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The syntheses of novel indicators and materials for chiral separation

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THE SYNTHESES OF NOVEL INDICATORS AND MATERIALS FOR CHIRAL SEPARATION

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

In

The Department of Chemistry

By
Rolanda Johnson
B.S., Southern University, Baton Rouge, Louisiana, 1998
May 2004
DEDICATION

This thesis is dedicated to my family who has given me countless support all of my life. First, to my mom and dad, thank you both for being my pillar of strength and my source of encouragement. You have both taught me well, to always strive for the best. I thank God for wonderful parents like you, for you two are truly the reason why I am here today. Next, to my brothers Ronald, Jr. and Rayland, thank you so much for allowing me to be a model for the two of you to follow. I love you both very much. To my grandmother, Ida Johnson, and my grandfather, Roosevelt Johnson, Sr. Every since I was a little girl I always looked at both of you as two very strong people. Thank you for passing that Johnson family strength on to me. Mama Ida, I also thank God for the happiness, the help, and the enjoyment you have brought into my life. You are truly a gem. To my fiancé Adrian Dunn, thank you for your love, support and encouragement throughout the years. I am glad I have you by my side. To the rest of my family, my grandparents, Aspazie and Rogers Batiste, my aunts, uncles and cousins, thank you for your advice, support and love. To the little ones, Kaitlyn, Donald, Layla, and Adrianna, I also dedicate this to you. I challenge you to always set your goals high and strive to be the very best you can be. I hope I have set a good example for you to follow.
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LIST OF ABBREVIATIONS

amu       Atomic Mass Units
BHT       Butylated hydroxytoluene, 2,6-Di-tert-butyl-4-methylphenol
calc.     Calculated
DCC       1,3-Dicyclohexylcarbodiimide
DCM       Dichloromethane
DMAP      4-Dimethylaminopyridine
DMF       N,N-Dimethylformamide
DMSO      Dimethyl sulfoxide
FAB       Fast Atom Bombardment
FDA       Federal Drug Administration
HOBT      1-Hydroxybenzotriazole
HCl       Hydrochloric acid
HPLC      High-Performance Liquid Chromatography
IUPAC     International Union of Pure and Applied Chemistry
MALDI     Matrix-Assisted Laser Desorption Ionization
MeOH      Methanol
MS        Mass Spectrometry
NaBH₄     Sodium borohydride
NaOH      Sodium hydroxide
NMR       Nuclear Magnetic Resonance
ORTEP     Oak Ridge Thermal Ellipsoid Plot
ppm       Parts Per Million
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<tr>
<td>PTZ</td>
<td>Phenothiazine</td>
</tr>
<tr>
<td>R_F</td>
<td>Ratio to Solvent Front</td>
</tr>
<tr>
<td>rt</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>r.t.</td>
<td>Retention time</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoro acetic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-Layer Chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>UV-Vis</td>
<td>Ultraviolet-Visible</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>Wavelength</td>
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ABSTRACT

The colorimetric properties of resorcinarene solutions had not been fully investigated since von Baeyer’s initial synthesis. We find that the solutions containing resorcinarene macrocycles develop color upon heating or standing. In the presence of saccharides, these solutions exhibit significant color changes which are readily observable by visual inspection. We determined that the solution color is due to macrocycle ring opening and oxidation. The optical responses to saccharides are due to complexation of the sugar with the acyclic chromophores. We have applied these mechanistic insights towards the challenging problems of the visual detection of saccharides and other important biologically analytes. In addition, we also report the first single crystal X-ray crystal structure determination of a rarely observed “diamond” resorcinarene stereoisomer.

The visual sensing of saccharides is of importance to medical diagnostics and industry. The synthesis of the diamine tripod and the diamine fluorescein compounds will be presented and their application towards the detection of saccharides and biomolecules of interest will be discussed. In addition to this, the synthesis of a new cationic chiral surfactant, the $l$-arginine methyl ester, for use in chiral separations will also be presented.
CHAPTER 1

INTRODUCTION

1.1 History of Resorcinarenes

In 1872 Adolf von Baeyer first synthesized resorcinarenes. He reported that an acid catalyzed condensation reaction of benzaldehyde and resorcinol gave a reddish resin which, upon the addition of base, changed to violet. In addition to the reddish resin, a crystalline compound was obtained when the mixture was heated. The unknown crystalline product was later determined to be an isomer of the red resin. Several years later, Michael determined the correct elemental composition of this slightly soluble, high melting crystalline compound \((C_{13}H_{10}O_{2})_n\) as well as its acetyl derivative \((C_{13}H_8(OCOCH_3)_2)_n\). Michael also reported that the product was formed by combination of an equal number of benzaldehyde and resorcinol molecules and the loss of an equal number of water molecules. Despite this, it took several decades to determine the structure of the product. Michael initially suggested structure 1.1 for the phenolic compound. Niederl and Vogel showed that the ratio between aldehyde and resorcinol in the product should be 4:4 according to molecular weight determinations. As a result, they proposed a cyclic tetramer 1.2, which is a structural analogue to porphyrins. Erdtman and coworkers finally proved its structure in 1968 with the aid of single crystal X-ray analysis.

Initially, Gutsche and Böhmer referred to the compounds as calix[4]resorcinarenes or resorcinol-derived calix[4]arenas. In 1994, Schneider suggested the name "resorcinarene". Resorcinarenes are also sometimes referred to as "Högberg compounds" or "octols" in the literature.
Figure 1.1. Structures of the crystalline compound obtained from Baeyer’s synthesis proposed by Michael (1.1), Nierdel and Vogel (1.2), R = aliphatic.

1.2 Synthesis of Resorcinarenes

The synthetic route of most resorcinarenes involves an acid-catalyzed condensation reaction between resorcinol and an aliphatic or aromatic aldehyde.\textsuperscript{1.9, 1.15} Generally, a cyclotetramer crystallizes from the reaction mixture, but in some cases the isolation of the condensation product requires the addition of water.\textsuperscript{1.13, 1.17} In the synthesis of resorcinarenes, an unsubstituted resorcinol (1,3 dihydroxybenzene) is usually used. The use of 2-methylresorcinol or pyrogallol (1,2,3-trihydroxybenzene) is reported to also yield significant amounts of tetrameric products.\textsuperscript{1.10, 1.18} When electron-
withdrawing substituents such as NO₂ or Br\textsuperscript{1.13} are present at the 2-position of the resorcinol derivatives, or when the hydroxyl groups are partially alkylated, the products will not be formed.\textsuperscript{1.19} For electron withdrawing groups such as NO₂ or Br, it appears that such groups deactivate the resorcinol nucleus as a nucleophile, resulting in partial condensation which occurs slowly.\textsuperscript{1.13} There is very little limitation to the structure of the aliphatic and aromatic aldehyde. However, the use of very sterically crowded aldehydes, like 2,4,6-trimethylbezaldehyde or aliphatic aldehydes with functionalities too close to the reaction center, such as ClCH₂CHO or glucose\textsuperscript{1.13}, provides an exception to this rule.\textsuperscript{1.19}

The mechanism of the acid-catalyzed condensation reaction for the formation of resorcinarenes has been thoroughly studied (Figure 1.2).\textsuperscript{1.19} The aldehyde is first protonated to serve as the initial electrophile which adds to resorcinol. The alcoholic hydroxyl of the subsequent adduct is protonated again generating a mole of water. A carbocation intermediate is afforded by the removal of water. This intermediate undergoes second electrophilic addition to another resorcinol to form a dimer. Coupling of the dimer with resorcinol units results in trimer, tetramer or higher oligomers containing more than four monomers. Under acidic conditions, the condensation reaction is reversible so most of the higher oligomers disappear towards the end of the reaction. However, they are present during the intermediate reaction time. Once they are formed in the reaction mixture, the acyclic tetr amers cyclize rapidly to form resorcinarenes. As a result of the immediate cyclization, the tetr amers can not be isolated. Due to the lack of conformational strain by the formation of hydrogen bonds between proximal phenolic
hydroxyl groups of adjacent resorcinol units in the folded structures, the rapid cyclization is favored.

**Figure 1.2.** Mechanism of the acid-catalyzed synthesis of resorcinarenes
1.3 The Stereochemistry of Resorcinarenes

The stereochemistry of resorcinarenes, which are non-planar, is generally defined based on three criteria. The first criterion is the macrocyclic ring conformation. As a result of the macrocycle ring having five highly symmetrical conformations: crown (C\textsubscript{4v}), boat (C\textsubscript{2v}), chair (C\textsubscript{2h}), diamond (C\textsubscript{s}), and saddle (D\textsubscript{2d}), resorcinarenes have five corresponding stereoisomers (Figure 1.3).

![Figure 1.3. Five stereoisomers of resorcinarene.](image-url)
The relative configuration of the substitutes at the methylene bridges, giving the all-cis (ccc), cis-cis-trans (cct), cis-trans-trans (ctt) and trans-cis-trans (tct) resorcinarene stereoisomers is the second criterion (Figure 1.4).

**Figure 1.4.** Relative configuration of the substituents at methylene bridges.

The individual configuration of methylene bridge substituents is the final criterion. They may be either axial or equatorial in conformations of the macrocycle with C symmetry. A combination of these three criteria results in a great number of possible stereoisomers. Experimentally, only four have been reported thus far. The boat conformation is usually reported as a crown conformation due partially to the presence of two boat isomers, which interconvert rapidly to give a time-averaged crown conformation. The interconversion between boat, chair and diamond diastereomeric isomers does not occur since it requires the breaking of at least two covalent bonds. Each of the stereoisomers can be produced in a reaction. The product ratio is mainly determined by the thermodynamic stability of the different isomers because the condensation reaction is reversible under homogeneous acidic conditions. The solubility of the different isomers in the reaction solvent play a key role in determining the product ratio if the reaction is performed under heterogeneous conditions. Therefore, the ratio of different diastereoisomers depends greatly on the reaction conditions used.
However, there are many other factors that may affect the presence or absence of a specific isomer.

