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DETECTION OF IONS AND SMALL MOLECULE TOXICANTS IN AQUEOUS
MEDIA USING NEW COLORIMETRIC AND FLUORIMETRIC METHODS

BY

TERESA LOUISE MAKO

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

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DOCTOR OF PHILOSOPHY DISSERTATION

OF

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UNIVERSITY OF RHODE ISLAND

2019

CHAPTER 1 ABSTRACT

Ultrasensitive Detection of Nitrite through Implementation of *N*-(1-Naphthyl)ethylenediamine-Grafted Cellulose into a Paper-Based Device

Reported herein is the immobilization of *N*-(1-naphthyl)ethylenediamine on cellulose via an epichlorohydrin-based covalent attachment and the implementation of the functionalized cellulose into an ultrasensitive, paper-based device for nitrite detection. There is high demand for affordable, robust, sensitive, selective, and user-friendly detection methods for nitrite, a nutrient which is harmful at high concentrations in both marine environments and physiological systems. The reported functionalization procedure resulted in a 12.9-fold higher functionalization density than previously reported procedures using epichlorohydrin, and the subsequent device allows for nitrite detection limits in synthetic freshwater and real seawater of 0.26 μM and 0.22 μM , respectively. The sensor is efficient in a wide range of temperature, humidity, turbidity, and salinity conditions and was successfully applied to real water samples.

CHAPTER 2 ABSTRACT

Highly Sensitive and Subtraction-Free Dual Detection of Nitrate and Nitrite using the Griess Assay and a Paper-Based Device

Reported herein is the development of a novel paper-based sensor for the dual detection of nitrate and nitrite, using the *N*-(1-naphthyl)ethylenediamine-functionalized paper disclosed in Chapter 1. The detection of nitrate requires that nitrate be reduced to nitrite before reaction with indicator molecules. The majority of colorimetric and spectrophotometric detection schemes cannot differentiate reduced nitrate from any nitrite present in the sample. This compounded sensor readout requires the subtraction of nitrite signal in order to quantify nitrate in the sample which is difficult to accomplish with the naked eye. However, the immobilization of *N*-(1-naphthyl)ethylenediamine in the detection zones and the subsequent immobilization of the colored product has allowed for a subtraction-free nitrate readout. With the introduction of a cadmium/platinum chloride reduction zone into the sensor, this subtraction-free method has achieved nitrite and nitrate detection limits of 1.1 μM and 0.61 μM, respectively.

CHAPTER 3 ABSTRACT

Design, Implementation, and Evaluation of Paper-Based Devices for the Detection of Acetaminophen and Phenacetin in an Advanced Undergraduate Laboratory

Reported herein is a multi-disciplinary experiment for senior-level undergraduate teaching laboratories in the synthesis of the analytes acetaminophen and phenacetin, the fabrication of paper-based devices using low-complexity techniques, and the application of these devices for successful qualitative and quantitative detection of the analytes. This experiment includes elements of organic, analytical, and materials chemistry, as well as mechanical engineering, and provides a strong pedagogical experience for the undergraduate student participants. The experiment was tested over two years in an Advanced Organic Laboratory, and 90% of students over the two years successfully completed all experimental objectives. The modular nature of the reported experiments and inexpensive costs of materials and instrumentation significantly enhances the practical applicability of this experiment and the likelihood of widespread adaptation.

CHAPTER 4 ABSTRACT

Supramolecular Luminescent Sensors

There is great need for stand-alone luminescence-based chemosensors that exemplify selectivity, sensitivity, and applicability, and that overcome the challenges that arise from complex, real-world media. Discussed herein are recent developments toward that goal in the field of supramolecular luminescent macrocycle chemosensors. Specific focus is placed on the development of new macrocycle hosts since 2010, coupled with considerations of the underlying principles of supramolecular chemistry.

CHAPTER 5 ABSTRACT

A Polycationic Pillar[5]arene for the Binding and Removal of Organic Toxicants from Aqueous Media

The ability to bind and detect small molecule analytes with high levels of selectivity, sensitivity and broad applicability for a variety of analytes in multiple complex environments is an essential goal in analytical chemistry, with applications in public health, environmental remediation, and medical diagnostics. The use of supramolecular chemistry to accomplish such detection, by binding a target analyte in a supramolecular host and transducing that binding into a measurable signal, has notable advantages, including straightforward tunability of the supramolecular sensor as well as the ability to rationally design highly effective hosts through an understanding of non-covalent interactions in supramolecular complexes. Reported herein is the design and use of pillar[5]arenes to accomplish precisely such supramolecular detection. A water-soluble pillar[5]arene containing ten cationic peripheral arms bound small molecule toxicants in their hydrophobic cores with association constants on the orders of 10^5 - 10^6 M⁻¹. When bound to a cationic exchange resin, the pillar[5]arene host allowed for effective toxicant removal and potential applications in water purification systems.

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CHAPTER 1 PREFACE

Ultrasensitive Detection of Nitrite through Implementation of N-(1-naphthyl)ethylenediamine-Grafted Cellulose into a Paper-Based Device includes contributions from Adelaide Levenson. This work, in combination with Chapter 2, is in preparation for submission to a peer-reviewed journal.

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CHAPTER 1

Ultrasensitive Detection of Nitrite through Implementation of *N*-(1-Naphthyl)ethylenediamine-Grafted Cellulose into a Paper-Based Device

1.1. Introduction

There is high demand for affordable, robust, sensitive, selective, and user-friendly detection methods for nitrite, a nutrient which is harmful at high concentrations in both marine and physiological systems. Due to the detrimental nature of nitrite to human health,¹ environmental well-being,² and global climate^{3,4} there is a great need for careful monitoring and control of nitrite and related nutrients, such as nitrate.^{5,6} These nutrients are introduced in large quantities into the environment and groundwater supplies by poor wastewater management, agricultural fertilizer use, and contaminating industrial processes.⁷⁻⁹ The ingestion of nitrite, and the endogenous conversion of consumed nitrate to nitrite,⁸ can negatively impact human health in a number of ways, including through the transformation of hemoglobin to methemoglobin via a reaction with nitrite, leading to reduced oxygen transport efficiency^{1,10,11} and the formation of carcinogenic *N*-nitroso-compounds.^{12,13} While these effects of nitrite and nitrate typically occur at low ppm levels, the maximum contaminant level (MCL) for nitrite in drinking water supplies legislated by the US EPA is 1 ppm (21.7 μ M).¹⁴ Therefore, ppb level detection methods are desirable for monitoring nitrite concentrations before they reach dangerous levels.

In the past century, the global nitrogen cycle has been disrupted by nitrogen-based pollution and CO₂-driven ocean acidification.^{3,4} In marine environments, even

miniscule, low ppb local amounts of nitrogen-based pollutants can lead to large fluxes in the nitrogen cycle, which in turn lead to coastal eutrophication, toxic algal blooms,¹⁵⁻¹⁹ hypoxic dead zones,²⁰ marine life toxicity,²¹⁻²³ and increases in the rate of release of the greenhouse gas N₂O into the atmosphere.²⁴ Analyses of the global ocean condition are limited, however, due to sparse measurements and lack of nitrogen influx quantification, leading to a need for highly portable and user-friendly sensors that can provide accurate, on-site characterization of nitrogen-based pollutants such as nitrite.²⁴

While nitrite detection at ppb levels can be accomplished in laboratory settings using spectroscopic techniques,²⁵ such techniques are not easily translocated for on-site, real-time measurements; they are expensive and require large instrumentation; and they are not easily utilized by citizen scientists. Most commercially available paper-based devices, while sufficient for the monitoring of drinking water supplies, cannot detect levels that are relevant for environmental monitoring, rely on qualitative comparisons to color charts rather than quantitative methods, and can have “bleeding” of reagents into the aqueous sample, compromising system sensitivity and ultimate system performance. Thus, a user-friendly and easily transported uniform system for the quantitative, colorimetric detection of nitrite across a wide concentration range is desired for widespread field measurements.²⁴

Reported herein is the development and implementation of a newly designed paper-based device, shown in Figure 0.1, to meet the aforementioned criteria, using an immobilized nitrite-selective indicator which directly enables the ultrasensitive (low ppb) detection of nitrite in aqueous media.

Figure 0.1. (a) An Adobe Illustrator generated image of the paper-based device; (b) a scanned image of the device with immobilized indicator after exposure to 150 μM nitrite

1.2. Paper-Based Device Design

Colorimetric nitrite detection schemes typically utilize two indicators, sulfanilamide and *N*-(1-naphthyl)ethylenediamine, termed the “Griess reagents”, which form a highly colored azo dye in the presence of nitrite (Figure 0.2).²⁶ Several paper-based devices^{27,28} for nitrite detection have been reported in recent literature,^{29,30,31} allowing for detection limits as low as 1.0 μM (46 ppb),³⁰ and 0.65 μM (30 ppb)³¹ which is still too high for real-world detection applications. Most of these devices suffer from poor device stability, with the Griess reagents degrading on the order of several days, which further limits long-term system performance.^{29,30}

Figure 0.2. *N*-(1-naphthyl)ethylenediamine and sulfanilamide are commonly used “Griess reagents” for the colorimetric detection of nitrite via the formation of a highly colored azo compound²⁶

In order to achieve a significant increase in sensitivity towards nitrite detection using a paper-based device, we envisioned a device that would allow a large sample volume to interact with the detection zone without dilution of the indicators or colored product due to solution flow or runoff. This was accomplished by the immobilization of a single indicator, and thus the colored product, at the detection zone. The difference between mobile and immobile indicator, shown in Figure 0.3, is the diffuse color obtained via transportation of the colored product throughout the length of the device with the mobile chromophore (Figure 0.3a) in contrast to the darker, localized coloration of the detection zone with the immobile indicator (Figure 0.3b). Of the two chromophores necessary for nitrite detection, *N*-(1-naphthyl)ethylenediamine was chosen as the molecule to graft to cellulose because sulfanilamide and nitrite react first to form a diazonium salt³² before the reaction with *N*-(1-naphthyl)ethylenediamine can occur. While immobilization of both indicators was considered, added difficulties arose from the necessary sulfanilamide protection before functionalization and sulfanilamide deprotection once

bound to the cellulose. Additionally, distance between potential functionalization sites and reduced flexibility of species upon binding may lead to inhibition of reaction between the two indicators.

Figure 0.3. Comparison of (a) mobile and (b) immobile *N*-(1-naphthyl)ethylenediamine when treated with 150 μ M nitrite

The paper-based device, shown in Figure 0.4, was designed with a sulfanilamide/nitrite sample mixing zone, followed by a *N*-(1-naphthyl)ethylenediamine-functionalized cellulose “bridge” detection zone, and ending with an extended wicking channel, which allows for the majority of added sample to flow past and interact with the immobilized chromophore. To integrate the immobilized *N*-(1-naphthyl)ethylenediamine into the device, the “bridge” detection zone was pre-printed with wax barriers then functionalized with *N*-(1-naphthyl)ethylenediamine prior to adherence to the device. Details about the extensive device architecture optimization studies can be found in the Supporting Information.

Figure 0.4. Expanded view of optimized device architecture

1.3. Functionalization of Cellulose

Immobilization of small molecules to cellulose has been previously achieved using a variety of methods,³³⁻⁴⁰ although only one example of functionalized cellulose for nitrite detection, using 1-naphthylamine, has been reported.⁴¹ This method, however, relied on procedures that were chemically detrimental to cellulose, utilized a carcinogenic chromophore (1-naphthylamine),¹⁸ and achieved low ppb detection only via absorbance spectroscopy or by treating the paper repeatedly with sample solution. A more favorable approach for the immobilization of *N*-(1-naphthyl)ethylenediamine is the use of the linker epichlorohydrin, which has been reported in the grafting of small molecules⁴²⁻⁴⁴ and macrocycles^{45,46} to cellulose, typically using aqueous sodium hydroxide conditions.⁴⁴ However, under these conditions, epichlorohydrin is known to undergo hydrolysis⁴⁷⁻⁵⁰ or form other unfavorable side products⁵¹ due to the presence of a strongly nucleophilic base and a nucleophilic solvent. Additionally, *N*-(1-

naphthyl)ethylenediamine has poor water solubility and degrades readily in the presence of water. Thus, new, more mild conditions were investigated using organic solvents and non-nucleophilic bases.

Grafting of cellulose with *N*-(1-naphthyl)ethylenediamine was achieved following conditions shown in Figure 0.5, using epichlorohydrin as a linker in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetonitrile, with a pre-functionalization sonication^{52,53} step designed to minimally degrade the cellulose to provide more sites for grafting.⁵⁴⁻⁵⁶ These conditions were superior, in terms of *N*-(1-naphthyl)ethylene diamine functionalization density, to the aforementioned aqueous sodium hydroxide conditions^{37,40} as indicated by both colorimetric and fluorimetric analyses. Detailed reaction optimization studies and procedures for colorimetric and fluorimetric analyses can be found in the Supporting Information.

Figure 0.5. The optimized method for the functionalization of cellulose with *N*-(1-naphthyl)ethylenediamine for nitrite detection

The functionalization density of *N*-(1-naphthyl)ethylenediamine on cellulose was calculated using solid-state fluorescence spectroscopy, for which calibration curves are shown in Figure 0.6 for Whatman #1 and Figure 0.20 for Whatman 602h. The functionalization densities achieved using various conditions are shown in Table 0.1.

Conditions using DBU as a base and acetonitrile as a solvent (Condition 2, Table 0.1) were 4.8-fold more effective, in terms of functionalization density, than aqueous sodium hydroxide conditions (Condition 1, Table 0.1). Further optimization of the DBU/acetonitrile conditions, including the use of sonication and Whatman 602h (Condition 4, Table 0.1), increased the functionalization density to 12.9 times that of the aqueous sodium hydroxide conditions. The small pore size (0.2 μm) of Whatman 602h²⁸ may contribute to the higher functionalization density observed. Corroborating these results, a more intense color change was produced when the optimally-functionalized paper was treated with sulfanilamide and nitrite in acidic conditions.

Figure 0.6. Fluorescence calibration curve for the determination of functionalization density on Whatman #1. An exponential curve model (red line) with an equation of: $y = A_1^{(-x/t_1)} + y_0$ was fit to the data where A_1 : 17895950 ($\pm$ 835101); t_1 : -17878871 ($\pm$ 831434); y_0 : 0.07176 ($\pm$ 0.00495); and $R^2 = 0.9984$

A comparison of cellulose and functionalized cellulose fabricated under optimal conditions was conducted using confocal Raman microscopy (CRM) (see Figure 0.40). Changes in the Raman signal can be seen as decreases in the Raman peaks at 1120 and 2901 nm and new peaks which appear at 1608 and 1788 nm. These changes likely represent the *N*-(1-naphthyl)ethylenediamine that has been covalently attached to the cellulose substrate.

Table 0.1. Calculated functionalization densities, using the calibration curve shown in Figure 0.6, of *N*-(1-naphthyl)ethylenediamine-grafted cellulose

Condition	Functionalization Density ($\mu\text{g}/\text{mm}^2$)
1	0.00693 ($\pm$ 0.0028)
2	0.0333 ($\pm$ 0.0015)
3	0.0650 ($\pm$ 0.0047)
4*	0.0891 ($\pm$ 0.0076)

Grafting Conditions: (1) Whatman #1 (50 mg), *N*-(1-naphthyl)ethylenediamine (4.3 mass equiv. to cellulose), epichlorohydrin (1.5 equiv. to *N*-(1-naphthyl)ethylenediamine), and 2.0 M NaOH (10 mL), 50 °C for 18 hours. (2) Whatman #1 (50 mg), *N*-(1-naphthyl)ethylenediamine (4.3 mass equiv. to cellulose), epichlorohydrin (1.5 equiv. to *N*-(1-naphthyl)ethylenediamine), DBU (2.0 equiv. to *N*-(1-naphthyl)ethylenediamine) and acetonitrile (10 mL) 50 °C for 18 hours. (3) Whatman #1 (50 mg), *N*-(1-naphthyl)ethylenediamine (0.833 mass equiv. to cellulose), epichlorohydrin (3.3 equiv. to *N*-(1-naphthyl)ethylenediamine), DBU (3.0 equiv. to *N*-(1-naphthyl)ethylenediamine) and acetonitrile (7.3 mL), 55 °C for 72 hours. (4) Conditions shown in Figure 0.5. *calculated using fluorescence calibration curve for Whatman 602h (Figure 0.20)

Of note, the stability of the *N*-(1-naphthyl)ethylenediamine increased upon its grafting to cellulose because the readily oxidized primary amine was transformed into

a much more stable secondary amine (Figure 0.5). Fluorescence studies (Figure 0.7) showed minimal changes in fluorescence over a 110-day period where the functionalized paper was stored in a capped clear vial under ambient temperature and lighting. If *N*-(1-naphthyl)ethylenediamine degradation or oxidation had occurred, a decrease in fluorescence (Figure 0.39) and discoloration of the functionalized paper would be evident.

Figure 0.7. Comparison of the fluorescence of functionalized paper when first synthesized (day 0) and 110 days later

1.4. Detection and Quantitation Limits

The identity of the acid medium in which the sulfanilamide is dissolved and deposited onto the paper-based device is a key contributor to the limits of detection and quantitation of this system. Previous reports have suggested the use of citric³⁰ and phosphoric acids,²⁹ however careful screening of acids (see section 1.4.8) identified

sulfuric acid and hydrochloric acid as superior candidates. Figure 0.8 shows a comparison of 1.0 M citric, phosphoric, sulfuric, and hydrochloric acid conditions upon treatment with 0 to 15 μM concentrations of nitrite. Linear curve fitting was applied, and the slopes of the linear fit lines clearly indicate the superior detection ability promoted by 1.0 M hydrochloric acid conditions.

Figure 0.8. Comparison of nitrite detection calibration curves using different acidic media for sulfanilamide deposition.

Differences in pH between these acids likely contribute significantly to the observed acid effect. Citric acid and phosphoric acid, being weak acids, have pH values between 1 and 2 at 1.0 M, whereas sulfuric acid and hydrochloric acid are substantially more acidic, having pH values of 0 at 1.0 M. The increased concentration of hydronium ions provided by stronger acids, particularly HCl, likely allows for a more sustained acidic environment on the paper device, which is necessary for an efficient reaction between nitrite and the indicator molecules. This is supported by increasing concentrations of

phosphoric acid (i.e. decreased pH) leading to darker sensor readout (Figure 1.46). The polyprotic nature of the less-effective acids may also contribute to their decreased sensor readout. Additionally, it is suspected that this pH dependence is accompanied by effects from viscosity and sulfanilamide solubility. Sulfuric acid and phosphoric acid are substantially more viscous than HCl, and this increased viscosity could hinder the even rewetting of the paper by the sample and reduce the sample flow, leading to decreased and uneven sensor readout. Finally, sulfanilamide, was observed to be much more soluble in HCl than in any of the other acid media, which is significant as sulfanilamide must be dissolved by the sample solution during the assay.

A color readout scale for the detection of nitrite in ultrapure water using the optimal conditions is shown in Figure 0.9, and the nitrite calibration curve using sulfanilamide dissolved in 1.0 M hydrochloric acid is shown in Figure 0.10. The limits of linearity were found to be between 15 and 20 μM for all calibration curves. Thus, limits of detection and quantitation were calculated using exponential decay curve fitting in order to extend the upper limit of detection (see section 1.4.9). The limits of detection (LOD) and limits of quantitation (LOQ) calculated using exponential decay curve fitting are shown in Table 0.2, with the lowest LOD and LOQ values, 0.087 and 0.29 μM , respectively, obtained when using 1.0 M hydrochloric acid conditions.

Figure 0.9. Visual color readout of the nitrite detection calibration curve, in ultrapure water, using 1.0 M hydrochloric acid for sulfanilamide deposition. Images collected 10 minutes after sample addition using an EPSON V19 Perfection scanner

Figure 0.10. Nitrite calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M HCl solution. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 1.51896 (\pm 0.25611)$; $t = 88.93514 (\pm 18.64398)$; $y_0 = -0.51443 (\pm 0.25616)$; and $R^2 = 0.99898$

Table 0.2. Limits of detection (LOD) and limits of quantitation (LOQ) calculated using exponential decay curve fitting of nitrite calibration curves using different acid media for sulfanilamide deposition.

Acid	LOD (μM)	LOQ (μM)
1.0 M citric acid	0.84	3.33
1.0 M phosphoric acid	1.05	3.81
1.0 M sulfuric acid	0.42	0.77
1.0 M hydrochloric acid	0.087	0.29

Detection efficacy was next compared in synthetic freshwater⁵⁷ and a real water sample from the Sargasso Sea,⁵⁸ which differ in both salinity and trace ion content. Calibration curves in both of these media are shown in Figure 0.11, and it is clear that salinity has a substantial effect on

the readout of the detection zone (*vide infra*). Despite this, the limits of detection and quantitation in these media are similar to that in ultrapure water, as shown in

Table 0.3.

Figure 0.11. Nitrite calibration curves, in synthetic freshwater (grey, from 5 to 87.5 μM) and Sargasso seawater (red, from 5 to 50 μM) fit to exponential decay curves

However, as the initial LOD and LOQ values calculated are lower than the ranges of these calibration curves, additional, more accurate, low μM calibration curves were generated. These data were fit to linear curves, shown in Figure 0.12, and similar LOD and LOQ values, 0.26 μM and 0.69 μM for synthetic freshwater and 0.22 μM and 0.89 μM for Sargasso seawater, were obtained (Table 0.3).

Table 0.3. Limits of detection (LOD) and limits of quantitation (LOQ) using different conditions and different media

Media	Range	LOD (μM)	LOQ (μM)
Synthetic Freshwater	5-50 μM	0.12	0.42
Sargasso Seawater	5-87.5 μM	0.15	0.52
Synthetic Freshwater	0.05-5 μM	0.26	0.69
Sargasso Seawater	0.05-5 μM	0.22	0.89

Figure 0.12. Low concentration nitrite calibration curves (from 0.05 to 5 μM), in synthetic freshwater (grey) and Sargasso seawater (red) fit to linear curves

1.5. Interference Studies

1.5.1. Environmental Interference

As the end goal of this sensor development is on-site application, the robustness of these devices to typical environmental conditions must be examined.²⁸ Certain environmental factors, namely temperature, humidity, salinity, and turbidity, have the potential to dramatically impact device performance.

As indicated by the differences in calibration curve slopes between freshwater and seawater media (*vide supra*), salinity has significant influence on sensor readout, which has previously been reported with Griess-based detection using paper-based microfluidic devices.^{59,60} With 10 μM nitrite (blue, Figure 0.13), the sensor readout begins to change at 0.5% salt content, yet from 0.5% to 4.5% salt content, the sensor readout stays relatively constant. Similarly, the sensor readout at 50 μM (maroon, Figure 0.13) is constant from 1.0 to 4.5% salinity. This is confirmed by comparison to the sensor readout in synthetic freshwater (green bars, Figure 0.13) and Sargasso seawater (grey bars, Figure 0.13) that were used for the calibration curves (*vide supra*). These ranges encompass normal ocean saline ranges (3.0% to 3.5%),⁶¹ brackish (0.3% to 2.0%),^{62,63} and briny (3.5% to 7.5%)⁶⁴ waters. Higher salinities, up to 15%, also followed these trends, however, extremely hypersaline water (30%), akin to Dead Sea⁶⁵ or Great Salt Lake⁶⁶ waters, led to near complete degradation of sensor readout (Figure 0.61)

Figure 0.13. Comparison of sensor readout for samples of 50 μM (red) or 10 μM (blue) nitrite in various saline solutions. The bars indicate the upper and lower bounds of the same measurements in Sargasso seawater (grey bars) and synthetic freshwater (green bars) from the average and standard deviation values

The saturation of paper in high humidity conditions effects not only the amount of sample evaporation, but also the speed and rate at which the sample flows through the device channels.⁶⁷ Temperature has been previously found to have an effect on the reaction kinetics of the Griess reaction at low (10 °C) and high (40 °C) temperatures.⁶⁸ At nitrite concentrations of 50 μM and below, relative humidity did not affect device performance between a range of 14 and 91% (Figure 0.14a). However, upon examination of 100 μM nitrite, increasing relative humidity led to increased device performance (i.e. lower normalized green value). Temperature had the opposite effect on device performance, with a temperature of 45 °C leading to decreased sensor readout

at all nitrite concentrations examined (Figure 0.14b). These interferences are potentially due to changes in device flow rate, with increased humidity leading to less sample evaporation, slower flow rate, and a darker sensor readout, while increased temperatures lead to more sample evaporation, faster flow rate, and lighter sensor readout. Thus, for nitrite concentrations of 50 μM or lower, these sensors can reasonably be used at all relative humidity and between temperatures of 15 and 35 $^{\circ}\text{C}$.

Figure 0.14. Comparison of device readouts, using 0, 10, 50, or 100 μM nitrite solutions, at a range of a) humidity and b) temperatures

Turbid water samples, i.e. those with suspended particulate matter, often require filtration before analytical techniques can be performed, especially when using optical methods,⁶⁹ but also when using certain paper-based devices,²⁹ especially when highly colored particulate matter may interfere with sensor readout.⁷⁰ However, the filtration ability of the paper substrate used in these devices eliminates the need for pre-filtration procedures.⁷¹ Supporting this, sensor performance, shown in Figure 0.62, was unaffected by low, moderate, and high turbidities, which were mimicked using Kaolin clay.⁷²

1.5.2. Chemical Interference

A variety of cations and anions were examined for sensor interference, including those that are commonly found in seawater, such as Na^+ , K^+ , Mg^{2+} , Cl^- , and SO_4^{2-} ,⁷³ ions that may be found in trace amounts in seawater, such as F^- , Br^- , NO_3^- , PO_4^{3-} , Co^{2+} , Zn^{2+} ,^{74,75} or that have been previously reported to be detrimental to the Griess detection scheme, such as acetate,³⁰ Cu^{2+} ,⁷⁶ S^{2-} , and I^- .²⁵ Upon examination of nitrite samples with equal concentrations of potential anion interferents, I^- , CO_3^{2-} , $\text{S}_2\text{O}_3^{2-}$, SO_4^{2-} , and SO_3^{2-} were found to moderately impact the sensor readout (Figure 0.15). Additionally, the presence of the cations Al^{3+} and Zn^{2+} led to minimal readout interference at the low concentrations examined (Figure 0.16).

