds, reducing vs. non-reducing sugars, and ketoses vs. aldoses are ongoing. The detailed characterization and analysis of the saccharide-receptor complexes employing a variety of conditions, including competitive binding studies of sugar mixtures and other polar biomolecules, is also in progress.

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3.13 The selective coloration is solvent sensitive. Boiling 5.2 mM solutions (3 min) of **3.1** in DMF with added H_2O and Na_2SO_4 produces a very pale pink solution coloration. This color is also observed when heating **3.1** in the presence of 3 equiv of added sucrose and glucose. In the presence of fructose, the solution color is pale peach. Boiling 5.2 mM solutions (3 min) of **3.1** in triglyme with added H_2O and Na_2SO_4 produces a very faint yellow tint which is also observed via heating in the presence of 3 equiv added glucose, fructose, and sucrose.

3.14 Heated 5.2 mM solutions of resorcinol or phenylboronic acid either alone or together in DMSO containing H_2O and Na_2SO_4 are colorless. Heating these solutions with added sucrose produces no color change. In the presence of glucose, only the mixed resorcinol/ phenylboronic acid solution develops a faint yellow tint. Added fructose results in a yellow coloration of the mixed resorcinol/ phenylboronic acid solution and a very faint yellow coloration of the solutions containing resorcinol or phenylboronic acid. These experiments demonstrate that the macrocyclic structure is a prerequisite for attaining the dramatic color changes observed. We are investigating the possibility of the role of sugar (beyond simple boronate ester formation and hydrogen bonding; e.g. furfural or other sugar-derived aldehyde condensation) reactions with **3.1** or oxidized, potentially ring opened **3.1**. In addition, comparative studies of the coloration process employing **3.1** and simple aliphatic and aromatic diols versus other hydroxy compounds, reducing versus nonreducing sugars, and ketoses versus aldoses in buffered solutions are in progress.

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CHAPTER 4

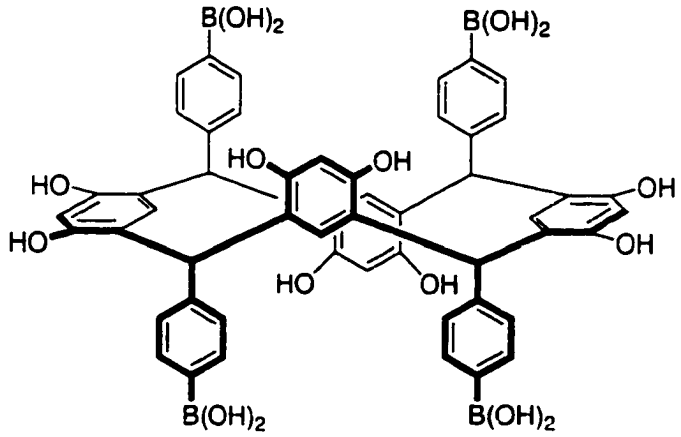
VISUAL SENSING OF SACCHARIDES PROMOTED BY RESORCINOL CONDENSATION PRODUCTS*

4.1 Introduction

The use of synthetic hosts for the recognition of saccharidesis is of great current interest.[4.1] Classical colorimetric methods are limited for the non-enzymatic detection of saccharides. For example, they might only detect reducing and non-reducing sugars.[4.2] Recently, Shinkai and coworkers reported the synthesis of a new visual receptor based on the affinity of nitrogen-containing arylboronic acid compounds.[4.3]

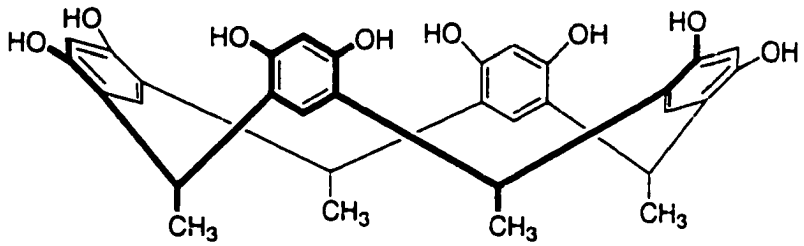
Adolf von Baeyer studied the condensation of benzaldehyde and resorcinol in 1872 .[4.4] He discovered that a reddish resin product was formed, and it turned to violet upon the addition of base. We recently reported that **4.1** promotes the visual differentiation of specific saccharide solutions via simple color changes.[4.5] Our methodology, involves heating aqueous DMSO solutions of **4.1** containing saccharides, which in turn produces characteristic color changes for specific carbohydrates, glucose phosphates, amino sugars and carboxylic acid sugars. As part of our ongoing investigations aimed at fully elucidating the mechanism, scope and limitations of this selective new coloration process we employed receptors **4.2**[4.6] and **4.3**.[4.7] Herein, we report the discovery of colorimetric properties observed with each resorcinol condensation product.

*Reprinted in part with permission from *Organic Letters*, **2000**, *Volume 2*, pages 589-592; Patrick T. Lewis, Claude J. Davis, Larry A. Cabell, Ming He, Mark W. Read, Matthew E. McCarroll, and Robert M. Strongin; Visual Sensing of Saccharides Promoted by Resoricnol Condensation Products.



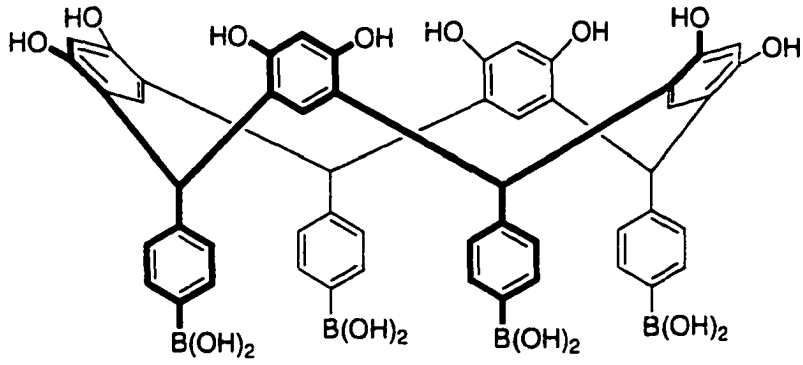
4.1

Figure 4.1. Chair resorcinarene colorimetric sensor for saccharides.



4.2

Figure 4.2. A new resorcinarene colorimetric sensor for saccharides.



4.3

Figure 4.3 Crown boronic acid resorcinarene colorimetric sensor for saccharides.

4.2 Results and Discussion

Compound **4.2**[4.6] is a readily available prototypical crown stereoisomeric resorcinarene.[4.8] Heating 5.2 mM of **4.2** (colorless after several recrystallizations from MeOH) in 1 mL of 9:1 DMSO:H_2O for 3 min to a gentle reflux followed by cooling to rt leads to a purple solution. The color formation can be monitored via a new absorption appearing at 536 nm. This result is consistent with the same experiment employing **4.1**.[4.5] Heating colorless solutions of **4.2** and 3.0 equiv of either D-(-)-fructose, α-D-glucose, sucrose or the glucose phosphates results in colors selective for each sugar; however, by visual inspection, the colors appear paler and less distinctive as compared to those from sensing experiments with **4.1** (Table 4.1). Colorless solutions (1 mL, 5.2 mM 9:1 DMSO:H_2O) of recrystallized crown resorcinarene **4.3** also develop color upon heating. The colors of sugar/**4.3** solutions are similar to those reported previously with stereoisomer **4.1**[4.5]; however, are they are more distinctively colored compared to the sugar/**4.2** solutions (Table 4.2). The aforementioned experiments

indicate that the colorimetric sensing of saccharides appears to be general to the resorcinarenes, including those without boronic acids such as **4.2**.

Table 4.1 Monitored λ, corresponding absorbances (A), and solution color observed upon heating 9:1 DMSO:H_2O 5.2mM solutions of **4.2** and 3 equiv added saccharides to a gentle reflux for 3 min. Values represent averages of three runs.

Added Sugar	λ(nm)	A	Color
None	536	0.472	Purple
Sucrose	536	0.329	Purple
α -D-Glucose	536	0.172	Yellow-orange
D-(-)-Fructose	536	0.128	Peach
α -D-Glucose-1-phosphate disodium salt hydrate	409	2.25	Orange-brown
	536	0.536	
D-Glucose-6-phosphate monosodium salt	452	0.680	Yellow-brown
	536	0.274	

Previously, we found that oxygen promoted the color development of solutions of **4.1** alone or in the presence of sugars.[4.5] Heating N_2-saturated samples of **4.2** or **4.3** with or without the five saccharides listed in Table 4.1 for 3 min results in a significant decrease in visible region absorbance intensity (decrease by 3-40 % [536 nm] and decrease by 47-96 % [536 nm]], respectively) as compared to samples heated without protection from air. This supports our prior proposal that color formation is promoted by oxidation.[4.5]

Table 4.2 Monitored λ, corresponding absorbances (A), and solution color observed upon heating 9:1 DMSO:H_2O 5.2mM solutions of **4.3** and 3 equiv added saccharides to a gentle reflux for 3 min. Values represent averages of three runs.

Added Sugar	λ (nm)	A	Color
None	536	0.548	Pink
Sucrose	536	0.540	Pinkish-purple
α -D-Glucose	536	0.328	Orange
D-(-)-Fructose	536	0.266	Yellow-gold
α -D-Glucose-1-phosphate disodium salt hydrate	536	1.38	Orange-amber
D-Glucose-6-phosphate monosodium salt	536	2.13	Amber

We next decided to examine the effect of acid and base on the colorimetric properties of **4.1**, **4.2**, and **4.3**. The solution colors of resorcinol condensation products have long been known to exhibit pH dependence.[4.4] Furthermore, each solution in Tables 4.1 and 4.2 exhibit a characteristic pH. We found that solutions of **4.1**-**4.3** (after exposure to O_2[4.5]) function as acid-base indicators, displaying sensitive changes in visible region absorbance intensities. Heated solutions of compound **4.1** (5.2 mM, 9:1 DMSO:H_2O) are pale yellow at pH 4.2-6.2, turn pinkish-orange at pH 8.34, pale pink (8.4 –10.2), and pink (pH 10.5-12.0). Heated solutions of compound **4.2** are yellow from pH 4.9-7.9, pale orange at pH 9.1, and purple (9.3-11.1). Upon heating, solutions of compound **4.3** are yellow below pH 8.1, pale pink at pH 9.1 and pinkish-purple from pH 9.9-11.1. The nominal pH readings for heated solutions of compounds **4.1**-**4.3** with specific saccharides are listed in Tables 4.3-4.5.