### 1.4 Complexation of Polar Organic Molecules by Resorcinarenes

There are eight hydroxyl groups at the upper rim of the resorcinarenes, which can complex organic molecules containing polar substituents. Aoyama et al. first recognized this feature a decade ago and they have studied this phenomenon extensively.\(^{1,21,1,22}\) The complexation behavior of resorcinarenes for a variety of guest molecules such as sugars and steroids,\(^{1,23,1,24,1,25}\) amino acids,\(^{1,26}\) triethylamine and [2,2,2] cryptand\(^{1,27}\) has been studied.

Following a study of the complexation of resorcinarenes with several cyclohexanediols, Aoyama found that, among all possible isomers, cis-1,4-cyclohexanediol was bound the most tightly and the binding is eight times stronger than that of the corresponding trans isomers.\(^{1,28}\) The selectivity results from the preferred geometry of the cis-isomer where one of two related hydroxyl is equatorial and the other is axial. This 1,4-cis selectivity is also very important in the case of carbohydrate complexation.\(^{1,23}\) Although D-ribose is almost insoluble in pure CCl\(_4\) it was found to be readily extracted from a concentrated resorcinarene solution in CCl\(_4\). NMR investigations clearly showed that D-ribose is bound to resorcinarenes only in the \(\alpha\)-pyranose form,\(^{1,23b}\) which has a cis orientation of the hydroxyl groups at C-1 and C-4 (Figure 1.5). Fucose and 2-deoxyribose were found more readily extracted than ribose, while xylose could not be extracted at all although only its configuration at C-3 is different. These findings suggest that a cis relationship between the C-3 and C-4 OH’s is also very important for
complexation. A \textit{trans} 3-OH simply gave unfavorable interactions with the aryl ring between the two binding sites. The OH at C-2 should also be \textit{cis} to the C-3 and C-4 OHs or absent to avoid unfavorable exposure to the apolar solvent. The substituents at C-5 interact only with the apolar solvent and therefore should be as hydrophobic as possible.

\begin{center}
\includegraphics[width=0.6\textwidth]{resorcinarene.png}
\end{center}

\textbf{Figure 1.5.} Structure of the complex between Resorcinarene and D-ribose.

Aoyama and co-workers discovered that the major binding force for complexation in apolar, organic solvent is hydrogen bonding to four pair of hydroxyl groups of the resorcinarenes. In addition to this, the interaction between an aliphatic moiety at the guest and the electron-rich aromatic rings in the host (CH-\(\pi\) interactions) also contributes to the binding.\textsuperscript{1.24, 1.29} In aqueous systems,\textsuperscript{1.26, 1.30} in the absence of hydrogen bonding as a driving force for complexation, the affinity of resorcinarenes for polar guests is mainly determined by hydrophobic interactions. Moreover, CH-\(\pi\) interactions play a very important role in the binding if the guest molecules are hydrophobic.\textsuperscript{1.29}
1.5 The Significance of Complexation of Boronic Acid to Saccharides

Boronic acids have been known since Michaelis and Becker first synthesized phenylboronic acid.\textsuperscript{1,31} Kuivila et al. published the first binding studies of diols with boronic acids in 1954\textsuperscript{1,32}, although borates were already known to be able to bind polyhydroxyl compounds at the beginning of last century.\textsuperscript{1,33} They postulated the formation of a cyclic boronic ester after they observed that boronic acids could solubilize saccharides and polyols. Now it is well known that boronic acids form covalent bonds with 1,2- or 1,3-diols to give five- or six-membered cyclic esters in both neutral nonaqueous and alkaline aqueous solutions (Figure 1.6). Norrild and Eggert reported the structures of the complexes of boronic acid with fructose and glucose under these conditions by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy.\textsuperscript{1,34}

![Figure 1.6. Boronate ester formation with phenylboronic acid in alkaline aqueous solution (top) and aprotic media (bottom).](image)

Hydrogen-bonding is the basis of the binding interactions between many synthetic molecular receptors and biologically important molecular species. In aqueous media, a serious drawback arises from the competitive hydrogen bonding by the solvent. The
ability of boronic acid to readily form cyclic ester with saccharides in aqueous media provides an important binding force in the recognition of saccharides and related molecular species. As saccharides play an important role in the metabolic pathway of living organism, determination of the presence and the concentration of sugars of biological importance (e.g., glucose, fructose) becomes necessary in the fields of medicine and industry.

Lorand and Edwards published the first quantitative evaluation of the interaction between boronic acid and saccharides in 1959. They reported the selectivity order of phenylboronic acid towards several monosaccharides: D-fructose > D-galactose > D-mannose > D-glucose. They also discovered that the rigid, vicinal cis diols of saccharides form more stable cyclic esters than simple acyclic diols such as ethylene glycol. A variety of receptors containing a boronic acid moiety have been synthesized in different laboratories and employed for the recognition of mono- and oligosaccharides. The applications of these kind of studies range from the monitoring of fermenting processes in industry to the establishment of the enantiomeric purity of synthetic drugs. Past enzymatic methods for sugar detection are limited in specificity. In addition to this, sterilization conditions were sometimes used in enzymatic methods, which make enzyme-based sensors unstable. As a result, our group has designed and synthesized relatively stable receptors based on boronic acid. This has led to useful colorometric detection of saccharides. Based on these results, it was our goal to determine the mechanism of color changes of our compounds in the presence of sugars for the purpose of designing new and improved sensors.
1.6 References


1.15 Pieroni, O. I.; Rodriguez, N. M.; Vuano, B. M.; Cabaleiro, M. C. *J. Chem. Research (S)* 1994, 188.


1.21 As a result of this extensive study, resorcinarenes were awarded “reagent of the year in 1993” by Fluka: *J. Org. Chem.* 1993, 58, 2A.


CHAPTER 2

CHROMOPHORE FORMATION IN RESORCINARENENE SOLUTIONS

2.1 Introduction

This was a collaborative project. My contribution to this project includes:

2.1.1 The identification of acyclic oxidized and unoxidized products from resorcinarene fragmentation.

2.1.2 The inhibition of resorcinarene fragmentation by free radical inhibitors.

2.1.3 The identification and first x-ray crystal structure of the diamond stereoisomer.

2.1.4 The identification of acid formation from the thermolysis of the resorcinarene macrocycle.

2.1.5 First x-ray crystal structure of trimethyl sulfonium methane sulfonate.

2.1.6 Identification of dihydroxy acetophenone from the fragmentation of a model acyclic oligomer.

2.2 Background

Adolf von Baeyer studied the condensation reaction of resorcinol and benzaldehyde in acidic media in 1872. Upon the addition of base, the red solution he obtained turned to violet. It is now known that Von Baeyer's reaction created macrocyclic compounds now called resorcinarenes.

The great importance of resorcinarenes have been discussed in past reviews. For example, resorcinarenes were the first compounds shown to bind sugars in apolar media. Lewis and Davis synthesized 2.1 and 2.2a and investigated their properties in the presence of sugars. They observed eleven different solution colors of eleven different heated sugar solutions containing 2.1. They studied neutral carbohydrates, glucose phosphates, carboxylic acid and amino sugars. The solution color changes were each rapid, quantifiable and reproducible. They also showed that solutions containing 2.2b
exhibited relatively paler color changes in the presence of sugars compared to those containing boronic acids 2.1 and 2.2a or 2.3a.²,⁶

Analyses of sugars are difficult due to their great structural similarity as well as transparency in most of the ultraviolet and in the visible region, (they lack chromophores or fluorophores). The sensing of specific saccharides could aid the monitoring of disease or industrial fermentation products.

In 1887, Seliwanoff reported a resorcinol color test which was followed by other resorcinol-derived methods.²,⁷ These latter and numerous other related reducing sugar assays, while based on simple reagents, typically require toxic materials, harsh and often tedious procedures.²,⁸

![Figure 2.1 Resorcinarenes and related condensation products that produce color changes in the presence of sugars.](image-url)
In the 1990's significant progress was made towards the improved selective and mild detection of monosaccharides via relatively strong solution color changes observable by visual inspection. The recent advances were due mainly to the pioneering efforts of Shinkai and coworkers. Their studies were based primarily on aniline-functionalized azo dyes containing appended arylboronic acids.2.9

Evidence that xanthenes form and serve as the active chromophores in resorcinarene solutions is presented.

2.3 The Formation and Structure of the Chromophore in Resorcinarene Solutions

Lewis and Davis\textsuperscript{2.4} found that colorless DMSO solutions of freshly crystallized 2.1 or 2.2a, (5.2 mM), upon standing in solution for several hours or upon heating at 90 °C for 1 min, developed a pinkish-purple color. The color formation was monitored via UV-vis spectroscopy. The appearance of a new $\lambda_{\text{max}}$ at 535 nm was accompanied by a less intense absorbance at 500 nm.\textsuperscript{5.5} Initial attempts at understanding the origin of the solution color involved heating solutions of 2.1 in the dark or in O$_2$ degassed conditions. In both cases they found that the color intensities diminished, as evidence by both visual inspection and UV-vis spectroscopy.\textsuperscript{2.5} For instance, heating a solution of 2.1 (5.2 mM in DMSO) under O$_2$ degassed conditions led to a 61% decrease in absorbance at 536 nm. Light and O$_2$ apparently promote color formation. In addition, upon acylation of the phenolic hydroxyls of 2.1 and heating a DMSO solution of the resultant octaacetate to reflux, the solution remained colorless.\textsuperscript{2.6} The phenolic hydroxyls thus also play a key role in chromophore formation. We reasoned that the chromophore arises via oxidation of a resorcinol moiety to a quinone.\textsuperscript{2.5,2.6}
Scheme 2.1. Dehydration and oxidation of methine-bridged resorcinol oligomers leading to a xanthene.

We also heated solutions of resorcinol or benzeneboronic acid separately or as an equimolar mixture using the aforementioned conditions and concentrations, with and without added monosaccharides. We observed only very faint solution colors by visual inspection. This result showed that a methine-bridged resorcinol/aldehyde condensation framework was needed for effective chromophore formation and optical sugar detection. Interestingly, methine-bridged condensation product resorcinarene substructures, of which 2.3a and 2.3b are examples, were noted as reaction intermediates in standard xanthene dye syntheses (e.g., the transformation of 2.4 to 2.5, n=m=0, Scheme 2.1).2,15

Xanthenes are some of the oldest known synthetic dyes such as fluorescein, rhodamine, ethyl eosin, 2.6a and 2.6b and as well as many others. Importantly, the colorimetric properties of xanthenes are a function of the ionization state of the C-6 moiety2,16 (Figure 2.2).