Figure 0.15. Comparison of sensor readouts for samples containing 50 μM sodium nitrite and 50 μM potential interferent anion

Figure 0.16. Comparison of sensor readouts for samples containing 50 μM sodium nitrite and 50 μM potential interferent cation

1.6. Environmental Sample Examination

Environmental samples from a variety of locations and containing differing levels of organic matter and suspended solids were successfully analyzed for the presence of nitrite using these devices, and nitrite concentrations were calculated using the appropriate calibration curve. The samples chosen were a home marine aquarium, which many current commercially available nitrite test strips are marketed towards, and the August 2017 Hurricane Harvey flood waters from Houston, Texas. Only minimal differences between filtered and unfiltered water samples from the same source were observed, further supporting the robustness of these devices towards turbidity and large particulate contamination (Figure 0.17). Confirmation of the quantification accuracy of these measurements will be conducted using Lachat ion chromatography.

Figure 0.17. Analysis and comparison of filtered (purple) and unfiltered (grey) real-world nitrite samples. The sensor readouts were compared to the appropriate calibration curves, pertaining to media type and estimated nitrite concentration, to calculate nitrite concentration: Home Aquarium: 5 – 50 μM Sargasso seawater; Houston 5 mi NW: 5 - 87.5 μM freshwater; Houston Downtown and Houston 5 mi SE: 0.05 – 5 μM freshwater.

1.7. Device Stability

Crucial to the commercialization and usability of such devices is their longevity. Although the covalent linkage of *N*-(1-naphthyl)ethylenediamine to cellulose effectively stabilizes that component of the Griess reaction (*vide supra*), the sulfanilamide component remains susceptible to degradation. Under ambient lighting and temperature conditions, the sulfanilamide was stable for less than 24 hours. Vacuum sealing of the device and storage in darkness did little to protect the sulfanilamide from degradation. Storage at $\leq 4\text{ }^{\circ}\text{C}$, however, extended the device lifetime to 3 days. This was determined both by sensor readout when treated with 50 μM nitrite solution (Figure 0.18), and by monitoring the discoloration of the sulfanilamide on the device prior to

use (Figure 0.64). These circumstances, very similar to component lifetimes reported by Jayawardane et al.³⁰ and Bhakta et al.,²⁹ are non-ideal, and further methods for sulfanilamide stabilization are currently underway.

Figure 0.18. Comparison of sensor readout, using 50 μM nitrite solution, after storage in different conditions: open air with light (grey), vacuum with light (red), vacuum with darkness (blue), and vacuum with refrigeration (green)

1.8. Conclusions

The procedure reported herein allows for the epichlorohydrin-based functionalization of cellulose with *N*-(1-naphthyl)ethylenediamine using new conditions that are 12.9-fold more effective than typical aqueous sodium hydroxide methods. The subsequent paper-based device implementing the functionalized cellulose allows for detection limits of 0.22 μM and 0.26 μM for nitrite in Sargasso seawater and synthetic freshwater, respectively, the lowest that have been seen using a colorimetric

paper-based device for this analyte, to the knowledge of the authors. The sensor readout is robust in a variety of environmental conditions and was successfully used to analyze several environmental samples without the need for prior sample filtration. In addition, grafting of *N*-(1-naphthyl)ethylenediamine to cellulose improved the stability of the *N*-(1-naphthyl)ethylenediamine in the presence of moisture and light.

We are continuing to advance this technology in several ways, including through the enhancement of sulfanilamide stability and device lifetimes, the implementation of a highly efficient nitrate detection scheme, and the application of a cell phone-based color analysis system.

1.9. Experimental

1.9.1. General Considerations

All chemicals and cellulose products were purchased through Fisher Scientific or Millipore Sigma and used as received. Synthetic freshwater was made following the EPA standard procedures.⁵⁷ Synthetic seawater with a salinity of 30.5 ppt was prepared using Red Sea Coral Pro Salt mix by dissolving 33.4 g of the salt mix in 1 L of ultrapure water. An ICP-MS analysis of the salt mixture was provided by Red Sea (Figure 0.19). Water from the Sargasso Sea (located in the North Atlantic near Bermuda, a typically low-nutrient environment⁵⁸) was filtered through a 0.2 μm filter to remove organic matter.

Name of product tested: Coral Pro Salt
Batch number: 1903170115

Tested element	Units	Acceptable Range	Batch Analysis
pH		8.2-8.5	8.30
Total Alkalinity	meq/l	4.15-4.45	4.24
Calcium Ca	mg/l	450-480	466.49
Magnesium Mg	mg/l	1350-1430	1389.82
Sulfur S	mg/l	870-930	883.00
Potassium K	mg/l	385-415	393.43
Bromine Br	mg/l	60-70	63.43
Strontium Sr	mg/l	8.5-10.5	10.11
Boron B	mg/l	4.45-4.95	4.73
Total ammonium NH ₄ /NH ₃	mg/l	≤0.1	≤0.1
Nitrate NO ₃	mg/l	≤0.3	≤0.3
Phosphate PO ₄	mg/l	≤0.03	≤0.03

Figure 0.19. ICP analysis provided by Red Sea MyBatch for the Coral Pro Salt mix used to create synthetic seawater. All numbers are based on a 35 ppt solution

Colorimetric analyses were conducted by treating the functionalized paper with an acidic solution of sulfanilamide and nitrite, to form the azo dye, and allowing the device to incubate for 10-30 minutes. The sensors were imaged using an EPSON V19 Perfection flat-bed scanner and the images were analyzed using ImageJ software (<https://imagej.nih.gov/ij/download.html>) on an 8-bit color scale (white = 255 a.u., black = 0 a.u.). Using ImageJ, the detection zone coloration was separated into average RGB channels and converted into Normalized Green Value (NGV) by dividing the Green Value (the color value that changed the most with an increase in magenta color) by Red Value (the color value that changed the least with an increase in magenta color). Pixel standard deviation (PSD), a measure of pixel color homogeneity⁷⁷ that was provided by the program was also used as a metric for analysis.

The fluorescence studies were conducted using a BioTek Instruments Synergy H1 microplate reader with the following parameters: excitation: 300 nm,

emission: 340 to 575 nm, gain: 45; data interval: 1 nm, read height: 10.68 mm. Each sample was measured four times from which averages of fluorescence integration were calculated and used for further comparisons. Fluorescence integrations were performed using OriginPro 2018 or OriginPro 2019. All colorimetric and fluorimetric experiments were repeated with at least three paper samples to ensure the reproducibility of the functionalization techniques and the precision of the colorimetric detection.

The paper-based devices were designed using Adobe Illustrator and printed using a Xerox ColorQube 8580. Fellowes® self-adhesive sheets and FLEXcon® FLEXmount® SELECT™ DF051521 clear 0.5 poly perm adhesive/ double faced liner were cut to the desired sizes using a Graphtec CE6000-40 cutting plotter.

1.9.2. Calibration Curve for Degree of Functionalization Calculations

To each of 84 wells of a BioTek 96 well plate was added a circular 6 mm piece of Whatman #1 or Whatman 602h. A solution of 0.52 mg naphthylethylenediamine in 1.0 mL ultrapure water was created, then diluted by serial dilution to concentrations of 0.48, 0.44, 0.40, 0.36, 0.32, 0.28, 0.24, 0.20, 0.16, 0.12, 0.08, 0.064, 0.048, 0.032, 0.016, 0.008, 0.004, and 0.002 mg/mL. To the first four wells was added 5 μ L of the 0.52 mg/mL solution, to the second four wells was added 5 μ L of the 0.48 mg/mL solution, etc., until all wells were filled, with 5 μ L of ultrapure water added to the last four wells. The solutions were allowed to dry for 2 hours in the dark, then the fluorescence of each well was analyzed using the BioTek. The fluorescence integration of each spectrum (fluorescence intensity by wavenumber) was obtained using OriginPro2018, and average and standard deviation values were obtained. OriginPro2018 non-linear curve

fitting was applied to the data and an exponential curve fitting was obtained. Values for degree of functionalization were calculated using Excel Solver and the obtained equation. See Figure 0.6 for Whatman #1 calibration curve and Figure 0.20 for Whatman 602h calibration curve.

Figure 0.20. BioTek fluorescence calibration curve for degree of *N*-(1-naphthyl)ethylenediamine functionalization of Whatman 602h. An exponential curve model (red line) with an equation of: $y = A_1^{(-x/t_1)} + y_0$ was fit to the data where $A_1 = -15569867 (\pm 582332)$; $t_1 = 0.07208 (\pm 0.00392)$; $y_0 = 15864232 (\pm 588103)$; and $R^2 = 0.99839$

1.9.3. Optimized Procedure for Cellulose Functionalization

The paper to be functionalized was patterned using a wax printer to create a 2.5 x 10 mm hydrophilic lane with 3.75 x 10 mm hydrophobic barriers on each side. The wax was melted in a 120 °C oven for 2.5 minutes. To an Erlenmeyer flask bearing a 24/40 ground glass joint and a stirbar was added the paper to be functionalized, *N*-(1-naphthyl)ethylenediamine·HCl (NED) (0.833 w/w% to cellulose) and acetonitrile

(0.022 M to NED). This solution was sonicated for 30 minutes, then 1,8-diazabicyclo-[5.4.0]undec-7-ene (3.0 equiv. to NED) was added and the solution was heated to 50 °C for 30 minutes with gentle stirring at 100 rpm. Epichlorohydrin (3.3 equiv. to NED) was then added, a condenser was attached to the Erlenmeyer flask, and the solution was heated to 55 °C for 72 h. The solution was then cooled to room temperature. The supernatant was decanted, and the functionalized paper was washed thoroughly with acetonitrile (2x), distilled water (2x), 1.0 M HCl (2x, 1 min each), and distilled water (4x). The functionalized paper was collected on a Buchner funnel and vacuum was pulled through for 30 minutes until dry. The paper was further dried in an oven at 50 °C for 30 minutes, then stored in a capped vial away from direct light.

1.9.4. Device Construction and Application

All devices were printed in triplicate for easier comparison of identical measurements. The device was designed to hold 50 µL of sample solution, with a sulfanilamide/nitrite sample mixing zone prior to the detection zone, and with an extended wicking zone. A fan-shaped wicking zone was chosen to promote sustained liquid flow through the device without requiring an absorbent pad.⁷⁸ A white “lip” was incorporated at the beginning of the detection zone to facilitate color analysis, and coloration was analyzed only in the section of the detection zone above the white background as indicated in Figure 0.1b. Devices were patterned in the dimensions shown in Figure 0.21 using a wax printer, then melted in a 120 °C oven for 2.5 minutes. Lamination was found to increase color consistency of the detection zone, but no-heat laminate was required to avoid thermal degradation of sulfanilamide. Self-adhesive no-heat laminate was cut using a Graphtec vinyl cutter to the dimensions shown in Figure

0.22. The laminate was placed on the front of the device, then the device was flipped over and 5 μ L of a 50 mM sulfanilamide solution (8.6 mg sulfanilamide per 1.0 mL of 1.0 M HCl solution) was added at the location indicated on the device shown in Figure 0.1a. The solution was allowed to dry for 30 minutes, then the functionalized paper “bridge” was adhered using double-sided tape to the underside of the device (see Figure 0.4 for a visual depiction). An uncut piece of self-adhesive no-heat laminate was added to the underside of the device and the device was sealed using a pressure laminator. To the sample loading zone of the device was added 50 μ L of aqueous sample. The device was allowed to develop for 10 minutes, then placed on a flat-bed scanner for image collection. Alternatively, naked-eye detection was achieved within 60 seconds.

Figure 0.22. Laminate dimensions for optimized architecture of triplicate devices

1.9.6. Optimizations and Analyses – Paper Functionalization

1.9.6.1. Initial Functionalization Conditions. The paper to be functionalized was patterned using a wax printer with a 10 mm x 10 mm wax square with a 6 mm diameter hydrophilic circle in the center. The wax was melted in a 120 °C oven for 2.5 minutes. To an Erlenmeyer flask bearing a 24/40 ground glass joint and a stir bar was added 50 mg of the paper to be functionalized, NED (0.25 – 2.0 mass equiv. to cellulose) and acetonitrile (to achieve a concentration of 0.022 M NED). 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1 - 6.0 mol. equiv. to NED) was added and the solution was heated to 50 °C for 30 minutes with gentle stirring at 100 rpm. Epichlorohydrin (1.0 – 4.0 mol equiv. to NED) was then added, a condenser was attached to the Erlenmeyer flask, and the solution was heated to 50 °C for a specified amount of time (1 - 72 hr). After the required time period, the solution was cooled to room temperature. The supernatant was decanted, and

the functionalized paper was washed with acetonitrile (2x), distilled water (2x), 1.0 M HCl (2x, 1 min of gentle stirring each), and distilled water (4x). The functionalized paper was collected on a Buchner funnel and vacuum was pulled on the paper for 30 minutes until dry. The paper was further dried in an oven at 50 °C for 30 minutes, then stored in a capped vial away from direct light.

1.9.6.2. Initial Device Analysis Procedure. Fluorimetric measurements were conducted by removing the hydrophilic barrier using a 6 mm diameter hole punch and placing the paper circles into a 96 well plate for BioTek measurements. Initial colorimetric measurements were conducted using a rudimentary device shown in Figure 0.23 with the functionalized paper adhered using FLEXcon® FLEXmount® SELECT™ DF051521 clear 0.5 poly perm adhesive/ double faced liner. 5 µL of a 50 mM solution of sulfanilamide in citric acid was added to the functionalized paper, then allowed to dry for 30 minutes. 50 µL of nitrite solution was added to the sample loading zone, then allowed to develop for 30 minutes before the image was collected using an EPSON V19 Perfection flat-bed scanner. Optimal conditions analyzed by colorimetry are marked with an asterisk (*).

Figure 0.23. Simple wax-printed device for initial colorimetric analyses

Figure 0.24. Colorimetric comparison of bases used for the deprotonation of *N*-(1-naphthyl)ethylenediamine and cellulose using 15 ppm nitrite and 5 μ L of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA: *N,N*-diisopropylethylamine; DMAP: 4-dimethylaminopyridine

Figure 0.25. BioTek fluorimetric comparison of bases used for deprotonation of *N*-(1-naphthyl)ethylenediamine and cellulose. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA: *N,N*-diisopropylethylamine; DMAP: 4-dimethylaminopyridine

Figure 0.26. Colorimetric comparison of equivalents of DBU required for *N*-(1-naphthyl)ethylenediamine and cellulose deprotonation using 15 ppm nitrite and 5 μ L of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

Figure 0.27. BioTek fluorimetric comparison of equivalents of DBU required for *N*-(1-naphthyl)ethylenediamine and cellulose deprotonation. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

Figure 0.28. Colorimetric comparison of equivalents of epichlorohydrin required for linking *N*-(1-naphthyl)ethylenediamine to cellulose using 15 ppm nitrite and 5 μ L of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid

Figure 0.29. BioTek fluorimetric comparison of equivalents of epichlorohydrin required for linking *N*-(1-naphthyl)ethylenediamine to cellulose

Figure 0.30. Colorimetric comparison of equivalents of *N*-(1-naphthyl)ethylenediamine required for linking reaction using 15 ppm nitrite and 5 μ L of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid

Figure 0.31. BioTek fluorimetric comparison of equivalents of *N*-(1-naphthyl)ethylenediamine required for linking reaction

Figure 0.32. Colorimetric comparison of reaction time required for linking *N*-(1-naphthyl)ethylene diamine to cellulose using 15 ppm nitrite and 5 μ L of an 50 mM solution of sulfanilamide in 1.0 M phosphoric acid

Figure 0.33. BioTek fluorimetric comparison of reaction time required for linking *N*-(1-naphthyl)ethylenediamine to cellulose

Figure 0.34. Colorimetric comparison of paper type and sonication conditions at: a) 10 ppm nitrite or b) 0.5 ppm nitrite (conducted using optimized device)

Figure 0.35. Comparison, by fluorescence spectroscopy, of types of paper with and without sonication conditions (conducted using optimized device)

1.9.6.3. Reproducibility Studies. Reproducibility studies of the functionalization reaction were conducted in an effort to determine: 1) whether all pieces of paper in the

same reaction flask were functionalized comparably and 2) whether separate trials of the functionalization reaction produced the same results. For fluorimetric measurements, each sample was measured four times and the average fluorescence intensity or fluorescence integration values were compared with other trials.

Figure 0.36. Reproducibility studies using fluorescence spectroscopy of four pieces of cellulose that were functionalized simultaneously. Each piece of functionalized cellulose was measured four times and the average fluorescence intensity values for each piece were compared

Figure 0.37. Reproducibility studies by colorimetry between three functionalization trials, each conducted in triplicate, using 5 μ L of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid

Figure 0.38. Reproducibility studies by fluorescence spectroscopy between three functionalization trials, each comprised of three samples. Each piece of functionalized cellulose was measured four times and the average fluorescence integration values for each piece were compared

1.9.6.4. Stability Studies. The stability of the functionalized paper was analyzed through comparison of newly made functionalized paper to 110-day old functionalized paper. This was also compared to free *N*-(1-naphthyl)ethylenediamine and free *N*-(1-naphthyl)ethylenediamine that was dried on paper then degraded by exposure to UV light for 5 hours.

Figure 0.39. Fluorescence comparison of grafted *N*-(1-naphthyl)ethylenediamine (NED) (blue line) to a piece of cellulose with 5 μ L of a 1 mg/mL solution of *N*-(1-naphthyl)ethylenediamine (NED) dried on it before (red line) and after degradation for 5 hours under UV light and in open air (black line)

1.9.6.5. Confocal Raman Microscopy Analysis. Confocal Raman microscopy measurements were collected using a WITec alpha 300R confocal Raman spectrometer with a 532 nm CW laser. Objective: Zeiss EC Epiplan-Neofluar 50x / 0.8; objective magnification: 50.0; integration time: 1.05468 seconds; number of accumulations: 100. For each spectrum shown, eight sites were analyzed and averaged.

Figure 0.40. Confocal Raman Microscopy comparison of unfunctionalized cellulose (top) and functionalized cellulose (bottom) showing differences (indicated by boxes) between the two substances

1.9.7. Optimizations and Analyses – Device Architecture and Fabrication

See section 1.4.4. for general fabrication procedures. Optimizations of device architecture included: device channel width, *N*-(1-naphthyl)ethylenediamine-functionalized paper “bridge” width, and length of sulfanilamide incubation channel. Optimization of device fabrication protocol included: location of sulfanilamide deposition, amount of sulfanilamide deposited, and device incubation time (i.e. length of time between sample deposition and image collection). Device performance was analyzed by examining the colorimetric response of the devices to three different

concentrations of nitrite: 10, 45, and 200 μM . Conditions indicated with an asterisk (*) in the figures below were determined to be optimal.

Figure 0.41. Comparison of four device channel widths, 1.5, 2.0, 2.5, and 3.0 mm, with four functionalized paper lane widths, 2.0, 2.5, 3.0, and 3.5 mm, by colorimetry using 200 μM nitrite and 5 μL of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid. A device with a 3.0 mm wide channel paired with a lane 2.5 mm (*) gave the most optimal coloration (darkness and evenness). 1.5 mm and 2.0 mm devices were not used because the detection zone was too small to be accurately characterized visually, and 1.5 mm devices gave highly variable coloration of the detection zone (i.e. large error bars)

Figure 0.42. Comparison of the length of sulfanilamide incubation channel (distance between sample loading zone and detection zone) by colorimetry using 200 μM nitrite and 5 μL of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid. A 10 mm distance (*) was chosen for optimal device

Figure 0.43. Comparison, by colorimetry, of the sulfanilamide application site (sample loading zone, detection zone, or halfway between), using 45 μM nitrite and 5 μL of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid

Figure 0.44. Comparison, by colorimetry, of the amount of sulfanilamide solution, 1.0, 2.5, 5.0, 7.5, and 10.0 µL, of a 50 mM solution of sulfanilamide in 1.0 M phosphoric acid. 200 µM nitrite was used. 7.5 and 10.0 µL solutions degraded (decolored) faster than other conditions

Figure 0.45. Comparison, by colorimetry, of different incubation times (i.e. time between sample addition and image collection), using 5 µL of a 50 mM solution of sulfanilamide in 1.0 M sulfuric acid and 50 µL of 35 µM sodium nitrite

1.9.8. Optimizations and Analyses – Acid Identity

It was found that the identity and concentration of the acid in which sulfanilamide is dissolved and deposited is crucial for color development both in terms of lowest NGV (darkest color) and lowest PSD (lowest pixel heterogeneity). Previous articles report the use of citric acid³⁰ or phosphoric acid,²⁹ yet the formation of the azo dye is best promoted by strongly acidic conditions.²⁵ Additionally, it was found that, in certain cases, lower NGV values promoted by stronger acids led to an increase in PSD, i.e. uneven detection zone coloration. Therefore, a variety of acids and acid mixes were analyzed and compared below. In the graphs below, the best acidic media is represented by both low NGV and low PSD values (i.e. closest to the bottom left of the graphs). Optimal paper functionalization and device fabrication procedures were used, and each device was treated with a 50 mM solution of sulfanilamide in the indicated acid and 50 μ L of 35 μ M sodium nitrite. 1.0 M hydrochloric acid was determined to be the best solvent for sulfanilamide loading.

Figure 0.46. Comparison by Normalized Green Value and Pixel Standard Deviation of different concentrations of phosphoric acid media for sulfanilamide loading

Figure 0.47. Comparison by Normalized Green Value and Pixel Standard Deviation of different concentrations of sulfuric acid media for sulfanilamide loading

Figure 0.48. Comparison by Normalized Green Value and Pixel Standard Deviation of a mix of 0.5 M citric acid and different concentrations of sulfuric acid media for sulfanilamide loading

Figure 0.49. Comparison by Normalized Green Value and Pixel Standard Deviation of a mix of 1.0 M citric acid and different concentrations of sulfuric acid media for sulfanilamide loading

Figure 0.50. Comparison by Normalized Green Value and Pixel Standard Deviation of a mix of 0.5 M sulfuric acid and different concentrations of phosphoric acid media for sulfanilamide loading

Figure 0.51. Comparison by Normalized Green Value and Pixel Standard Deviation of a mix of 1.0 M sulfuric acid and different concentrations of phosphoric acid media for sulfanilamide loading

Figure 0.52. Comparison by Normalized Green Value and Pixel Standard Deviation of different concentrations of hydrochloric acid media for sulfanilamide loading

1.9.9. Detection and Quantitation Limits

All limits of detection (LOD) and limits of quantification (LOQ) were obtained using the optimal device architecture and optimal functionalization conditions. Solutions of nitrite of the concentrations: 100, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, and 5 μM were created by serial dilution from a 14.5 mM sodium nitrite (1 mg/mL) solution. 50 μL of these solutions were applied to the paper-based sensors which were allowed to incubate for 10 minutes, then imaged using an EPSON v19 Perfection flatbed scanner. The images were analyzed using ImageJ to obtain Normalized Green Values (NGV) and Pixel Standard Deviations (PSD). OriginPro 2018 non-linear curve fitting models were applied to the data until the most optimal R^2 value was obtained. Excel Solver was used, with the equation obtained from the non-linear curve fitting, to find the concentration of nitrite corresponding to the limit of detection (LOD), using $\text{LOD} = \text{AVG}_{\text{blank}} - 3 \times \text{STD}_{\text{blank}}$, and the limit of quantitation (LOQ), using

$LOQ = AVG_{blank} - 10 * STD_{blank}$, where AVG_{blank} is the average value of the blank measurement (i.e. no nitrite) and STD_{blank} is the standard deviation of the blank measurement. Three replicates were conducted for each measurement in ultrapure water and six replicates were conducted for each measurement in synthetic freshwater or Sargasso seawater.