Table 4.3 Monitored the nominal pH and solution color observed upon heating 9:1 DMSO:H_2O 5.2mM solutions of **4.1** and 3 equiv added saccharides to a gentle reflux for 3 min.

Added Sugar	Color	pH
None	Pinkish-purple	9.39
Sucrose	Pinkish-purple	9.65
α -D-Glucose	Peach	8.53
D-(-)-Fructose	Yellow	8.01
α -D-Glucose-1-phosphate disodium salt hydrate	Deep orange	10.7
D-Glucose-6-phosphate monosodium salt	Amber	8.48

Table 4.4 Monitored the nominal pH and solution color observed upon heating 9:1 DMSO:H_2O 5.2mM solutions of **4.2** and 3 equiv added saccharides to a gentle reflux for 3 min.

Added Sugar	Color	pH
None	Purple	10.6
Sucrose	Purple	10.8
α-D-Glucose	Yellow-orange	8.4
D-(-)-Fructose	Peach	9.2
α -D-Glucose-1-phosphate disodium salt hydrate	Orange-brown	8.3
D-Glucose-6-phosphate monosodium salt	Yellow-brown	6.7

Table 4.5 Monitored the nominal pH and solution color observed upon heating 9:1 DMSO:H_2O 5.2mM solutions of **4.3** and 3 equiv added saccharides to a gentle reflux for 3 min.

Added Sugar	Color	pH
None	Pink	10.7
Sucrose	Pinkish-purple	11.1
α -D-Glucose	Orange	9.9
D-(-)-Fructose	Yellow-gold	7.8
α -D-Glucose-1-phosphate disodium salt hydrate	Orange-amber	10.0
D-Glucose-6-phosphate monosodium salt	Amber	8.5

4.3 Conclusions

Several conclusions can be made from the present studies. First, the visual sensing of saccharides appears to be applicable to a variety of readily-available resorcinol condensation products.[4.8a] Secondly, changing the receptor framework can alter the color patterns observed for the various sugars. Third, colored solutions containing **4.1-4.3** can function as acid-base indicators. [4.5] Fourth, oxygen promotes the solution color formation with each receptor. This is consistent with our prior mechanistic proposal that oxidation of the receptors is a key factor in producing solution color.[4.5] Ongoing studies are aimed at further probing the mechanism and scope of biomolecule visual sensing with resorcinol condensation products. Our efforts include examining the role of pH, aggregation-deaggregation,[4.1a,4.5] oxidation[4.5,4.9] and covalent[4.1a,4.10] and/or noncovalent[4.1b,4.8] analyte/receptor interactions.[4.1,4.8,4.11,4.12] We will report further details of the color sensing mechanism in due course.

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4.12 Addition of 3 equiv of sucrose, glucose, or fructose to colored (preheated) 10% aqueous DMSO solutions containing 5.2 mM **4.1** affords characteristic color changes (purple, peach, and yellow for sucrose, glucose, and fructose respectively, as described in ref. 5) upon standing at room temperature overnight. Interestingly, addition of preheated (6 min at gentle reflux) 10% aqueous DMSO solutions containing 3 equiv of each of the three sugars to colored (preheated) solutions of **4.1** also affords solution colors similar to those reported in ref 5, but within 1 min at room teperature. The absorbance intensity monitored at 538 nm diminishes corresponding to the previously observed order: sucrose (A = 0.546) > glucose (A = 0.493) > fructose (A=0.174).

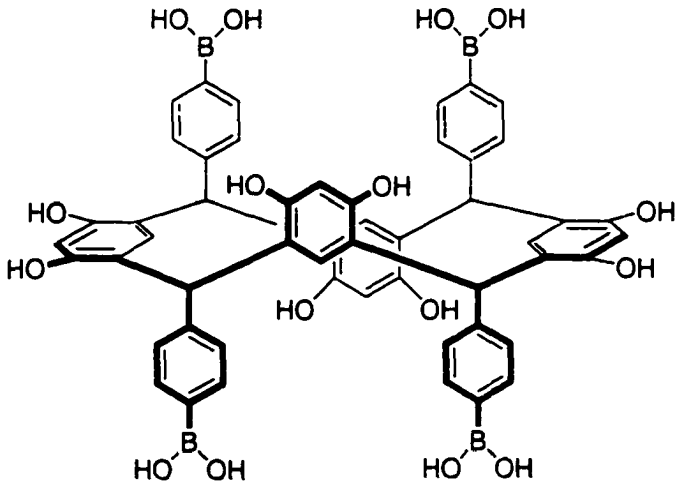
CHAPTER 5

SOLID STATE SUPRAMOLECULAR STRUCTURES OF RESORCINOL-ARYLBORONIC ACID CONDENSATION PRODUCTS

5.1 Introduction

The controlled formation of self-assembling supramolecular solids poses a great challenge to the scientific community.[5.1] Two-dimensional hydrogen-bonded networks are of current interest to serve as templates for the design and construction of supramolecular assemblies. A pre-organized two-dimensional array allows for the assembly of three-dimensional networks via controlled "stacking" of the two-dimensional arrays. This affords one dimensional crystal engineering, which promotes the predictability of crystal structures.[5.2] Well-ordered, porous organic solids that incorporate receptor and/or catalytic elements are particularly attractive targets. Binding and/or catalysis often occurs within their cavities.[5.3]

A two-dimensional network could be advantageous, due to a lack of dense packing that often limits the cavity size in the more prevalent three-dimensional systems. One of the major culprits in this process is self-interpenetration. The "arms" of adjacent molecules are used to increase the packing efficiency or even strengthen the molecular interactions, often filling voids to form cavities. The incorporation of multiple binding sites and/or rigid frameworks can aid in overcoming this trend.[5.4] Aoyama recently reported the creation of bis(resorcinol) derivatives of anthracene or anthraquinone, which form hydrogen-bonded columns that can include guests and serve as catalysts.[5.5]

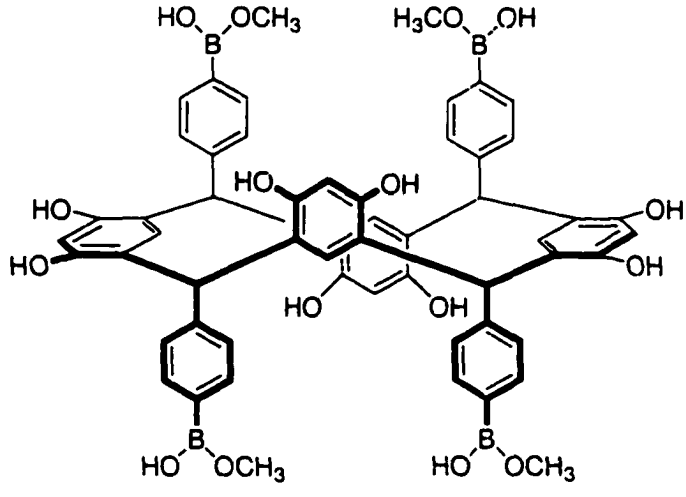


5.1

Figure 5.1 Chair arylboronic acid resorcinarene.

We have been investigating the properties of new materials incorporating arylboronic acid and resorcinol functionality. Our boronic acid-derived resorcinarenes have been employed as both chiral and achiral molecular hosts, as well as substrates for the creation of deep-cavity polyaromatic hosts.[5.6] We have recently reported the discovery that these materials can function as color sensing agents for saccharides.[5.7] Our solid-state studies of resorcinol derivatives in conjunction with the historic role of arylboronic acids in molecular recognition and catalysis has focused our efforts toward understanding how polytopic resorcinol-boronic acid materials interact to form supramolecular arrays.[5.8] Herein, we report the X-ray crystal structure of the supramolecular solid-state structure of the C_2h stereoisomeric macrocycle **5.1** (Figure 5.1), previously synthesized in our laboratory (Figure 5.1).[5.6a, 5.7b] Interestingly, we find that **5.1** crystallizes as its corresponding half methyl ester **5.2** (Figure5.2) from

methanol. This results in the formation of infinite, antiparallel two-dimensional hydrogen-bonded columns with a single macrocycle at the focal point. Our findings differ from Böhmer's, where he reported that a chair resorcinarene formed hydrogen-bonded columns that were "wrapped" by layers of solvent or was either completely solvated .[5.9] Recently, Atwood reported the crystal structure of a boat resorcinarene formed in a one dimensional hydrogen-bonded array, which serves as a "T-shaped" building block in the solid state.[5.10]



5.2

Figure 5.2 Chair half-methyl ester resorcinarene.

5.2 Results and Discussion

A slow recrystallization of **5.1** from methanol at room temperature for seven days yielded colorless crystals of **5.2** that were of suitable size and shape for X-ray structure analysis. The crystals were somewhat more stable to solvent loss than those of **5.1**, surviving for several minutes in ambient conditions. X-ray structure analysis shows

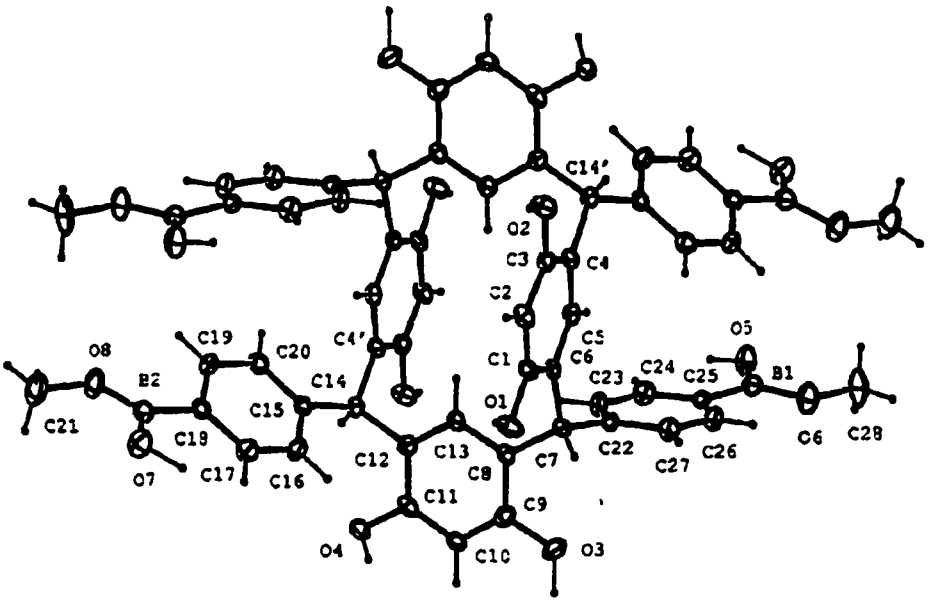


Figure 5.3 Crystal structure of half methyl ester **5.2**.