Figure 2.2 Xanthene dyes 2.6a and 2.6b.
They typically exhibit two absorbance maxima in the visible region. The absorption spectrum of 2.6b (5.0 x 10^{-6} M) in 9:1 DMSO:H₂O is shown in Figure 2.2. It exhibits a λ_{max} at 530 nm and a less intense λ_{max} at 500 nm. Interestingly, the λ_{max} absorbance values and spectral features are strikingly similar to those observed for colored DMSO solutions of 2.1 as well as 2.2a, 2.2b and 2.3a which we previously reported.

![Figure 2.3](image_url)

**Figure 2.3**  2.2a (1.0 mg) and 2.3a (1.0 mg) each in 0.9 mL DMSO were heated to gentle reflux over two minutes and cooled to room temperature before 0.1 mL H₂O was added to each solution. The final concentrations of 2.2a and 2.3a in 9:1 DMSO:H₂O are 1.03 x 10^{-3} M and 1.96 x 10^{-3} M respectively. A solution of 2.6b (5.0 x 10^{-6} M) was prepared at rt in 9:1 DMSO:H₂O.

Incorporation of a planar xanthene within a resorcinarene macrocycle framework via the transformation shown in Scheme 2.1 would lead to a considerable increase in strain energy. Simulations (Sybil 6.6) done by Jorge Escobedo show that an increase in strain energy of 34.2 kcal/mol would occur upon formation of a xanthene substructure within 2.2b (Figure 2.4). Prior studies of the related calixarenes (macrocycles formally derived from phenol/formaldehyde condensations) showed that xanthenes did not form in cyclic tetrameric structures.
Ring opening to acyclic oligomers could thus be a prerequisite for xanthene formation from resorcinarenes. It is known that the condensation reactions producing resorcinarenes are reversible under acidic conditions.\textsuperscript{2,2} The detailed mechanism of resorcinarene macrocycle genesis has been studied thoroughly by Weinelt and Schneider.\textsuperscript{2,18} They found that 2.2b and its macrocyclic stereoisomers interconverted via the intermediacy of acyclic oligomers. Their studies included the rapid quenching of condensation reactions between resorcinol and either acetaldehyde or paraldehyde in MeOH in the presence of anhydrous HCl (Scheme 2.2).

![Energy-minimized structure (SYBYL® 6.6) of a hypothetical macrocyclic xanthene derived from 2.2b](image)

**Figure 2.4** Energy-minimized structure (SYBYL® 6.6) of a hypothetical macrocyclic xanthene derived from 2.2b

Since the opening of a resorcinarene ring has only been previously shown to occur upon the addition of strong acid, our hypothesis of acyclic oligomer formation in aqueous or neat DMSO solutions without added acid warrants further analysis.
We observed that $^1$H and $^{13}$C NMR spectra of DMSO-$d_6$ solutions of 2.1 (1.2 mM), heated at 90 °C for 3 min (our initial sugar colorimetric detection conditions) exhibited no readily observable change in chemical shifts or peak area integrals compared to fresh, colorless samples. Xanthenes are strongly absorbing materials which need be only produced in trace (ca. 0.5 % conversion; see, for example, the concentrations and absorbances shown in Figure 2.3) amounts to afford solution colors under our conditions.

![Diagram of the reaction of paraldehyde and resorcinol showing the reversible formation of a variety of intermediates in acidic media including acyclic oligomers and resorcinarenes as reported by Weinelt and Schneider.](image)

See Figure 1.4 for relative configurations of stereoisomers (rccc, rcct, rctt, and rtct).

**Scheme 2.2** Diagram of the reaction of paraldehyde and resorcinol showing the reversible formation of a variety of intermediates in acidic media including acyclic oligomers and resorcinarenes as reported by Weinelt and Schneider.\(^2,18\)
2.4 Evidence for Acid Formation in DMSO Solutions

As a result of our experimental investigations, I found that more vigorous thermolytic conditions are necessary to afford conversion to significant amounts of products. Heating a DMSO (10 mL) solution of freshly recrystallized 2.2b (100 mg, 18.4 mM) for 8 h at 120 °C followed by analysis via reversed phase high-performance liquid chromatography reveals the formation of numerous new products representing a 74 % conversion of 2.2b to products based on relative peak areas (Figure 2.5). An HPLC trace of the pure macrocycle would only contain a peak at approximately 32 minutes.

Strong literature precedent allows us to propose that acyclic oligomers arise from 2.2b via the in situ formation of strong acids. It is known that acid production from DMSO is promoted by the presence of O₂ and peroxides. In addition, in situ acid formation has been attributed as the cause of certain oxidations in DMSO. We have noted the effect of O₂ on resorcinarene solution color intensity.

Figure 2.5 HPLC Trace of the thermolysis of the acetaldehyde derived macrocycle.
Acid formation observed during DMSO decomposition has been inhibited by free radical scavengers.\textsuperscript{2.19c} If the decomposition of DMSO is producing acid in our systems, and the presence of acid is resulting in the formation of multiple products, then the addition of free radical inhibitors to our reaction conditions should inhibit product formation. I tested this hypothesis in our reactions. Under the same thermolysis conditions as noted above, but in the presence of free radical scavengers (either butylhydroxy toluene (BHT) or phenothiazene (PTZ), 10 mol %), I observed less than 28 % conversion to products by HPLC analysis (Figure 2.6).

Further evidence that strong acids form under our conditions was presented in our recent report describing the first X-ray crystal structure of trimethysulfonium methane sulfonate \textsuperscript{2.7}, \((\text{CH}_3)_3\text{S}^+\text{CH}_3\text{SO}_3^-\) (Figure 2.7). \textsuperscript{1.20} I was able to obtained this compound from a related thermolysis reaction of \textsuperscript{2.2b} in DMSO. It is known that \((\text{CH}_3)_3\text{S}^+\text{CH}_3\text{SO}_3^-\) forms, along with \(\text{CH}_3\text{SO}_3\text{H}\), \(\text{CH}_3\text{SO}_2\text{H}\) and \(\text{CH}_3\text{SOH}\) (and several other products) via the radical and acid promoted decomposition of DMSO.\textsuperscript{2.21}

![Figure 2.6](image)

**Figure 2.6** Top HPLC trace shows product inhibition by the addition of PTZ and bottom HPLC trace shows product inhibition by BHT.
Following the aforementioned result, I then turned my attention to identifying the products of macrocycle ring opening. I isolated 2.8 (Figure 2.8), a rarely observed "diamond" resorcinarene stereoisomer,\(^2\)\(^{22}\) in 2.3 % yield from the thermolysis of 2.2b in DMSO, via flash column chromatography. The structure of 2.8 was previously assigned (as the octabutyrate derivative) via NMR evidence during the acid-catalyzed condensation/isomerization studies of Schneider.\(^2\)\(^{18}\)

As a result of obtaining single crystals suitable for X-ray analysis, grown via slow evaporation of a 9:1 CH\(_2\)Cl\(_2\)::MeOH solution of 2.8, I was able to report the first known crystal structure of any resorcinarene diamond isomer. The macrocycle molecule lies on a mirror plane in the crystal, with three methyl groups (C10, C8, and its mirror-related equivalent) relatively syn. The fourth methyl group, C18, lies on the mirror, and is anti to the other three. The resulting conformation is such that OH groups O1 and O4 both form intramolecular hydrogen-bonding contacts with their mirror-related equivalents on O3 and O5, respectively.
adjacent aromatic rings. The H atoms in these contacts are disordered, with the two O atoms alternately donor and acceptor. The O…O distances are 2.712(2) Å for O1 and 2.671(2) Å for O4. There are two independent methanol molecules, both lying on mirrors and forming hydrogen bonds with external macrocyclic OH groups O2 and O3. Importantly, stereoisomer 2.8 can only form from 2.2b via bond rupture and reformation. If 2.8 were a conformer of 2.2b, the methyl group (C18), would reside outside, rather than above the plane of the macrocycle cavity.

Acyclic products are also observed during the thermolysis of 2.2b. A key reaction product, 2.3b is found in a broad HPLC fraction eluting from 16-19 min (Figure 2.9).

![Figure 2.8 Compound 2.8 and ORTEP.](image-url)
Figure 2.9 Top: Chromatogram of a reaction of resorcinol (rt=13.5 min) and acetaldehyde quenched after 10 min according with the procedure reported by Weinelt and Schneider\textsuperscript{2.18} showing the formation of 2.3\textit{b} (rt=17.7 min) Bottom: Chromatogram of the thermolysis of 2.2\textit{b} (rt=30 min) showing the formation of 2.3\textit{b} (rt=18 min).