Table 0.4. Data for the nitrite detection calibration curve, in ultrapure water, for devices constructed using 50 mM sulfanilamide in 1.0 M citric acid solution

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.01029	0.00379
5	0.95209	0.00405
10	0.90705	0.00424
15	0.86486	0.00847
20	0.81186	0.00434
25	0.78805	0.01659
30	0.74412	0.00936
35	0.71586	0.00762
40	0.70798	0.02041
45	0.60811	0.02184
50	0.6061	0.02285
55	0.60385	0.00702

Figure 0.53. Nitrite calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M citric acid solution. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 0.70747 (\pm 0.08594)$; $t = 64.18914 (\pm 12.37246)$; $y_0 = 0.30069 (\pm 0.09047)$; and $R^2 = 0.99954$. The LOD and LOQ values were calculated to be 0.84 μM and 3.33 μM , respectively

Table 0.5. Data for the nitrite detection calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M phosphoric acid solution

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.01029	0.00379
5	0.96389	0.00674
10	0.91415	0.00677
15	0.87027	0.00973
20	0.81629	0.0214
25	0.77817	0.00766
30	0.74307	0.00946
35	0.70012	0.00911
40	0.68379	0.00203
45	0.63408	0.05899
50	0.61447	0.00816
55	0.56796	0.00354

Figure 0.54. Nitrite calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M phosphoric acid solution. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 1.20451 (\pm 0.23337)$; $t = 122.40866 (\pm 30.21403)$; $y_0 = -0.19526 (\pm 0.23678)$; and $R^2 = 0.99978$. The LOD and LOQ values were calculated to be 1.05 μM and 3.81 μM , respectively

Table 0.6. Data for the nitrite detection calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M sulfuric acid solution

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.00432	0.00065
5	0.9365	0.00711
10	0.89807	0.00821
15	0.85037	0.00943
20	0.77369	0.00711
25	0.7086	0.02046
30	0.69304	0.03974
35	0.66724	0.02178
40	0.62579	0.02491
45	0.5849	0.03419
50	0.59666	0.03147
55	0.51248	0.03841

Figure 0.55. Nitrite calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M sulfuric acid solution. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 0.7709 (\pm 0.14399)$; $t = 57.91361 (\pm 15.96034)$; $y_0 = 0.23713 (\pm 0.14918)$; and $R^2 = 0.99953$. The LOD and LOQ values were calculated to be 0.42 μM and 0.77 μM , respectively

Table 0.7. Data for the nitrite detection calibration curve for devices constructed using 50 mM sulfanilamide in 1.0 M HCl solution

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.00455	0.00050
5	0.92475	0.01203
10	0.83622	0.00678
15	0.74663	0.00782
20	0.71671	0.00605
25	0.63506	0.03251
30	0.56766	0.01194
35	0.50206	0.00686
40	0.48787	0.01326
45	0.39869	0.0051
50	0.37175	0.03668
55	0.28689	0.05198

Table 0.8. Data for the nitrite detection calibration curve for devices constructed using 50 mM sulfanilamide solution in a mixture of 1.0 M citric acid and 0.25 M sulfuric acid

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.003252	0.000384
5	0.934942	0.003073
10	0.881022	0.003107
15	0.819796	0.033176
20	0.737478	0.019568
25	0.708931	0.006568
30	0.630364	0.037578
35	0.626183	0.01016
40	0.548602	0.033031
45	0.486057	0.061036
50	0.446383	0.053046
55	0.386995	0.163772

Figure 0.56. Nitrite calibration curve for devices constructed using 50 mM sulfanilamide solution in a mix of 1.0 M citric acid and 0.25 M sulfuric acid. The data were fit to a linear curve: $y = mx + b$ where $m = -0.01173 (\pm 0.0002475)$; $b = 1.00307 (\pm 0.00062108)$; and $R^2 = 0.99557$. The LOD and LOQ values were calculated to be 0.098 μM and 0.33 μM , respectively

Table 0.9. Data for the nitrite detection calibration curve, from 5 – 87.5 μM , in synthetic freshwater for devices constructed using the optimal methods

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.00391	6.91866E-4
5	0.90982	0.01344
10	0.8426	0.00846
15	0.75805	0.03182
20	0.72225	0.02546
25	0.69703	0.04034
30	0.61046	0.01583
35	0.56402	0.03024
40	0.54325	0.03469
45	0.51168	0.02542
50	0.44733	0.04462
62.5	0.37719	0.053
75	0.2487	0.05894
87.5	0.22507	0.03786

Figure 0.57. Nitrite calibration curve, from 5 to 87.5 μM , in synthetic freshwater, for devices constructed using the optimal conditions. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 0.995562 (\pm 0.06177)$; $t = 56.53845 (\pm 5.21821)$; $y_0 = 0.04824 (\pm 0.0619)$; and $R^2 = 0.99783$. The LOD and LOQ values were calculated to be 0.12 μM and 0.41 μM respectively

Table 0.10. Data for the nitrite detection calibration curve, from 0.05 – 5 μM , in synthetic freshwater for devices constructed using the optimal methods

[Nitrite] (μM)	NGV	NGV standard deviation
0	1.00255	0.00156
0.05	1.00242	0.00132
0.1	1.00262	0.00168
0.25	1.00136	0.00101
0.5	0.99421	0.00217
0.75	0.99138	0.00163
1	0.98904	0.00214
1.25	0.97882	0.00326
1.5	0.97624	0.00525
2	0.96799	0.00654
3.5	0.94018	0.01057
5	0.91561	0.0159

Figure 0.58. Nitrite calibration curve, from 0.05 to 5 μM , in synthetic freshwater, for devices constructed using the optimal conditions. The data were fit to a linear curve: $y = mx + b$, where $m = -0.017422 (\pm 0.00102)$; $b = 1.00426 (\pm 0.00058537)$; and $R^2 = 0.96675$. The LOD and LOQ values were calculated to be 0.26 μM and 0.69 μM respectively

Table 0.11. Data for the nitrite detection calibration curve, from 5 – 50 μM , in Sargasso seawater for devices constructed using the optimal methods

[Nitrite] (μM)	NGV	NGV standard deviation
0	0.99995	0.00135
5	0.86101	0.01602
10	0.7553	0.01126
15	0.64813	0.01458
20	0.56135	0.0305
25	0.51689	0.07002
30	0.41377	0.09217
35	0.31187	0.05733
40	0.15831	0.0542
45	0.13339	0.04322
50	0.05295	0.0233

Figure 0.59. Nitrite calibration curve, from 5 to 50 μM , in Sargasso seawater, for devices constructed using the optimal conditions. The data were fit to an exponential decay curve: $y = A^{(-x/t)} + y_0$ where $A = 1.92658 (\pm 0.15965)$; $t = 74.37635 (\pm 7.79546)$; $y_0 = -0.9267 (\pm 0.15972)$; and $R^2 = 0.99918$. The LOD and LOQ values were calculated to be 0.15 μM and 0.52 μM respectively

Table 0.12. Data for the nitrite detection calibration curve, from 0.05 – 5 μM , in Sargasso seawater for devices constructed using the optimal methods

[Nitrite] (μM)	NGV	NGV standard deviation
0	0.99667	0.00257
0.05	0.99153	8.18304E-4
0.1	0.99347	0.00158
0.25	0.99055	0.00201
0.5	0.98472	0.00109
0.75	0.97633	0.00238
1	0.96111	0.0066
1.25	0.95035	0.00565
1.5	0.94326	0.00641
2	0.92775	0.00987
3.5	0.90033	0.0112
5	0.85462	0.01256

Figure 0.60. Nitrite calibration curve, from 0.05 to 5 μM , in Sargasso seawater, for devices constructed using the optimal conditions. The data were fit to a linear curve: $y = mx + b$, where $m = -0.0268 (\pm 0.00233)$; $b = 0.995 (\pm 0.0011)$; and $R^2 = 0.92972$. The LOD and LOQ values were calculated to be 0.22 μM and 0.89 μM respectively

1.9.10. Interference Studies

1.9.10.1. Salinity. Samples of nitrite in solutions of known salinity were created using Coral Pro Sea Salt batch number 1903170115. A sample with a salinity of 4.5% (45 ppt) was created by dissolving 0.491 g of salt mix in 10 mL of a solution of 50 μ M nitrite in ultrapure water. Concentrations of 4.0, 3.5, 3.3, 3.0, 2.5, 1.5, and 0.5% salt were then created by serial dilution from the 4.5% solution using a solution of 50 μ M nitrite in ultrapure water to dilute. A sample with salinity of 30 % (300 ppt) was created by dissolving 3.71 g of salt mix in 10 mL of a solution of 50 μ M nitrite in ultrapure water. The sample was sonicated for 30 minutes, though full dissolution of the salt was not achieved. Samples of 15 % and 7.5% were created by serial dilution from the 30 % solution using a solution of 50 μ M nitrite in ultrapure water to dilute. The devices were prepared using the optimal paper functionalization and device construction procedures. The devices were treated with 50 μ L of the appropriate solution, allowed to incubate at ambient conditions for 10 minutes, then scanned using a flatbed scanner.

Figure 0.61. Comparison of sensor readout for samples of 50 μM nitrite in high salinity % solutions akin to briny or hypersaline water⁶⁵

1.9.10.2. Temperature and Relative Humidity. The temperature was controlled in a Boekel Scientific Digital Incubator and the relative humidity was adjusted using desiccant and water as needed to reach the desired relative humidity. Temperature and relative humidity were monitored using an AcuRite Digital Humidity and Temperature Comfort Monitor. Devices were prepared using the optimal paper functionalization and device construction procedures. The devices were then incubated under the desired testing conditions for 30 minutes to acclimate, then 50 μL of sample solution (0, 10, 50, or 100 μM nitrite in ultrapure water) were added and the device was allowed to further incubate in the testing conditions for 10 minutes, then scanned using a flatbed scanner.

1.9.10.3. Turbidity. Suspensions of 1 mg/mL, 5 mg/mL, and 10 mg/mL of Kaolin clay⁷² in nitrite sample solution (0, 10, 50, 100 μM) were created, then allowed to stir vigorously overnight. Devices were prepared using the optimal paper functionalization and device construction procedures, then tested with 50 μL of the appropriate sample solution, incubated for 10 minutes, then scanned using a flatbed scanner.

Figure 0.62. Comparison of sensor readouts for nitrite concentrations of 0, 10, 50, or 100 μM in solutions of various turbidities (mg/mL) created using Kaolin clay

Figure 0.63. Picture of actual unfiltered samples from the Houston Hurricane Harvey flood waters (from left to right: downtown Houston, 5 miles northwest of Houston, and 5 miles southeast of Houston) analyzed with the reported device

1.9.10.4. Chemical. 100 μM solutions of potential ion interferents were created, then combined with equal amounts of 100 μM sodium nitrite solution in ultrapure water to

create solutions of 50 μ M nitrite + 50 μ M interferent. Devices were prepared using the optimal paper functionalization and device construction procedures, then tested with 50 μ L of the appropriate sample solution, incubated for 10 minutes, then scanned using a flat-bed scanner. Additionally, 50 μ M solutions of silver nitrite and potassium nitrite were created and tested using the optimal devices and conditions.

1.9.11. Stability Studies

Devices were prepared using the optimal paper functionalization and device construction procedures. Those stored under ambient temperature and lighting conditions were left on a lab bench with occasional direct sunlight. The other devices were vacuum sealed using a White Dolphin automatic vacuum sealer model number 02G and Nutri-Lock Vacuum Sealer Bags. These devices were placed in ambient temperature and lighting conditions, darkness, a fridge, or a freezer as necessary. When ready for testing, cold devices were allowed to acclimate for 30 minutes to ambient temperatures before the packages were opened. The devices were scanned to observe discoloration, then the devices were then treated with 50 μ L of the 50 μ M nitrite in ultrapure water solution, incubated for 10 minutes, then scanned using a flat-bed scanner.

Figure 0.64. Time-dependent discoloration of sulfanilamide on the optimal device after storage in open air and light (grey), vacuum and light (red), vacuum and darkness (blue), and vacuum and refrigeration (green)

1.10. References

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CHAPTER 2 PREFACE

Highly Sensitive and Subtraction-Free Dual Detection of Nitrate and Nitrite using the Griess Assay and a Paper-Based Device was supported by the National Science Foundation under EPSCoR Cooperative Agreement #OIA-1655221. This work, in combination with Chapter 1, is currently in preparation for submission to a peer-reviewed journal.

CHAPTER 2

Highly Sensitive and Subtraction-Free Dual Detection of Nitrate and Nitrite using the Griess Assay and a Paper-Based Device

2.1. Introduction

The detection of nitrate and nitrite, prevalent environmental contaminants¹⁻⁴ that are released to the environment by human activities such as wastewater treatment, agricultural activities, and industrial processes,⁵⁻⁷ can successfully be quantified at sub-micromolar levels using techniques such as capillary electrophoresis, spectrophotometry, electrochemical detection, and ion chromatography.^{8,9} While these techniques are highly useful in laboratory settings, in most cases they are not easily translocated for on-site, real-time measurements, despite the need to detect nitrate and nitrite in the field.¹⁰ In recent years, point-of-care devices, specifically paper-based devices, have gained significant attention, attributed to a report on such devices that was published in 2007 by Whitesides and coworkers, with the overarching goal of developing cost-effective detection methods for rapid and inexpensive on-site detection.¹¹ These devices require microliter quantities of sample, as opposed to milliliter volumes required for instrumentation-based quantification,¹² and often can be analyzed using naked-eye detection, smart phones,^{13,14} or flatbed scanners.¹⁵⁻¹⁸ Paper-based devices often rely on precisely patterned hydrophilic channels through which sample solutions flow, facilitated by capillary action. Sequential timed delivery of reagents, and thus multistep processes, can be mediated by this controlled flow.¹² These channels can be utilized in order to eliminate sample pretreatments, such as purification,

concentration, dilution, or reagent addition, that are often required prior to instrumentation-based techniques.

Point-of-care devices are most useful when they adhere to the ASSURED criteria, developed by the World Health Organization initially for medical diagnostics, where ASSURED stands for: i) affordable, ii) sensitive, iii) specific, iv) user-friendly, v) rapid and robust, vi) equipment-free, and vii) deliverable.¹⁰ The authors followed these criteria to develop a paper-based assay for the detection of nitrate and nitrite. The most attractive analytical method to achieve this is the colorimetric Griess method,¹⁹ which allows for simple computer-based or naked eye quantitation; and the most attractive device substrate is paper, as it is inexpensive, ubiquitous and easy to pattern with hydrophobic channels to control sample flow.¹⁰

The Griess reaction typically utilizes two indicators, sulfanilamide and *N*-(1-naphthyl)ethylenediamine, which, in the presence of nitrite, form a highly colored azo dye (Figure 2.1) that is used for colorimetric quantitation.²⁰ Sulfanilamide reacts with nitrite to form a diazonium salt intermediate which rapidly undergoes a nucleophilic aromatic substitution with *N*-(1-naphthyl)ethylenediamine to produce the azo dye.²¹ This method has been used for a variety of spectrophotometric detection systems²² as well as naked-eye detection schemes, and most commercially available devices are based on these reagents.^{23,24} While similar reagents can, and have, been used,^{21,25} these reagents are commonly regarded as the optimal choice. *N*-(1-naphthyl)ethylenediamine is the most sensitive, rapid, and pH tolerant of the known potential candidates,²² and sulfanilamide reacts rapidly with *N*-(1-naphthyl)ethylenediamine and nitrite to produce a stable colored product.²⁵

Figure 2.1. Griess reagents, *N*-(1-naphthyl)ethylenediamine and sulfanilamide, were used for the detection of nitrate and nitrite

While the detection of nitrite with this method is straightforward, the detection of nitrate requires that the nitrate be reduced to nitrite prior to detection (Figure 2.1). Because of this, any nitrate signal generated has the potential to be compounded by the presence of nitrite in the sample and thus many detection schemes rely on the subtraction of nitrite signal from nitrate signal to achieve accurate quantitation.⁹

A variety of methods have been examined for the reduction of nitrate to nitrite including metals, enzymes,²⁶ and organic reductants such as hydrazine.²⁷ Most commonly, cadmium or copperized-cadmium reducing agents^{19,28,29} are used to convert nitrate to nitrite, but zinc^{29,30} or metal salts such as titanium trichloride³¹ and vanadium trichloride³² have also been reported. Issues arise in the reduction of nitrate due to the propensity of nitrite to be further reduced to other species that are not detectable by the Griess method, with nitrate to nitrite reduction often being the rate-determining step.³³ Additionally, the dissociation of nitrite from metal surfaces typically has high energy barriers. This leads to inaccessibility of nitrite to the Griess reagents as well as

promotion of further reduction of nitrite. Cadmium-based reduction is often found to be most ideal because nitrate to nitrite reduction is thermodynamically favored, and further reduction of nitrite is kinetically disfavored, however, reaction conditions such as mixing time, cadmium surface area, and solution pH all play a significant role in determining reduction efficiency.³⁴ A computational study by Goldsmith and coworkers indicates the potential for selective nitrate to nitrite reduction systems using Fe, Co, Pt, and Rh in acidic systems due to high nitrate to nitrite activity and low nitrite dissociation barriers.³³ In addition, palladium catalysts³⁵ have been shown to provide selective nitrate to nitrite reduction in aqueous solution.

A range of promising paper-based devices utilizing the Griess method have already been developed, reporting micromolar detection limits for nitrite.^{13,15-18,36,37} However, very few of these devices are used for the detection of nitrate¹⁵ and, like the vast majority of nitrate detection techniques, nitrite signal subtraction is required for accurate nitrate quantitation.⁹ In one of these methods a zinc channel was successfully used for nitrate reduction.¹⁵ However, while zinc is the least toxic of potential candidates, it is not the most efficient.²⁸

The device reported herein was designed to provide a highly efficient sensor platform for nitrate, using the Griess method, without the need for nitrite signal subtraction. Through modification of the device reported in Chapter 1 with a cadmium/platinum chloride reduction zone, a maximum reduction efficiency of 32% for nitrate was reached, and nitrite and nitrate detection limits of 1.1 μM and 0.61 μM were achieved.

2.2. Dual Nitrate/Nitrite Detection Device

The paper-based nitrite sensor first described in Chapter 1 was further modified for dual nitrite/nitrate reduction. The immobilization of the nitrite sensing molecule *N*-(1-naphthyl)ethylenediamine and the subsequent immobilization of the colored product to the detection zone effectively removes nitrite from the sample as it moves through the device. Therefore, only nitrate remaining in the sample reaches the reduction zone, and only nitrite formed by nitrate reduction reaches the second detection zone. Thus, the sensor readout for nitrate is not compounded by the presence of nitrite in the sample, and subtraction of nitrite signal is not required during device analysis. This is a significant improvement over previously reported and commercially available colorimetric sensors for nitrate. The dual detection device, shown in Figure 2.2, was constructed based on the initial nitrite sensor reported in Chapter 1, and construction details can be found in Section 2.4.2.

Figure 2.2. a) dimensions of dual nitrite/nitrate sensor and b) sensor readout when treated with 50 μL of aqueous sample containing 45 μM nitrite and 90 μM nitrate

2.2.1. Nitrate Reduction

The nitrate reduction zone was designed as a 5 mm x 2.5 mm hydrophilic lane, pre-printed with wax barriers parallel to the lane, which was infused with a metal reductant, then adhered to the device overlapping the nitrite detection zone (Figure 2.8, Section 2.4). Nitrate reduction efficiency of each fabricated reductant zone was determined by the colored readout of the sensor, i.e. amount nitrite produced, and was calculated using the ultrapure water/1.0 M HCl calibration curve from Chapter 1.

Reduction zone preparation was initially accomplished by soaking or sonicating the lanes in a 3.0 M metal slurry for two minutes, followed by a thorough rinse with ultrapure water. The lanes were laid flat and allowed to dry completely (about 2 hours)

before adherence to the device shown in Figure 2.8. The reduction zone was treated with 1.0 μL of 1.0 M HCl in order to remove any oxide layers and to provide a source of H^+ to enhance reduction efficiency (see Figure 2.9 for comparison). Initial studies revealed a nitrate reduction efficiency from the cadmium reduction chamber of 21%, with the next highest nitrate reduction efficiency, 6.9%, from the zinc reduction chamber (Figure 2.3). As expected based on previous reports,³³ reduction efficiency was determined for iron (1.8%), platinum (0.62%), and rhodium (0.33%) reduction chambers, though minimal, and it is unclear whether this minimal nitrate reduction is occurring or whether over reduction is producing other species that are not detectable by the Griess method.³³

Figure 2.3. Reduction efficiencies of nitrate reduction chambers fabricated by sonicating Whatman #4 in 0.30 M slurries of the indicated metals in ultrapure water

Studies of preparation conditions indicated that sonication is detrimental to paper infusion (Figure 2.10), and further infusions were accomplished simply by soaking the paper in the metal slurry. Optimization of cadmium concentration in the slurry identified 0.075 M cadmium in ultrapure water as the best conditions for infusion (Figure 2.4).

Figure 2.4. Optimization of cadmium slurry molarity for impregnation of paper by soaking

The infusion of the detection zone with a slurry containing both cadmium (0.075 M) and a metal additive (0.035 M) did not increase reduction efficiencies (Figure 2.5a). Decreased reduction efficiencies were found for mixes of cadmium with copper, titanium, and zinc, indicating that these metals are likely over-reducing the nitrite. Examination of metal salts (0.0075 M) yielded similar results, with most salts decreasing reduction efficiency (Figure 2.5b), except platinum chloride, which minimally enhanced efficiency. Further examination of platinum chloride as a co-reductant revealed the optimal co-reductant ratio of 20 mol% (Figure 2.5).

Figure 2.5. Nitrite reduction efficiency comparisons of a cadmium reduction zone with a) metal co-reductants, b) metal salt co-reductants, and c) different quantities of PtCl₂ co-reductant

2.2.2. Dual Detection

Several device architectures were examined, with the device shown in Figure 2.2a providing higher reduction efficiency (32%) compared to the initial device architecture (27%) (Figure 2.12). This device was used for subsequent calibration curve generation.

Calibration curves were generated for these devices using known concentrations of nitrite (5-75 mM) and nitrate (10-175 mM) in ultrapure water (Figure 2.13) leading to limits of detection and limits of quantitation of 1.4 μ M and 3.0 μ M for nitrite, and 3.3 μ M and 5.1 μ M for nitrite, respectively. Variances in nitrate detection zone color (purple

vs. pink readout) and unevenness (high pixel standard deviation)³⁸ in the nitrate detection zone were corrected with the application of a surfactant, tetrabutylammonium bromide, at the beginning of the nitrate detection zone to aid in even rehydration of the paper during sample flow.³⁹ The resulting calibration curve indicated more favorable limits of detection and quantitation for nitrite of 1.1 μM and 3.4 μM , and 0.61 μM and 2.2 μM for nitrate, respectively.

Table 2.1. Limit of detection (LOD) and limit of quantitation (LOQ) values for nitrite and nitrate

Surfactant	Nitrite LOD	Nitrite LOQ	Nitrate LOD	Nitrate LOQ
none	1.4 μM	3.0 μM	3.3 μM	5.1 μM
TBAB	1.1 μM	3.4 μM	0.61 μM	2.2 μM

Figure 2.6. Calibration curves for nitrite and nitrate, with TBAB used as a color stabilizer, fit to exponential decay curves with the formula: $y = A_1 e^{(-x/t)} + y_0$. For nitrite, $A_1 = 0.76502$; $t = 52.453$; $y_0 = 0.23462$; and $R^2 = 0.99973$. For nitrate, $A_1 = -126.126$; $t = -20638.6$; $y_0 = 127.149$; $R^2 = 0.99992$

2.3. Conclusions

While this preliminary work indicates a promising approach to a subtraction-free nitrite/nitrate dual sensor, many studies and optimizations are still underway. Further investigations include examining: the use of alkaline cadmium-infused paper and other reduction zones,¹⁹ the effects of environmental conditions and chemical interferents, the decrease of cadmium reduction efficiency over time, and the applicability of the devices to real world samples. In addition, the upper limits of nitrite and nitrate detection (i.e. the concentration at which the presence of one affects the signal readout of the other) will be determined. Overall, we hope to fully develop these sensors to the point where they can rival commercially available devices and state-of-the-art literature.

2.4. Experimental

2.4.1. General Considerations

All chemicals and cellulose products were purchased through Fisher Scientific or Millipore Sigma and used as received.

The sensors were imaged using an EPSON V19 Perfection flatbed scanner and the images were analyzed using ImageJ software (<https://imagej.nih.gov/ij/download.html>) on an 8-bit color scale (white = 255 a.u., black = 0 a.u.). Using ImageJ, the detection zone coloration was separated into average RGB channels and converted into Normalized Green Value (NGV) by dividing the Green Value (the color value that changed the most with an increase in magenta color) by Red Value (the color value that changed the least with an increase in magenta color). Pixel standard deviation (PSD),³⁸ a measure

of pixel color homogeneity that was provided by the program was also used as a metric for analysis.

The paper-based devices were designed using Adobe Illustrator and printed using a Xerox ColorQube 8580. Fellowes® self-adhesive sheets and FLEXcon® FLEXmount® SELECT™ DF051521 clear 0.5 poly perm adhesive/ double faced liner were cut to the desired sizes using a Graphtec CE6000-40 cutting plotter.

2.4.2. Optimized Device Construction

All devices were printed in triplicate for easier comparison of identical measurements. The device was designed to hold 50 μ L of sample solution, with a sulfanilamide/nitrite sample mixing zone prior to the nitrite detection zone, overlapped (1.5 mm) by a reductant-loaded paper zone, which in turn was overlapped (1.5 mm) by a nitrate detection zone. A fan-shaped wicking zone was chosen to promote sustained liquid flow through the device without requiring an absorbent pad.⁴⁰ A white “lip” was incorporated at the beginning of the both detection zones to facilitate color analysis, and coloration was analyzed only in the section of the detection zone above the white background. Reference lines were used to guide the adherence of *N*-(1-naphthyl)ethylenediamine functionalized paper (yellow) and the reduction channel (red lines).

Devices were patterned using a wax printer in the dimensions shown in Figure 2.2 then melted in a 120 °C oven for 2.5 minutes. Lamination was found to increase color consistency of the detection zone, but no-heat laminate was required to avoid thermal degradation of sulfanilamide. Self-adhering no-heat laminate was cut using a Graphtec vinyl cutter to the dimensions shown in Figure 2.7.

To construct the device, the laminate was first placed on the front of a printed and melted device, then the device was flipped over and 5 μL of 50 mM sulfanilamide solution in 1.0 M HCl was added at the location indicated by a blue asterisk on the device shown in Figure 2.2. The solution was allowed to dry for 30 minutes, then the functionalized paper “bridge” to be used for nitrite detection was adhered using double-sided tape to first location indicated by yellow reference lines, shown in Figure 2.2. A reduction zone “bridge” was placed on the device, in the location indicated by red reference lines, shown in Figure 2.2, to overlap the end of the nitrite detection zone by 1.5 mm, using double sided tape to adhere. A second 5 μL aliquot of 50 mM sulfanilamide solution in 1.0 M HCl was added to the center of the reduction zone and allowed to dry for 1 hour. A second functionalized paper “bridge” to be used for nitrate detection was placed on the device, in the second location indicated by yellow reference lines, shown in Figure 2.2, to overlap the end of the reduction zone by 1.5 mm, using double sided tape to adhere. An uncut piece of self-adhering no-heat laminate was added to the underside of the device and the device was sealed using a pressure laminator. To the sample loading zone of the device was added 50 μL of aqueous sample. The device was allowed to develop for 15 minutes, then placed on a flatbed scanner for image collection.

Figure 2.7. Laminate dimensions for optimized architecture of triplicate devices

2.4.3. Initial Device Construction

This initial dual nitrite/nitrate detection device for initial reduction channel screening was patterned with the dimensions shown in Figure 2.8, printed using a wax printer, then melted at 120 °C for 2.5 minutes. A piece of no-heat laminate was placed, dimensions shown in Figure 2.8, was placed on the front of the device. The device was flipped over, and 5 μ L aliquots of a 50 mM solution of sulfanilamide in 1.0 M HCl was added to both of the locations indicated by blue asterisks and allowed to dry for 30 minutes.