5.2 to be a resorcinarene incorporating four half-phenylboronic acid/half-methyl boronate ester moieties. The molecule has crystallographic inversion symmetry and approximate C_{2h} symmetry, with the chair conformation, as shown in Figure 5.3. This is an example of a potential half-boronic acid/half-boronate ester prototype (Figures 5.4 and 5.5). Two opposite resorcinol rings of the macrocyclic framework are nearly coplanar with the resorcinarene best plane, and the two remaining resorcinol rings are almost perpendicular to this plane, with their hydroxyl groups pointing in opposite directions. Due to the presence of the cystallographic inversion center, the opposite resorcinol units are rigorously parallel. The C1-C6 resorcinol ring forms a dihedral angle of 89.0 (1)° with the C8-C13 ring. The phenylboronic acid moieties at the

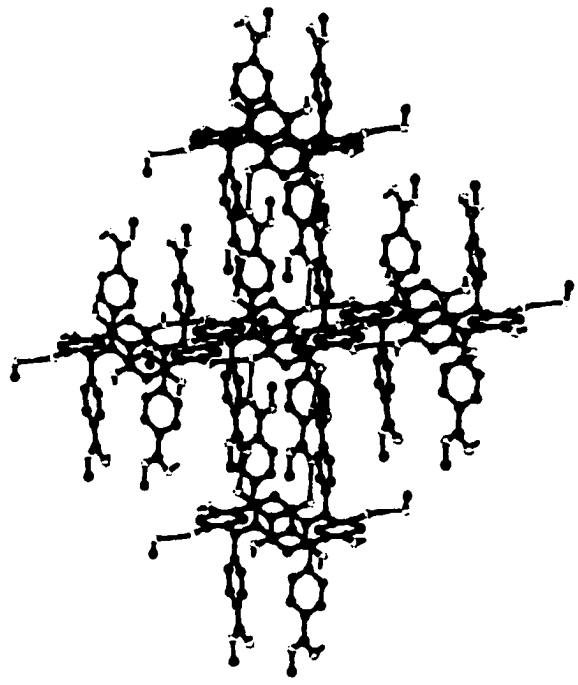


Figure 5.4 Supramolecular hydrogen-bonded array of **5.2**.

methylene bridges assume the axial position, with two units pointing up and two of them down, roughly perpendicular to the coplanar resorcinol units (dihedral angles 75.2 (2) and 86.1 (2)°). The phenyl rings of the phenylboronic moieties are not parallel, forming a dihedral angle of 40.0 (1)°. No intramolecular hydrogen-bonding exists; however, all potential donors are involved in intermolecular hydrogen bonds. Each molecule of **5.2** forms 18 intermolecular hydrogen bonds, including 12 to four other molecules of **5.2** and 6 to solvent molecules. Central macrocyclic unit **5.2** is hydrogen bonded about an inversion center to a unit of **5.2** (right side) via phenolic OH groups (O4---O2, 2.821 (4) Å), and also to the molecule of **5.2** on the left by the same interactions. The central macrocyclic unit **5.2** is connected to a third unit of **5.2** (top) via

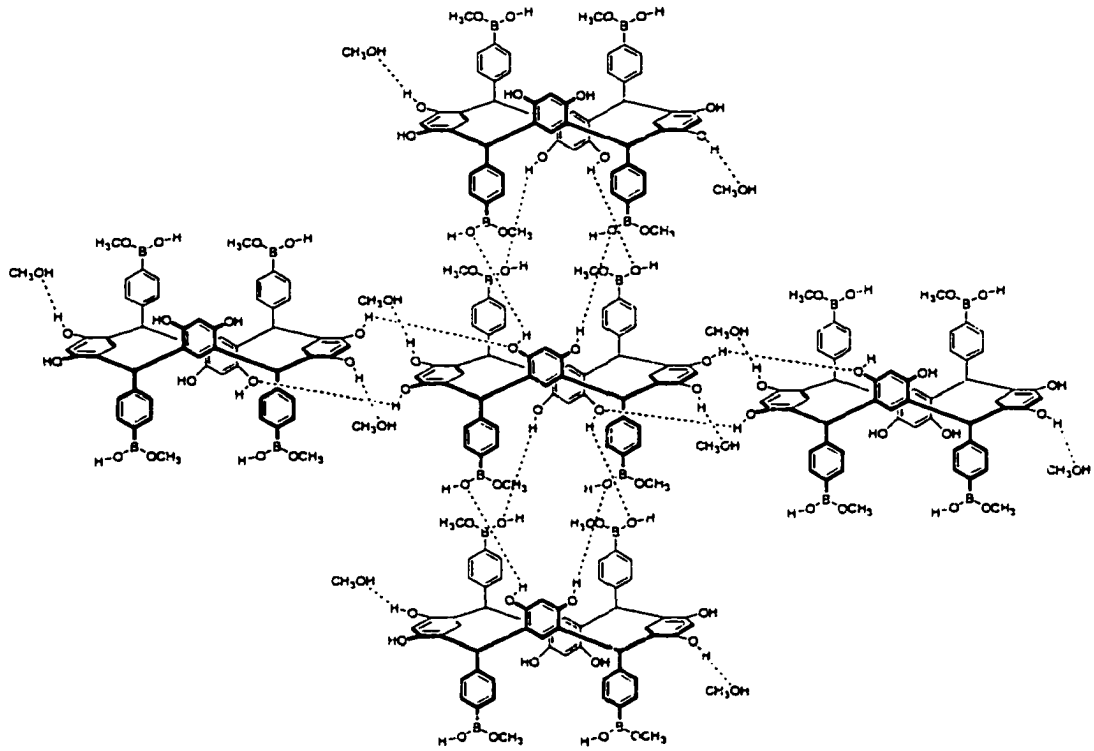


Figure 5.5 Intermolecular hydrogen-bonding of **5.2**.

four phenolic/boronic acid interactions (O1---O5, 2.753 (4) Å; O2---O7', 2.698 (4) Å; and their equivalents). A fourth unit of **5.2** (bottom) is connected to the central unit **5.2** by the same phenolic/boronic acid interactions (O1---O5 and O2---O7). Each molecule of **5.2** also donates two hydrogen bonds to solvent molecules via phenolic OH (O3---O 2.677 (5) Å) and four hydrogen bonds via B-OH units to solvent (O5---O 2.748 (6); O7---O 2.669 (5) Å). Two other independent solvent molecules are disordered and do not hydrogen bond to **5.2**.

5.3 Conclusions

In conclusion, resorcinol/arylboronic acid materials form unique hydrogen-bonded supramolecular arrays. These findings suggest the great potential of utilizing these compounds for designing and tailoring solid state materials for molecular recognition and catalysis. Currently we are synthesizing and studying guest-bound supramolecular structures based on **5.1** and congeners.

5.4 Experimental Procedures

General. All chemicals were reagent grade (Aldrich or Lancaster) and used without further purification. The ^{1}H NMR spectra were obtained with a Bruker AM-400 spectrometer. Residual ^{1}H signals from deuterated solvents were used as a reference unless TMS (δ 0.00) was present. ^{13}C NMR spectra were acquired with a Bruker AM-400 spectrometer. MALDI experiments were performed with a PerSeptive Biosystems Voyager linear mass spectrometer employing a nitrogen laser with a wavelength of 337 nm. A Perkin-Elmer spectrophotometer was used to obtain uv spectra.

X-ray. Data for all three compounds were collected at low temperature on an Enraf-Nonius CAD4 equipped with Moka radiation (λ = 0.71073 A) and a graphite monochromator, **5.2** at 150 K. Data for **5.2** were corrected for absorption using Ψ scans. Structures were solved by direct methods and refined by full-matrix least squares. Final R values are 0.084 (4789 data) for **5.2**. The crystallographic data for **5.2** can be found in Appendix A.

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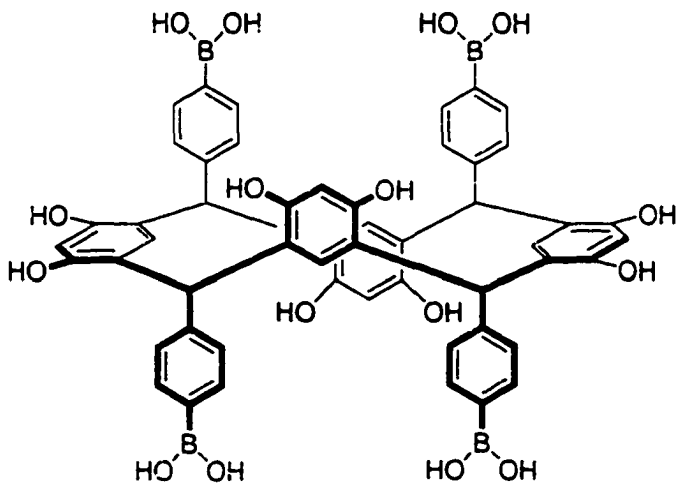
CHAPTER 6

FUTURE WORK

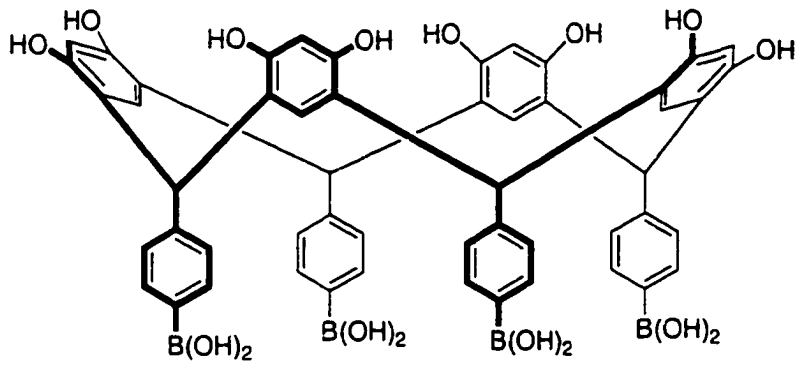
6.1 Specific Aims

We have recently reported that resorcinarene receptors **6.1-6.3** (Figures 6.1 and 6.2) synthesized in our laboratories afford the most versatile color sensing of specific saccharides observed to date.[6.1,6.2] Sugars are a very challenging class of compounds to analyze due to their similarity in structure. A visual sensing test for specific saccharides should allow for improved monitoring of disease states as well as the products of fermentation processes. Our preliminary studies indicate that this fundamentally new methodology could potentially have broad applicability. The unprecedented color responses to saccharides are sensitive to variations in receptor structure and

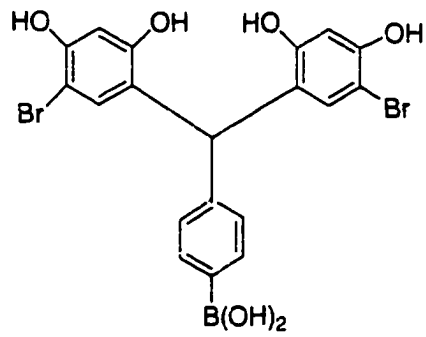


6.1

Figure 6.1 Resorcinarene colorimetric sensor.