The \textsuperscript{1}H NMR spectrum of the isolate exhibits several peaks including each of the resonances associated with 2.3\textit{b}\textsuperscript{2.18} (CH\textsubscript{3}OD $\delta$ 1.46, d, $^3J = 7.3$ Hz, 4.53, q, $^3J = 7.3$ Hz, 6.18-6.22, m, 6.89, d, $^3J = 8.0$ Hz). Overlay of the \textsuperscript{1}H NMR spectrum of the HPLC isolate with a sample of independently synthesized and isolated 2.3\textit{b} confirms the assignment (Figure 2.10). In addition, the MALDI MS of the HPLC fraction contains a peak at 245.59 amu (246.26 amu calcd). The production of compounds 2.3\textit{b} and 2.8 under our conditions constitutes an important initial link between our investigations and the prior acid-catalyzed macrocycle genesis mechanism studies\textsuperscript{2.18}.
I was also able to find evidence for higher order oligomer production under our conditions (*vide supra*) involving thermolysis of 2.2b in DMSO. At least five sets of doublets appear between 0.72 and 1.53 ppm in the $^1$H NMR of each of two flash column fractions (TLC $R_f=0.54$ and 0.63, 9:1 CH$_2$Cl$_2$:CH$_3$OH, δ 1.53, 1.08, 1.01, 0.97, 0.83, 0.72 ppm, and δ 1.29, 1.15, 1.00, 0.89, 0.84 ppm, CH$_3$OD, respectively). In addition, the MALDI mass spectrum (anthracene matrix) of other fractions ($R_f=0.29$ and 0.44) exhibit peaks for higher homologues of 2.3b (entries 1 and 2, Table 2.1). MALDI MS evidence also suggests the formation of xanthene materials not previously reported in previous fragmentation and equilibration studies of 2.2b (entries 3-6, Table 2.1).$^{23,24}$
Table 2.1. MALDI MS Evidence for the Formation of Acyclic Oxidized and Unoxidized Products from the Thermolysis of 2.2b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>TLC R$_F$</th>
<th>(m/z) calcd</th>
<th>(m/z) obsd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.4, R=Me, m=1, n=0</td>
<td>0.29</td>
<td>382.41</td>
<td>381.89</td>
</tr>
<tr>
<td>2</td>
<td>2.4, R=Me, m=3, n=2</td>
<td>0.44</td>
<td>926.36</td>
<td>926.28</td>
</tr>
<tr>
<td>3</td>
<td>2.6a</td>
<td>0.44</td>
<td>226.23</td>
<td>225.61</td>
</tr>
<tr>
<td>4</td>
<td>2.5, R=Me, m+n=4</td>
<td>0.26</td>
<td>906.01</td>
<td>906.33</td>
</tr>
<tr>
<td>5</td>
<td>2.5, R=Me, m+n=3</td>
<td>0.84</td>
<td>770.79</td>
<td>770.82</td>
</tr>
<tr>
<td>6</td>
<td>2.5, R=Me, n=1, m=0</td>
<td>0.79</td>
<td>362.51</td>
<td>361.38</td>
</tr>
</tbody>
</table>

In order to study the formation of the oxidation products, in this case, the formation of xanthenes, I heated 2.3b, the parent acyclic unoxidized homolog attained via ring-opening of 2.2b. Heating an air saturated solution of 2.3b (0.880 g, 3.576 mmol) dissolved in DMSO (78 mL) at 100 °C for 28 h leads to the formation of several products. The complex $^1$H NMR of the crude mixture reveals the presence of resorcinol as the predominant (90 %) product as well as minor conversion to 2,4-dihydroxyacetophenone 2.9 (ratio of integrals of resorcinol triplet 6.94 ppm to 2.9 doublet at 7.76 ppm is 153:1, CH$_3$OD) and very small traces of xanthene 2.6a (d, 7.65 ppm).

![2.9](image)

Figure 2.11 2,4-dihydroxyacetophenone (2.9) formed upon oxidation of a DMSO solution of 2.3b.
The production of resorcinol and 2.9 (Figure 2.11) is consistent with the reversible opening and fragmentation of the resorcinarenes in acidic media.\textsuperscript{2,18} This result also complements our recent report describing the production of 4-formylphenylboronic acid from 2.3c.\textsuperscript{2,25} Furthermore, in acidic media, the addition of water at the methine carbon of 2.4 (R=Ar, n=0, m=0) followed by elimination has been described as an intermediate step in the synthesis of xanthenes.\textsuperscript{2,26}

We attain better conversion to xanthene 2.6a from 2.3b by limiting thermolysis time to 2 h. The $^1$H NMR spectrum (DMSO-$d_6$) of the crude reaction mixture clearly shows a doublet at 7.65 ppm characteristic of 2.6a with improved S/N compared to the 28 h experiment (\textit{vide supra}). Resonances centered at 5.26, 6.49 and 6.60 ppm are also discernable, overlaying with the $^1$H NMR of an analytical sample\textsuperscript{2,26} of 2.6a. Since oxidation to xanthenes can be promoted by peroxides and acid,\textsuperscript{2,26, 2,27} we should attain better conversion to xanthenes upon addition of these latter reagents.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.12.png}
\caption{Acid and peroxide formation increases formation of xanthene.}
\end{figure}
Indeed, K. Kim found that heating a solution of 2.3b (50 mg, 0.203 mmol), H₂SO₄ (0.15 mL) and K₂S₂O₈ (1.0 mg) in 1.5 mL MeOH at reflux for 2h produces the most significant conversion (4 % yield) of 2.3b to 2.6a we have observed to date (Figure 2.12).

We have shown that xanthenes form in solutions containing resorcinarene macrocycles (Scheme 2.1). The O₂-induced radical decomposition of DMSO leads to in situ strong acid formation. The acid catalyzes a reverse condensation reaction to afford acyclic oligomers. The acyclic oligomers undergo oxidation also via the action of acid and peroxide.

2.6 Conclusion

We have presented strong evidence that the color observed in Baeyer’s initial resorcinarene condensation reaction\(^2\) was due to the presence of xanthenes. In other words, he had created xanthen dye at apparently low levels. Interestingly, Fischer, who won the Nobel Prize for sugar research, presented his doctoral thesis to Baeyer in 1874 on fluorescein and orcinol dyes.\(^2\)

We have shown that the colored products existing in solutions of resorcinarene macrocycles can serve as colorimetric indicators. I have also provided the first mass spectral evidence of higher order oligomers, the first evidence of xanthenes from resorcinarene fragmentation, the first x-ray structure of any resorcinarene “diamond” stereoisomer and the first x-ray crystal structure of trimethylsulfonium methane sulfonate. The main findings of the present study include (i) the determination of the origin and structure of the active chromophores, and (ii) elucidation of mechanisms associated with the solution color changes induced by sugars.

The investigation of the colorimetric and fluorimetric properties of resorcinarenes, xanthenes and related chromophoric materials is ongoing in our
laboratory. Our efforts are now guided by the mechanistic studies described herein. Xanthene dyes containing well-positioned boronic acid or related binding moieties should find application as powerful receptors for saccharides and other polar analytes such as carboxylates and phosphates.

The resorcinarenes, however, do offer potential advantages compared to functionalized dye materials. A great attraction is their ease of synthesis in one step on ca. 200 g scale.\textsuperscript{2,2d} Having addressed many of the main mechanistic issues associated with the colorimetric sugar detection process, we are now also focusing on the study and optimization of important applied sensing parameters such as detection selectivity, sensitivity and reversibility in aqueous and biological media.

2.7 Experimental Section

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. FT-IR spectra were recorded at room temperature on a Perkin-Elmer 1760X FT-IR spectrophotometer. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 µm particle size, 60Å). Analytic and preparative-scale HPLC were performed on a CM4000 multiple solvent delivery system (Milton Roy) and a Spectromonitor 5000 photodiode array detector (LDC Analytical) using a Dynamax 60Å C18 (21.4 mm ID x 25 cm L) with a flow rate of 5 mL/min. and a gradient of 50% water/MeOH to 100% MeOH in 20 min. unless otherwise stated. The following compounds were prepared according to literature methods: \textsuperscript{2.1,2,4} \textsuperscript{2.2a,2,4} \textsuperscript{2.2b,2,32} \textsuperscript{2.3a,2,6} \textsuperscript{2.3b,2,18} \textsuperscript{2.6a,2,15} Isotopically
labeled D-fructose-2-$^{13}$C was purchased from Isotec. All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD$_3$OD, CH$_3$OD or DMSO-$d_6$ on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All $\delta$ values are reported with (CH$_3$)$_4$Si at 0.00 ppm or DMSO at 2.45 ppm as references.

**X-ray crystallographic data.** Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoK$\alpha$ radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller. Data collection parameters and crystallographic data are provided in Supporting Information. Absorption and decay effects were negligible. The structure was solved by direct methods, using SIR97$^{30}$ and refined using SHELXL97. H atoms were observed in difference maps, but were constrained to be in idealized positions in the refinement. OH hydrogen atoms are all disordered into two sites, all of which were treated as half populated. O-H distances were constrained to be 0.84 Å, but otherwise, these H positions were refined.

### 2.8 References


2.22 For the structures of the different possible resorcinarene stereoisomers see reference 2.3d.

2.23 In the previous work (reference 2.19), acyclic oligomeric products (2.3b and two stereoisomeric trimeric compounds, three resorcinol rings, 2.4, R=Me, m=1, n=0, Scheme 2.1) were isolated and characterized. Higher order acyclic oligomers (e.g., pentamers and hexamers) were also observed as major reaction products. Methyl $^1$H NMR resonances, appearing as several doublets between 0.7 and 2.0 ppm (CD$_3$OD) that corresponded to neither 2.3b, 2.4 (R=Me, m=1, n=0), or resorcinarene macrocycles, thus were assigned to acyclics with five or more resorcinol moieties.

2.24 Flash column chromatography and TLC analysis of the thermolysis products of 2.2b were complicated by the multiple product formation and fraction streaking.


2.29 Fischer, E. Ph.D. Dissertation, Strasbourg University, Strasbourg, France, 1874


2.31 Sheldrick, G. SHELXL97, University of Göttingen, Germany, 1997.

CHAPTER 3
SYNTHESIS OF METHYL RESORCINOL-FORMALDEHYDE OLIGOMERS
AS NOVEL INDICATORS

3.1 Introduction

The mechanism accounting for the color changes in resorcinarene solutions was explained in the previous chapter. In this mechanistic study, it was also found that aldonic acids, formed from reducing sugars in situ upon heating in DMSO, promoted solution color changes via a charged hydrogen bonding interaction with the xanthene chromophore. This latter interaction perturbed the ionization state of the C-6 hydroxyl of the dye (Figure 3.1). As a result of this study, attention was next turned to the synthesis of new indicators which would enhance the optical response to the colored solutions of the sugars. The target indicators were in this case methyl resorcinol-formaldehyde oligomers.