N-(1-naphthyl)ethylenediamine bridges (10 mm x 10 mm square pre-printed with wax to form a 10 mm x 2.5 mm hydrophilic lane) were adhered, using double-sided tape, to the locations indicated by yellow reference lines. The nitrate reduction zone was

adhered, using double sided tape, to the location indicated by red reference lines, overlapping the nitrite detection zone by 1.0 mm. The reduction zone was then treated with 1.0 μL of 1.0 M HCl, and this was allowed to dry for 15 minutes. An uncut piece of laminate was placed on the back of the device, and pressure lamination was used to seal the device. Application of 50 μL of sample solution and a 15-minute incubation period was followed by image collection using a flatbed scanner.

Figure 2.8. Dimensions of the initial device, printed in triplicate, for dual nitrite/nitrate detection

2.4.4. Optimized Loading of Metal Reductant

To a small beaker was added six pieces of 10 mm x 10 mm Whatman # 4 patterned with 10 mm x 2.5 mm hydrophilic lanes. 40 mg of -325 mesh cadmium powder, 20 mg platinum chloride, and 4 mL of ultrapure water were added. The solution was shaken to fully immerse the paper and distribute the solids, then was allowed to sit for 1 hour at

room temperature. The paper was removed with tweezers and immersed and swirled in ultrapure to rinse. The paper was laid flat and allowed to dry for 2 hours before use, then adhered to the device following the procedures indicated above. Each device was treated with 50 μL of a 100 μM solution of nitrate in ultrapure water. The colored readout was compared to the ultrapure water/1.0 M HCl calibration curve from Chapter 1 ($y = 1.519(x^{88.935}) - 0.5144$), and Excel Solver was used to solve for x . This readout was divided by the initial about, 100 μM and multiplied by 100% to obtain reduction efficiency values.

Figure 2.9. Reduction efficiencies of nitrate reduction chambers fabricated by sonicating Whatman #4 in 0.30 M slurries of the indicated metals in ultrapure water with no acid pretreatment

Figure 2.10. Evaluation of the use of sonication in the preparation of metal zones with 0.075 M cadmium slurry

Figure 2.11. Evaluation of different paper types in the preparation of metal zones with 0.075 M cadmium slurry (CP = carbon paper)

Figure 2.12. Comparison of reduction efficiencies by architecture. Architecture 1 is shown in Figure 2.8, Architecture 2 is shown in Figure 2.2

Table 2.2. Data for the detection of nitrite and nitrate at various concentrations, in ultrapure water, using the optimal device and conditions, including the use of TBAB as a rehydrating agent, recorded as Normalized Green Value (NGV) and standard deviation of NGV (STD)

[Analyte]	Nitrite		Nitrate	
	NGV	STD	NGV	STD
0	0.99773	0.00457	0.97265	0.00139
5	0.93906	0.0039		
10	0.85867	0.00905	0.93072	0.0099
15	0.8051	0.00405		
20	0.75597	0.01097	0.84167	0.01413
25	0.72033	0.01698		
30	0.66714	0.05332	0.77216	0.00601
35	0.61947	0.00903		
40	0.61649	0.01199	0.70865	0.05853
45	0.52919	0.02006		
50	0.51832	0.02638	0.69144	0.02896
60			0.62231	0.04086
62.5	0.50222	0.03408		
70			0.49996	0.05088
75	0.41132	0.01828		
80			0.52755	0.09101
87.5	0.37982	0.01736		
90			0.46292	0.02475
100			0.45155	0.04202
125			0.20272	0.05787
150			0.05017	0.0023

Table 2.3. Data for the detection of nitrite and nitrate at various concentrations, in ultrapure water, using the optimal device and conditions, recorded as Normalized Green Value (NGV) and standard deviation of NGV (STD)

[Analyte]	Nitrite		Nitrate	
	NGV	STD	NGV	STD
0	1.00468	0.00109	0.98431	0.00425
5	0.91787	0.01212		
10	0.85388	0.00735	0.9108	0.01374
15	0.79163	0.01864		
20	0.6812	0.00467	0.88624	0.00465
25	0.67203	0.03715		
30	0.59371	0.01744	0.79589	0.05172
35	0.56616	0.03836		
40	0.48742	0.04227	0.74518	0.03099
45	0.50667	0.00729		
50	0.44273	0.01165	0.68339	0.09372
60			0.64208	0.0243
62.5	0.41199	0.00216		
70			0.61412	0.07819
75	0.33029	0.01873		
80			0.46141	0.06541
87.5				
90			0.50783	0.04536
100			0.43635	0.09603
125			0.46771	0.07699
150			0.33571	0.16205
175			0.01479	0.00753

Figure 2.13. Calibration curves for nitrite and nitrate fit to exponential decay curves with the formula: $y = A_1^{(-x/t)} + y_0$. For nitrite, $A_1 = 0.74355$; $t = 37.733$; $y_0 = 0.26676$; and $R^2 = 0.99976$. For nitrate, $A_1 = 130.351$; $t = 23432.23$; $y_0 = -129.364$; $R^2 = 0.99987$

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CHAPTER 3 PREFACE

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Student experimental procedures, notes to instructors, and suggested student report instructions have been excised for the purposes of this thesis, but can be found in the peer-reviewed manuscript.

CHAPTER 3

Design, Implementation, and Evaluation of Paper-Based Devices for the Detection of Acetaminophen and Phenacetin in an Advanced Undergraduate Laboratory

3.1. Introduction

The development and implementation of solid-state detection systems for broad varieties of analytes is useful in a number of real-world scenarios, including in public health,¹ national security,² and environmental remediation applications.³ Moreover, it also requires significant training in a number of sub-disciplines, including analytical chemistry, materials chemistry, and organic and/or inorganic synthesis. The topic of solid-state detection is not often taught at the undergraduate level, likely because of the complexity of the topic and because this topic does not fall into one of the traditional chemistry sub-disciplines (organic, inorganic, physical, or analytical chemistry). While interdisciplinary chemistry research, including in the area of chemical detection⁴ (and especially solid-state detection),⁵ has experienced a resurgence in recent decades, interdisciplinary chemistry education has been slower to follow suit.⁶⁻⁹ The lack of interdisciplinary education means that graduates of traditional chemistry programs may not have the skills necessary to engage in interdisciplinary chemistry research, and will be ill-prepared for professional employment and/or for a graduate career in such areas.

To address this gap between significant interdisciplinary work in the chemical enterprise and less interdisciplinary undergraduate chemistry education, our laboratory has developed a number of new experiments for the undergraduate teaching laboratory

that have a strong interdisciplinary focus and substantial pedagogical advantages. In particular, we have previously reported the synthesis and analysis of a near-infrared emitting squaraine fluorophore;¹⁰ the synthesis and characterization of a fluorescent conjugated polymer and the subsequent fabrication of nanoparticles and thin films;¹¹ and the synthesis, analysis, and practical applications of a cyclodextrin-containing metal-organic framework for environmental pollutant removal.¹²

In continuation of our goals to create relevant and interdisciplinary experiments for undergraduate teaching laboratories, we focused next on the area of colorimetric chemical detection, an active research topic in our own group.¹³⁻¹⁵ Chemical detection, while a highly active research area in general,¹⁶⁻¹⁸ has only been reported for undergraduate teaching laboratories in isolated cases,¹⁹⁻²⁴ and the scope of analytes and detection methods have been fairly limited. Colorimetric detection, or detection based on the changes in color of a transducing signaling element, has a number of advantages in practical detection applications due to the ability to observe color changes using naked eye detection.²⁵ This also has been introduced, in limited examples, in the undergraduate²⁶ (and even high school)²⁷ laboratories, usually in analytical chemistry settings, for the detection of a variety of high impact analytes. Moreover, paper-based devices have become widely used materials for qualitative and quantitative colorimetric chemical detection in the industry.²⁸⁻³³ Therefore, this area was deemed important for inclusion in an undergraduate curriculum, with the goal of introducing students to state-of-the-art technologies that could be applicable to their future careers.

Reported herein is the design, implementation, and evaluation of an interdisciplinary experiment for the undergraduate chemistry laboratory focused on paper-based devices.

This integrated experiment includes two topics that are of substantial interest in both the chemistry education and chemistry research communities: solid-state (in particular paper-based) device fabrication³⁴ and colorimetric detection.³⁵ As part of the experiment, students synthesize and purify acetaminophen and phenacetin (Figure 3.1a), two compounds that are of interest in forensic analyses because they can be used to adulterate illicit materials, that are subsequently detected using the chromophore 1,2-naphthoquinone 4-sulfonate (Figure 3.1b).³⁶ To achieve detection, students fabricate paper-based devices using an inexpensive filter paper medium with hydrophilic barriers formed from wax-based eyeliner,^{35,37} acrylic spray paint,^{38,39} or wax printing⁴⁰ (three technically easy and robust methods for doing so), then introduce a color-changing chromophore to the paper-based device and use the colorimetric response of the chromophore as a way to monitor and detect the presence of the newly synthesized analytes. This experiment has elements of organic chemistry (in the synthesis and purification of analytes), analytical chemistry (in the color-based analyte detection system), materials chemistry (in the device fabrication), and colorimetric analysis in the design and use of the color-changing chromophore, which together provides a truly unique, interdisciplinary educational experience for undergraduate students. This combination of paper-based devices, colorimetric detection, and analyte synthesis is relatively unique in the chemical literature, and has robust pedagogical advantages associated with this interdisciplinary approach.

Figure 3.1. a) Synthesis of acetaminophen and phenacetin and b) detection of acetaminophen and phenacetin using the chromophore 1,2-naphthoquinone-4-sulfonate

3.2. Pedagogical Goals

This experiment teaches a number of important laboratory techniques and requires student knowledge in a number of key chemistry subject areas, including organic, materials, and analytical chemistry, leading to a high pedagogical impact of this experiment for upper-level chemistry majors who are preparing for future employment or graduate school, where they will likely use many of these interdisciplinary techniques. The introduction of the chromophoric (i.e. color-changing) element required discussion around the mechanism of the reaction between the analyte and the chromophore, and how the electronic and chemical structure of the reaction product relates to its coloration. The students were also introduced to paper-based devices and microscale reactions for the first time, prompting discussions regarding the immobilization of the microscale reaction on a paper substrate using simple hydrophobic barriers, the ease and cost-effectiveness of such devices, and their

usefulness in situations where more expensive, instrumentation-based analyses cannot be implemented. Finally, the students were asked to create serial dilutions of their synthesized analytes in order to create calibration curves for their detection with 1,2-naphthoquinone-4-sulfonate. Through this, the students realized how analytical techniques are typically used for unknown identification

The detection of phenacetin and acetaminophen in basic conditions using sodium 1,2-naphthoquinone-4-sulfonate chromophore on a paper-based device has been reported,³⁶ and was modified by the authors for use in this undergraduate laboratory experiment. In particular, the first part of the experiment requires chemical synthesis of the analytes (Figure 3.1a). Acetaminophen and acetaminophen isomers were formed from reacting the appropriate isomer of aminophenol (*o*-, *m*-, or *p*-) with acetic anhydride in 200 proof ethanol.⁴¹ After stirring at room temperature, the crude products were isolated and recrystallized. In the same lab period, the students synthesized phenacetin and phenacetin isomers by placing their acetaminophen product into a round-bottom flask with *N,N*-dimethylformamide, bromoethane, and potassium carbonate. While this reaction is reportedly conducted at elevated temperatures for several hours,⁴² it was found to be efficient at room temperature over five to seven days. Typically, the majority of acetylation and alkylation reactions gave 80-90% yields, with the acetylation reaction to produce *o*-acetaminophen and the alkylation reaction to produce *m*-phenacetin producing slightly lower yields between 40 and 60%. The students collected ¹H and ¹³C NMR spectra and IR spectra of their products, examples of which can be found in the Section 3.5. All students were able to determine purity of the products using their NMR spectra by identifying all relevant peaks in both the ¹H

and ^{13}C spectra. Isomers could clearly be differentiated by differences in the aromatic regions of the ^1H and ^{13}C NMR spectra, and the full conversion of acetaminophen to phenacetin was evident due to the disappearance of the alcohol peaks in the IR spectrum and the appearance of ethyl proton peaks in the ^1H spectrum.

This synthesis provides an opportunity for the instructor to review important concepts in organic synthesis, including the reactivity of all starting materials compared to products; the stoichiometry, solvent choice, and reaction conditions used under the optimized conditions; and the purification techniques used, including rotary evaporation and recrystallization. Many of the students collected ^{13}C NMR spectra for the first time in this portion of the experiment and were asked to analyze their products for purity before continuing onto the detection portion of this experiment, an important practice to instill in teaching laboratories. All students in the laboratory were able to accomplish the synthesis successfully, although some struggled with the purification of phenacetin when residual *N,N*-dimethylformamide solvent resulted in an oily crude product, an issue which can be solved by taking the phenacetin up in ethyl acetate and washing several times with large amount of water. This yielded product that was sufficiently pure for the next step of the project.

Figure 3.2. Mechanism for the formation of the colored product from the reaction of phenacetin with 1,2-naphthoquinone-4-sulfonate

The formation of acetaminophen by an amine acylation and the formation of phenacetin by a nucleophilic addition of the phenol alcohol with bromoethane are mechanisms that the students will have learned in sophomore organic chemistry. The mechanism for the formation of the colored product, however, is more complex (Figure 3.2), and first involves the acid-promoted deprotection of the acyl amine of either of the analytes to form the primary amine. Following this, in basic conditions, the primary amine acts as a nucleophile in a Michael-type addition to 1,2-naphthoquinone-4-sulfonate. The sulfonate group is then removed in the reforming of the α,β -unsaturated ketone. The basicity of the solution then promotes the formation of an imine in conjugation with an enolate and thus the final product. It is important for students to realize the highly conjugated nature of the product and the connection between conjugation and visible color. The reported reaction products of acetaminophen and phenacetin with sodium naphthoquinone-4-sulfonate are dark blue/purple and red, respectively.³⁶ Using modified versions of these analytes (i.e. with *ortho*- and *meta*-

substitution rather than *para*-) resulted in differently colored products (Figure 3.3) which introduced students to the relationship between electronic structure in conjugated small molecules and observable colors. Students realized that differences in the electronic structure of an analyte changes the electronic structure, and therefore the color, of the product.

Figure 3.3. Differences in product color when the analytes are reacted with 1,2-naphthoquinone-4-sulfonate

The fabrication of devices introduced students to important concepts in hydrophobic and hydrophilic surfaces, including the fact that the Whatman Filter paper is hydrophilic, that the eyeliner, spray paint, and wax are all hydrophobic, and that simple heating of the hydrophobic barriers is generally sufficient to fix the barriers in place, immobilize the reagents, and prevent mixing between sampling sites. Students were intrigued by the fact that materials they had seen previously (especially the eyeliner)

could be used to accomplish an important scientific objective. Pictures of devices created by students are shown in Figure 3.4. Although many of these techniques for device fabrication and hydrophobically-driven immobilization are standard in materials science and solid-state chemistry, it was the first time the students had fabricated such devices, and the pedagogical opportunities around solid-state chemistry were abundant. The use of the wax printer and Adobe Illustrator to make devices and ImageJ to analyze devices provided additional pedagogical opportunities for the instructor to introduce students, often for the first time, to technologies that are common in solid-state detection.

Figure 3.4. Student-created paper-based devices made from a) wax-printing, b) spray-painting, and c) eyeliner

The final component of this laboratory, the colorimetric detection of analytes, included significant amounts of information pertaining to analytical chemistry and colorimetric detection methods, including the use of mean grey values (MGV), obtained from RGB analysis, and the application of calibration curves for quantitative colorimetric detection. The students were introduced to the rigorous analytical techniques required to create serial dilutions, the methods for application of those serial

dilutions to the creation of a calibration curve, and finally, the use of that calibration curve for the quantitative analysis of an unknown sample provided by the Teaching Assistant. Using ImageJ, the MGV of each of the hydrophilic zones was obtained. Graphing the average MGV against the known analyte concentrations provided linear curves for which trendlines were found using Excel (examples of which can be found in the ESI). The trendlines were then used to find the concentration of unknown samples based on the MGV. This quantitative analysis was compared against student's initial, qualitative assessment of the unknown concentration, reaffirming the concept that pairing a color-changing detection scheme with computer-based analysis leads to more accurate quantitation. An example of student calibration curves and unknown comparison is shown in Figure 3.5.

Figure 3.5. Student-created *p*-acetaminophen and *p*-phenacetin calibration curves and unknown comparison scanned using a flat-bed scanner

3.3. Student Responses

This experiment was first tested as a final, collaborative experiment in the Advanced Organic Chemistry Laboratory at the University of Rhode Island in the Fall of 2017, where various methods for the fabrication of the wax barriers on paper-based devices were tested, including the use of wax-based eyeliner, acrylic spray paint, and a wax printer. The nine students in the class were split into three groups, with each student in the group beginning with a different starting material (*o*-, *m*-, or *p*-aminophenol), and using a different method for wax barrier formation (wax-based eyeliner, spray paint, or wax printing). The experiment was summarized in a formal lab report in which the grouped students share results to answer a series of in-depth discussion questions on the outcome of using different analytes and different methods for paper-based device fabrication. Of the students in the Fall 2017 laboratory, 100% of them successfully fabricated the devices; 100% made and purified the analytes; and 77% were able to detect the analytes using the devices they had made. Issues with the analyte detection component stemmed from student error in formulating correct concentrations of the chromophore, which we plan to address with the use of more accurate balances in the laboratory. More accurate balances could not be incorporated into the Fall 2018 semester, however, and thus correctly prepared solutions of the chromophore were provided by the Teaching Assistant (T. Mako).

In the Fall 2018 Advanced Organic Chemistry Laboratory, the experiment was incorporated as a regular experiment module. Based on Fall 2017 student feedback and input from the Teaching Assistant (T. Mako), wax printing was identified as the optimal method of device fabrication, and *p*-aminophenol as the optimal starting material for

organic syntheses, as the *para*- isomers generally led to higher product yields and darker colors upon reacting with NQS, and these were used for the entire student population in the Fall 2018 laboratory. Of the students in the Fall 2018 laboratory, 100% of them successfully fabricated the devices; 100% made and purified acetaminophen; 50 % made and purified phenacetin (with the relatively low percentage attributed to technical difficulties in the laboratory not associated with the experimental procedure); and 92% were able to detect the analytes using the devices they had made, with errors here stemming from students using micropipettes incorrectly. In this second iteration, a calibration curve and unknown concentration analysis was implemented with the goal of achieving quantitative detection, and 50% of students accurately determined the concentration of their unknown solution. Overall, student feedback from both years was highly positive, and included positive statements such as, “I enjoyed seeing the color change.” 100% of the respondents across both years of implementation agreed or strongly agreed with the statement, “I think the instructor should use the solid-state sensing experiment in future classes.”

3.4. Conclusions

This experiment is highly modular, in that it can be adapted for laboratories that wish to focus more specifically on one area. For example, an analytical laboratory could purchase the required analytes, thereby skipping the synthetic component, and focus entirely on colorimetric analysis and detection. A materials science laboratory can focus more on the optimization of device fabrication methods, and less on both synthesis and colorimetric analysis. Significant cost savings are also accessible through the use of

inexpensive eyeliner-based devices while still largely accomplishing the same pedagogical objectives.

In conclusion, the highly interdisciplinary experiment reported herein contains important aspects of a variety of areas of chemistry, including synthetic organic chemistry, materials science, and analytical chemistry, and fills a pedagogical need for teaching truly interdisciplinary science to undergraduate chemistry students. Based on our implementation of this experiment over two years in the advanced undergraduate organic laboratory in our department, we have demonstrated high modularity of the experiment, a variety of experimental options for fitting time, budgetary, and pedagogical constraints, and strong positive feedback from students who participated in the experiment. Current efforts in our laboratory are focused on ways to continue to develop interdisciplinary undergraduate experiments, and the results of these and other investigations will be reported in due course.

3.5. Experimental Procedures

3.5.1. Materials and Methods

All chemicals were received from Sigma-Aldrich or from Fisher Scientific and were used as received. IR spectra were acquired using a Shimadzu IRAffinity-1S FT IR spectrometer and Miracle 10 single reflection ATR accessory. NMR spectra were acquired using a Bruker Ascend 400 MHz spectrometer. Eyeliner (Wet n Wild H2Oproof Liquid Eyeliner), 6 mm diameter stickers (hole punched from a larger sticker using a 6 mm hole puncher), clear packing tape, and black Valspar High-Gloss Lacquer were obtained from a local CVS Pharmacy or hardware store. Whatman #4 filter paper

was obtained from Fisher Scientific both as 55 mm circles, for the spray-painting procedure, and as 460 mm x 570 mm sheets that were cut into 8.5 in x 11 in sheets for use in the wax printer or 2 in x 2 in sheets for use in the eyeliner procedure. A Xerox Color Qube 8580 was used for wax printing. A free trial of Adobe Illustrator was downloaded for use in the wax printing part of this experiment, and the free program ImageJ was downloaded for the color analysis part of this experiment. Micropipettes were purchased from Fisher Scientific and used as received.

3.5.2. Analyte Synthesis

1.00 gram of the assigned aminophenol (*ortho*, *meta*, or *para*) and an equimolar amount of acetic anhydride were combined in absolute (200 proof) ethanol and allowed to mix at room temperature for 30 minutes to form acetaminophen or an acetaminophen structural isomer. Details of the reaction workup varied depending on the aminophenol starting material but included rotary evaporation of the ethanol solvent and recrystallization of the crude reaction product to obtain pure material. A small amount of this material (25-50 mg) was set aside for later detection. The phenacetin analyte was formed by combining the remaining acetaminophen, or acetaminophen analog, with an equimolar amount of bromoethane and three equivalents of potassium carbonate in dimethylformamide. The solution was left to stir at room temperature for five days (until the next lab period), when it was extracted into ethyl acetate and isolated via rotary evaporation. All intermediates and final products were characterized by ^1H NMR and ^{13}C NMR (both in $\text{DMSO-}d_6$) and IR spectroscopy, and copies of student-acquired spectra are included in the electronic supporting information. The samples were then treated with 1.0 M HCl at 40 °C (at a concentration of 1 mg analyte/mL 1.0 M HCl) for

two days in order to deprotect the amine moiety in preparation for the reaction with sodium 1,2-naphthoquinone-4-sulfonate.

3.5.3. Fabrication of Paper-Based Devices

The fabrication of paper-based devices was testing using three distinct procedures in the first year of implementation, with the wax printing method (#3) used exclusively in the second year.

1. Using eyeliner: Nine 6 mm diameter stickers were placed on a 2" x 2" piece of Whatman #4 filter paper in a 3 x 3 array of 6 mm stickers, and liquid eyeliner was used to draw borders (approximately 2 mm thick) around the edge of each sticker. After removal of the stickers via tweezers, the colored filter paper was heated in an oven at 125 °C for 10 seconds to partially melt the wax in the eyeliner and fix the position of the circles. Clear packing tape was used to coat the back of the device so that the solution would not bleed through.
2. Using acrylic lacquer: Nine 6 mm diameter stickers were placed in a 3 x 3 array on a 55 mm circle of Whatman #4 filter paper, with space between each sticker. The filter paper was flipped over, and nine additional stickers were placed on the opposite side of the paper in exactly the same positions as the first 9 stickers. The filter paper was then placed on a Buchner filter funnel that was large enough to fit the full paper without bending the edges, the vacuum was turned on fully, and acrylic lacquer was used to spray each side of the paper. After full drying of the lacquer, all stickers were removed. Clear tape was again placed on the back of the device to ensure that the solution does not bleed through.

3. Using a wax printer (2017 semester): Adobe Illustrator was used to pattern a wax printed device with a 3 x 3 pattern of 6 mm diameter circles, and a wax printer that was connected to Illustrator was used to print the wax device as designed on the program. Once printed, the wax device was heated at 125 °C for 2 minutes in the oven to ensure that all barriers were fully melted and that the pattern was set on the filter paper. Clear packing tape was placed on the back of the device to ensure that solution will not bleed through.
4. Using a wax printer (2018 semester): Adobe Illustrator was used to pattern two wax printed devices with a 3 x 6 pattern of 6 mm diameter circles (for the calibration curves), and one device with a 3 x 3 pattern of 6 mm diameter circles (for the unknown analysis), and a wax printer that was connected to Illustrator was used to print the wax device as designed on the program. Once printed, the wax device was heated at 125 °C for 2 minutes in the oven to ensure that all barriers were fully melted and that the pattern was set on the filter paper. Clear packing tape was placed on the back of the device to ensure that solution will not bleed through.

3.5.4. Use of Paper-Based Devices

Each patterned device was treated with 6 μ L of the chromophore solution (2.0 mg/mL of sodium 1,2-naphthoquinone 4-sulfonate in DI water) and 6 μ L of sodium hydroxide solution (27.2 mg/mL in DI water). Without allowing the device to dry, 4 μ L of the phenol analytes (1 mg/mL solution in 1.0 M HCl) were added to each of the chromophore spots, following the general schematic shown in Figure 1, with the three circles per row used for triplicate measurements of the same sample. Finally, 2 μ L of

cetyltrimethylammonium bromide (2.0 mg/mL in DI water) was added as a color stabilizer. After drying of those analytes and comparison to a control sample of 4 μ L of 1.0 M HCl (lacking any phenol analyte but using otherwise identical conditions), a scan of the filter paper-based device was taken, using an EPSON flatbed scanner, and the colors in the photo were used to indicate the presence of the target analyte. This procedure was also used for unknown analysis (*vide supra*).