6.2



6.3

Figure 6.2 Other resorcinol-based colorimetric sensors.

experimental parameters. We can optimize both host structure and experimental conditions[6.1,6.2] in an effort to visually sense a variety of biologically significant molecules. There are three problems of current interest that the future work of this research will address. One is the selective sensing of fructose in plasma and sweet foods and beverages. Another is the sensing of sialic acid in gangliosides, and the last is oligosaccharide detection in post-column effluents. Each of these specific aims builds upon our prior successes in the area of visible region sensing.

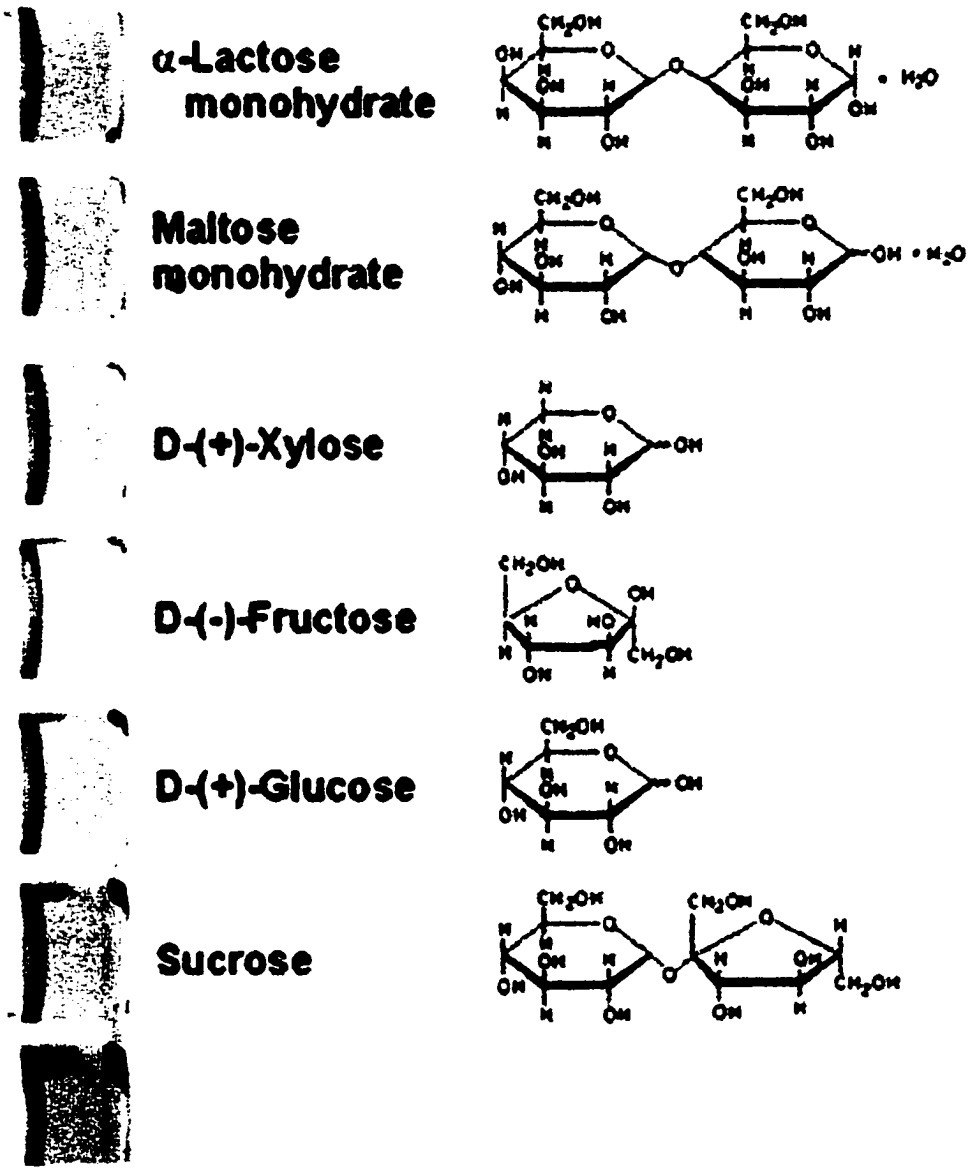


Figure 6.3 Preheated 5.2 mM aqueous DMSO solutions of **6.2** (unlabeled) were cooled to room temperature and stirred in the presence of 3 equiv of carbohydrates for five minutes.

6.2 Selective Color Sensing of Fructose

Fructose is an important energy source and sweeter, which is metabolized at a high rate in humans and animals. The elucidation of the biochemical role of D-fructose requires better methods of analysis. For example, the determination of relatively low levels of fructose in human plasma cannot be performed in a reliable manner due, in large part, to an excess of glucose.[6.3] The reported fructose levels vary substantially among laboratories and on the technique employed, including enzymatic detection.[6.4] Most methods of detection are GC or HPLC based determinations, and they often involve tedious sample preparation and derivatization.[6.4] Preliminary studies suggest that resorcinarene sensor **6.2** could potentially serve as a selective color sensing agent (Figure 6.3) for the determination of fructose in plasma and sweet foods and beverages. This simple, rapid, and inexpensive color test, which does not use corrosive or degradable materials, could be of global benefit to industry and medicine.

6.3 Selective Color Sensing of Sialic Acid

Sialic acids are components of glycoproteins, glycopeptides, and glycolipids. They play a key role in cell to cell communication in the human body. Imbalances in sialic acid levels can have clinical manifestations such as alterations in cell adhesions. This condition is implicated in some cancers and graft rejections. Importantly, an increase in the levels of both soluble and cellular sialic acid can be a marker for cancer diagnosis.[6.5] The most prevalent and significant sialic acid is *N*-acetylneuramic acid, followed by *N*-glycoloylneuramic acid.[6.5] The function of sialic acids in gangliosides is presently not completely understood. The gangliosides embody relatively simpler structures compared to other sialic acid-containing biomolecules. Sialic acids appear to

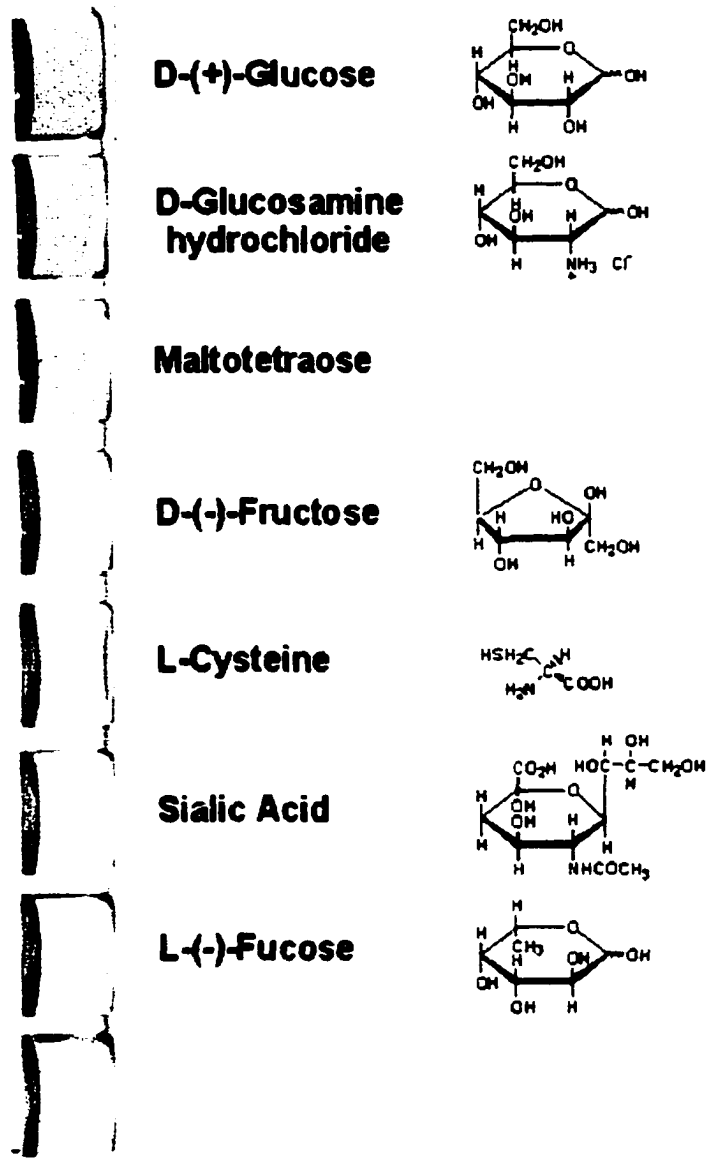


Figure 6.4 Preheated 5.2 mM aqueous DMSO solutions of **6.3** (unlabeled) were cooled to room temperature and stirred in the presence of 3 equiv of carbohydrates for 10 minutes.

be essential to the biological effects of gangliosides, as the amphiphilic donor of negative charge to the cell surface.[6.6] Based on preliminary results, it appears that our resorcinol-based sensor **6.3** could potentially serve as a selective color sensing agent for sialic acid (Figure 6.4).