![Figure 3.1](image)

**Figure 3.1** Charged hydrogen bonding between carbohydrates and proximal hydroxyls of 3.1 and 3.2.

Resorcinol-formaldehyde resins have been of great importance to the rubber industry for over 40 years. Rayon, nylon, fiberglass, polyester, steel, and aramid cords
have been successfully bonded to rubber with resorcinol-based adhesives.\textsuperscript{3.2-3.8} Improvements in these products and wider utilization of these products have necessitated a more complete understanding of how these materials function. The ability to analyze the structure of these resins is very important because the resin structure is closely related to resin function. In this reaction, resorcinol reacts with formaldehyde in alkaline medium at low temperatures. The reaction products are mixtures of addition and condensation compounds which react further to form high molecular compounds, mostly infusible and insoluble.\textsuperscript{3.9} Characterization of these resins has been very difficult in the past, owing to the complexity of these systems and to inherit limitations of the methods of analysis.\textsuperscript{3.10-3.19} \textsuperscript{13}C NMR has been most successful analytical tool used to characterize phenol-formaldehyde resins, and to a much lesser extent resorcinol-formaldehyde resins.\textsuperscript{3.20-3.24}

In our study however, we decided to utilize the synthesis of resorcinol-formaldehyde oligomers for a very different aim. We sought to overcome the obstacles previously occurred in the synthesis and characterization of resorcinol-formaldehyde resins for the purpose of utilizing the polymers as indicators which will selectively detect sugars. However, instead of using resorcinol in our studies, the selected material was 2-methyl resorcinol. The structure of the polymer is the main reason we sought to utilize it as a potential indicator. The polymer structure is analogous to the linear oligomeric products we identified in the fragmentation of the resorcinarene macrocycle. Knowing that the ionization state of the C-6 moiety is a direct function of the colorimetric properties of xanthene dyes and the oligomeric products of the resorcinarene macrocycle, we reasoned that the presence of several hydroxyl groups on the oligomeric chain would result in better selectivity in the detection of sugars (Figure 3.2). Utilization of the
oligomers as indicators depended upon the isolation and characterization of the oligomers, which in the past has been proven to be very difficult.\textsuperscript{3,4}

\[
\text{Figure 3.2 Structure of 2-methyl resorcinol-formaldehyde oligomers 3.3 compared to oligomeric products of resorcinarene fragmentation 3.4}
\]

3.2 Results and Discussion

In an effort to synthesize the 2-methyl resorcinol-formaldehyde oligomer, a model reaction was studied. This model study consisted of reproducing the resorcinol-formaldehyde resin. In addition to obtaining the oligomeric products, I was also able to obtain a crystal structure of one of the oligomers (Figure 3.3). As a result of the successful synthesis of the model resorcinol-formaldehyde oligomers, I sought to synthesize the 2-methyl resorcinol formaldehyde oligomers.

\[
\text{Figure 3.3 Crystal structure of resorcinol-formaldehyde oligomer (Sybyl 6.6)}
\]
**Scheme 3.1** describes the synthesis of the 2-methyl resorcinol-formaldehyde oligomers. The starting material was 2-methyl resorcinol 3.5, which was allowed to react with formaldehyde 3.6 in MeOH. After cooling the solution and dilution with water, the desired products 3.3 was obtained in a 78% yield.

![Scheme 3.1 Synthesis of 2-methyl resorcinol-formaldehyde oligomers 3.3](image)

In an effort to characterize the oligomeric products, I first analyzed the product by TLC. Analysis by TLC showed evidence of several products, which had very close R_f values. 1H NMR spectrum of the product proved difficult to analyze as a result of the complex mixture. This prompted me to analyze the product by MALDI MS and FAB. By MALDI MS and FAB, there is evidence of several oligomeric products (Table 3.1).

**Table 3.1** MALDI MS and FAB Evidence for the Formation of unoxidized 2-methyl resorcinol-formaldehyde oligomeric products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>(m/z) calcd</th>
<th>(m/z) obsd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3, n=0</td>
<td>260.29</td>
<td>259.30</td>
</tr>
<tr>
<td>2</td>
<td>3.7, n=2</td>
<td>532.58</td>
<td>532.65</td>
</tr>
<tr>
<td>3</td>
<td>3.8, n=3</td>
<td>668.73</td>
<td>668.73</td>
</tr>
<tr>
<td>4</td>
<td>3.9, n=4</td>
<td>804.88</td>
<td>804.80</td>
</tr>
<tr>
<td>5</td>
<td>3.10, n=5</td>
<td>941.02</td>
<td>941.00</td>
</tr>
</tbody>
</table>
There is also evidence by MALDI MS and FAB of the formation of oxidized 2-methyl resorcinol-formaldehyde oligomers. MALDI MS and FAB peaks at 241.9 amu and 513 amu indicate the presence of the oxidized dimer and tetramer with calculated amu of 240.25 and 512.55 respectively.

I attempted to isolate the oligomeric products by flash column chromatography, however this attempt was unsuccessful. I then turned my attention towards the separation and isolation of the oligomeric products via HPLC (Figure 3.4). As a result of each of the products eluting at very close times, successful separation was not achieved. Although eluting times 13.5, 20.9, and 31.4 seem to be well resolved, when isolated, these products consist of oligomeric mixtures.

![HPLC Chromatogram of 3.3](image)

**Figure 3.4** HPLC Chromatogram of 3.3

### 3.3 Conclusion

In summary, I have synthesized 2-methyl resorcinol-formaldehyde oligomers. However, due to the difficulty in separating the various oligomeric products, which is common in resorcinol-formaldehyde resins, we have not yet used this product for the
detection of saccharides. Future work involves isolation of the oligomeric products and utilization of these products towards the detection of sugars.

3.4 Experimental Section

**General.** Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. Analytical thin-layer chromatography (TLC) was performed using general purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 µm particle size, 60Å). Analytic and preparative-scale HPLC were performed on a CM4000 multiple solvent delivery system (Milton Roy) and a Spectromonitor 5000 photodiode array detector (LDC Analytical) using a Dynamax 60Å C18 (21.4 mm ID x 25 cm L) with a flow rate of 5 mL/min. and a gradient of 50% water/MeOH to 100% MeOH in 20 min. unless otherwise stated. All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD3OD, CH3OD or DMSO-d6 on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All δ values are reported with (CH3)4Si at 0.00 ppm or DMSO at 2.45 ppm as references.

**Compound 3.3** (Oxidized and unoxidized oligomeric compounds) To a solution of 2-methyl resorcinol 3.5 (1g, 8.06 x 10⁻³ mol) and in methanol (3 mL) was added 37% formaldehyde 3.6 (0.21 mL, 0.2221 mol). The mixture was stirred 1.5 hours at 80 °C. Following heating, the mixture was allowed to cool to room temperature and was diluted with water (7 mL). This mixture was then allowed to sit at room temperature overnight. The solution afforded 0.8 g (80.0 %) of a light pink solid, which was filtered and dried under vacuum. ¹H NMR (250 MHz; CD3OD δ: 2.09 (q, J= 4.98 Hz, 4H), 3.68 (d, J= 3.99 Hz, 2H), 6.30 (q, J= 11.33 Hz, 4H), 6.77 (q, J= 8.46 Hz, 4H)
3.5 References


3.6 Whitby, G. S. *Synthetic Rubber*, 1954, 698.


3.9 Werstler, D. D *Polymer*, 1986, 27, 767.


3.11 Vorontsova, J. A.; Gadyuchenko, V. A.; Subgrua, C. A; Vzina, P. V. *Proiza Shin RTI ATI* 1975, 7, 31.


CHAPTER 4

THE SYNTHESIS OF NOVEL INDICATORS FOR SIMPLE AND RAPID VISUAL SENSING OF SACCHARIDES AND BIOMOLECULES OF INTEREST

4.1 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. Materials such as this could lead to improved indicators relative to degradable enzyme-based systems or to those requiring complex and expensive syntheses or instrumentation.

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. Other resorcinol-based color tests for sugars were later developed. These tests and other related reducing sugar assays however were based on harsh methods which included high toxicity, corrosiveness, and heating. Some of the past methods also suffered from harsh interference from compounds such as neutral carbohydrates, cysteine, thiols, proteins and certain metal ions. Great progress has been made towards the enhanced selective visible detection of saccharides via the pioneering studies of Shinkai and coworkers. A previous review underscored the lack of sugar receptors that promote dramatic color changes in the presence of individual analytes. Detecting the presence and concentration of biologically important sugars such as glucose, fructose, and galactose is necessary in many medicinal and industrial applications. D-glucose recognition is also of interest because the breakdown of glucose transport in humans has been correlated with many diseases.
Building on our mechanistic knowledge which was reported in Chapter 2, our goal was directed towards the synthesis of new and improved indicators which would be more powerful, selective, rapid and efficient. To this end, the synthesis of two novel indicators which have potential applications towards the detection of saccharides and also biowarfare molecules will be discussed.

4.2 Synthesis of Diamine Tripod

Scheme 4.1 describes the synthesis of the diamine 4.4. The reaction began with a known synthesis by Tunstad and co-workers\(^4\) to obtain 4.3. The starting material was 2-nitroresorcinol 4.1 which was allowed to react with acetaldehyde 4.2 in ethanol to form 4.3.\(^4\) After reducing 4.3 in the presence of sodium borohydride and palladium on carbon (10%) in water, the product was extracted in ether, dried and stabilized by acidification. Following drying, the desired compound 4.4 was obtained in a good yield (80%).

\[\text{Nitroresorcinol} + \text{Acetaldehyde} \rightarrow \text{Intermediate} \rightarrow \text{Product} \]

\[\text{EtOH} \quad 87\% \]

\[\text{Product} \quad \text{NaBH}_4, \text{NaOH} \rightarrow \text{Compound} \quad \text{Ar(g), Pd/C} \quad 80\% \]

Scheme 4.1 Synthesis of 4.4

I successfully obtained crystals of the acid of 4.4 (Figure 4.1) following protonation with concentrated HCl. Compound 4.4 will be utilized as a synthetic building block for the synthesis of larger compounds as indicators.
4.3 Synthesis of Diamine Fluorescein (DAF) Compound

As a result of successfully synthesizing the diamine tripod, our efforts turned towards the synthesis of a more powerful dye which did not require extensive functionalization in order to be utilized as an indicator. To this end, I have synthesized the diamine fluorescein compound 4.6. The synthesis of 4.6 was achieved by reducing 4,5-dinitro fluorescein 4.5 in the presence of sodium borohydride and paladium on carbon (10%) in water at room temperature while stirring overnight (Scheme 4.2). The product was then extracted in ether, dried and stabilized by acidification. After drying, the desired compound 4.6 was obtained (85%).