Figure 3.6. Placement of blank and analyte solutions on the paper-based devices for analysis

3.5.5. Generation of Calibration Curves

Analyte solutions of the concentrations 0.5 mg/mL, 0.25 mg/mL, 0.125 mg/mL, and 0.0625 mg/mL in 1.0 M HCl were created by serial dilution from the previously prepared 1 mg/mL solution for both acetaminophen and phenacetin. The first 3 x 6 patterned device was treated with 6 μ L of the chromophore solution (2.0 mg/mL of sodium 1,2-naphthoquinone-4-sulfonate in DI water) and 6 μ L of sodium hydroxide solution (27.2 mg/mL in DI water). Without allowing the device to dry, 4 μ L of the acetaminophen solutions, or 4 μ L of 1.0 M HCl (for the control) were added to each of the hydrophilic zones, following the general schematic shown in Figure 2, with the three circles per row used for triplicate measurements of each sample. Finally, 2 μ L of cetyltrimethylammonium bromide (2.0 mg/mL in DI water) was added as a color stabilizer to each hydrophilic zone. This procedure was repeated on the second 3 x 6

patterned device for the phenacetin solutions. After the devices had dried completely, scans were taken using an EPSON flatbed scanner, and ImageJ was used to collect the Mean Grey Value (MGV) for each individual zone. The average values for each trial were used to create a calibration curve, and the trendline of the curve, found using Excel, was used for unknown quantification.

Figure 3.7. Placement of blank and analyte solutions on the paper-based devices for calibration curve

3.6. Copies of Student Spectra and Images

Figure 3.8. ¹H NMR spectrum of *o*-acetaminophen

Figure 3.9. ¹³C NMR spectrum of *o*-acetaminophen

Figure 3.10. IR spectrum of *o*-acetaminophen

Figure 3.11. ¹H NMR spectrum of *o*-phenacetin

Figure 3.12. ^{13}C NMR spectrum of *o*-phenacetin

Figure 3.13. IR spectrum of *o*-phenacetin

Figure 3.14. ^1H NMR spectrum of *m*-acetaminophen

Figure 3.15. ^{13}C NMR spectrum of *m*-acetaminophen

Figure 3.16. IR spectrum of *m*-acetaminophen

Figure 3.17. ¹H NMR spectrum of *m*-phenacetin

Figure 3.18. ^{13}C NMR spectrum of *m*-phenacetin

Figure 3.19. IR spectrum of *m*-phenacetin

Figure 3.20. ^1H NMR spectrum of *p*-acetaminophen

Figure 3.21. ^{13}C NMR spectrum of *p*-acetaminophen

Figure 3.22. IR spectrum of *p*-acetaminophen

Figure 3.23. ¹H NMR spectrum of *p*-phenacetin

Figure 3.24. ^{13}C NMR spectrum of *p*-phenacetin

Figure 3.25. IR spectrum of *p*-phenacetin

Figure 3.26. Student acetaminophen calibration curve from 2018 semester

Figure 3.27. Student phenacetin calibration curve from 2018 semester

3.7. References

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CHAPTER 4 PREFACE

Supramolecular Luminescent Sensors is a comprehensive review article prepared with contributions from Joan Racicot and Dr. Mindy Levine which was published in the peer-reviewed journal *Chemical Reviews* in 2019. Sections that were primarily written by J. Racicot and M. Levine (luminescent nanomaterial and polymer sensor sections) and sections that were not deemed relevant for this dissertation (analyte and fluorophore sections and certain subsections of the macrocycle section) have been removed.

CHAPTER 4

Supramolecular Luminescent Sensors

4.1. Introduction

The ability to detect a broad variety of analytes under a wide variety of real-world conditions is critical for a number of applications and in a wide range of scientific, medical, political, and security realms. Broadly speaking, chemists have been highly successful at developing detection methods for small organic molecules,^{1,2} anions^{3,4} and cations;^{5,6} biological macromolecules including peptides,^{7,8} and oligonucleotides;⁹ and whole cells^{10,11} and organisms, including bacteria^{12,13} and fungi.^{14,15} Notable successes include the use of these systems for the detection of 2,4,6-trinitrotoluene (TNT)^{16,17} in the air above land mines,¹⁸ for demarcation of tumor boundaries to enable highly effective tumor resection surgeries,¹⁹ and for the detection of bacteria in food,²⁰ liquid,²¹ and the human body.²²

In all cases, the rational design of chemical sensors, or chemosensors, for detection applications requires thorough consideration of all system components: (1) the analyte, defined as the target for detection; (2) the recognition element, defined as the part of the sensor that recognizes the analyte; (3) the transducer, defined as the sensor component that responds to the presence of the analyte with a change in signal; (4) the environment (solvent²³ and/or solvent additives;²⁴ gas-phase environment;²⁵ solid-state backing),²⁶⁻²⁸ and (5) all other experimental parameters, including the system temperature²⁹ and the concentrations of all components.³⁰

Figure 4.1. Examples of recently developed chemosensors that have all three aspects of an ideal chemosensor: selectivity, sensitivity, and applicability^{31-32,33}

One classification system for understanding sensor platforms is to divide such platforms into two categories: those that are sensitive and those that are selective. Selective sensor platforms, in this classification, refer to those that detect only one analyte, whereas sensitive platforms refer to those that use multidimensional analyses for the (often simultaneous) detection of multiple analytes.³⁴ Selective detection schemes require sensor molecules, such as antibodies,^{35,36} enzymes,^{37,38} or aptamers,^{39,40} that are specific for binding and detecting one analyte. Such systems have strong commercial successes in pregnancy tests,^{41,42} HIV diagnostic systems,^{43,44} and glucose monitoring equipment.^{45,46} all of which require specificity for one analyte. However,

since most analytes share similar structural features with a large range of other molecules, identifying a sensor that binds only a single target analyte is often impractical, and sensitive detection can be the most feasible option. To accomplish such sensitive detection, array-based statistical analytical methods are used to create unique fingerprints for the desired analytes, which are then used for accurate unknown identification.⁴⁷

Overarching goals of sensor chemistry is to develop sensors that have general applicability in multiple environments, high levels of sensitivity for low concentrations of the target analyte, and good selectivity in distinguishing that analyte from other, often structurally related or commonly co-existing compounds (Figure 4.1). Often, in controlled lab settings, sensitive detection platforms will fare well, only to fall short in circumstances where multiple analytes are present or in relatively complex environments. Selective sensors are generally more successful in complex environments because of the extremely strong analyte-sensor binding displayed by the sensor elements, but there is a relatively small range of molecules that can be detected by selective methods. As discussed in a recent review by Rotello and coworkers,³⁴ a key challenge in sensor development is the design, optimization, and implementation of systems that are highly selective, highly sensitive, and work well in real-world environments.

Supramolecules are molecular assemblies that are held together by intermolecular forces rather than by covalent bonds. Several features inherent to such systems make them ideal candidates for use as chemosensors, including:⁴⁸ (1) Ease of formation: Supramolecules are able to form highly ordered and complex systems without the need

for covalent bond formation, which avoids lengthy synthetic processes, and facilitates rapid sensor development;⁴⁹ and (2) Adaptive nature: The relatively weak nature of the intermolecular interactions that underlie supramolecular assemblies means that the assemblies are adaptive, and can change their configurations in response to a variety of external stimuli, including the introduction of the target analyte. Such configurational changes, in turn, often lead to a measurable change in an optical signal, including fluorescence and absorption changes. High levels of reversibility, another feature of supramolecular assemblies that is a consequence of the labile intermolecular interactions, means that once the external stimulus is removed, the supramolecular host can reorder to its original state.⁵⁰ Supramolecular luminescent sensors often rely on non-covalent supramolecular interactions in all areas of the sensor system, including in sensor-analyte, sensor-fluorophore, and fluorophore-analyte interactions.^{51,52} System reversibility provides significant practical advantages, especially compared with sensors that rely on covalent bond formation, which is often irreversible and leads to single-use sensors.⁵³ This review will discuss luminescent supramolecular macrocycles and their use in chemosensor design. Although metal organic frameworks are also prominent luminescent supramolecular hosts, they will not be discussed in this review, and the authors direct interested readers to several other reviews on the topic.⁵⁴⁻⁵⁸ We would also like to apologize to any researcher whose work has been inadvertently overlooked.

Changes in a detectable signal that occur in the presence of the analyte can refer to a broad variety of signaling elements and various types of read-outs, including changes in color (for colorimetric or absorption-based detection);⁵⁹⁻⁶¹ changes in the Raman spectral signal (for Raman-based detection);^{62,63} changes in the mass of the sensor after

a target analyte binds (for quartz crystal microbalance detection);⁶⁴⁻⁶⁶ or changes in any other spectroscopic,⁶⁷ quantitative,⁶⁸ or analytical property.⁶⁹ Luminescence-based chemosensors refer to those sensors that respond to the presence of the target analyte with a detectable change in the luminescence signal, with the main types of luminescence being fluorescence, characterized as an allowed, singlet-to-singlet relaxation with photon emission, and phosphorescence, characterized as a forbidden, triplet-to-singlet relaxation with photon emission. More details about the mechanism of fluorescence and phosphorescence are discussed in Section 4.3, below. Luminescent chemosensors require a component that is photophysically active, in order for the target analyte to induce a measurable change in that photophysical activity.⁷⁰ The change of photophysical activity may occur through a change in the magnitude of emission intensity, the wavelength of the emission maximum, the quantum yield, or the relative ratios of various fluorescence/phosphorescence-emitting components.⁷¹ Multiple types of emission changes can also occur simultaneously,^{72,73} especially in complex detection environments.⁷⁴

This review begins with a review of some of the underlying principles of chemosensors, including the non-covalent forces that govern such systems, and the mechanisms of recognition between an analyte and chemosensor via non-covalent interactions. From there, we will review particular classes of luminescent cavitand macrocycles. Fluorescent chemosensors are much more common than those based on other types of luminescence, and thus the majority of discussions herein are focused on fluorescence. The concluding section of the review article includes a discussion of

unsolved issues in the field of chemosensors, and how future directions of luminescent chemosensors might address those issues.

Of note, the field of chemosensors in general, and fluorescent chemosensors in particular, is highly active with significant numbers of chemists publishing in this field. Readers are directed to other reviews on this important topic to supplement this one, including reviews by Anslyn,^{75,76} Rotello,^{77,78} Gibb,^{79,80} Rebek,^{81,82} Liu,^{83,84} and Swager.⁸⁵⁻⁸⁷

4.2. Non-Covalent Interactions in Supramolecular Systems

In order for a chemosensor to detect an analyte of interest, the presence of the analyte must induce a measurable change in a read-out signal that can be detected by a user, or operator, of the sensing device. This requires association between the analyte and the chemosensor, which can occur either via covalent⁸⁸ or non-covalent interactions.⁸⁹ Association via non-covalent interactions in sensor design is significantly more common in the scientific literature compared with covalent association,^{90,91} because covalent association is often irreversible (with the exception of dynamic covalent chemistry), leading to single-use sensors. Common non-covalent interactions between the analyte and the chemosensor include: hydrophobic association,⁹² electrostatic interactions,^{93,94} intermolecular hydrogen bonding,⁹⁵ cation- π ⁹⁶ and anion- π ⁹⁷ interactions, and other aromatic interactions, including π - π stacking⁹⁸ and edge-face interactions.⁹⁹ When designing a sensor, it is important to note that very rarely do supramolecular complexes rely on just one non-covalent interaction.¹⁰⁰ Combinations of several interactions are often present, and efforts toward designing a system to achieve a myriad of non-covalent interactions are complex and varied. Examples of such

cooperativity include: a combination of π - π interactions and weak hydrogen bonding allowing for the formation of oligophenyleneethynylene-based amphiphilic platinum(II) complexes;¹⁰¹ and a combination of cation- π , anion- π , and intermolecular hydrogen bonding facilitating the assembly of ternary complexes of 1,3,5-triamino-2,4,6-trinitrobenzene, an anion, and a cation.¹⁰²

4.2.1. Hydrophobic Association

Hydrophobic association refers to favorable interactions that exist between two non-polar molecules when they are found in an aqueous environment,¹⁰³ with the two molecules associating in a geometry that allows the exclusion of water.¹⁰⁴ Fewer interactions between the aqueous solvent and the non-polar molecules result in a more energetically favorable system¹⁰⁵ because water molecules at the interface with the non-polar molecules are highly ordered, and hydrophobic association reduces the size of that interface. The history of the hydrophobic effect began in earnest in the biochemistry community in the 1960s, with very few examples reporting hydrophobic association before that decade.¹⁰⁶⁻¹⁰⁸ In 1967, a biochemist named Bernard Randall Baker first reported the existence of hydrophobic association as key factor in facilitating enzyme-substrate binding and enzymatic catalysis.¹⁰⁹ Other biochemists soon reported similar effects,¹¹⁰⁻¹¹² highlighting the ubiquity of this interaction in biological systems. Soon after that, in 1970, Ronald Breslow and coworkers reported the first synthetic use of the hydrophobic effect to drive the design and performance of a cyclodextrin-based artificial enzyme.^{113,114}

Examples of hydrophobic association between a supramolecular host and a target analyte include cyclodextrin binding a hydrophobic guest in its hydrophobic interior

cavity,^{115,116} which results in displacing high energy water from the cavity¹¹⁷ (so named because of its inability to form the full complement of hydrogen bonds, (Figure 4.2)^{118,119} and an overall energetically favorable binding. Such binding has been used in chemical sensors, in cases where the binding of an analyte induces changes in the fluorescence emission signal of a fluorophore bound (covalently^{120,121} or non-covalently)^{122,123} in close proximity, in cases where analyte binding induces displacement of a photophysically active guest from the cavity; and in cases where the analyte itself is photophysically active and displays photophysical changes as a result of encapsulation in the cyclodextrin cavity.

Figure 4.2. “High energy” water, i.e. water without a full complement of intermolecular hydrogen bonds, in a single-file arrangement inside of a single-walled carbon nanotube. Reproduced from Ref. 124. Copyright 2017 American Chemical Society

Cucurbiturils (CBs) are another class of macrocyclic chemosensors that rely on hydrophobic association to bind a small-molecule analyte in the interior of the cavity. As with cyclodextrins, these interactions are favored due to the displacement of high-energy water from the macrocycle cavity. Many isomers of these compounds exist, with the most common ones being CB[6], CB[7],¹²⁵ and CB[8].¹²⁶ Isaacs,^{127,128} Masson,^{129,130} Nau,¹³¹ Kaifer,⁵³ and others¹³² have demonstrated unprecedentedly high levels of affinity between the CB hosts and small molecule guests. Although these supramolecular hosts are often not photophysically active (with few exceptions),^{133,134} the attachment of a photophysically active moiety to the CB core results in a read-out signal that changes in the presence of the target analyte. Synthetic cavitands, including those developed by Gibb,^{135,136} Rebek,^{137,138} and Anslyn,^{75,76} demonstrate markedly improved hydrophobic association and binding affinities compared to naturally-occurring and synthetically-modified cyclodextrins and cucurbiturils. Many of these synthetic cavitands have significant conformational rigidity,¹³⁹ which eliminates undesired flexibility in the cavity and facilitates extremely strong binding.¹⁴⁰

Hydrophobic association also occurs for polymeric chemosensors.^{141,142} In one example, researchers reported the use of highly hydrophobic nanostructures derived from block copolymers for the detection of small-molecule nitroaromatics.¹⁴³ These nanostructures were rendered water dispersible as a result of the inclusion of non-conjugated segments, and were highly fluorescent due to their poly(*p*-phenylenevinylene) block components. Analyte-induced quenching of the nanostructure's fluorescence was used to detect nitroaromatics at 0.5 ppm in fully aqueous environments. A variety of other examples have also been reported.^{144,145}

Of note, the strength of hydrophobic association between two non-polar molecules is intimately dependent on the solvent composition,¹⁴⁶ which must be highly polar (usually aqueous) in order to favor solvent exclusion between the non-polar molecules.^{147,148} Moreover, a variety of solvent additives can be used to tune the strength of the effective hydrophobic interactions, with additives such as chaotropic agents decreasing the effective hydrophobicity,¹⁴⁹ and additives such as kosmotropic agents increasing it.¹⁵⁰

Hydrophobic interactions are highly prevalent in well-solubilized solutions, but they can also occur in the solid-state, at interfaces, or in a variety of other situations. For example, at the air-water interface, hydrophobic interactions occur between non-polar molecules.¹⁵¹ These interactions drive the self-assembly of ionic liquids,¹⁵² determine how amino acids interact with lipid monolayers,¹⁵³ and are instrumental in determining the three-dimensional conformation of enzymes.¹⁵⁴ Computational investigations of molecules at the air-water interface point to factors such as significant aqueous surface tension,¹⁵⁵ relatively high polarity of the air,¹⁵⁶ and the decreases in entropy associated with organized assemblies of molecules¹⁵⁷ as factors that determine molecular and supramolecular behavior at these interfaces.¹⁵⁸ In highly polar solid matrices, two non-polar analytes associate with energetics and geometries that closely mimic solution-state hydrophobic binding.¹⁵⁹ By contrast, hydrophobic interactions in the gas state are almost unheard of,¹⁶⁰ due to the lack of an energetic driving force to compel two non-polar molecules into close proximity.¹⁶¹

Classical hydrophobic interactions are entropy-driven and occur due to the increase in the disorder of water molecules when they are removed from the well-ordered

interface with the non-polar analyte and become part of the bulk aqueous solvent. Of note, small enthalpic contributions are generally also present.^{162,163} Rigorous studies of certain systems, such as the inclusion complexes formed between bile salts and β -cyclodextrin,¹⁶⁴ have described non-classical hydrophobic effects that are driven by enthalpy.¹⁶⁵ Because the energetic driving force of hydrophobic association can have both entropic and enthalpic contributions, the primary thermodynamic driving force for a given host-guest system cannot be fully assumed unless proper studies are conducted, including isothermal titration calorimetry (ITC)¹⁶⁴ and computational studies.¹⁶⁶

Hydrophobic interactions are usually measured by determining the strength of binding between two non-polar molecules and conducting rigorous experiments to rule out other possible interactions, thus determining by exclusion that hydrophobic interactions must be occurring. Various types of computational modeling have also been used to support the existence of a hydrophobic interaction, although questions about the simplifying assumptions inherent in such computational methods remain, as do questions about the accuracy of some of the results.^{167,168} These questions arise because although computational work can be highly accurate for extremely small systems, the significant computing resources required to achieve similar accuracy for larger systems is often prohibitive, resulting in the use of multiple simplifying assumptions. To address this issue, Chia-en Chang¹⁶⁹⁻¹⁷¹ and others^{172,173} have developed new computational models that are particularly effective at predicting hydrophobic association, especially in large, flexible supramolecular structures such as cyclodextrins.

4.2.2. Electrostatic Interactions

Electrostatic interactions are significantly stronger than interactions involved in intermolecular hydrophobic association, with gas-phase binding strengths that approach covalent bond interactions, although they are often weakened in water due to ion solvation.^{174,175} Examples of using electrostatic interactions in luminescent chemosensors include the use of fluorescent cationic polyelectrolytes, developed by Bazan,^{9,176,177} Heeger,^{178,179} LeClerc,¹⁸⁰ and Liu,^{181,182} to bind polyanionic DNA and transduce that binding into noticeable photophysical changes.

One weakness that is traditionally associated with electrostatically-driven chemosensors is that of low selectivity, because electrostatic interactions are highly promiscuous.^{183,184} Oftentimes, selectivity in chemosensors needs to be balanced against sensitivity in the same systems, as factors that benefit one of these elements can work against the other.³⁴ Selectivity is particularly challenging for high strength, promiscuous interactions such as electrostatic interactions, especially in complex environments.¹⁸⁵ In the use of cationic polyelectrolytes to bind polyanionic DNA, the authors achieve reasonable selectivity through the use of multiple favorable electrostatic interactions,^{186,187} which act cooperatively to enable high selectivity to occur.^{188,189}

Non-classical electrostatic interactions have been reported by Flood and coworkers in which two or more anions were found to stabilize each other through the formation of anti-electrostatic hydrogen bonds.¹⁹⁰ For example, dimers or multimers of bisulfate⁴ or phosphate,¹⁹¹ chaotropic anions, were stabilized by encapsulation in a macrocyclic cavity, leading to the formation of stable 2:2 and higher order, host-guest complexes. A crystal structure that shows an example of this binding is shown in Figure 4.3. Other

anions, including I^- , ClO_4^- , and NO_3^- , formed 1:1 host-guest complexes with cyanostars, with anion dimers not forming due to their lack of hydrogen atoms.¹⁹²

Figure 4.3. A crystal structure of three phosphate anions stacked inside four cyanostar hosts as reported by Flood and coworkers. Reproduced with permission from Ref. 191. Copyright 2018 Royal Society of Chemistry

The strength of electrostatic interactions, much like that of hydrophobic interactions, are intimately dependent on the solvent environment.^{193,194} Highly polar solvents interact directly with the charged components, and as a result partially mitigate the charge that is felt by the other system component, resulting in a lower “effective” charge.¹⁹⁵ Aqueous solvents, for example, orient water around both cations¹⁹⁶ and anions¹⁹⁷ in a way that facilitates solvation of the anions but decreases the effective charges and the strength of the electrostatic interactions.¹⁹⁸ Electrostatic interactions in non-polar solvents, by contrast, are generally magnified, due the inability of the solvent to solvate charged species effectively.^{199,200}

Electrostatic interactions exist in non-solution-state systems and are often stronger in these systems due to lack of solvent interference. In particular, solid-state fluorescent

chemosensors use electrostatic interactions to bind polyanionic dengue viral DNA²⁰¹ and polycationic serine-containing proteases.²⁰² Electrostatic interactions also exist in the gas phase,²⁰³ and have been studied using gas-phase IR multiple photon dissociation (IRMPD) spectroscopy, ion mobility-mass spectrometry (IM-MS),²⁰⁴ and various UV and other IR techniques.²⁰³

4.2.3. Intermolecular Hydrogen Bonding

The traditional definition of an intermolecular hydrogen bond is a favorable interaction between a hydrogen atom attached to an electronegative atom on one molecule, termed the hydrogen bond donor, and an atom with a lone pair of electrons on a different molecule, termed the hydrogen bond acceptor (Figure 4.4).²⁰⁵ These interactions are generally weaker than electrostatic interactions, but stronger than hydrophobic and other non-polar interactions. Of note, recent work has expanded the traditional definition of a hydrogen bond to include a greater variety of hydrogen bond donors, as long as the atom directly attached to the participating hydrogen has significant electronegative character.²⁰⁶ Hydrogen bonding under this expanded definition has been reported between a C-H bond and an iodide anion,²⁰⁷ between a molybdenum and phenol proton,²⁰⁸ between an sp³-hybridized C-H proton and aromatic ring,²⁰⁹ and between carboranes and aromatic rings.²¹⁰

Figure 4.4. Electrostatic potential map of the intermolecular hydrogen bonding between Coumarin 30 and tetrahydrofuran (THF). Adapted with permission from Ref. 211. Copyright 2018 Springer

Some structural motifs typically used in hydrogen bonding include squaramides,²¹² ureas,²¹³ and thioureas.²¹⁴ Often, these motifs are used to drive self-assembly,²¹⁵ including the self-assembly of supramolecular hosts.^{216,217} In one example, Bruce Gibb reported the design, synthesis, and applications of a series of self-assembled supramolecular cavitands,²¹⁸⁻²²⁰ where the driving force for self-assembly is through intermolecular hydrogen bonding.^{221,222} In another example, hydrogen bond-driven chemosensors in chloroform were reported by Zimmerman and coworkers.^{223,224} Such self-assembled architectures bound a variety of small molecule guests, including nitroaromatics,²²⁵ guanosine,^{226,227} and other nucleotide bases²²⁸ with extremely high

affinities, due to favorable binding of host and guest molecules with alternating donor and acceptor groups.

Unlike intermolecular hydrophobic association, hydrogen bonding is primarily driven by enthalpy, although highly solvent dependent²²⁹ enthalpy/entropy compensation balances have also been reported.²³⁰ A report by Ross and Subramanian studied the thermodynamics of protein association, discovering a temperature-dependent system in which the processes are driven by entropy and hydrophobic associations at low temperatures, and by enthalpy and hydrogen bonding at high temperatures.²³¹ The researchers asserted that the presence of hydrogen bonding can be revealed by negative values of entropy and enthalpy, indicating that hydrogen bonds produce favorable enthalpic contributions. David van der Spoel and coworkers employed classical molecular dynamic simulations of alcohol/water mixtures to derive thermodynamic parameters of the hydrogen bonds present in the solvent mixtures.²³² In these situations, the formation of hydrogen bonds was almost always enthalpically favorable and for higher concentrations of alcohol in water, entropic barriers were present. Leung, Peng, Chou and coworkers developed a series of oligo- α -aminopyridines with a high propensity for hydrogen bond-promoted dimerization, finding that increasing the number of hydrogen bonding sites present led to significant enthalpic stabilization of the dimers.²³⁰

The existence of hydrogen bonding can be inferred through solid-state X-ray crystallography,^{233,234} although not visualized directly, because hydrogen atoms are generally too small to be seen.²³⁵ Moreover, the existence of hydrogen bonding in the solid state does not provide direct information about solution-state hydrogen bonding,

even when comparing the same molecule, as ample literature precedent supports the fact that intermolecular interactions in the two states can differ widely.^{236,237} Direct solution-state measurements of intermolecular hydrogen bonding generally rely on spectroscopic measurements including ^1H NMR²³⁸ and near-²³⁹ and far-infrared spectroscopy.²⁴⁰

4.2.4. Cation- π Interactions

The history of the cation- π interaction began in 1981, when chemists found that the gas-phase interaction between a potassium cation and benzene was stronger than the gas-phase interaction between the potassium cation and water.²⁴¹ Similar results were measured for the interactions of other cations, including sodium and lithium cations, with benzene, demonstrating the generality of this phenomenon and pointing to the existence of favorable cation- π interactions. Following this initial discovery, Dougherty and coworkers used such interactions to bind a positively charged quaternary amine guest, adamantyltrimethylammonium iodide, inside an aromatic catenane.^{242,243} An example of a cation- π interaction between benzene and NH_4^+ is shown in Figure 4.5.