6.4 Selective Color Sensing of Oligosaccharides

Currently, there are no useful direct color tests for the detection of higher molecular weight oligosaccharides.[6.7] Their current detection methods require complete hydrolysis to monosaccharides or covalent attachment to a chromophore.[6.7] The classical color tests for monosaccharides simply fail to directly detect oligosaccharides containing more than three residues.[6.8] The color response is only related to the molar concentration of oligosaccharide, not the concentration by weight. For instance, maltohexaose's response is only 18 % of the same weight of glucose.[6.8]

"Detection of oligosaccharides eluting from HPLC columns is the biggest challenge and weakest link in the analysis of oligosaccharides."[6.8] Thus a simple test method is needed for the visible detection of oligosaccharides. We have developed a simple color test for the detection of oligosaccharides. Our preliminary studies with sensor **6.2** and the maltose oligomers, which are composed of glucose monomers, appears to be a breakthrough in the detection of oligosaccharides (Figure 6.5). Oligosaccharides up to seven residues were studied. This test is effective without prior hydrolysis or chemical modification of the oligosaccharides with a chromogenic reagent.

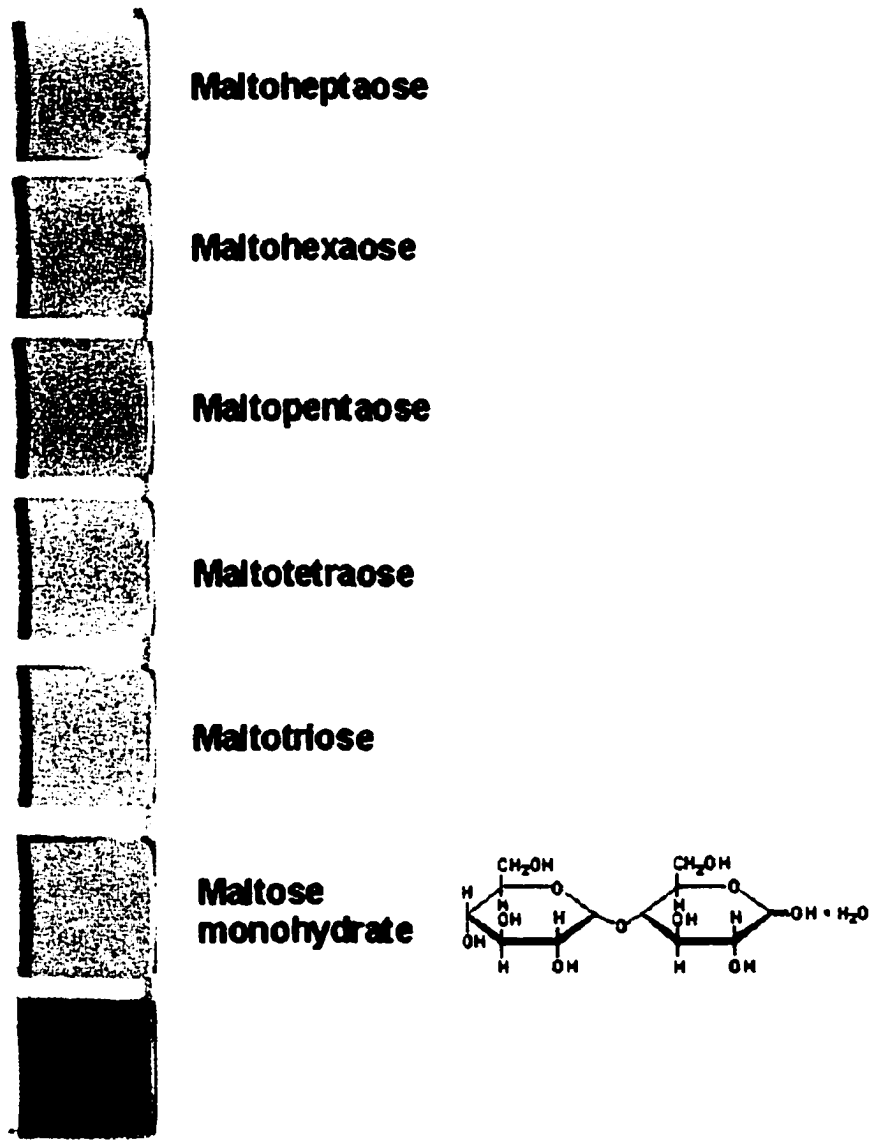


Figure 6.5 5.2 mM aqueous DMSO solutions of **6.2** (unlabeled) were heated to reflux in the presence of 2 mg of oligosaccharides for 3 minutes.

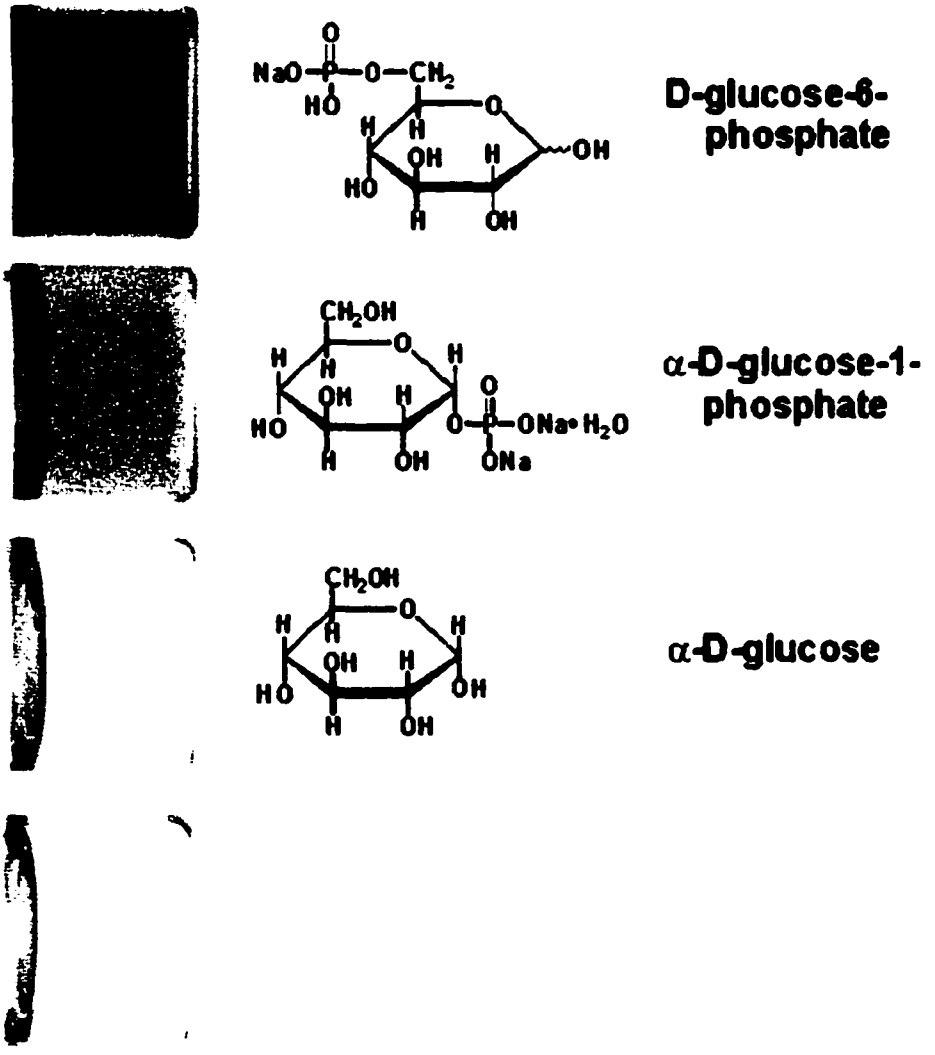
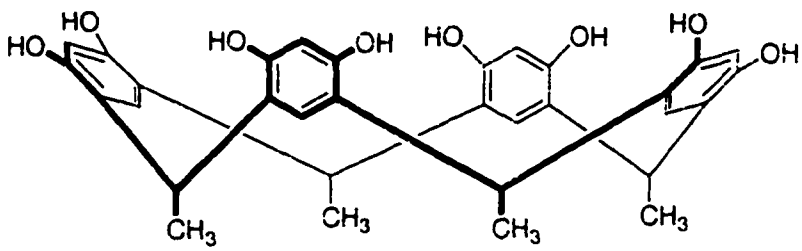


Figure 6.6 5.2 mM aqueous DMSO solutions of **6.2** (unlabeled) were heated to reflux with 3 equiv of saccharides in the presence of 40 equiv HEPES buffer for 3 minutes.

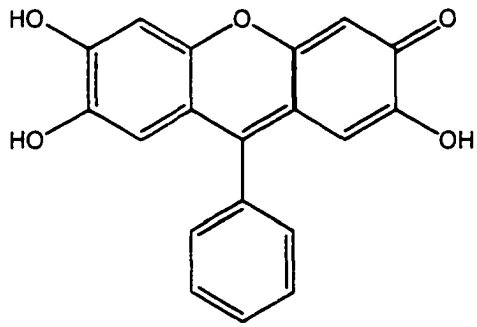
6.5 Additional Color Sensing Studies

We also decided to investigate the effect of altering the conditions of our colorimetric test on the resorcinarene sensors. In addition to extending the scope of our colorimetric sensing methodology beyond saccharides. Heating solutions of **6.2** (5.2 mM, 9:1 DMSO:H_2O, 1mL) and 3 equiv of glucose-1-phosphate and glucose-6-phosphate in the presence of 40 equiv of HEPES buffer (pH 7.5) at reflux for three minutes results in selective coloration (Figure 6.6). The glucose phosphates are important intermediates in the biosynthetic pathway of glycogen. As a result of this study, **6.2** could potentially serve as a sensing agent for glucose phosphates under controlled pH conditions. Prior success with resorcinol-based receptors without arylboronic acids prompted us to extend our studies of their properties. These studies yielded selective coloration with analytes other than saccharides. The aforementioned **6.2**, methyl resorcinarene **6.4** (Figure 6.7), and the commercially available xanthene dye **6.5** (9-phenyl-2,3,7-trihydroxy-6-flurone; Figure 6.8) were subjected to our thermolysis conditions (heated at reflux for 3 min), and the results are listed in Tables 6.1-6.3.



6.4

Figure 6.7 Methyl resorcinarene sensor.



6.5

Figure 6.8 Commercial xanthene dye.