Scheme 4.2 Synthesis of the diamine fluorescein (DAF) compound 4.6
4.4 Application of DAF Toward the Detection of Saccharides

It is a well-known fact that under certain conditions saccharides form colored complexes with amines. This reaction is known as the Maillard reaction, which is also referred to as non-enzymatic browning. It is actually a complex set of reactions that takes place between amines usually from proteins and carbonyl compounds, generally sugars, especially glucose, fructose, maltose or lactose.

The initial step involves the reaction between a reducing sugar and a primary amino acid. Loss of water from this molecule produces an imine or the Schiff base that is able to cyclize, resulting in the formation of an N glycoside (a sugar attached to an NR₂ group) which is a yellow color (Scheme 4.3).

Scheme 4.3 Maillard Reaction

Upon prolonged heating this product turns a dark brown color. This process is very important for food preparation and processing because it results in desirable browning, for example, during baking, roasting of meat, and malt preparation but also in discoloration, which is observed in heat-treated milk products, among others.

Since our diamine fluorescein compound is a dye and also possesses primary amines, we decided to react this compound with sugars in order to obtain a color change. This was achieved by reacting with glucose in methanol to obtain the Schiff base product 4.7. Compound 4.7 was then reacted with potassium cyanide, a soft nucleophile,
in methanol to obtain the more stable and newly colored complex 4.8 (Scheme 4.4) along with other side products, which are not shown.

Scheme 4.4 Reaction of DAF 4.6 with glucose

The Schiff base product can be mono-substituted or di-substituted. The mono-substituted product was confirmed by MALDI MS (Figure 4.2). The top $^1$H NMR indicates the diamine fluorescein compound, the middle $^1$H NMR indicates the presence of the Schiff base 4.7 and the bottom $^1$H NMR indicates the final product after the addition of cyanide (aminonitrile 4.8). The two singlets at 6.8 ppm possibly indicate the Schiff base product. Upon the addition of cyanide, these two singlets disappear, further indicating the conversion to the aminonitrile product 4.8. These results can be observed visually as shown in Figure 4.3.

This reaction (Scheme 4.4) can also be monitored by UV-vis where upon the addition of potassium cyanide to the vials, an increase in absorbance is observed at 550 nm, indicating the presence of sugars (Figure 4.4).
Figure 4.2 $^1$H NMR and MALDI MS of 4.6-4.8. MALDI MS indicates the mass of the mono-substituted product. Top $^1$H NMR (a): DAF starting material. Middle $^1$H NMR (b): Schiff base product. Circled are two peaks, which are possibly indicative of the Schiff base product. Bottom $^1$H NMR (c): Final product 4.8, after the addition of cyanide. There is an absence of the two possible Schiff base peaks and an upfield shift after the addition of cyanide.

Figure 4.3 Visual Detection of Saccharides with DAF. Vial #1 first contained DAF, vial #2 contained DAF + glucose, and vial #3 contained DAF + fructose. Upon the addition of potassium cyanide to all three vials, there is a selective color change distinguishing the presence of the sugars.
**Figure 4.4** UV-vis data displaying the interaction of DAF with saccharides in methanol at room temperature. Line 1: DAF with KCN; line 2: DAF with KCN and D-glucose, line 3: DAF with KCN and D-fructose. Concentration of DAF is $5.5 \times 10^{-4}$ mol/L. Concentration of saccharides is $4 \times 10^{-3}$ mol/L.

### 4.5 Detection of Saccharides via Periodate Oxidation

It is known that sugars can be oxidized using periodate (Scheme 4.5). Hydroxyl groups in non-reducing sugars are converted to aldehyde groups by periodate oxidation, followed by further conversion to carboxyl.\textsuperscript{4,10} This method of oxidation has been and is currently being utilized in the sensing of saccharides. However, known methods have limitations.

In 1996 Masuda and co-workers developed a method using postcolumn fluorescent derivatization for the detection of sugar in vegetables.\textsuperscript{4,11} Sugar types and concentrations in vegetables affect their taste. Thus, the measurement of taste-related sugars such as sucrose, D-fructose, and D-glucose is indispensable for quality evaluation.
Scheme 4.5 Oxidation of Sugars with Periodate (dialdehyde major product)

Masuda’s method however, involved producing fluorescent derivatives of guanidine by heating the oxidized derivatives of sugars in alkaline solution.\textsuperscript{4,11} Other methods which involved periodate oxidation for the detection of sugars include normal phase chromatography on amino-bonded silica (NH\textsubscript{2} type) columns using acetonitrile-water as mobile phase with refractive index detectors.\textsuperscript{4,12} This procedure provides advantages of high resolution of various sugars and repeated analysis without initialization of the column condition. However, detection is not specific for sugars, and other components such as organic acids and amino acids interfere with the measurements. Fluorophore labeled carbohydrate electrophoresis also utilizes oxidized saccharides for detection. This method involves several steps, which include labeling of carbohydrates, separation of the saccharide by polyacrylamide gel and then imaging.\textsuperscript{4,13}

We have accomplished a means to effectively detect saccharides by oxidation visually and rapidly. This is accomplished by first oxidizing the sugar with sodium periodate to form a dialdehyde and other byproducts such as formaldehyde and formic
acid. The dialdehyde is then reacted with DAF 4.6 in water to obtain a Schiff base product (Scheme 4.6). The formation of the aldehyde by periodate oxidation was proven by $^1$H NMR. Although the final Schiff base product 4.8a was not isolated or proven by $^1$H NMR, we are able to base the product formation on similar reactions that are found in the literature.\textsuperscript{4.8, 4.12, 4.14}

**Scheme 4.6** Detection of Saccharides Using DAF and Periodate Oxidation

**Figure 4.5** Visual Detection of Saccharides Using DAF and Periodate Oxidation; control solution consisted of DAF and sodium periodate
These results can also be observed visually (Figure 4.5), where upon the addition of the oxidized saccharides to the control solution which is yellow, there is an immediate color change to deep purple. In addition to its efficiency and rapidness, a major benefit of this method is its ability to take place in aqueous conditions.

4.6 Application of DAF Toward the Detection of Cyanide

In lieu of September 11, 2001, there is a growing effort to synthesize compounds for the fast detection of biomolecules of interest. In addition to this, exposure to cyanide originating from industrial processes, tobacco smoking, drug administration and dietary intake of cyanogenic glucosides is a problem related to human health because of its high toxicity and there have been several studies on the analysis of biological fluids, especially blood, for cyanide.\textsuperscript{4.15-4.17}

Scheme 4.7 Detection of Cyanide with DAF
Further, in biological analysis for cyanide, the previous methods of detection such as spectrophotometric methods using pyridine and various other compounds, suffer from insensitivity or instability of the reaction products.\textsuperscript{4,18}

In addition to utilizing DAF \textbf{4.6} for the detection of saccharides, we are also able to visually and rapidly detect cyanide with DAF \textbf{4.6}. This was attained by reacting hydroxy substituted aldehydes with \textbf{4.6} in methanol at room temperature to obtain the Schiff base \textbf{4.9}. Compound \textbf{4.9} is then reacted with potassium cyanide to achieve the more stable and newly colored complex \textbf{4.10} (Scheme 4.7). The formation of \textbf{4.10} was supported by analytical techniques such as such \textsuperscript{1}H NMR and also MALDI MS (Figure 4.6).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{\textsuperscript{1}H NMR and MALDI MS data for \textbf{4.10}. Spectra A indicates the presence of aldehyde and Schiff base peaks in the starting products. Spectra B displays the absence of aldehyde and Schiff base peaks.}
\end{figure}
This reaction can also be monitored by UV-vis. Upon the addition of cyanide to the DAF/aldehyde complex in methanol, there is an increase in absorbance at 414 and 540 nm (Figure 4.8).
4.7 Conclusion and Future Work

The synthesis of two new compounds which have applications as indicators has been described. The diamine tripod 4.4 has potential applications for sensing. Future studies involve its utilization as a building block for the synthesis of larger compounds as indicators. The diamine fluorescein 4.6 successfully detects the presence of glucose and fructose under two different conditions, the first being in the presence of potassium cyanide and the second involves the detection of saccharides via periodate oxidation. These two new methods successfully detect saccharides visually, rapidly and efficiently without requiring a laborious synthetic route in order to achieve the target indicator. Future studies will involve the establishment of the detection limits and also a complete analysis of compounds that may cause interference.

Compound 4.6 also detects cyanide. The method of detection that we have established has potential applications toward the fast detection of cyanide in biological
fluids and biowarfare weapons. Other ongoing projects include the use of DAF for the detection of various compounds such as saccharides, amino acids and anions by complexation with various metals.

4.8 Experimental Section

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. Analytical thin-layer chromatography (TLC) was performed using general purpose silica gel on glass (Scientific Adsorbants). All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD$_3$OD or DMSO-$d_6$ on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All δ values are reported with (CH$_3$)$_4$Si at 0.00 ppm or DMSO at 2.45 ppm as references. UV-visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices).

X-ray crystallographic data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoKα radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller. Data collection parameters and crystallographic data are provided in Supporting Information. Absorption and decay effects were negligible. The structure was solved by direct methods, using SIR97$^{30}$ and refined using SHELXL97.$^{31}$ H atoms were observed in difference maps, but were constrained to be in idealized positions in the refinement. OH hydrogen atoms are all disordered into two sites, all of which were treated as half populated. O-H distances were constrained to be 0.84 Å, but otherwise, these H positions were refined.
**Compound 4.4** A suspension of 10% Pd/carbon (0.69g) in 40 ml H₂O was added in a 250 ml round bottom flask. To this, a solution of NaBH₄ (1.46g, 0.014 mol) in 70 ml of H₂O was added. The mixture was stirred under Ar(g). A solution of 1,1-Bis (2,4-dihydroxy-3-nitrophenyl)ethane 4.1 (1g, 0.006 mol) in 22 ml of NaOH (3M) was added to the solution dropwise. The mixture was allowed to stir at room temperature for 24 h.