Figure 4.5. Electrostatic potential map of the cation- π interaction between benzene and NH_4^+ . Reproduced from Ref. 243. Copyright 2013 American Chemical Society

Scientific consensus about the nature of the cation- π interaction is that it is primarily an electrostatic interaction between a positively charged cation and the negative charge density that exists above an aromatic ring.²⁴⁴ Like most electrostatic interactions, larger ions produce weaker interactions because of lower charge densities.²⁴⁵ Therefore, in the gas phase, the strength of cation- π interactions follows the following order, with the smallest cation (lithium) participating in the strongest cation- π interactions:²⁴⁶

The use of the cation- π interactions in fluorescent chemosensor design focuses on the detection of cations including potassium,²⁴⁷ mercury,²⁴⁸ and cesium.²⁴⁹ Such chemosensors have been designed to take advantage of cation- π interactions, including in the development of a supramolecular hydrogel containing an aromatic pillar[5]arene with pendant naphthalimide arms that bind, detect, and remove mercury cations;²⁴⁸ and with the use of a naphthylamine-derived host for the selective detection of copper.²⁵⁰

The existence of cation- π interactions has been measured with a variety of methods, including the imaging of charge transfer in a cation- π system in the gas phase.²⁵¹ Initial gas-phase measurements of cation- π interactions were much higher in magnitude than subsequent solution-phase measurements due to the solvation of cations that occurs, to varying degrees, in virtually all solvents investigated. Nonetheless, solution-phase cation- π interactions are particularly favored in non-polar and aprotic solvents that have limited interactions with the cation.²⁵²⁻²⁵⁴ Particular examples of such interactions in biological systems have been reported,^{255,256} including as essential components in the formation of tertiary protein structures.²⁵⁷

Moreover, solid-state cation- π interactions have also been measured, and include examples such as interactions between aromatic triphenylene and potassium cations,²⁵⁸ between a cationic surfactant and aromatic PAHs in a clay matrix,²⁵⁹ and between alkali metal cations and an aromatic macrocyclic host.²⁶⁰ The limited mobility of the cations and the aromatic moieties within the matrix limits the ability to voluntarily adopt the most favorable intermolecular distances, but systems that position each component in the appropriate location can use these interactions to achieve highly stable multicomponent architectures.²⁶¹

4.2.5. Anion- π Interactions

The anion- π interaction⁹⁷ is a relatively newly investigated intermolecular phenomenon, especially compared to many of the aforementioned non-covalent interactions,^{262,263} and there was initially some controversy around the legitimacy of such interactions, due to their counterintuitive nature,²⁶⁴ when they were first introduced.^{265,266} A crystal structure demonstrating a close-range interaction between an anion and aromatic ring, reported in 2004, unambiguously proved that anion- π interactions exist in the solid state.²⁶⁷ Following that report, evidence of solution-state anion- π interactions was discovered via spectroscopic methods,²⁶⁸ and computational methods were used to obtain significantly improved understanding of such forces.^{269,270} In contrast to the negative electron density that exists over an unsubstituted benzene ring, a significant region of positive electron density exists over aromatic rings with highly electronegative substituents, such as hexafluorobenzene.^{271,272} This positive region of electron density can, in turn, bind to a broad variety of anions in a phenomenon termed an “anion- π interaction” (Figure 4.6).

Figure 4.6. Electrostatic potential maps of benzene, hexafluorobenzene, and trifluorotriazine and (b) modes of anion- π interactions as reported by Hay²⁷³ and Albrecht.²⁷⁴ Reproduced from Ref. 263. Copyright 2013 American Chemical Society

Anion- π interactions are particularly useful in designing sensors that can detect anions, including those with significant public health, agricultural, and security interests such as fluoride,²⁷⁵ nitrate,²⁷⁶ and perchlorate.²⁷⁷ Of note, because anions are generally strongly solvated in aqueous solutions, anion binding motifs generally need to be designed to either bind solvated anions or to strip (or partially strip) the aqueous solvation shell prior to binding.²⁷⁸ The extent to which anions are solvated/desolvated and how such solvation impacts binding affinities and selectivities is a highly active research area.^{279,280}

4.2.6. π - π Interactions

π - π Interactions refer to the interaction between the negative electron density of one aromatic ring and a second aromatic ring to form one of three possible structures:²⁸¹ a sandwich structure,²⁸² a T-shaped structure,^{283,284} or a parallel displaced structure²⁸⁵ (Figure 4.7). The actual structure of the dimer that forms depends on a number of experimental and structural parameters, with two benzene molecules in the gas phase interacting in a T-shaped geometry,²⁸⁶ where the negative electron cloud on one molecule interacts with a proton (with partial positive charge) on the second aromatic molecule. In contrast, differently substituted aromatic rings, especially those with widely disparate charge densities, will interact to form a sandwich structure. For example, benzene and hexafluorobenzene, with significantly different charge densities, crystallize in infinite stacks with alternating benzene and hexafluorobenzene moieties.²⁸⁷ This phenomenon was first reported in 1960, where the mixture of C_6H_6 and C_6F_6 was characterized as a “molecular complex.”²⁸⁸ The third possible geometry, parallel displaced structures, is extremely rare for single-ring aromatic moieties, and is markedly more prevalent in intermolecular interactions involving medium and large-sized polycyclic aromatic compounds.^{289,290}

Figure 4.7. Depictions of sandwich, T-shaped, and parallel displaced modes of π - π stacking^{286,291}

π - π interactions are extremely useful in sensing applications, especially for the sensing of aromatic analytes.²⁹² For example, Stoddart and coworkers have synthesized a variety of aromatic hosts that are capable of binding aromatic guests with high affinities via π - π stacking.²⁹³ There are large varieties of aromatic guests that are important targets for detection due to their environmental prevalence and high toxicities to humans, including polycyclic aromatic hydrocarbons,²⁹⁴ polychlorinated biphenyls,²⁹⁵ bisphenol A and other bisphenol analogues,²⁹⁶ and aromatic pesticides such as DDT.²⁹⁷ Work in the Levine group has included the design and synthesis of aromatic ring-containing macrocycles, which have demonstrated enhanced binding affinities for aromatic guests compared to non-aromatic cyclodextrin hosts,²⁹⁸ and more efficient energy transfer between an aromatic analyte and high quantum yield aromatic fluorophore when both are bound in the macrocycle's interior.²⁹⁹ Much of this enhanced performance is attributed to favorable π - π stacking interactions, and computational modeling of the complexes supports favorable and close-range interactions between the aromatic rings in the various system components.³⁰⁰

4.2.7. Halogen Bonding

Halogen bonding, which is defined as the non-covalent interaction between a Lewis acidic halogen and a Lewis base, has gained significant attention in recent years due to its utility in supramolecular sensing (specifically anion recognition), templated self-assembly, and catalysis.^{301,302} Halogen atoms, due to their high electronegativity, can participate as electron donors in interactions with electron acceptors including hydrogen atoms, alkali metals, or alkaline earth metals.³⁰² In cases where the halogen atom is bound covalently to another atom, the electron density about the halogen atom becomes

anisotropically distributed, as shown in Figure 4.8. A band of increased electronegativity about the center of the halogen atom, orthogonal to the covalent bond, is formed, while the end of the atom becomes electropositive. This electropositive region is then able to form non-covalent interactions with electron-rich sites, such as other halogen atoms. This model of explaining halogen bonding is referred to as a sigma-hole model.³⁰³ Other models, including a lump-hole model,³⁰⁴ have been proposed, and significant theoretical efforts to fully explain the halogen bonding interaction have also been reported.³⁰⁵

Figure 4.8. Depiction of anisotropic distribution in a halogen atom covalently bound to another atom. Reproduced from Ref. 302. Copyright 2016 American Chemical Society

Efforts to use non-covalent halogen bonding in supramolecular chemical sensing have taken a variety of forms. Diedrich and co-workers reported the use of halogen bonding for directing the self-assembly of complex resorcinarene cavitands,³⁰⁶ with interactions gained from a single halogen bond competitive enthalpically with that of an intermolecular hydrogen bond.³⁰⁷ Halogen bonding has also found utility in luminescent chemical sensing in cases where halogen bonding can trigger assembly and/or disassembly of a sensing element;³⁰⁸ in the detection of anions in which halogen

bonding between the anion and sensor is used to achieve high selectivity;³⁰⁹ and in the development of sensors for biological processes, through use of halogen bonding to modulate molecular conformations and achieve target selectivity.³¹⁰

4.3. Mechanisms of Fluorescence

The process of luminescence is characterized by the radiative release of a photon from a molecule as it transitions from an excited state back to its ground state configuration.^{175,311,312} Fluorescence and phosphorescence, the two main categories of luminescence, are differentiated based on the excited state from which the photon is released. The Jablonski diagram, shown in Figure 4.9, illustrates the difference in these two phenomena. When a molecule is irradiated, it transitions from the ground S_0 state to the excited S_1 state. In many cases, the molecule transitions back to the ground state via a non-radiative pathway, known as internal conversion, in which no photon is emitted and luminescence is not observed.³¹¹ Alternatively, radiative decay can occur as the molecule relaxes from S_1 to S_0 . During this process, termed fluorescence, a photon is released. This radiative decay is promoted by conjugation of the molecule or the presence of inherently luminescent atoms such as terbium or europium.³¹² In a final instance, the molecule can undergo the spin-forbidden transition from an excited singlet state, S_1 , to an excited triplet state, T_1 , through non-radiative intersystem crossing. Because this is technically a forbidden transition, the likelihood of this transition occurring is generally low, although it can be increased in cases of similarity between the molecular geometry and vibrational levels of the molecule's excited singlet and triplet states, as well as in cases where strong spin-orbit coupling, often due to the heavy atom effect, is possible and can promote the necessary spin flip.¹⁷⁵ Spin-orbit coupling

is the mixing of the spin and orbital quantum numbers of a molecule, and heavier atoms have a higher mixing of these two states than do lighter atoms. After undergoing the forbidden transition, the molecule then relaxes from T_1 to S_0 in a radiative pathway referred to as phosphorescence. Due to the spin-forbidden nature of phosphorescence, the lifetimes of fluorescent and phosphorescent emissions are vastly dissimilar, with the former occurring on micro- or nano-second timescales and the latter on millisecond-to-second timescales. It is very common to observe a change in the fluorescence or phosphorescence emission spectra upon the formation of a host-guest association complex; however, host-guest complexation can also lead to measurable changes in phosphorescence lifetimes, allowing for time-gated detection³¹³⁻³¹⁷ in which the presence of an analyte can be detected based on the longevity of a phosphorescence signal.¹⁷⁵

Figure 4.9. Jablonski Diagram illustrating the electronic transitions that lead to absorbance, fluorescence, and phosphorescence^{175,311,312}

Luminescent supramolecular detection schemes often rely on the ability of an analyte to change the fluorescent or phosphorescent emission of a sensor molecule through the transfer of energy.³¹² There are several different mechanisms by which this energy transfer can occur: Förster resonance energy transfer (FRET), photo-induced electron transfer (PET), and electron exchange (EE). Of note, in any given system, multiple energy transfer mechanisms can occur simultaneously, and the possibility of multiple coexisting mechanisms should be explicitly considered in any mechanistic investigation. The transfers are characterized based on differences in the electron movements between the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) of the participating molecules as illustrated in Figure 4.10, as well as by the observed changes in the emission profile.¹⁷⁵ The fluorescent or phosphorescent molecule in a host-guest complex can be either the energy donor, energy acceptor, or both, depending on the electronics of the system, and thus the aforementioned transitions can lead to either emission quenching or emission enhancement. Emission quenching occurs via the transfer of energy to the excited state of a molecule that undergoes non-radiative decay as it transitions back to the ground state. Conversely, emission enhancement occurs when energy is transferred to a molecule that undergoes a radiative transition from an excited state to the ground state. Ratiometric changes in emission can also occur, in which one peak in the emission spectrum decreases while a new peak at a significantly different wavelength increases.³¹² Often, this type of emission change is a result of the formation of aggregates of excited state molecules. One such type of aggregate, termed an exciplex, is a complex formed from the excited states of the donor and acceptor molecules.

Excimers, in contrast, refer to aggregates of the excited states of two of the same molecule. Other aggregates, including H-aggregates and J-aggregates, can also form.³¹⁸ H-aggregates are characterized by co-facial stacking between the monomeric units that results in hypsochromic shifts (or H-shifts) in the absorption spectra relative to the monomeric species.³¹⁹ J-aggregates, in contrast, are slipped-stack arrangements of monomeric units that have bathochromic shifts in their absorption spectra and increased extinction coefficients in those bathochromically-shifted bands.³²⁰

Figure 4.10. Molecular orbital diagram representations of the mechanisms of a) resonance energy transfer (RET); b) photo-induced electron transfer (PET) between LUMOs; c) photo-induced electron transfer (PET) between HOMOs; and d) electron exchange (EE)

The molecular orientation between the donor and acceptor can have profound effects on the efficiency of energy transfer processes, with the effects intimately dependent on the particular energy transfer mechanism. Specifically, Förster resonance energy transfer theory considers the relative orientation of the donor and acceptor explicitly in the Förster equation as the orientational factor, κ^2 .^{321,322} Most commonly this

orientational factor is approximated to have a value of $2/3$, which is accurate in cases where there is unrestricted movement of both the donor and acceptor dipoles and where the movement is markedly faster than the fluorescence lifetime of the donor.³²³ Additional mathematical relationships between the energy transfer efficiency and the orientation of the donor and acceptor dipoles have been derived in cases where these experimental conditions cannot be guaranteed,³²⁴ and the ability of the orientational factor to reveal important information about the system geometry and other system-wide structural features has also been demonstrated.³²⁵

For energy transfer that proceeds via a photoinduced electron transfer mechanism, energy transfer efficiencies are maximal for a co-facial, pi-stacked relationship between the electron donor and electron acceptor.³²⁶ This orientation allows for direct orbital overlap between the two system components, and directly enables effective electron transfer to occur.³²⁷ Such co-facial relationships have been found in a broad variety of biologically-relevant^{328,329} and materials science-related systems.^{330,331} Similarly, energy transfer that results from direct electron exchange between the donor and acceptor is most efficient for co-facially arranged donor and acceptor moieties.^{332,333}

4.3.1. Förster Resonance Energy Transfer (FRET)

Förster resonance energy transfer, or FRET, is governed by the Förster energy transfer mechanism¹⁷⁵ which treats the energy donor and acceptor as two interacting dipoles.³³⁴ Although commonly known as fluorescence resonance energy transfer, this mechanism is also applicable to phosphorescence and other types of luminescence. FRET occurs when there is an energy match and spectral overlap between the fluorescent emission of the donor molecule and the absorption of the acceptor

molecule.³¹² When this resonance condition is met, photons emitted by the donor are absorbed by the acceptor (Figure 4.10a), raising the acceptor to an excited state. The acceptor then fluoresces or phosphoresces at its characteristic wavelength, even without direct excitation. In cases where the acceptor is not emissive, however, fluorescence quenching due to energy transfer is observed. The extent of this energy transfer is determined by the degree of spectral overlap between the emission and absorption profiles of the donor and acceptor, respectively, referred to as the spectral overlap integral, or J .³³⁵ As a result, the energy transfer mechanism can be assessed by using the same energy donor in combination with a broad variety of fluorophores, calculating the spectral overlap integral for each donor-acceptor combination, and comparing that to the efficiency of the energy transfer.³³⁶ If Förster resonance energy transfer is the predominant mechanism, the ratio of energy transfer efficiency to spectral overlap integral should be constant.³³⁷ Additionally, FRET is operative over relatively long-range distances,³³⁸ and is inversely proportional to R^6 , where R is the average distance between the energy donor and energy acceptor.³³⁹ An example of a FRET-based sensing mechanism is shown in Figure 4.11.

Figure 4.11. Example of a FRET-based sensing mechanism. Cationic ethylene diamine appendages of a carbon dot were encapsulated in a crown ether affixed to a graphene oxide surface, leading to quenching by FRET from the carbon dot to graphene oxide. Addition of potassium cation displaced the carbon dot, prohibiting FRET and increasing fluorescence. Adapted with permission from Ref. 340. Copyright 2012 Royal Society of Chemistry

Practical ramifications of Förster energy transfer in detection systems relates to the spectral overlap requirement of Förster theory, which often has, as an unintended consequence, spectral overlap between the emission spectrum of the donor and the emission spectrum of the acceptor.³⁴¹ This emission spectra overlap means that for sensing systems that respond to the presence of an analyte with an increase in the acceptor emission signal, residual emission from the donor is often observed even in the absence of the target analyte. System sensitivity in such cases is compromised, often times severely, by the inability to achieve a completely dark background. As a result, energy transfer that operates with reduced spectral overlap between the donor and acceptor can potentially lead to higher system performance,³⁴² and efforts towards the development of such systems have been reported.

The inner filter effect (IFE) also describes a phenomenon wherein spectral overlap between two species leads to the emission of an energy donor being absorbed by an energy acceptor. In this case, however, the energy acceptor is not the luminophore, and absorption of excited state energy by the energy acceptor prevents the excitation energy from reaching the luminophore, resulting in a filtering of the excited state energy and a lower overall amount reaching the target compound.^{343,344} Although IFEs have been seen in many cases as an undesirable mechanism, it is quickly emerging as an important non-irradiative energy conversion model. IFE is commonly observed with nanomaterial detection platforms,^{345,346} as the nanomaterials have high absorbing capacity and extinction coefficients.³⁴³

4.3.2. Photo-Induced Electron Transfer (PET)

Photo-induced electron transfer, or PET, occurs when a donor-acceptor complex is formed in which an electron can shuttle from the donor directly to the acceptor, unlike FRET in which no electron is transferred.³⁴⁷ In PET, an electron is relocated directly from the LUMO of the excited state donor to the LUMO of the ground state acceptor, in the case where the LUMO of the donor is higher in energy than that of the acceptor (Figure 4.10b); or when an electron moves from the ground state HOMO of the donor to the excited state HOMO of the acceptor, when the former is higher in energy than the latter (Figure 4.10c). Both instances of PET result in the donor having a singly occupied HOMO and the acceptor having a full HOMO and singly occupied LUMO.¹⁷⁵ Close proximity of the acceptor and donor is required, and the use of covalently linked donor-acceptor pairs increases the likelihood of PET occurring. The distance dependence of the donor and acceptor in energy transfer schemes depends largely on the operative

energy transfer mechanism. Photoinduced electron transfer in particular requires close proximity between the donor and acceptor in order for effective orbital overlap to occur.³⁴⁸ Of note, the exploitation of such strong distance dependence to determine key structural information about a variety of experimental systems has also been reported.^{349,350} In some cases, the charge transfer complex undergoes a non-radiative transition back to the ground state and no emission profile is seen. A common mode of supramolecular sensing involves a host that has internal PET between covalently linked donor and acceptor moieties that quenches the emission of the species. Upon complexation with an analyte, the PET is disrupted, leading to an increase in fluorescence.³¹² In other cases, the charge transfer complex can undergo a radiative transition to the ground state. An example of a PET-based chemosensor is shown in Figure 4.12.

Figure 4.12. A calixarene host in which PET existing between the imine nitrogen lone pair and the coumarin fluorophore is interrupted by the presence of Cu^{2+} , leading to an increase in fluorescence³⁵¹

Other electron transfer mechanisms that can be considered classes of PET are internal (or intramolecular) charge transfer (ICT) and metal-ligand charge transfer (MLCT), and twisted internal (or intramolecular) charge transfer (TICT) in which the

fluorescence of a compound, such as thioflavin T,^{352,353} is related to the rotary motion of certain bonds on the molecule.³⁵⁴ The former case typically involves conjugated π -systems in which an electron donor and an electron acceptor are bridged by conjugation, which allows for the migration of an excited state electron.³⁵⁵ In the excited state, many conjugated systems, including those with heteroatoms, have larger dipoles than in their ground state, allowing for enhanced charge transfer.³⁵⁶ Due to these strong dipoles, these species generally aggregate in solution. MLCT describes the charge transfer that occurs from a ligand to the metal. The efficiency of MLCT is strongly dependent on a number of experimental parameters, including the solvent environment³⁵⁷ and the identity of the metal center, which is often a transition metal.^{358,359}

4.3.3. Electron Exchange (EE)

Electron exchange (EE), or Dexter-type interactions, rely on the quantum mechanical interactions of donor and acceptor molecules when they are in close proximity.¹⁷⁵ In such interactions, an electron is transferred from the LUMO of the excited donor to the LUMO of the acceptor. Simultaneously, an electron is transferred from the HOMO of the acceptor to that of the donor, (Figure 4.10d). This exchange of electrons, rather than the transfer of one single electron, is what differentiates this mechanism from PET. In contrast to FRET, Dexter energy transfer requires close-range interactions between the donor and acceptor to enable direct orbital overlap between the interacting moieties,³⁶⁰ and the efficiency of such energy transfer decreases dramatically as the distance between the donor and acceptor increases.^{348,361,362} Collisions of the donor and acceptor molecules induce direct interactions of the wavefunctions of the molecules, which is necessary for the electron exchange to occur, and which requires

close intermolecular distances.³¹¹ In order to ensure close proximity between the molecules and induce Dexter interactions, donor and acceptor molecules can be held in fixed media such as frozen solvents or polymeric scaffolds.¹⁷⁵ A particularly useful application of EE involves electron transfer between the triplet states of the donor and acceptor molecules in a process called “sensitization.”¹⁷⁵ Sensitization is useful in instances where an acceptor molecule cannot undergo intersystem crossing, but instead EE from a donor molecule allows for the phosphorescence of the acceptor molecule.

4.3.4. Chelation and Aggregation Fluorescence Mechanisms

Other phenomena commonly cited in the publications reviewed herein as inducing changes in fluorescent or phosphorescent emission are: chelation enhanced fluorescence (CHEF), chelation enhanced fluorescence quenching (CHEQ), and aggregation-induced emission (AIE). CHEF and CHEQ describe the occurrence of fluorescence enhancement³⁶³⁻³⁶⁵ or quenching³⁶⁶⁻³⁶⁸ upon the chelation of a metal center to the sensor molecule, and thus are mentioned primarily in cation detection schemes. The chelation of a metal center changes the electronic structure of the molecule, allowing one or more of the aforementioned processes to take place. AIE refers to the aggregation of molecules, often induced by complexation with a guest for the most effective detection schemes, to produce an emission response, again most likely through one of the aforementioned mechanisms.³⁶⁹⁻³⁷¹

4.3.5. Fluorescence Enhancement of Encapsulated Dyes

In the majority of cases, binding of a small molecule fluorophore inside the hydrophobic cavity of a macrocycle host results in enhancement of the fluorophore’s

emission, with concomitant attenuation of the fluorescence signal upon displacement from the cavity. The mechanisms that underlie such fluorescence changes strongly depend on the chemical structures, and can occur via sterically-induced blocking of single bond rotation,³⁷² and/or blocking the formation of a non-radiative charge transfer excited state.³⁷³ For hydrophobically-driven inclusion complexes in particular, the non-polar environment around a complexed fluorophore can also contribute to increases in the fluorophore's emission intensity through inducing changes in the fluorophore's observed dipole moment³⁷⁴ and through blocking interactions between the fluorophore and the bulk solvent.³⁷⁵ The ability of macrocycle complexation to lead to decreased aggregation of the fluorophore and concomitant fluorescence enhancements has also been reported.³⁷⁶ These effects combine with the increased steric hindrance that occurs when the fluorophore is complexed inside the macrocycle's cavity to lead to the overall observed fluorescence enhancement.

4.4. Quantifying Supramolecular Complexation

4.4.1. Benesi-Hildebrand Binding Constants

In 1948, Benesi and Hildebrand realized that association complexes were forming between iodine and aromatic hydrocarbons, based on the formation of a new absorption peak when both species were combined.³⁷⁷ In a subsequent publication, the same authors reported an equation to quantify the equilibrium constant, defined as the binding strength between iodine and an aromatic hydrocarbon, with the numerical representation of such a binding strength now recognized as an association constant.³⁷⁸ Many variations of the Benesi-Hildebrand equation have developed since the initially reported

equation (Equation 1, below), in which $[G]$ is the initial concentration of guest, $[H]$ is the initial concentration of host, I is the signal intensity in the presence of guest (reported as absorbance, luminescence, fluorescence, or phosphorescence values), I_0 is the signal intensity in the absence of guest, ε_0 is the molar extinction coefficient, and K is the association constant.

$$(1) \quad \frac{[G] \cdot l}{\log(I_0/I)} = \left(\frac{1}{K\varepsilon_0} \right) \frac{1}{[H]} + \frac{1}{\varepsilon_0}$$

Practically, the numerical data represented in this equation is often derived by plotting $1/[Host]$ on the x -axis and $1/\Delta I$ on the y -axis. If a linear relationship is obtained, the slope of this line is taken to represent the association constant.^{379,380,381} While useful, this method is only valid in cases where the concentration of host is much higher than the concentration of the complex, and is typically only used for 1:1 host-guest complexes,³⁷⁸ although other binding stoichiometries have also been reported.³⁸²

4.4.2. Stern-Volmer Quenching Constants

The Stern-Volmer equation, first reported in 1920,³⁸³ describes the quenching of a fluorophore through a dynamic, or collisional, quenching process as a result of diffusive interactions between the fluorophore and quencher.³⁸⁴ The Stern-Volmer relationship is expressed by Equation 2, below, where F_0 is the fluorescence intensity in the absence of quencher, F is the fluorescence intensity in the presence of quencher, $[Q]$ is the quencher concentration, and K_{SV} is the Stern-Volmer constant.⁸⁵

$$(2) \quad \frac{F_0}{F} = (1 + K_{SV}[Q])$$

This relationship can also be expressed in terms of luminescence lifetimes, as shown by Equation 3, below, where τ_0 is the luminescence lifetime in the absence of quencher,

τ is the luminescence lifetime in the presence of quencher, and k_q is the diffusional quenching constant.⁸⁵

$$(3) \quad \frac{\tau_0}{\tau} = (1 + k_q \tau_0 [Q])$$

A linear relationship is obtained in instances where dynamic quenching is the only process occurring, and thus K_{SV} and k_q can be calculated by plotting F_0/F vs. $[Q]$ or τ_0/τ vs. $\tau_0[Q]$, respectively. However, in some cases, static quenching, in which the fluorophore forms a stable non-fluorescent ground state complex with a quencher, is occurring simultaneously.³⁸⁵ This results in a nonlinear relationship between F_0/F and $[Q]$, which can be described by Equation 4, below, where K_S represents the static quenching constant and K_D represents the dynamic quenching constant.

$$(4) \quad \frac{F_0}{F} = (1 + K_S [Q])(1 + K_D [Q])$$

Despite its widespread usage throughout the fluorescence sensor literature, the Stern-Volmer relationship is based on a number of assumptions, including that of a pseudo-first order quenching mechanism and an assumption of a 1:1 relationship between fluorophore and quencher molecules.³⁸⁶ Thus, a number of fluorescence systems in which analyte-induced quenching occurs cannot be described via the Stern-Volmer relationship.