Table 6.1 Thermolysis of aqueous DMSO solutions of **6.4**.

Added Analyte	A (532 nm)	Color
None	0.1915	Faint purple
Acetone	0.2613	Faint pink
Acetaldehyde	0.1300	Pale yellow
Benzaldehyde	0.2485	Faint orange
Furan	0.3296	Pale orange-yellow
Et_3N	1.143	Purple
Bn_3N	0.4661	Pinkish-purple
$Bu_4N^+Br^-$	0.3585	Faint pink
Acetylcholine iodide	0.1881	Faint yellow
$Bu_4N^+F^-$	3.3077	Amber

Table 6.2 Thermolysis of aqueous DMSO solutions of **6.5**.

Added Analyte	A (538 nm)	Color
None	0.1836	Pink
Acetone	2.0880	Bright pink
Acetaldehyde	0.1947	Pale yellow
Benzaldehyde	0.6299	Peach
Furan	1.4241	Peach
Et_3N	2.6409	Bright pink
Bn_3N	0.4819	Pale orange
$Bu_4N^+Br^-$	2.4454	Bright pink
Acetylcholine iodide	0.6698	Peach
$Bu_4N^+F^-$	0.2966	Yellow

Table 6.3 Thermolysis of aqueous DMSO solutions of **6.2**.

Added Analyte	A (533 nm)	Color
None	1.6117	Bright pink
Acetone	1.8333	Bright pink
Acetaldehyde	0.3452	Yellow gold
Benzaldehyde	0.7570	Orange
Furan	1.5003	Bright peach
Et_3N	2.4513	Bright peach

(table continued)

Bn_3N	1.5682	Bright pink
$Bu_4N^+Br^-$	1.6713	Bright pink
Acetylcholine iodide	1.4181	Bright peach
$Bu_4N^+F^-$	3.2928	Dark red

6.6 Conclusions

The visual determination of saccharides has been of great interest for more than a century. In 1887, Seliwanoff reported a resorcinol color test that was specific for ketoses.[6.9] The other non-enzymatic assays for sugars are based on harsh methods and some encounter interference from other species present. An example is the general phenol-sulfuric acid assay[6.10] for reducing sugars, which is hampered by mixed responses from different classes of sugars and reproducibility depends on the manner of sulfuric acid addition. The Carbazole assay for uronic acids[6.11] is limited due to interference from neutral carbohydrates, cysteine, other thiols, and proteins. Reproducibility is also a problem with this assay. Another example is the Warren assay for sialic acid,[6.12] which employs toxic sodium arsenate and encounters interference from fucose and fructose. Our synthetic receptors afford a color specificity for fructose and sialic acid under the proper conditions. We are the only research group to report a simple, rapid, inexpensive, and fully reproducible colorimetric test for saccharides with great versatility.[6.1]

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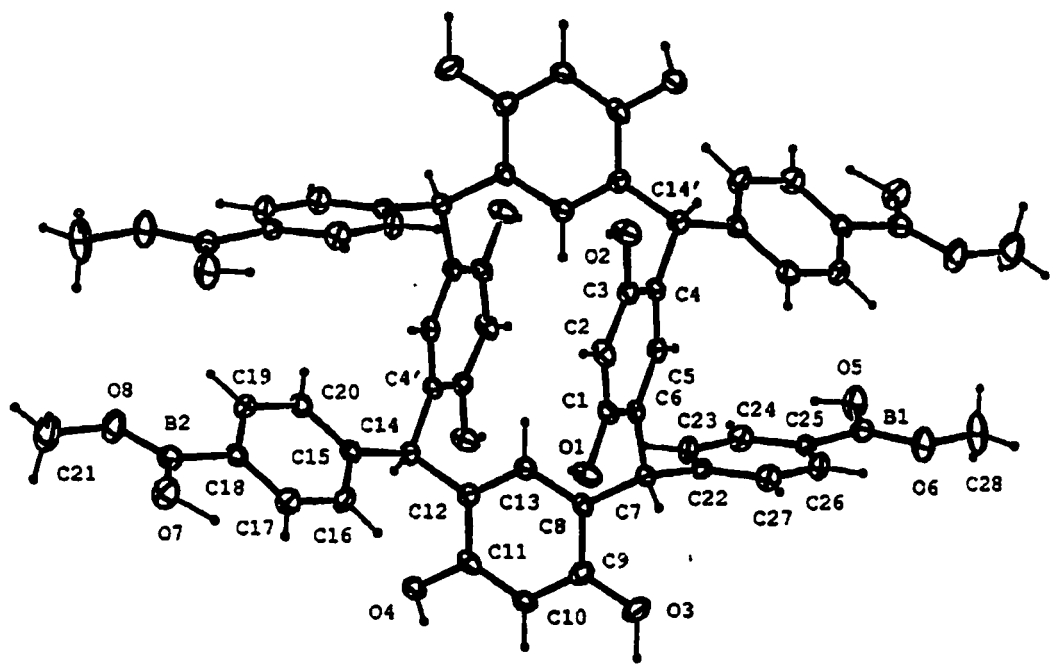
APPENDIX A: CRYSTALLOGRAPHIC DATA



A.1 Crystal data and structure refinement for **5.2**.

Identification code	C2BOMe
Empirical formula	$C_{70}\ H_{100}\ O_{26}\ B_4$
Formula weight	1400.8
Temperature	150 K
Wavelength	0.71073 Å (Mo Kα)
Crystal system	Triclinic
Space group	P-1

Unit cell dimensions	a = 12.105(1) Å	α= 74.72(2)°
	b = 12.145(4) Å	β= 66.281(8)°
	c = 13.547(2) Å	γ = 81.38(2)°
Volume	1756.8(7) $Å^3$	
Z	1	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	748	
Crystal size	0.40 x 0.47 x 0.59 mm^3	
Theta range for data collection	2.5 to 28.3°	
Index ranges	-15<=h<=16, 0<=k<=16, -17<=l<=18	
Reflections collected	9081	
Independent reflections	8678 (R_{int} = 0.023)	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4789 / 0 / 480	
Goodness-of-fit on F^2	3.697	
Final R indices [I>2sigma(I)]	R1 = 0.084, wR2 = 0.089	
R indices (all data)	R1 = 0.151 wR2 = 0.095	
Largest diff. peak and hole	1.25and -0.15 e.$Å^{-3}$	

A.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5.2**.

	x	y	z	U(eq)
O1	0.4081(2)	0.1237(2)	0.2100(2)	0.032(1)
O2	0.4377(2)	-0.2806(2)	0.3582(2)	0.028(1)
O3	0.6387(3)	0.3943(3)	0.1386(2)	0.032(2)
O4	0.3878(2)	0.4946(2)	0.4851(2)	0.026(1)
O5	1.1951(2)	0.0674(3)	0.2120(2)	0.035(2)
O6	1.2148(2)	0.0704(3)	0.0326(2)	0.033(2)
O7	-0.2302(2)	0.3069(3)	0.6607(2)	0.033(2)
O8	-0.2418(2)	0.2613(3)	0.8442(2)	0.033(2)
C1	0.4631(3)	0.0292(3)	0.2580(3)	0.021(2)
C2	0.4182(3)	-0.0787(4)	0.2881(3)	0.025(2)
C3	0.4784(3)	-0.1720(3)	0.3308(3)	0.020(2)
C4	0.5822(3)	-0.1615(3)	0.3480(3)	0.018(2)
C5	0.6226(3)	-0.0508(3)	0.3188(3)	0.020(2)
C6	0.5671(3)	0.0459(3)	0.2718(3)	0.018(2)
C7	0.6206(3)	0.1616(3)	0.2282(3)	0.019(2)
C8	0.5540(3)	0.2482(3)	0.2988(3)	0.019(2)
C9	0.5684(3)	0.3657(4)	0.2494(3)	0.024(2)
C10	0.5132(3)	0.4480(3)	0.3102(3)	0.022(2)
C11	0.4442(3)	0.4153(3)	0.4223(3)	0.023(2)

C12	0.4290(3)	0.3001(3)	0.4757(3)	0.019(2)
C13	0.4846(3)	0.2188(3)	0.4114(3)	0.020(2)
C14	0.3582(3)	0.2667(3)	0.6001(3)	0.019(2)
C15	0.2216(3)	0.2633(3)	0.6337(3)	0.019(2)
C16	0.1673(3)	0.3201(4)	0.5603(3)	0.024(2)
C17	0.0424(3)	0.3238(4)	0.5916(3)	0.028(2)
C18	-0.0338(3)	0.2724(3)	0.6966(3	0.021(2)
C19	0.0221(3)	0.2154(4)	0.7702(3)	0.024(2)
C20	0.1465(3)	0.2110(4)	0.7395(3)	0.025(2)
C21	-0.3710(4)	0.2799(5)	0.8857(4)	0.044(3)
C22	0.7551(3)	0.1516(3)	0.2037(3)	0.018(2)
C23	0.8005(3)	0.1566(4)	0.2821(3)	0.024(2)
C24	0.9241(3)	0.1353(4)	0.2609(3)	0.029(2)
C25	1.0060(3)	0.1113(3)	0.1619(3)	0.019(2)
C26	0.9597(3)	0.1110(4)	0.0820(3)	0.025(2)
C27	0.8367(3)	0.1300(4)	0.1030(3)	0.025(2)
C28	1.3427(4)	0.0447(5)	0.0002(4)	0.045(3)
B1	1.1432(4)	0.0831(4)	0.1362(4)	0.024(2)
B2	-0.1736(4)	0.2796(4)	0.7341(4)	0.026(2)
O1S	0.6730(3)	0.6184(3)	0.0604(3)	0.051(2)
C1S	0.7332(5)	0.6606(5)	0.1127(5)	0.065(4)
O2S	0.0935(6)	0.4428(7)	1.0986(5)	0.172(6)
C2S	0.0811(6)	0.5756(5)	1.0642(5)	0.071(4)

C3S	0.0953(5)	0.5992(5)	0.9392(5)	0.068(4)
O3S	0.3304(8)	0.3448(8)	0.1460(6)	0.239(7)
C4S	0.2679(6)	0.3965(6)	0.2429(6)	0.116(4)
C5S	0.1446(6)	0.3453(7)	0.2868(5)	0.095(5)
O4aS	0.0975(5)	0.1186(5)	0.4171(4)	0.064(3)
O4bS	0.0918(8)	0.018(1)	0.4338(7)	0.067(6)
C6S	0.1698(5)	0.0727(5)	0.4757(4)	0.070(3)
O5S	0.1350(4)	0.6304(6)	0.5598(4)	0.137(4)
C7S	0.120(1)	0.5972(7)	0.6532(6)	0.142(7)