After 24 h, the carbon was filtered out of the mixture. The filtrate was then acidified with 2M HCl, followed by neutralization using 3M NaOH. The mixture was extracted with ether (3X, 200 ml), dried with MgSO₄ then filtered. The filtrate was acidified with concentrated HCl, and stored at 4°C for 24 h. Thus affording a cloudy yellow layer, which was decanted. The solvent was removed from the decanted solution and dried to give 1.10 g of diamine tripod 4.4. ¹H NMR (250 MHz, DMSO-d₆) δ: 1.33 (d, J=6.45 Hz, 3H); 4.91 (q, J=6.95 Hz, 1H); 6.49 (d, J=8.4 Hz, 1H); 6.82 (d, J=8.65 Hz, 1H); 9.51 (s, 1H), 10.44 (s, 1H), 10.64 (s, 1H). ¹³C NMR (250 MHz, DMSO-d₆) δ: 20.5, 35.0, 110.0, 110.6, 121.2, 130.1, 150.0, 154.3. MALDI MS calcd for C₁₄H₁₆N₂O₄: 274.0 m/z; observed: 276.29 m/z.

**Compound 4.6** A suspension of 10% Pd/carbon (0.25g) in 25 ml H₂O was added in a 250 ml round bottom flask. To this, a solution of NaBH₄ (0.54g, 0.015 mol) in 50 ml of H₂O was added. The mixture was stirred under Ar(g). A solution of 2,5-dinitrofluorescein 4.5 (1g, 0.002 mol) in 25 ml of NaOH (3M) was added to the solution dropwise. The mixture was allowed to stir at room temperature for 24 h.

After 24 h, the carbon was filtered out of the mixture. The filtrate was then acidified with 2M HCl, followed by neutralization using 3M NaOH. The mixture was extracted with ether (3X, 200 ml), dried with MgSO₄ then filtered. The filtrate was acidified with
concentrated HCl, thus affording a yellow solid, which immediately precipitated out of 
solution. The product mixture was then stored at 4°C for 24 h.

After 24 h, the solid was then filtered and dried under vacuum. The product was 
then isolated by flash column chromatography (gradient elution of 10% MeOH/ 90% 
DCM). The isolated product was dried to give 0.78g. 1H NMR (MeOH-d6) δ: 2.15 (s, 1H); 
6.75 (d, J= 8.807, 1H); 6.85 (d, J= 8.768, 1H); 7.28 (d, J= 6.125, 1H); 7.78 (m, 2H); 8.04 
(d, J= 7.008, 1H). 13C NMR (250 MHz, DMSO-d6) δ: 36.4, 108.3, 111.9, 115.6, 126.5, 
127.7, 129.6, 130.0, 130.7, 132.3, 143.0, 147.2, 150.1, 169.2. MALDI MS calcd for 
C20H14N2O5: 362.3 m/z; observed: 362.04 m/z.

4.9 References


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4.7 Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. 

49, 1966.


4.14 Work on characterizing 4.8a is currently in progress.


CHAPTER 5

THE SYNTHESIS OF A NEW CATIONIC CHIRAL SURFACTANT

5.1 Introduction

Surfactant molecules consist of a polar or ionic group (head) and a hydrophobic tail.\textsuperscript{5.1} At low concentrations, surfactants are dispersed in solution.\textsuperscript{5.2} However, at higher concentrations, above what is known as the critical micelle concentration (CMC),\textsuperscript{5.2} self-assembly occurs and micelles are formed. Thus, “normal” micelles consist of a hydrophobic core, with the polar groups at the surface. The average number of surfactants molecules which form a micelle is defined as the aggregation number (N). Small micelles typically have N values in the range of 40-140.\textsuperscript{5.3} Surfactants are classified according to the type of polar head group, i.e. anionic (R-X\textsuperscript{−}M\textsuperscript{+}), cationic (R-N\textsuperscript{+}(CH\textsubscript{3})\textsubscript{3}X\textsuperscript{−}), zwitterionic (R-N\textsuperscript{+}(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}X\textsuperscript{−}), or non-ionic (R-(OCH\textsubscript{2}CH\textsubscript{2})\textsubscript{n}OH), where R is a long aliphatic chain; M\textsuperscript{+} is typically a metal ion; X\textsuperscript{−} is typically a halogen, carboxylate, sulfonate or sulfate, and the subscript “n” is an integer.\textsuperscript{5.3,5.4}

The structure of the micelle is determined by an equilibrium between repulsive forces (ionic) and short-range attractive forces (van der Waals). The size and shape of the micelle is somewhat uncertain and has been discussed and debated on in the past.\textsuperscript{5.5-5.10} Despite the varying views of micelles in terms of size and shape, neutron small-angle scattering experiments on sodium dodecyl sulfate (SDS) and other ionic micelles support that of a spherical micelle.\textsuperscript{5.11-5.13}

It has been established that dynamic equilibria between surfactant monomers and micelles inhibit accurate estimation of the shape of the micelle.\textsuperscript{5.14} For this reason, Kammer and Elias\textsuperscript{5.14} suggested to lock the micellar structure by polymerizing the amphiphiles which make up this structure. This process requires that the surfactants contain...
polymerizable groups. Past studies suggest that polymeric surfactants possess properties similar to conventional (non-polymeric) micelles.\textsuperscript{5.15-5.16} Moreover, due to the covalent bonding of polymeric surfactants, some unique properties and potential applications exist in areas such as analytical separations, catalysis, and drug delivery systems. Some of the differences between polymeric surfactants and conventional micelles are outlined in Table 5.1.

Table 5.1 Properties of Polymeric Surfactants Compared to Conventional Micelles

<table>
<thead>
<tr>
<th>POLYMERIC SURFACTANTS</th>
<th>CONVENTIONAL MICELLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenous: can be purified due to stability</td>
<td>Heterogeneous: cannot be purified due to dynamic equilibrium</td>
</tr>
<tr>
<td>Stable below CMC</td>
<td>By definition, unstable below CMC</td>
</tr>
<tr>
<td>Stable below CMC</td>
<td>Micelle concentration varies with concentration of organic solvent</td>
</tr>
<tr>
<td>Stable in presence of inclusion molecules such as cyclodextrins</td>
<td>Micelle concentration varies with concentration of inclusion molecules such as cyclodextrin due to inclusion of monomer</td>
</tr>
<tr>
<td>Properties can be manipulated and then fixed through polymerization</td>
<td>Properties can be manipulated, but not fixed</td>
</tr>
</tbody>
</table>

Another major comparison of polymeric surfactants to conventional micelles is that polymeric surfactants must be synthesized. Numerous synthetic organic reagents are produced and used because of their many advantages over naturally occurring reagents.\textsuperscript{5.13,5.15}

The separation of enantiomeric mixtures into individual optical isomers is one of the most challenging problems in analytical chemistry. Many researchers have focused much of
their careers into understanding and achieving these challenging problems.\textsuperscript{5.16-5.18} This interest focuses on practical considerations which are important to many areas of science, particularly the pharmaceutical and agricultural industries. For example, it is apparent that many drugs are chiral and therefore most formulations of these chiral drugs involve racemic mixtures rather than a pure form of the drug. The problem is that one optical form of a racemic mixture may be medicinally useful while the other optical form may be very toxic, as in the case of thalidomide.\textsuperscript{5.19-5.20} In other cases, one form may have no medicinal value or an entirely different medicinal property. These observations have resulted in the recent release of new FDA guidelines regulating the marketing of chiral drugs. Such regulation has suggested a potential for growth in the chirotechnology industry, particularly in the area of chiral drug separations.\textsuperscript{5.21}

The concerns with optical purity have resulted in chiral drugs being extensively evaluated prior to large-scale manufacturing. These evaluations have focused on a heightened concern for drug efficacy and a minimization of the toxic side-effects which may be attributed to a particular enantiomer or to the interaction of both enantiomers in a racemic mixture. The resolution of individual optical isomers has in the past required considerable time, effort, and expense. Thus, there continues to be a growing need for the development of new methodologies for improved chiral separations.

A continuous effort is being made by an analytical group at Louisiana State University toward the development of organized media for better analytical measurements. This effort is primarily in the area of separation science via the utilization of polymeric surfactants. To date, most of their studies have employed anionic micelles. The anionic micelles have proved fruitful for analyses of cationic and neutral analytes, however they were sometimes limited for the analyses of anionic analytes due to charge repulsion. A solution to this problem is the use of cationic micelles. To this end, we are working in
collaboration with an analytical group at Louisiana State University in order to synthesize new cationic chiral surfactants.

Herein, the synthesis of two new cationic chiral surfactants is presented. The surfactants will subsequently be polymerized by the analytical group and utilized for chiral separation via capillary electrochromatography (CEC). This is achieved by flashing a capillary which has been coated with silanol groups. Following coating of the cationic polymer the capillary will be coated with an anionic polymer to achieve a negative-positive, negative-positive effect (Figure 5.1).

**Figure 5.1** Scheme of the capillary profile. Capillary wall consisting of silanol groups is represented in layer (1), cationic polymeric surfactant (2), anionic surfactant (3)

**5.2 Synthesis of A New Chiral Cationic Surfactant**

The synthesis of L-arginine methyl ester surfactant is described in Scheme 5.1. The target compound 5.3 is achieved (70% yield) by reacting L-arginine methyl ester 5.1 and
undecylenic acid 5.2 in the presence of isobutyl chloroformate and N-methylmorpholine in THF.

$$\text{H}_2\text{N} - \begin{array}{c} \equiv \text{N} \end{array} - \text{H} \quad \text{O}$$

5.1

$$\text{H}_2\text{N} - \begin{array}{c} \equiv \text{N} \end{array} - \text{H} \quad \text{O}$$

5.2

[N-methylmorpholine, THF 70%]

$$\text{Cl} - \begin{array}{c} \equiv \text{C} \end{array} - \text{O}$$

Scheme 5.1 Synthesis of L-arginine methyl ester surfactant 5.3

In order to polymerize the surfactant for utilization in capillary electrochromatography separations a certain degree of solubility is necessary. Currently, these studies are ongoing in order to achieve effective polymerization.

5.3 Conclusion and Future Work

A new cationic chiral surfactant 5.3 has been synthesized. The surfactant will be polymerized by collaborators and examined as mobile phase additives to achieve chiral separations. Polymeric surfactants are stable under many conditions where normal micelles are known to decompose, as a result of this it is believed that a polymeric chiral surfactant will have stronger chiral recognition properties than a conventional (non-polymerized) chiral micelle.