4.4.3. Association/Binding Constants

While Benesi-Hildebrand and Stern-Volmer constants are widely recognized as sufficient estimations of binding constants, it has been realized that much more complicated intermolecular interactions are commonly present, and thus more detailed equations that account for this complexity are required for the calculation of more

accurate binding constants. Furthermore, with the advent of more advanced computer technologies that can process more complex equations, researchers are moving towards the use of these equations that can provide more accurate information.³⁸⁷ Because these calculations can be difficult or time consuming, a number of computer programs have been devised for the purpose of analyzing data and determining accurate association constants, including Hyperquad^{363,388,389} and Specfit.^{390,391} Readers who are interested in determining association constants manually are directed to an excellent tutorial review by Thordarson.³⁸⁷

4.4.4. Job's Plots

The aforementioned Benesi-Hildebrand and Stern-Volmer relationships generally rely on the assumption of a 1:1 host-guest binding stoichiometry, yet in many instances of supramolecular binding events formation, other stoichiometries are favored, including 1:2 complexes, 2:1 complexes, and complicated combinations of simultaneous, co-occurring multiple stoichiometries. In 1928, Paul Job described a method to determine the stoichiometry of a binding event,³⁹² and this method is now known as Job's plot, Job's method, or the method of continuous variation. To use this method, the total concentration of a solution of A and B is held constant, while the relative proportions of A and B are varied.³⁹³ The mole fraction of A (χ_a) is then plotted versus the normalized physical parameter (P), which is obtained using a variety of spectroscopic techniques (fluorescence, absorbance, NMR, etc.). In cases where a 1:1 AB stoichiometry is in effect, $P_{\max}$ occurs when $\chi_a = 0.5$. Likewise, $P_{\max}$ occurs at $\chi_a = 0.67$ with an A_2B binding mode and at $\chi_a = 0.33$ with an AB_2 binding mode. However, care must be taken when utilizing this method, as more complicated stoichiometric

combinations, or instances where multiple stoichiometries are present, cannot be determined using this method. These plots are also useful in gaining a rough estimation of host-guest association constants, in that sharper peaks generally correspond to higher constants and broader peaks correspond to lower constants.³⁹³

4.4.5. Limits of Detection and Quantification

Determining a detection limit, the smallest amount of analyte that will give an unmistakable signal, and a quantification limit, the smallest amount of analyte that can be accurately quantified, of a given system is invaluable for the analysis of any sensor that could potentially have any commercial or industrial application.³⁹⁴ The most common approach is to obtain a calibration line of the system in question and to use the equation of that line to calculate the concentration of analyte at the point where the signal is three times the standard deviation of the blank, for detection limit, or ten times the standard deviation of the blank, for quantitation limit. However, there are numerous methods for the determination of these limits, many of which are described in a review by Belter et al.³⁹⁴

4.5. Luminescent Cavitand Macrocyclic Sensors

In general, many classes of macrocycles are particularly amenable to binding small molecule organic compounds, which can associate with the macrocycle host via a variety of non-covalent interactions. These non-covalent host-guest interactions are particularly strong in cases where the macrocycle is rigid, such as for cucurbiturils (*vide infra*),¹³² but also operate with reasonable strength and concomitant binding affinities in more flexible macrocycles such as cyclodextrin.³⁹⁵ Compared to other luminescent

supramolecular sensors, macrocycles offer the ability to accomplish binding and detection that is highly tailored for the particular analyte of interest. The oftentimes straightforward nature of synthetic modifications for the macrocycle provides an additional advantage to further tailor the system components in order to achieve optimal sensor performance.^{396,397}

In contrast to many other macrocycle hosts that bind small molecule organic analytes with high affinities, crown ethers and crown ether-derived macrocycle hosts are particularly well suited for the binding of metal cations.³⁹⁸ Such binding and concomitant detection relies on strong interactions between the cation and the chelating heteroatoms, including oxygen, nitrogen, and sulfur (*vide infra*).³⁹⁹

Cavitands are cyclic molecules with enforced nanometer-sized cavities large enough to bind small molecule guests.^{400,401} In general, these molecules are basket- or container-shaped, either comprised of a wide upper rim and a narrower lower rim, like cyclodextrins and calixarenes; or with a symmetrical inner cavity, like cucurbiturils and pillararenes. Rational design of cavitand supramolecular hosts allows for sophisticated control over intermolecular host-guest interactions and enables selective small molecule recognition.⁴⁰² The relative rigidity of these structures compared to acyclic molecules promotes highly selective guest binding, although different classes of cavitands have widely disparate rigidities, binding strengths, and binding selectivities.⁴⁰⁰ A variety of macrocycle classes are discussed below.

4.5.1. Cyclodextrins

Cyclodextrins are cyclic oligoamyloses^{403,404} composed of glucose monomers, that adopt toroidal three-dimensional structures,^{405,406} with a narrow upper rim and a wider

lower rim. A broad variety of cyclodextrin isomers occur naturally in corn and other starch sources,⁴⁰⁷ with the most common structural isomers being α -cyclodextrin,⁴⁰⁸ β -cyclodextrin,⁴⁰⁹ and γ -cyclodextrin,⁴¹⁰ with six, seven, and eight glucose moieties, respectively (Figure 4.13). The internal cavities of the cyclodextrins have hydrophobic character,⁴¹¹ whereas the hydroxyl moieties on the exterior of the cavity confer relative hydrophilicity and reasonable aqueous solubilities.⁴¹² Interestingly, the solubility of β -cyclodextrin is markedly lower than that of the other two commonly occurring isomers, due the fact that strong intramolecular hydrogen bonds in the β -cyclodextrin create a relatively rigid structure that is poorly solvated.^{413,414}

Figure 4.13. The α -,⁴⁰⁸ β -,⁴⁰⁹ and γ -⁴¹⁰ isomers of cyclodextrin

Compared to other macrocycle hosts (such as cucurbiturils^{415,416} and synthetic cavitands⁴¹⁷), cyclodextrins have relatively flexible structures.⁴¹⁸ This flexibility can complicate spectral analysis of their molecular structures and host-guest complexation behaviors, with many of the key structural components undergoing rapid motion on the experimental time scale.^{419,420} Attempts to obtain X-ray crystal structures of cyclodextrin complexes suffer from similar challenges, with the high flexibility of the molecule leading to relatively poor structural resolution.⁴²¹ Finally, computational work

involving cyclodextrin host-guest complexes is also complicated by having to account for cyclodextrin structural flexibility, although more recent efforts in the development of novel computational methods have demonstrated promising success.⁴²²

Covalently attached cyclodextrin-fluorophore conjugates can obviate many of the challenges associated with non-covalent complexes,⁴²³ mostly around the ambiguity of complexation structure and the distances between the fluorophore and analyte. Moreover, in non-covalent cyclodextrin-fluorophore-analyte systems, the analyte requires stronger binding affinities than the fluorophore in order to bind in cyclodextrin and displace the fluorophore, which can be a challenging condition to meet.⁴⁴⁹ Covalent cyclodextrin-fluorophore constructs, by contrast, contain a fluorescent transducer moiety at a relatively well-defined location relative to the cyclodextrin cavity, with the flexibility of the linker between the cyclodextrin and the fluorophore affecting the fluorophore mobility.⁴²⁴ Such covalently-linked architectures have been made with both β -cyclodextrin⁴²⁵ and γ -cyclodextrins,⁴²⁶ with single fluorophores and multiple fluorescent moieties covalently attached to the cyclodextrin hosts, and with both monomeric cyclodextrin hosts as well as higher order cyclodextrin architectures (dimers,⁴²⁷ trimers,⁴²⁸ and polymers).⁴²⁹ Cyclodextrins can be modified via a broad variety of chemical reactions,⁴³⁰ and many of the synthetic derivatives are commercially available, including randomly methylated β -cyclodextrin, with an average of 1.8 methyl groups per monomer unit, permethylated β -cyclodextrin, and 2-hydroxypropyl- β -cyclodextrin.⁴³¹ Selective synthetic modification to access non-commercially available derivatives often begins with full protection of all the hydroxyl groups,⁴³² followed by selective deprotection⁴³³ and further reaction at the target sites of interest.⁴³⁴ Other

protecting group strategies are also available.^{435,436} Using these methods, selective mono-functionalized,⁴³⁷ di-functionalized,⁴³⁸⁻⁴⁴⁰ tri-functionalized,⁴⁴¹ and tetra-functionalized cyclodextrins^{442,443} have been synthesized. Synthetic modifications to the cyclodextrin structure have the ability to dramatically change the sterics,⁴⁴⁴ hydrophobicity,⁴⁴⁵ and charge density⁴⁴⁶ of the cyclodextrins, and have enabled the installation of covalently-linked aromatic moieties.⁴⁴⁷ Of interest for purposes of this review, photophysically active (usually fluorescent) transducer moieties^{448,449} have been attached to cyclodextrin via covalent modification.^{450,451} The functionalization of the larger secondary face⁴⁵²⁻⁴⁵⁴ of cyclodextrins, so named because it contains secondary hydroxyl groups, is more challenging than the functionalization of the narrow primary face,^{455,456} which contains more reactive, more sterically accessible primary alcohols. Thus, secondary face modifications typically begin with the protection of the primary face. Several advances⁴⁵⁷ in secondary face modification strategies have been reported, including total functionalization by epoxidation⁴⁵³ or copper catalysis,⁴⁵⁴ and selective modification of the secondary face by mechanochemical means.⁴⁵⁸

Cyclodextrins are well-known for their ability to bind a variety of non-polar small molecule guests in their hydrophobic interiors.⁴⁵⁹⁻⁴⁶¹ In the absence of any guest molecules, the cavity of cyclodextrin is filled with high-energy water molecules,⁴⁶² so named because their inability to form a full complement of hydrogen bonding results in water molecules that are of higher energy compared to the bulk solvent.⁴⁶³ This water is typically displaced by a small molecule guest upon binding, which results in a thermodynamically favored process as the water returns to the lower energy bulk solvent state. Such cyclodextrin host-guest binding has been used for a broad variety of

applications, including in the solubilization of pharmaceutically active agents for effective drug delivery,⁴⁶⁴⁻⁴⁶⁶ in the environmental remediation of toxic chemicals,^{467,468} fuel,⁴⁶⁹ and oil^{470,471} through binding the toxicants in the cyclodextrin, in odor neutralization^{472,473} in functionalized filters⁴⁷⁴ and membranes,⁴⁷⁵ and in chiral chromatography.⁴⁷⁶

Cyclodextrin host-guest complexes have been used as fluorescent chemosensors, and these chemosensors can be divided into two categories: (a) covalently modified cyclodextrins, with covalently tethered fluorescent moieties that respond to binding of the analyte with a change in the fluorescence signal;⁴⁷⁷ and (b) cyclodextrin association complexes, with non-covalently attached fluorophores that respond to the presence of the analyte with non-covalent, analyte-specific interactions.

4.5.2. Modified Cyclodextrins⁴⁷⁸

Major challenges in the covalent modification of cyclodextrin focus on the synthesis and purification of these complex supramolecular architectures, with singly functionalized cyclodextrin moieties generally accessible via global protection of the hydroxyl moieties,⁴⁷⁹ followed by selective deprotection to reveal a single site for functionalization.⁴³³ Doubly functionalized cyclodextrins can also be realized by judicious choice of deprotection agent; using diisobutyl aluminum hydride (DIBAL), for example, results in a di-deprotected β -cyclodextrin analogue with the sites of deprotection on opposite sides of the cyclodextrin host.⁴⁸⁰⁻⁴⁸³ Other di-deprotected isomers have also been reported.⁴⁸⁴ Selective functionalization of a cyclodextrin host with more than two fluorophore appendages requires complex syntheses as well as often tedious purification procedures.¹ Of note, particular challenges of cyclodextrin

purification result from their large size, highly polar functionalities, and plethora of hydroxyl groups that can complicate chromatographic purification.⁴⁸⁵⁻⁴⁸⁷

Efforts in the Levine group have enabled the synthesis of monomeric β -cyclodextrin moieties with covalently attached fluorophores, either with one (compound **1**) or two (compound **2**) appended fluorophore units (Figure 4.14).¹ Compared to the non-covalent cyclodextrin-fluorophore system, the covalently linked architectures had significantly improved selectivity in response to a broad range of isomeric and analogous hydrophobic toxicants, including aliphatic alcohols, DDT and related analogues, and PCB congeners, with 100% differentiation via array-based analysis observed. Micromolar detection limits were found for the majority of analytes, and the discrimination of 1:1 binary mixtures of aromatic alcohols was achieved. This improved selectivity was evident in the significant changes in fluorophore emission that occurred upon analyte introduction for the covalently linked adducts, which were markedly higher than the changes observed for the non-covalent adducts.

Further efforts by the same group led to the synthesis of covalently linked cyclodextrin dimers, where the fluorophore moieties were incorporated as part of the linker backbone.⁴⁸⁸ These photophysically active cyclodextrin dimers (Figure 4.14), bearing pyridine,⁴⁸⁹ **3**, naphthalene,⁴⁹⁰ **4**, or anthracene,⁴⁹¹ **5**, linkers, formed inclusion complexes with squaraine fluorophores, resulting in notable fluorescence changes. Displacement of the squaraine following analyte introduction resulted in significant changes in fluorescence emission as well as notable color changes, observed through naked eye detection, UV-visible spectroscopy, and quantitative RGB (red-green-blue) analyses.⁴⁹²

Figure 4.14. Cyclodextrin hosts modified to bear fluorescent appendages, **1** and **2**,¹ or fluorescent linkers, **3**, **4**, and **5**⁴⁸⁸

Another noteworthy application of covalently-linked cyclodextrin constructs is in the detection of biologically relevant analytes. Yang et al. functionalized an adenosine aptamer fragment with β -cyclodextrin and the complementary aptamer fragment with a

dansyl fluorophore, which is known to form a strong inclusion complex with β -cyclodextrin (Figure 4.15).⁴⁹³ The presence of adenosine, the essential nucleoside for energy production in cells, brings the two nucleic acid fragments, and thus the dansyl and cyclodextrin fragments, into close proximity, leading to the association of the dansyl and β -cyclodextrin functionalities and a subsequent increase in dansyl fluorescence emission. The estimated detection limit for adenosine using this system was calculated to be 1 μ M. The authors surmised that changing the aptamer could enable detection of a variety of additional analytes.

Figure 4.15. Representation of the ability of dansyl- and β -cyclodextrin appended aptamer fragments to encapsulate adenosine and lead to a fluorescence response using A) mono-functionalized and B) di-functionalized adenosine aptamer fragments. Reproduced from Ref. 493. Copyright 2015 American Chemical Society

The modification of β -cyclodextrin to include negatively charged pendant arms led to the selective detection of cationic amino acids by Pettiwala et al. (Figure 4.16).⁴⁴⁶ An association complex of Thioflavin-T and the polyanionic cyclodextrin allowed for the ratiometric sensing of lysine and arginine, with detection limits of 40 μM and 50 μM , respectively. It was hypothesized that the cationic ends of the amino acids associated with the anionic side chains of the macrocycle, allowing for the inclusion of the neutral segment of the analyte in the cyclodextrin cavity. In addition to detecting lysine and arginine in purified buffer solution, this detection system also operated efficiently in fetal bovine serum.

Figure 4.16. Representation of the use of a β -cyclodextrin modified with cationic pendant arms for the encapsulation and detection of arginine and lysine by indicator displacement. Reproduced from Ref. 446. Copyright 2017 American Chemical Society

Click chemistry has been used to synthesize several fluorophore-modified cyclodextrins, including tetraphenylethylene-functionalized **6**,⁴⁹⁴ pyrene-functionalized **7** and **8**,⁴⁹⁵ and cyclodextrin dimer **9** (Figure 4.17).⁴⁹⁶ Compound **6** was used for the selective detection of cadmium by Zhang et al., where the addition of Cd^{2+} led to the formation of **6** aggregates through cadmium-induced π - π stacking of the terphenylene

moieties, resulting in fluorescence enhancements.⁴⁹⁴ The system demonstrated a low detection limit for Cd^{2+} (0.01 μM), and high levels of selectivity, with only Ag^+ impeding effective cadmium detection. He et al. used modified macrocycles **7** and **8** in combination with fluorophores **10** and **11** for the detection of lectins, proteins found in legumes and grains that display strong binding to sugars. Such lectins include soybean agglutinin (SGA) and wheat germ agglutinin (WGA), both of which can be detected with nanomolar detection limits.⁴⁹⁵ The **8** host and **10** fluorophore combination led to the lowest detection limit, 260 nM, of SGA via fluorescence enhancement. Similar lectins, including WGA, concanavalin A, lentil lectin, and pea lectin had no effect on the SGA-induced fluorescence increases. Similarly, a combination of **7** and **11** could detect WGA at concentrations as low as 735 nM without interference from the aforementioned species. An array of cyclodextrin dimers, including **9**, was used by Martos-Maldonado et al. for the detection of bile salts, namely sodium chlorate and sodium deoxycholate, through salt-induced fluorescence increases of the dimer in aqueous media.⁴⁹⁶

Figure 4.17. A series of modified cyclodextrins, **6**,⁴⁹⁴ **7**,⁴⁹⁵ **8**,⁴⁹⁵ and **9**,⁴⁹⁶ that were synthesized using click chemistry, and two novel fluorophores, **10** and **11**,⁴⁹⁵ with glucose-like appendages

Another example of a cyclodextrin modified with a signaling unit was reported by Feng et al.⁴⁹⁷ In this case, fluorescein-bound **12** (Figure 4.18), was used for the sensitive detection of TNT, a nitroaromatic explosive, in aqueous media (20 nM detection limit). The inclusion of TNT in the cyclodextrin cavity decreased the fluorescence of the system through TNT-induced fluorescence quenching with a Stern-Volmer constant of

$3.79 \times 10^5 \text{ M}^{-1}$. In one final example, a series of cyclodextrin-based ruthenium complexes were synthesized by Zhang et al. and were used for highly selective detection of lysozyme, an antimicrobial enzyme, through the binding of a lysozyme aptamer to the metallacyclodextrin host (Figure 4.19).⁴⁹⁸ The higher order cyclodextrin-ruthenium complex, containing six cyclodextrin moieties, enabled a limit of detection (48 pM) several orders of magnitude lower than its three-cyclodextrin and one-cyclodextrin analogues (27 nM and 239 nM, respectively).

Figure 4.18. Fluorescein modified **12** used for the detection of TNT⁴⁹⁷

Figure 4.19. Ruthenium metallacyclodextrin complexes used by Zhang et al. for the detection of lysozyme through the favorable binding of the complex to the lysozyme aptamer. Reproduced with permission from Ref. 498. Copyright 2015 Royal Society of Chemistry

4.5.3. Ternary Cyclodextrin Association Complexes

Non-covalent cyclodextrin-fluorophore association complexes rely on the binding of a fluorophore in or around the cyclodextrin cavity. The introduction of an analyte to the system then causes either the displacement of the fluorophore from the cavity, co-binding of the fluorophore and analyte in the cavity to create a ternary (i.e. three-component complex),⁴⁹⁹ or another permutation of the environment around the fluorophore⁵⁰⁰ that results in a measurable change in the fluorophore emission signal, either in its intensity, position, or signal spectral shape.⁵⁰¹

Challenges around the use of non-covalent cyclodextrin-fluorophore complexes include ambiguity about the geometry of the guest(s) in the cavity. Moreover, ternary complexes are common only for γ -cyclodextrin (and larger) isomers, which have cavity sizes that can readily accommodate two small molecule guests simultaneously.⁵⁰²⁻⁵⁰⁴

The use of the more common β -cyclodextrin generally utilizes analyte-induced displacement of the fluorophore from the cavity. This competitive displacement requires the analyte to have a stronger affinity for the hydrophobic cyclodextrin cavity than the fluorophore, which is only true in some cases. Isolated cases of ternary complexation inside a β -cyclodextrin cavity have been reported, although generally only for small analytes.^{505,506}

The Levine group has developed non-covalent cyclodextrin sensors based on ternary complexation between γ -cyclodextrin, a high quantum yield fluorophore, and a target analyte, with binding of the photophysically active analyte resulting in highly efficient, cyclodextrin-promoted analyte-to-fluorophore energy transfer.⁵⁰⁷ The resulting fluorophore emission via analyte excitation was used as a highly sensitive and selective signal for analyte detection. Even in cases where the analyte was not photophysically active, binding of the analyte in the cyclodextrin cavity resulted in proximity-induced, analyte-specific changes in the fluorophore emission signal that were used for sensitive and selective detection.^{508,509}

In particular, γ -cyclodextrin was used by the Levine group to promote energy transfer from five common polycyclic aromatic hydrocarbons (PAHs) to near-infrared emitting squaraine dyes, as illustrated in Figure 4.20, with a detection limit of 1.1 μM for the anthracene analyte.⁵¹⁰ Fluorescent dyes Rhodamine 6G and BODIPY were also found to act as efficient energy acceptors in combination with PAHs and polychlorinated biphenyl (PCB) energy donors, with ppm detection levels observed.⁵⁰⁷ The system was successfully employed for the sequential cyclodextrin-promoted extraction and detection of PAHs from a variety of oils, including motor oil, pump oil,

and vegetable oil, as well as from oil-contaminated seawater samples.⁴⁷¹ Additionally, BODIPY and Rhodamine 6G acted as efficient energy acceptors, inducing analyte-specific fluorescence responses, in a broad variety of complex media, including coconut water,⁵¹¹ complex oils,^{512,513} samples from environmental contamination scenarios,⁴⁶⁹ samples collected from oil spill sites,⁵¹⁴ human plasma,⁵¹¹ human urine,⁵¹⁵ and human breast milk,⁵¹⁶ all with mid- to low- micromolar detection limits. These techniques rely on unique fluorescence modulation by each analyte and the use of multiple analyte-fluorophore combinations for the creation of array-based detection schemes. Notably, this array-based detection was used for the 96% accurate discrimination of 30 organic pollutants in purified buffer solution and 92% accurate discrimination in human urine.¹²³

Figure 4.20. Illustration of a ternary complex in which energy transfer between the electron-rich analyte and electron-deficient fluorophore is promoted by cyclodextrin encapsulation. Reproduced with permission from Ref. 510. Copyright 2012 Taylor & Francis

In addition to PAH detection using cyclodextrin-based ternary complexes, the Levine group also demonstrated the detection of pesticides and alcohols via analogous

methods. The array-based detection of aromatic pesticides using BODIPY as an energy acceptor and a variety of cyclodextrins as supramolecular hosts allowed for the 100% successful discrimination of structurally analogous pesticide analytes.⁵¹⁷ Aliphatic analytes, including aliphatic pesticides and alcohols, could be detected using cyclodextrin-promoted fluorescence modulation, with high sensitivity and selectivity obtained.^{508,509,122}

A ternary complex similar to that shown in Figure 4.15⁴⁹³ (vide supra) was reported by Jin et al., in which two fragments of an adenosine binding aptamer were functionalized with pyrene.⁵¹⁸ As shown in Figure 4.21, in the presence of adenosine triphosphate (ATP), the aptamer fragments were brought in close proximity. This facilitated the formation of a pyrene excimer inside the γ -cyclodextrin cavity, leading to the observed excimer emission. In the absence of cyclodextrin, by contrast, only weak excimer fluorescence emission was observed. This ratiometric scheme detected ATP with an 0.08 μ M detection limit. Of note, structurally similar triphosphates did not produce analogous fluorescence changes, nor did they interfere with the detection of adenosine, and the system was effective in both Tris-HCl buffer and in human serum.

Figure 4.21. Pyrene appended to ATP aptamer fragments in conjunction with γ -cyclodextrin for the detection of ATP. Adapted with permission from Ref. 518. Copyright 2013 Elsevier

Murudkar et al. used the ultrafast molecular rotor Thioflavin-T (ThT), in combination with γ -cyclodextrin, for the fluorescence detection of surfactants containing long alkyl chains.³⁸⁰ Binding of the surfactant alkyl chain in the cyclodextrin cavity led to the formation of a ternary complex and provided sufficient steric hindrance to ThT to prevent its non-emissive torsional motion, resulting in surfactant-induced fluorescence enhancement.