A.3. Bond lengths [Å] for **5.2.**

O1 C1	1.382(5)
O1 H1OH	0.87(6)
O2 C3	0.382(5)
O2 H2OH	0.72(6)
O3 C9	1.373(4)
O3 H3OH	1.05
O4 C11	1.373(5)
O4 H4OH	0.72(5)
O5 B1	1.366(7)
O5 H5OH	0.90(5)
O6 C28	1.438(5)

O6 B1	1.356(5)
O7 B2	1.369(7)
O7 H7OH	1.11(4)
O8 C21	1.438(5)
O8 B2	1.358(5)
C1 C2	1.390(6)
C1 C6	1.395(6)
C2 C3	1.376(5)
C3 C4	1.396(6)
C4 C5	1.402(6)
C4 C14	1.518(5)
C5 C6	1.396(5)
C6 C7	1.507(6)
C7 C8	1.526(6)
C7 C22	1.517(5)
C8 C9	1.412(6)
C8 C13	1.389(5)
C9 C10	1.383(6)
C10 C11	1.387(5)
C11 C12	1.396(5)
C12 C13	1.403(6)
C12 C14	1.524(5)
C14 C15	1.533(5)

C15 C16	1.387(6)
C15 C20	1.388(4)
C16 C17	1.394(6)
C17 C18	1.383(5)
C18 C19	1.403(6)
C18 B2	1.555(6)
C19 C20	1.388(6)
C22 C23	1.396(7)
C22 C27	1.390(5)
C23 C24	1.402(6)
C24 C25	1.383(5)
C25 C26	1.405(7)
C25 B1	1.557(6)
C26 C27	1.394(6)
O1S C1S	1.42(1)
O2S C2S	1.56(1)
C2S C3S	1.58(1)
O3S C4S	1.48(1)
C4S C5S	1.53(1)
O4aS O4bS	1.19(1)
O4aS C6S	1.374(9)
O4bS C6S	1.57(1)
O5S C7S	1.17(1)

A.4. Bond angles [°] for **5.2**.

C1 O1 H1OH	110(3)
C3 O2 H2OH	116(4)
C9 O3	115
C11 O4 H4OH	105(4)
B1 O5 H5OH	114(3)
C28 O6 B1	122.1(4)
B2 O7 H7OH	113(3)
C21 O8 B2	122.0(4)
O1 C1 C2	121.0(4)
O1 C1 C6	117.5(4)
C2 C1 C6	121.5(4)
C1 C2 C3	119.6(4)
O2 C3 C2	120.8(4)
O2 C3 C4	117.3(3)
C2 C3 C4	122.0(4)
C3 C4 C5	116.4(3)
C3 C4 C14	119.7(4)
C5 C4 C14	123.9(4)
C4 C5 C6	123.8(4)
C1 C6 C5	116.7(4)
C1 C6 C7	120.3(3)
C5 C6 C7	122.8(4)

C6 C7 C8	114.5(3)
C6 C7 C22	111.4(3)
C8 C7 C22	112.2(4)
C7 C8 C9	118.7(3)
C7 C8 C13	124.0(3)
C9 C8 C13	117.2(4)
O3 C9 C8	117.0(4)
O3 C9 C10	121.8(3)
C8 C9 C10	121.2(3)
C9 C10 C11	119.9(3)
O4 C11 C10	121.5(3)
O4 C11 C12	117.4(3)
C10 C11 C12	121.2(4)
C11 C12 C13	117.6(3)
C11 C12 C14	119.9(4)
C13 C12 C14	122.4(3)
C8 C13 C12	122.9(3)
C4 C14 C12	110.5(3)
C4 C14 C15	115.6(3)
C12 C14 C15	114.4(4)
C14 C15 C16	120.3(3)
C14 C15 C20	122.2(4)
C16 C15 C20	117.4(3)

C15 C16 C17	121.2(3)
C16 C17 C18	122.2(4)
C17 C18 C19	116.1(4)
C17 C18 B2	122.8(4)
C19 C18 B2	121.0(3)
C18 C19 C20	122.0(3)
C15 C20 C19	121.2(4)
C7 C22 C23	122.0(3)
C7 C22 C27	119.9(4)
C23 C22 C27	118.0(4)
C22 C23 C24	120.5(4)
C23 C24 C25	122.2(5)
C24 C25 C26	116.8(4)
C24 C25 B1	124.0(4)
C26 C25 B1	119.3(4)
C25 C26 C27	121.5(4)
C22 C27 C26	121.0(4)
O5 B1 O6	118.2(4)
O5 B1 C25	124.1(4)
O6 B1 C25	117.7(5)
O7 B2 O8	119.0(4)
O7 B2 C18	122.7(4)
O8 B2 C18	118.3(5)

O2S	C2S	C3S	103.5(6)
O3S	C4S	C5S	99.2(7)

A.5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5.2.**

	U^{11}	U^{22}	U^{33}
O1	0.027(1)	0.025(2)	0.045(1)
O2	0.022(1)	0.022(1)	0.047(1)
O3	0.045(2)	0.028(2)	0.027(1)
O4	0.026(1)	0.021(1)	0.033(1)
O5	0.020(1)	0.062(2)	0.036(1)
O6	0.017(1)	0.061(2)	0.036(1)
O7	0.020(1)	0.049(2)	0.037(1)
O8	0.017(1)	0.061(2)	0.034(2)
C1	0.019(2)	0.021(2)	0.024(2)
C2	0.016(2)	0.027(2)	0.033(2)
C3	0.017(2)	0.020(2)	0.024(2)
C4	0.014(2)	0.020(2)	0.022(2)
C5	0.014(2)	0.027(2)	0.021(2)
C6	0.015(2)	0.019(2)	0.019(2)
C7	0.015(2)	0.020(2)	0.021(2)
C8	0.013(2)	0.022(2)	0.024(2)
C9	0.021(2)	0.027(2)	0.025(2)

C10	0.024(2)	0.015(2)	0.031(2)
C11	0.018(2)	0.020(2)	0.035(2)
C12	0.014(2)	0.023(2)	0.023(2)
C13	0.013(2)	0.021(2)	0.027(2)
C14	0.014(2)	0.022(2)	0.023(2)
C15	0.015(2)	0.019(2)	0.023(2)
C16	0.017(2)	0.037(3)	0.021(2)
C17	0.021(2)	0.037(3)	0.028(2)
C18	0.017(2)	0.021(2)	0.027(2)
C19	0.022(2)	0.027(2)	0.022(2)
C20	0.022(2)	0.028(2)	0.025(2)
C21	0.025(2)	0.073(4)	0.047(3)
C22	0.017(2)	0.018(2)	0.020(2)
C23	0.019(2)	0.034(2)	0.020(2)
C24	0.027(2)	0.034(2)	0.026(2)
C25	0.018(2)	0.019(2)	0.022(2)
C26	0.020(2)	0.035(2)	0.023(2)
C27	0.021(2)	0.035(2)	0.022(2)
C28	0.018(2)	0.089(4)	0.056(3)
B1	0.020(2)	0.024(3)	0.030(2)
B2	0.021(2)	0.025(3)	0.034(2)
O1S	0.087(2)	0.034(2)	0.045(2)
C1S	0.061(3)	0.046(4)	0.100(4)

O2S	0.124(5)	0.309(8)	0.133(4)
C2S	0.100(5)	0.037(3)	0.097(4)
C3S	0.067(3)	0.063(4)	0.073(3)
O3S	0.287(8)	0.205(8)	0.232(7)
C4S	0.069(4)	0.152(5)	0.151(4)
C5S	0.107(5)	0.109(6)	0.073(4)
O4aS	0.044(3)	0.093(4)	0.064(3)
O4bS	0.058(5)	0.158(9)	0.034(4)
C6S	0.097(4)	0.069(4)	0.051(3)
O5S	0.151(3)	0.331(7)	0.051(2)
C7S	0.38(1)	0.081(5)	0.094(5)

A.6. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5.2** continued.

	U^{12}	U^{13}	U^{23}
O1	0.0250(9)	0.004(1)	0.005(1)
O2	0.002(1)	0.0205(9)	0.006(1)
O3	0.011(1)	0.002(1)	0.000(1)
O4	0.009(1)	0.008(1)	0.000(1)
O5	0.013(1)	0.016(1)	0.001(1)
O6	0.009(1)	0.016(1)	0.002(1)
O7	0.006(1)	0.015(1)	0.005(1)
O8	0.006(1)	0.004(2)	0.000(1)

C1	0.011(1)	0.006(2)	0.006(2)
C2	0.015(1)	0.011(2)	0.002(2)
C3	0.003(2)	0.006(1)	0.006(1)
C4	0.009(1)	0.004(1)	0.002(1)
C5	0.001(1)	0.008(1)	0.009(1)
C6	0.005(1)	0.008(1)	0.001(1)
C7	0.008(1)	0.003(1)	0.001(2)
C8	0.008(1)	0.007(1)	0.002(1)
C9	0.006(2)	0.008(1)	0.001(2)
C10	0.001(2)	0.010(1)	0.004(2)
C11	0.014(1)	0.011(1)	0.002(2)
C12	0.003(1)	0.009(1)	0.003(1)
C13	0.001(1)	0.008(1)	0.004(2)
C14	0.003(1)	0.008(1)	0.004(1)
C15	0.008(1)	0.005(1)	0.000(1)
C16	0.003(2)	0.005(1)	0.002(2)
C17	0.015(1)	0.001(2)	0.000(2)
C18	0.009(1)	0.005(2)	0.001(2)
C19	0.003(2)	0.004(1)	0.003(2)
C20	0.012(1)	0.005(2)	0.004(2)
C21	0.004(3)	0.003(2)	0.009(3)
C22	0.000(2)	0.007(1)	0.000(2)
C23	0.001(2)	0.003(1)	0.010(2)