In order to synthesize a surfactant with a higher degree of solubility, the L-arginine methyl ester monomethyl ether surfactant 5.12 was proposed. This surfactant should prove
to have better solubility as a result of the presence of the glycol group. Scheme 5.2 describes the synthesis of target compound 5.7.

Scheme 5.2 Synthesis of compound 5.7

N-Boc-N-nitro-L-arginine 5.4 would be used as a starting material for this synthesis. Compound 5.4 can then be reacted with trimethylene glycol mono methyl ether 5.5 in the presence of DMAP 4-(Dimethylamino)-pyridine, DCC 1,3-Dicyclohexylcarbodiimide, and HOBT 1-Hydroxybenzotriazole in DMF to yield 5.6. Compound 5.6 would be subsequently deprotected in TFA and chloroform to obtain 5.7. After coupling 5.7 with undecylenic acid in the presence of isobutyl chloroformate and N-methylmorpholine in THF, compound 5.8 can be produced. Compound 5.8 then undergo catalytic hydrogenation to form the target compound 5.9 (Scheme 5.3). As a result of synthesizing the proposed surfactant 5.9, the time spent on optimizing the solubility properties could be negated.
Scheme 5.3 Synthesis of L-arginine methyl ester monomethyl ether surfactant 5.8

5.4 Experimental Section

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. Analytical thin-layer chromatography (TLC) was performed using general purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 µm particle size, 60 Å). All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD$_3$OD or DMSO-$d_6$ on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All δ values are reported with (CH$_3$)$_4$Si at 0.00 ppm or DMSO at 2.45 ppm as references.

Compound 5.3 To a solution of the undecylenic acid (1.43 ml, 7.08 mmol) in dry THF at 20°C, N-methylmorpholine (0.65 ml, 5.9 mmol) and isobutyl chloroformate (0.765 ml, 5.9 mmol) was added. The mixture was stirred at that temperature for 15 minutes, followed by the addition of L-arginine methyl ester (1.54g, 5.9 mmol) and sodium bicarbonate (0.50g, 5.9 mmol) in 15 ml of water at 0°C. Stirring was continued at 0°C for 1 hour. After 1 hour, the solvents were removed and the product was dried under vacuum. The product purified
by column chromatography (gradient elution of 10% MeOH/90% Chloroform). The isolated product was dried to give 1.15 g. 

$^1$H NMR (MeOH) $\delta$: 1.34 (m, 12H); 1.63 (m, 6H); 2.02 (t, $J=6.905$, 2H); 2.25 (t, $J=14.722$, 2H); 3.72 (s, 3H); 4.92 (t, $J=1.27$, 1H); 5.80 (m, 1H). $^{13}$C NMR (250 MHz, MeOH-d$_6$) $\delta$: 25.5, 26.1, 29.3, 29.5, 29.7, 29.8, 34.2, 36.5, 41.5, 52.5, 54.8, 114.6, 139.5, 157.7, 173.4, 175.2. MALDI MS calcd for C$_{18}$H$_{35}$N$_4$O$_3$: 355.2 m/z; observed: 355.98 m/z.

5.5 References


5.8 Harkins, W. D. J. Chem. Phys. 1948, 16, 156.


APPENDIX A: CHARACTERIZATION DATA FOR COMPOUND 2.7 AND 2.8

Figure A.1  $^1$H NMR of Compound 2.8

A.2  CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.7

data_2.7
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;
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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_symmetry_cell_setting 'Orthorhombic'

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'-x, -y, -z'
'x-1/2, y, -z-1/2'
'-x-1/2, y-1/2, z-1/2'
'x, -y-1/2, z'

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_diffrn_reflns_number  7642
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H1B H 0.7715(17) 0.152(3) 0.050(3) 0.039 Uiso 1 1 d . .
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and torsion angles; correlations between esds in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell esds is used for estimating esds involving l.s. planes.

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C1 H1B 0.95(2) . ?
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S2 C3 1.781(2) . y
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C2 H2A 1.06(3) .
C2 H2B 0.95(2) .
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O2 S1 O2 113.45(12) 8_565 . y
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O2 S1 C1 106.11(8) 8_565 .
O2 S1 C1 106.11(8) . y
S1 C1 H1A 105.8(18) .
S1 C1 H1B 107.2(13) .
H1A C1 H1B 109.6(15) .
C3 S2 C3 101.31(15) . 8_575 y
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S2 C2 H2B 106.1(13) .
H2A C2 H2B 114.7(16) .
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S2 C3 H3B 106.4(15) .
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H3A C3 H3C 115(2) .
H3B C3 H3C 111(2) .

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A.4 CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.8

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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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'x-1/2, y, -z-1/2'
'x, -y-1/2, z'

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on F, with F set to zero for negative F^2^>. The threshold expression of
F^2^ > 2\sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
not relevant to the choice of reflections for refinement. R-factors based
on F^2^ are statistically about twice as large as those based on F, and R-
factors based on ALL data will be even larger.
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MOLECULAR GEOMETRY

_allgeom_special_details

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C1 C2 C3 C4 2.6(2) . . . . ?
C2 C3 C4 O2 177.29(15) . . . . ?
C2 C3 C4 C5 -2.7(3) . . . . ?
O2 C4 C5 C6 -178.70(15) . . . . ?
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C3 C4 C5 C6 1.2(2) . . . . ?
O2 C4 C5 C9 -2.9(2) . . . . ?
C3 C4 C5 C9 177.06(15) . . . . ?
C4 C5 C6 C1 0.2(2) . . . . ?
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C6 C1 C7 C8 39.7(2) . . . . ?
C2 C1 C7 C8 -141.78(18) . . . . ?
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C4 C5 C9 C11 -81.35(19) ... ?
C6 C5 C9 C10 -29.8(2) ... ?
C4 C5 C9 C10 154.61(16) ... ?
C5 C9 C11 C16 -20.7(2) ... ?
C10 C9 C11 C16 104.92(19) ... ?
C5 C9 C11 C12 161.88(16) ... ?
C10 C9 C11 C12 -72.5(2) ... ?
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C9 C11 C12 O3 -5.2(3) ... ?
C16 C11 C12 C13 -2.5(3) ... ?
C9 C11 C12 C13 175.08(16) ... ?
O3 C12 C13 C14 -177.17(16) ... ?
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O4 C14 C15 C16 179.17(16) ... ?
C13 C14 C15 C16 -2.3(3) ... ?
O4 C14 C15 C17 -0.6(3) ... ?
C13 C14 C15 C17 177.90(17) ... ?
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APPENDIX B: MALDI, FAB AND CRYSTALLOGRAPHIC DATA FOR OLIGOMERS

**Figure B.1** MALDI data for Oligomers (asterisks indicate observed oligomeric peaks, see Table 3.4)

**FIGURE B.2** FAB data for Oligomers (asterisks indicate observed oligomeric peaks; see Table 3.4)
FIGURE B.3 FAB data for Oligomers (asterisks indicate observed oligomeric peaks; see Table 3.4)

FIGURE B.3 FAB evidence of xanthene moiety of oligomeric products
B.4 CRYSTALLOGRAPHIC DATA FOR COMPOUND RESORCINOL FORMALDEHYDE OLIGOMERS

data_resorcinol-formaldehyde oligomer

#==================================#

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;?

_chemical_name_common ?
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'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
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  '-x, -y, -z'
  'x, -y, z-1/2'
  '-x+1/2, -y+1/2, -z'
  'x+1/2, -y+1/2, z-1/2'

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F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
not relevant to the choice of reflections for refinement. R-factors based
on F^2^ are statistically about twice as large as those based on F, and R-
factors based on ALL data will be even larger.
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C13 0.047(2) 0.036(2) 0.044(2) -0.0063(17) 0.0186(17) -0.0045(17)
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MOLECULAR GEOMETRY

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C13 C8 C7 121.9(3) . . ?
C9 C8 C7 121.4(3) . . ?
O3 C9 C10 120.0(3) . . ?
O3 C9 C8 118.1(3) . . ?
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APPENDIX C: CHARACTERIZATION DATA FOR COMPOUND 4.4 AND 4.6

FIGURE C.1: $^1$H NMR of Compound 4.4

FIGURE C.2: MALDI data for compound 4.4
C.3 CRYSTALLOGRAPHIC DATA FOR COMPOUND 4.4

data_compound 4.4

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MOLECULAR GEOMETRY

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C13 C12 N2 117.7(2) . . ?
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O4 C13 C12 114.7(2) . . ?
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FIGURE C.4: $^{1}$H NMR of compound 4.6

FIGURE C.5: MALDI MS data for compound 4.6
APPENDIX D: CHARACTERIZATION DATA FOR SURFACTANT

FIGURE D.1 $^1$H NMR of Compound 5.3

FIGURE D.3 MALDI data for compound 5.3
APPENDIX E: LETTERS OF PERMISSION

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Sincerely,

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Phone: (225) 578-9696
Fax: (225) 578-3458
E-mail: rjohn17@lsu.edu
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VITA

Rolanda Jeanette Johnson was born in Baton Rouge, Louisiana on July 29, 1977. She graduated with a Bachelor of Science degree in chemistry from Southern University in Baton Rouge, Louisiana. At Southern University she was the recipient of many awards and honors, of which included being an Honors College graduate and a Timbuktu Academy Scholar. In 1999, Rolanda was awarded the Huel D. Perkins Fellowship which afforded her the opportunity to be enrolled in the doctoral program at Louisiana State University in Baton Rouge, Louisiana. While at LSU, she has been involved in many projects under the supervision of Dr. Robert Strongin, giving support to her research group and other groups in the Chemistry Department. She has been involved in mechanistic studies and the synthesis of indicators and materials for chiral separation. In 2003 she was selected as a participant at the Procter and Gamble Research and Technical Careers in Industry Conference. She is a member of the American Chemical Society and the National Organization for the Professional Advancement of Black Chemist and Chemical Engineers. Rolanda Jeanette Johnson is currently a candidate for the degree of Doctor of Philosophy in organic chemistry, which will be awarded at the May 2004 Commencement.