C24	0.002(2)	0.014(1)	0.007(2)
C25	0.001(2)	0.007(1)	0.001(2)
C26	0.002(2)	0.005(1)	0.008(2)
C27	0.013(1)	0.005(2)	0.001(2)
C28	0.006(2)	0.037(2)	0.009(2)
B1	0.003(2)	0.010(2)	0.003(2)
B2	0.002(2)	0.012(2)	0.004(2)
O1S	0.024(2)	0.008(2)	0.012(2)
C1S	0.009(3)	0.026(3)	0.005(3)
O2S	0.019(5)	0.034(3)	0.069(5)
C2S	0.006(3)	0.022(4)	0.022(3)
C3S	0.011(3)	0.024(3)	0.014(3)
O3S	0.140(5)	0.010(6)	0.001(7)
C4S	0.051(3)	0.101(3)	0.023(4)
C5S	0.034(3)	0.024(4)	0.003(5)
O4aS	0.030(2)	0.047(2)	0.015(3)
O4bS	0.057(5)	0.019(3)	0.005(5)
C6S	0.012(3)	0.037(2)	0.012(3)
O5S	0.149(3)	0.043(2)	0.026(3)
C7S	0.094(6)	0.047(4)	0.037(7)

A.7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **5.2**.

	x	y	z	U(eq)
H1OH	0.347(4)	0.104(4)	0.201(4)	0.1013
H2OH	0.382(4)	-0.285(4)	0.351(4)	0.1013
H3OH	0.6571	0.4809	0.1064	0.1013
H4OH	1.146(4)	0.088(4)	0.276(4)	0.1013
H7OH	-0.167(4)	0.325(4)	0.573(4)	0.1013
H2	0.3464	-0.0880	0.2793	0.0304
H5	0.6917	-0.0410	0.3317	0.0249
H7	0.6098	0.1921	0.1603	0.0250
H10	0.5226	0.5267	0.2752	0.0307
H13	0.4743	0.1402	0.4464	0.0267
H14	0.3720	0.3206	0.6331	0.0252
H16	0.2161	0.3570	0.4874	0.0355
H17	0.0083	0.3629	0.5390	0.0368
H19	-0.0266	0.1786	0.8432	0.0333
H20	0.1809	0.1715	0.7917	0.0323
H21a	-0.4022	0.2626	0.9643	0.0685
H21b	-0.3913	0.3576	0.8592	0.0685
H21c	-0.4049	0.2320	0.8611	0.0685
H23	0.7473	0.1744	0.3504	0.0328

H24	0.9526	0.1375	0.3162	0.0359
H26	1.0136	0.0976	0.0121	0.0351
H27	0.8082	0.1281	0.0476	0.0327
H28a	1.3767	0.0392	-0.0750	0.0704
H28b	1.3791	0.1037	0.0088	0.0704
H28c	1.3567	-0.0259	0.0455	0.0704
H1OS	0.7544	0.6013	-0.0096	0.1013
H1aS	0.7554	0.5992	0.1624	0.0938
H1bS	0.6809	0.7143	0.1524	0.0938
H1cS	0.8037	0.6969	0.0582	0.0938

A.8. Torsion angles [°] for **5.2.**

C28 O6 B1 O5	-1.9(7)
C28 O6 B1 C25	179.8(4)
C21 O8 B2 O7	-5.8(7)
C21 O8 B2 C18	172.2(4)
O1 C1 C2 C3	176.8(3)
C6 C1 C2 C3	-1.2(6)
O1 C1 C6 C5	-179.0(3)
O1 C1 C6 C7	-4.2(5)
C2 C1 C6 C5	-0.8(5)
C2 C1 C6 C7	173.9(3)

C1 C2 C3 O2	-178.0(3)
C1 C2 C3 C4	1.9(6)
O2 C3 C4 C5	179.5(3)
C2 C3 C4 C5	-0.5(5)
C3 C4 C5 C6	-1.8(5)
C4 C5 C6 C1	2.4(5)
C4 C5 C6 C7	-172.2(3)
C1 C6 C7 C8	77.3(4)
C1 C6 C7 C22	-154.0(3)
C5 C6 C7 C8	-108.3(4)
C5 C6 C7 C22	20.4(5)
C6 C7 C8 C9	-158.5(4)
C6 C7 C8 C13	25.3(6)
C22 C7 C8 C9	73.2(5)
C22 C7 C8 C13	-102.9(5)
C6 C7 C22 C23	-92.0(5)
C6 C7 C22 C27	84.0(4)
C8 C7 C22 C23	37.9(5)
C8 C7 C22 C27	-146.1(4)
C7 C8 C9 O3	2.5(6)
C7 C8 C9 C10	-178.0(4)
C13 C8 C9 O3	178.9(4)
C13 C8 C9 C10	-1.6(6)

C7 C8 C13 C12	176.7(4)
C9 C8 C13 C12	0.5(6)
O3 C9 C10 C11	-179.2(4)
C8 C9 C10 C11	1.3(7)
C9 C10 C11 O4	-179.8(4)
C9 C10 C11 C12	0.0(7)
O4 C11 C12 C13	178.8(4)
O4 C11 C12 C14	-3.4(6)
C10 C11 C12 C13	-1.0(6)
C10 C11 C12 C14	176.7(4)
C11 C12 C13 C8	0.7(6)
C14 C12 C13 C8	-177.0(4)
C11 C12 C14 C15	86.8(5)
C13 C12 C14 C15	-95.5(5)
C12 C14 C15 C16	-19.1(6)
C12 C14 C15 C20	165.3(4)
C14 C15 C16 C17	-176.1(4)
C20 C15 C16 C17	-0.3(7)
C14 C15 C20 C19	175.8(4)
C16 C15 C20 C19	0.0(5)
C15 C16 C17 C18	0.5(7)
C16 C17 C18 C19	-0.4(7)
C16 C17 C18 B2	177.7(4)

C17 C18 C19 C20	0.2(6)
B2 C18 C19 C20	-178.0(4)
C17 C18 B2 O7	19.5(7)
C17 C18 B2 O8	-158.5(4)
C19 C18 B2 O7	-162.5(4)
C19 C18 B2 O8	19.6(7)
C18 C19 C20 C15	0(1)
C7 C22 C23 C24	173.4(4)
C27 C22 C23 C24	-2.7(6)
C7 C22 C27 C26	-174.6(4)
C23 C22 C27 C26	1.6(6)
C22 C23 C24 C25	1.4(7)
C23 C24 C25 C26	1.1(6)
C23 C24 C25 B1	-177.8(4)
C24 C25 C26 C27	-2.2(6)
B1 C25 C26 C27	176.7(4)
C24 C25 B1 O5	7.0(7)
C24 C25 B1 O6	-174.7(4)
C26 C25 B1 O5	-171.8(4)
C26 C25 B1 O6	6.4(6)
C25 C26 C27 C22	0.9(7)

APPENDIX B: LETTERS OF PERMISSION

American Chemical Society

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DATE: November 14, 2000
MEMORANDUM

TO: Claude J. Davis, Louisiana State University, Chemistry Department
232 Choppin Hall, Baton Rouge, LA 70803

FROM: C. Arleen Courtney, Assistant Copyright Administrator C. Arleen Courtney

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Department of Chemistry

November 14, 2000

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To Whom It May Concern:

I am writing to obtain permission for the use of my contributions to an article published in The Journal of Organic Chemistry. I am a graduate student in the Department of Chemistry at Louisiana State University. I am the second author on the article and would like to include my contributions to the article in my doctoral dissertation. The article is "Tetraarylboronic Acid Resorcinarene Stereoisomers. Versatile New Substrates for Divergent Polyfunctionalization and Molecular Recognition," Vol. 62, No. 18, pp. 6110-6111.

Thank you for your consideration of this request.

Sincerely,

Clamde J. Davis

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LOUISIANA STATE UNIVERSITY
AND AGRICULTURAL AND MECHANICAL COLLEGE
Department of Chemistry

November 14, 2000

American Chemical Society
1155 16th St., N.W.
Washington, DC 20036

To Whom It May Concern:

I am writing to obtain permission for the use of two articles published in Organic Letters. I am a graduate student in the Department of Chemistry at Louisiana State University. I am the first author on the first article and would like to include the article in my doctoral dissertation. The first article is "Simple and Rapid Visual Sensing of Saccharides", Vol. 1, No. 2, pp. 331-334. I am second author on the second article and would like to include my contributions to the article in my doctoral dissertation. The second article is "Visual Sensing of Saccharides Promoted by Resorcinol Condensation Products", Vol. 2, No. 5, pp. 589-592.

Thank you for your consideration of this request.

Sincerely,

Claude J. Davis

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VITA

Claude Joseph Davis was born in New Orleans, Louisiana, on January 1, 1972. He graduated fourth in the class of 1990 at Joseph S. Clark High School in New Orleans, Louisiana. He was the recipient of a myriad of awards and honors including a United Negro College Fund Scholarship. In the fall of 1990, he enrolled at Xavier University of Louisiana (XU) in New Orleans, Louisiana. While at XU, Claude conducted a teratology study under the direction of Dr. W. Brian Howard. He also worked on an environmental project under the direction of Dr. Howard Mielke. His senior research project, funded by the Minority Biomedical Research Support Program, involved organometallic synthesis under the direction of Dr. Teresa Birdwhistell. He also performed chemistry demonstrations at the Louisiana Children's Museum in New Orleans under the direction of the XU Department of Chemistry. Claude received the XU Award for Excellence in Advance Synthesis, XU Language Award for German, and the XU Hypercube Scholarship Award. A *cum laude* and chemistry honors graduate, he received a bachelor of science degree in chemistry (American Chemical Society certified) in 1995.

In the fall of 1995, Claude entered the graduate program in the Department of Chemistry at Louisiana State University (LSU) in Baton Rouge, Louisiana. While at LSU, he developed a colorimetric test for saccharides under the supervision of Dr. Robert M. Strongin. He received the LSU Teaching Award in chemistry and the Charles Harrington Outstanding Graduate Student Award. Claude married Kim Conner in July of 2000. He serves as a volunteer at the American Diabetes Association and the

March of Dimes in Baton Rouge. He is a member of the National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE), the American Chemical Society, and Alpha Phi Alpha Fraternity, Incorporated. Claude is currently a candidate for the degree of Doctor of Philosophy in organic chemistry. After graduation, he plans to begin a career as a research engineer at Kraft Foods, Incorporated, in Glenview, Illinois.

DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Claude J. Davis

Major Field: Chemistry

Title of Dissertation: Resorcinol Condensation Products:
A New Class of Colorimetric Sensors for Saccharides

Approved:

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Date of Examination:

December 4, 2000