Ternary cyclodextrin complexes with metal cations have also been reported for cation sensor applications. In one example, 80% of the fluorescence emission of a 1,2-dihydroxyanthraquinone: β -cyclodextrin association complex was quenched upon addition of Co^{2+} to form a ternary complex in aqueous solution,¹¹⁵ leading to a 22.7 nM detection limit. The ternary host-dye-cobalt system was then used to detect nitrate with a 2.4 nM detection limit, which the authors propose occurred via quaternary complex formation. Exogenous Co^{2+} and NO_3^- could also be detected following incubation of the host in HeLa cells. In a report by Khan et al., copper was detected with an association

complex of β -cyclodextrin and novel coumarin derivative **13** (Figure 4.22).⁵¹⁹ The addition of Cu^{2+} to the system resulted in formation of a ternary complex and quenching of the coumarin fluorophore. Of note, all other metal cations studied resulted in fluorescence emission increases, and the presence of these cations did not interfere with sensitive (ca. 25 nM) copper detection. Because the association complex was non-toxic to HeLa cells, in vivo Cu^{2+} detection was also obtained. Moreover, Jullian et al. reported that, in the absence of a supramolecular host, the emission of fluorophore **14** decreased only slightly in the presence of Cu^{2+} .⁵²⁰ Yet, when dimethyl- β -cyclodextrin was present, the fluorescence of **14** was decreased by both Cu^{2+} and Ni^{2+} , and the system could thus be used for the detection of both cations, with extremely low detection limits for nickel (65 ppb) obtained. Finally, Pd^{2+} was detected by Stalin and coworkers using an inclusion complex of β -cyclodextrin and **15**, with a detection limit of 1.0 μM obtained.⁵²¹

Figure 4.22. Various novel fluorophores used in ternary (compounds **13**,⁵¹⁹ **14**,⁵²⁰ and **15**⁵²¹) and binary (compound **16**)⁵²² cyclodextrin detection schemes

4.5.4. Binary Cyclodextrin Association Complexes

Binary cyclodextrin complexes have also been used as sensing platforms. For example, an indicator displacement assay was used for the detection of salicylaldehyde, a commonly used precursor in industrial processes, by Liu et al.⁵²² The target analyte displaced **16** from the cavity of β -cyclodextrin, resulting in analyte-induced

fluorescence quenching. A sensitive detection limit of 10 nM was reported, although selectivity for salicylaldehyde compared to other analytes was not discussed. Cyclodextrins have also been used for the detection of photophysically active analytes without the use of fluorescent dye transducers, such as in the detection of desipramine, an antidepressant,⁵²³ and *p*-aminohippuric acid, a kidney diagnostic agent.⁵²⁴ In the presence of β -cyclodextrin, Jalili et al. were able to detect 70 nM of desipramine,⁵²³ and Alremrithi et al. achieved the detection of *p*-aminohippuric acid at concentrations as low as 1 μ M.⁵²⁴ Similarly, Abdel-Aziz et al. were able to detect nanomolar amounts of benzo[*a*]pyrene, a highly carcinogenic and photophysically active PAH, using both β -cyclodextrin and calix[8]arene as supramolecular hosts.⁵²⁵

Additionally, Martínez-Tomé et al.⁵²⁶ and Ning et al.⁵²⁷ reported that 2-hydroxypropyl- β -cyclodextrin increased the fluorescence emission of naphthotriazole and benzotriazole, respectively. Such systems were used for nitrite detection, in which the reaction of nitrite with 1,2-diaminonaphthalene⁵²⁶ or 1,2-diaminobenzene⁵²⁷ formed the corresponding triazole that bound in the cyclodextrin, resulting in fluorescence increases only in the presence of the nitrite reactant. Detection limits of 13 nM and 2.0 nM were observed for naphthotriazole and benzotriazole, respectively. The derivatizing agents, 1,2-diaminonaphthalene and 1,2-diaminobenzene, were also found to react with Se^{4+} , leading to some erroneous results in the presence of this interferent.⁵²⁶ In a final example of binary complex formation for analyte detection, the encapsulation of fluorescent 2-hydroxy-1,4-naphthoquinone in β -cyclodextrin increased the solubility and stability of the dye, and facilitated its use as a fluorescent pH sensor.⁵²⁸

An interesting sensing application of cyclodextrins is in their employment as organic modifiers for capillary electrophoresis coupled with laser-induced fluorescence detection. The premise of this technique is that a mixture of analytes can be separated chromatographically by their differential complexation with cyclodextrin modifiers, and subsequently identified using fluorescence detection.⁵²⁹ Delaunay and coworkers have used cyclodextrin-modified capillary electrophoresis for the separation and identification of PAHs.^{529,530} In this case, 19 PAHs could be separated and identified with ppb level detection limits in aqueous solution⁵²⁹ and in complex edible oils.^{529,530} In another example, amino acids were derivatized with fluorescein isothiocyanate, **17** (Figure 4.23), and detected using cyclodextrin-modified capillary electrophoresis by Liang et al. with detection limits in the low pM levels.⁵³¹ Derivatization with a different fluorescent modifier, naphthalene-2,3-dicarboxaldehyde, **18** (Figure 4.23), resulted in pM limits of detection,⁵³² and in selectivity in separating of the D- and L- enantiomers of aspartic acid.

In a separate example, the enantiomeric purity of magnesium bis(L-hydrogenaspartate) dihydrate, a pharmaceutical agent, was determined through derivatization with *o*-phthaldialdehyde, **19** (Figure 4.23), followed by cyclodextrin-modified capillary electrophoresis.⁵³³ Trace levels of both L-aspartic acid and D-aspartic acid can contaminate this drug, although only the latter has deleterious effects on the human body. The authors were able to detect the presence of D-aspartic acid in levels as low as 0.003%, with full differentiation from its enantiomer observed. Liu et al. also detected amino acids using analogous methods and a rhodamine-based derivatizing agent.⁵³⁴ Stephen et al. reported the detection of the nucleosides adenosine

and inosine with detection limits of 1.6 μM and 4.0 μM , respectively, using derivatization with 2,4,6-trinitrobenzene sulfonic acid **20** (Figure 4.23),⁵³⁵ in the complex media of frozen rat brain tissue. Moreover, inhibitory neurotransmitter γ -aminobutyric acid was derivatized with 4-chloro-7-nitro-2,1,3-benzoxadiazole **21** (Figure 4.23), by Shi et al. and detected by laser-induced fluorescence.⁵³⁶ Of note, capillary electrophoresis was used to separate the functionalized derivative from the heads of houseflies and moths, with low detection limits (16 nM) reported. In a final example of the use of cyclodextrin-modified capillary electrophoresis coupled with laser-induced fluorescence detection, berberine, an established herbal remedy, could be identified in solution with a 15.7 ppb detection limit.⁵³⁷

Figure 4.23. Derivatizing agents that have been used for the separation and identification of similar analytes by cyclodextrin-modified capillary electrophoresis coupled with laser-induced fluorescence detection^{531-533,535,536}

4.5.5. Calix[n]arenes

Calixarenes⁵³⁸ are cyclic oligomers that are readily synthesized⁵³⁹ from the hydroxyalkylation reaction of a phenol and an aldehyde,⁵⁴⁰ resulting in the preferential formation of the thermodynamically favored, four benzene ring-containing product.⁵⁴¹ These molecules adopt vase conformations, with a wide upper rim and narrow lower

rim.⁵⁴² Although unsubstituted calixarenes suffer from significant insolubility in organic solvents,⁵⁴³ the inclusion of *tert*-butyl substituents confer reasonable solubility.⁵⁴⁴ Alternatively, the addition of hydrophilic substituents can be used to lend enhanced water solubility to these species,⁵⁴⁵ and amphiphilic calixarenes have been used for drug delivery applications.⁵⁴⁶ Calixarenes are generally used in sensing applications as scaffolds on which transducing elements are appended.⁵⁴⁷⁻⁵⁴⁹

A common use of calixarenes as supramolecular hosts for fluorescence detection is as receptors for metal cations such as copper, zinc, mercury, and lead. Chawla and coworkers developed a series of calixarenes with fluorescent appendages derived from fluorescein,⁵⁵⁰ coumarin,³⁵¹ and hydroquinoline⁵⁵¹ for the fluorescence detection of copper. Copper binding to photophysically active supramolecular sensors in general, and calixarene sensors in particular, can result in fluorescence enhancement, fluorescence quenching, and/or more complex changes to the fluorescence emission spectrum of the host, depending on the host structure and the mechanism of electronic interaction between the host and the copper analyte. The majority of calixarene-based copper sensors respond to the presence of copper with a noticeable quenching of the fluorescence emission.^{552,553} This behavior is in line with other reports where the presence of copper induces fluorescence quenching, in both biological⁵⁵⁴ and non-biological systems,⁵⁵⁵ and is thought to be a result of energy transfer from the fluorescent energy donor to the non-fluorescent metal-ligand bonds,⁵⁵⁶ or charge-transfer type interactions.⁵⁵⁷ Less common copper-induced fluorescence enhancement, such as seen using host **23**,³⁵¹ can occur via copper-induced aggregation, in cases where such aggregates display aggregation-induced emission;⁵⁵⁸ copper-induced formation of

a metal-to-ligand charge transfer band, for the right combination of copper salt and copper-chelating ligand;⁵⁵⁹ and copper-induced structural rigidification of an already existing fluorophore, resulting in potentially significant fluorescent enhancements.⁵⁶⁰ While other metal cations can display similar behaviors, the effects of copper on either fluorescence quenching or fluorescence enhancements are highly pronounced and can have potentially significant applications in biochemically-relevant sensing schemes.

Fluorescein-bearing species **22** (Figure 4.24) responded to the presence of Cu^{2+} with an increase in fluorescence emission, resulting in sensitive (10 nM) Cu^{2+} detection.⁵⁵⁰ Of note, this method was sensitive for copper ions in the presence of a variety of other potentially interfering species. The addition of copper to coumarin-appended **23** (Figure 4.24) was also characterized by an emission increase, as well as by a 90 nm bathochromic shift in the position of the emission maximum.³⁵¹ In a third report, **24** (Figure 4.24) was able to detect Cu^{2+} in tetrahydrofuran with a 0.5 μM detection limit.⁵⁵¹ However, this system was not fully selective, as Ni^{2+} , Zn^{2+} and Mn^{2+} interfered with effective detection. Emission of pyrene-appended **25** (Figure 4.24), synthesized by Maher et al., was fully quenched upon the addition of Cu^{2+} perchlorate, leading to an 0.22 μM detection limit and a Stern-Volmer constant of $4.5 \times 10^4 \text{ M}^{-1}$.⁵⁶¹ In a final example, bis-calix[4]arene tetra-triazole macrocycle **26** (Figure 4.24) formed a 1:3 host-guest complex with Cu^{2+} , resulting in 40 nM detection limits.⁵⁶² Of note, slightly basic pH conditions were required to produce the optimal response, and the macrocycle could cross T-cell membranes without leading to cell death, indicating potential biocompatibility and future biological applications.

Figure 4.24. Calixarenes that have been employed for Cu^{2+} detection^{351,550,551,561,562}

Rao and coworkers developed two fluorescence-based systems for the detection of copper with benzothiazole-appended calixarene **27**⁵⁶³ and benzimidazole-bearing **28**⁵⁶⁴ (Figure 4.25). An 8-fold decrease of the emission of **27** was observed in the presence of 10 equivalents of Cu^{2+} , and the quenching was not affected by the presence of up to 50

equivalents of other metal cations.⁵⁶³ A detection limit for copper of 403 ppm was achieved in acetonitrile. Compound **28** was found to produce a selective ratiometric response to Cu^{2+} , with no other cation leading to the formation of a new emission band.⁵⁶⁴ A 1:1 host-guest complex was the predominant species at lower concentrations of Cu^{2+} , and a 1:2 host-guest binding mode predominated at higher Cu^{2+} concentrations, with association constants of $7.24 \times 10^9 \text{ M}^{-1}$ and $1.80 \times 10^{10} \text{ M}^{-1}$ for the first and second binding event, respectively. Competition experiments in methanol indicated that moderate fluorescence perturbations could occur in the presence of other metal cations, with the addition of Hg^{2+} leading to a full fluorescence quenching of both the excimer and monomer peaks. However, in HEPES-buffered water, mercury did not perturb the system fluorescence. Xie et al. developed calixarene **29**⁵⁶⁵ (Figure 4.25), which was semi-selective for the detection of copper, and Sahin and coworkers synthesized **30**⁵⁶⁶ and **31**⁵⁶⁷ (Figure 4.25), which exhibited good and moderate selectivities for copper, respectively. A final example of Cu^{2+} detection was published by Maity et al. in which pyrenyl-bearing **32** (Figure 4.25) was selectively quenched by Cu^{2+} in a 4:1 THF/ H_2O solvent mixture.⁵⁶⁸

Figure 4.25. Calixarenes that have been used for Cu^{2+} detection⁵⁶³⁻⁵⁶⁸

Rao and coworkers developed a system for the fluorescent detection of zinc in human blood serum using **33** (Figure 4.26).⁵⁶⁹ Of 17 metal ions tested, zinc was the only species that increased the fluorescence emission, with a ten-fold increase in quantum yield observed in the Zn-complexed species. Compound **33** was able to detect Zn^{2+} in a buffer-methanol mixture with a detection limit of 36 ppb. A 1:1 binding stoichiometry was calculated along with a Benesi-Hildebrand binding constant of $1.49 \times 10^5 \text{ M}^{-1}$. Of note, strong sensitivity was maintained in human blood serum, with a 332 ppb detection limit observed (corresponding to approximately $1.2 \mu\text{M}$). Sutariya et al., using host **34** (Figure 4.26), were able to detect zinc in human blood serum at a level of $8.7 \mu\text{M}$, which decreased to 33 nM in acetonitrile solvent.⁵⁷⁰ In another example, trioxacalix[3]arene **35** bearing anthracenyl units was synthesized by Jiang et al (Figure 4.26).⁵⁷¹ Although

this macrocycle demonstrated inherently weak fluorescence in the uncomplexed state due to PET, it was able to detect Cd^{2+} and Zn^{2+} via fluorescence increases, with a detection limit of 0.38 μM for the latter in acetonitrile. 1:1 binding stoichiometries were observed for both systems, and Benesi-Hildebrand binding constants of **35** with Cd^{2+} and Zn^{2+} were reported to be $4.06 \times 10^4 \text{ M}^{-1}$ and $1.44 \times 10^4 \text{ M}^{-1}$, respectively. However, competing metal cations, including Cu^{2+} and Fe^{3+} , hindered the zinc-induced emission enhancement.

Compound **36** (Figure 4.26), a biscalixarene species with iminophenolate linkers developed by Ullman et al., selectively detected Zn^{2+} and Mg^{2+} in organic solvents.⁵⁷² The two analytes increased the emission of the macrocycle by inhibiting PET from the imines to the fluorescent phenols. Of note, each analyte caused a unique fluorescence emission signal, with a 15 nm difference between the emission maxima, which enabled accurate differentiation between the two cations. The reported detection limit for Zn^{2+} was 0.15 ppb, which is two to three orders of magnitude smaller than previously reported limits using mono-calixarenes with iminophenolate pendant arms.⁵⁷³⁻⁵⁷⁵ Naphthyl-bearing thiacalix[4]arene, **37** (Figure 4.26) was found by Darjee et al. to be a selective sensor for zinc, even in the presence of other metal cations.⁵⁷⁶ The 1:1 host-guest system enabled a broad linear detection range for Zn^{2+} (1 to 740 nM), and a binding constant was determined by Stern-Volmer analysis to be $3.16 \times 10^5 \text{ M}^{-1}$. Additional calixarene-based zinc sensors containing bispyridine and terpyridine units were developed by Zhang et al.⁵⁷⁷ and Li et. al.⁵⁷⁸ The bispyridine-modified calixarenes **38** and **39** (Figure 4.26) formed 1:2 host-guest complexes with zinc, leading to unique emission changes.⁵⁷⁷ Terpyridine-appended **40** (Figure 4.26) formed 1:1 host-guest

complexes with Zn^{2+} and Cd^{2+} with a relatively high binding constant of $>10^6 \text{ M}^{-1}$ for the former.⁵⁷⁸

Figure 4.26. Calixarenes that have been used for the detection of zinc^{569-572,576-578}

Calixarenes with covalently attached fluorescent units have also been used for the detection of toxic heavy metals such as mercury, lead, and cesium. In one example,

BODIPY-modified calixarene host **41** (Figure 4.27) responded to the presence of as little as 28 μM of Hg^{2+} by fluorescence quenching, with a Stern-Volmer quenching constant of $3.42 \times 10^7 \text{ M}^{-1}$, as a result of the formation of a 1:1 host-guest complex.⁵⁷⁹ Of note, the recognition ability of **41** toward mercury in a 9:1 methanol/water mixture was not significantly hindered by other metal cations. Arena et al. developed host **42** (Figure 4.27), whose fluorescence was quenched in acetonitrile by the addition of Hg^{2+} , Cd^{2+} , and Pb^{2+} , with a 60% to 70% quenching efficiency.⁵⁸⁰ When a 1:1 mixture of acetonitrile and water was employed as the solvent, however, only mercury effectively quenched the emission of **42** and a relatively low 1.6 μM detection limit was observed. This system was also sensitive to pH, with acidic conditions decreasing the quantum yield of the complex, and basic conditions leading to displacement of the bound analyte and an increase in fluorescence. In another example, fluorescence quenching was observed during the titration of dansyl-bearing calixarenes, such as **43** (Figure 4.27), with metal cations. Although not selective, the quenching ability of the metal cations increased in the following order: alkali metals < alkaline earth metals < transition and heavy metals.⁵⁸¹ Sulfonated, water-soluble, dansyl-bearing calixarenes **44** and **45** (Figure 4.27) could sense the presence of Hg^{2+} , with detection limits of 11.4 μM and 34.2 μM , respectively,⁵⁸² and the sensing ability was maintained in live cells. Benesi-Hildebrand binding constant values were calculated to be 666.7 M^{-1} and 733.3 M^{-1} for hosts **44** and **45**, respectively. One shortcoming of this research is that the response of the calixarenes to other metal cations was not reported. In one final example, Erdemir and coworkers found that triphenylamine-bearing calixarene **46** (Figure 4.27), was

moderately selective for the FRET-based fluorescence detection of mercury over other cations with a Benesi-Hildebrand binding constant of $7.52 \times 10^4 \text{ M}^{-1}$.⁵⁸³

Figure 4.27. Calixarenes that have been reported for the sensing of mercury and other metals⁵⁷⁹⁻

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Pyrene-affixed calixarenes have been reported for the detection of Pb^{2+} by the Kumar⁵⁸⁴ and Sahin⁵⁸⁵ research groups. Kumar and coworkers developed **47** and **48** (Figure 4.28), for the ratiometric (for **47**) and “turn-off” (for **48**) fluorescence detection of Pb^{2+} .⁵⁸⁴ Ratiometric detection of Pb^{2+} with **47** occurred through lead-induced disruption of the pyrene excimer, resulting in a decrease in the excimer emission and concomitant increase in monomer emission, and a detection limit of $0.49 \mu\text{M}$. In competition experiments with other metal cations, Hg^{2+} was the only other metal cation to induce ratiometric fluorescence changes, although of substantially lower magnitude than the lead-induced changes. For the quenching-based detection of lead using sensor **48**, nearly complete fluorescence quenching was observed in the presence of 10

equivalents of lead cation. Again, some Hg^{2+} interference was observed, although 100 equivalents of mercury were required to reach only a 25% fluorescence quench. Of note, the detection limit of sensor **48** towards Pb^{2+} was 0.29 μM , and reversibility was demonstrated through using EDTA to remove and sequester Pb^{2+} from the **48** cavity. Compounds **49** and **50** (Figure 4.28), were used for semi-selective Pb^{2+} detection, with fluorescence quenching of **49** caused by Pb^{2+} and Zn^{2+} , and quenching of **50** caused by Pb^{2+} and Cu^{2+} .⁵⁸⁵ The fluorescence response of these hosts was thought to proceed through a PET mechanism, with metal coordination inhibiting charge transfer from the pyrene moieties to the amine nitrogen atoms, leading to the observed fluorescence decreases. Stern-Volmer quenching constants of **49** with Pb^{2+} and Zn^{2+} were found to be $3.15 \times 10^4 \text{ M}^{-1}$ and $3.15 \times 10^5 \text{ M}^{-1}$, respectively, while the Stern-Volmer constants of **50** with Cu^{2+} and Pb^{2+} were $1.49 \times 10^4 \text{ M}^{-1}$ and $8.15 \times 10^3 \text{ M}^{-1}$.

Cesium was successfully detected by several calixarene-crown ether macrocycles.^{586,587} In one example, BODIPY-bearing species **51** and **52** (Figure 4.28) bound to both K^+ and Cs^+ , with a stronger binding to Cs^+ observed due to steric complementarity between the size of the host cavity and the cesium atomic radius. The complexation of Cs^+ with **51** led to a bathochromic shift and small increase in emission, whereas complexation with **52** led to a hypsochromic shift and slightly larger emission increase.⁵⁸⁶ In a later publication, coumarin-containing **53** (Figure 4.28) was integrated into a microfluidic device that detected Cs^+ with a 1.4 μM detection limit.⁵⁸⁷ Competition experiments indicated that 0.02 equivalents of other cations (relative to cesium) did not compromise the **53** detection sensitivity.

Figure 4.28. Pyrene-bearing calixarenes and crown-ether-modified calixarenes that have been used for heavy metal detection⁵⁸⁴⁻⁵⁸⁷

Other metal cations that have been detected by calixarenes include iron, chromium, gold, silver, and aluminum. In one example, Zhan et al. used a calixarene with pyridine-containing arms, **54** for the sensitive (0.5 μM detection limit) and selective detection of Fe^{3+} by iron-induced fluorescence quenching, with the proposed mechanism of quenching due to the reversal of PET.⁵⁸⁸ An association constant of $1.76 \times 10^4 \text{ M}^{-1}$ was calculated using the Benesi-Hildebrand equation for the binding of **54** with Fe^{3+} . Using nanoparticles of **54** rather than the monomeric calixarene caused an increase in the

fluorescence detection limit, to 125 μM . Zheng et al. discovered that Fe^{3+} could also be detected by **55**, a rhodamine-armed thiocalixarene, although with some loss of selectivity observed, as evident by signal changes in the presence of Cr^{3+} .⁵⁸⁹ The addition of these metal cations to **55** leads to the ring opening of the spirolactam and a concomitant increase in fluorescence emission due to increased conjugation. This transformation was reversible with the addition of diethylenetriamine, which sequestered the cations and re-formed the spirolactam. Detection limits for Fe^{3+} and Cr^{3+} were 35 nM and 160 nM, respectively, and the system maintained high detection performance even in tap water samples.

Lotfi et al. discovered that, upon the addition of Ag^+ to **56**, a unique hypsochromic shift in emission occurred, allowing for selective detection that was minimally affected by competing cations (Figure 4.29).⁵⁹⁰ In simulated physiological conditions ($[\text{Na}^+] = 145 \text{ mM}$, $[\text{K}^+] = 5 \text{ mM}$, $[\text{Mg}^{2+}] = 2 \text{ mM}$, and $[\text{Ca}^{2+}] = 5 \text{ mM}$), the detection limit of Ag^+ was 23 μM , somewhat higher than the 6.3 μM observed in a 3:7 HEPES buffer/methanol mixture. In another example, Memon et al. developed systems for the detection of Au^{3+} ⁵⁹¹ and Al^{3+} ⁵⁹² using calixarenes **57** and **58**, respectively (Figure 4.29). The addition of Au^{3+} to **57** led to moderate quenching of the system, and allowed for a detection limit of 15 μM and a quantification limit of 52 μM .⁵⁹¹ The addition of 32 potential interfering cations had no effect on the detection ability of the system. Compound **58** was found to detect Al^{3+} at concentrations as low as 2.8 μM via an increase in fluorescence emission.⁵⁹² Other cations did not perturb the emission spectrum of **58** or interfere with Al^{3+} detection.

Figure 4.29. Calixarenes that have been used as sensors for metal cations⁵⁸⁸⁻⁵⁹²

Several of the systems discussed above for the detection of metal cations have also been used for the detection of anions, especially of fluoride, an anion with significant public health relevance.⁵⁹³ Compound **24** (Figure 4.24), was reported as a ratiometric sensor for F^- , which responded to the presence of fluoride anion with a quenching of the excimer peak and enhancement of the monomer peak.⁵⁵¹ The system allowed for the detection of F^- with a limit of 0.7 μM , and other anions were found to have limited interference with the detection ability toward F^- . Compound **34** (Figure 4.26) was sensitive to the presence of F^- , with a detection limit of 22 nM in wastewater samples and 8 nM in acetonitrile.⁵⁷⁰ However, the system was not selective for F^- . Fluoride ions could also be detected by the fluoride-induced fluorescence quenching of **30** (Figure 4.25), reported by Sahin and coworkers, although other anions (NO_3^- and $H_2PO_4^-$)

interfered with the fluorescence response.⁵⁶⁶ Compound **46** (Figure 4.27), was quenched in the presence of F^- . The authors propose a quenching mechanism that includes fluoride-induced deprotonation of the amide NH and phenolic OH of the host. Although other basic conditions are expected to lead to the same deprotonations, such conditions were not examined.⁵⁸³ The emission of fluorenone-bearing **59** (Figure 4.30), was quenched in the presence of F^- , as reported by Nemati et al.⁵⁹⁴ The same group also reported the ratiometric sensing of F^- by **60** (Figure 4.30). Other anions induced similar effects on the emission profiles of both calixarenes, and the detection limit for F^- in the presence of **59** was calculated to be 32 nM.

Previously mentioned **57** (Figure 4.29) was fully quenched in the presence of 10 equivalents of iodide, with a low detection limit of 1.6 μ M and a quantification limit of 4.5 μ M, and no observed effects by any other anion investigated.⁵⁹⁰ In another report, Gómez-Machuca et al. reported the use of calixarenes **61-63** (Figure 4.30), for the semi-selective detection of I^- , with fluorescence quenching also observed for NO_2^- , SCN^- , NO_3^- , and N_3^- .⁵⁹⁵ Iodide detection limits of 1.81 ppm, 0.23 ppm, and 0.22 ppm were found for **61**, **62**, and **63**, respectively. Kim et al. reported that the inherent PET present between the pendant amine donor and pyrene acceptor units of calixarene **64**, (Figure 4.30) which resulted in excimer emission in the absence of analyte, was disrupted by iodide and bromide, allowing for their detection via the analyte-induced quenching of that emission.⁵⁹⁶ In another example of anion detection by calixarenes, dihydrogen phosphate anion was ratiometrically detected by Chen et al. using naphthol-armed hosts **65** and **66** (Figure 4.30).⁵⁹⁷ Ratiometric responses were also observed upon the addition of F^- , yet these hosts were much more sensitive toward $H_2PO_4^-$ (1.5-2.5 equivalents of

H_2PO_4^- required to induce a fluorescence response; 6-9 equivalents of F^- anion for the same effect). Benesi-Hildebrand constants were calculated to be $2.13 \times 10^3 \text{ M}^{-1}$ and $2.70 \times 10^3 \text{ M}^{-1}$ for the binding of H_2PO_4^- with hosts **65** and **66**, respectively; and constants of $1.61 \times 10^3 \text{ M}^{-1}$ and $4.16 \times 10^2 \text{ M}^{-1}$ were reported for the binding of F^- with **65** and **66**, respectively. The emission of **58** (Figure 4.29) was increased in the presence of disulfate anion but quenched in the presence of all other anions examined, with a calculated detection limit of $0.26 \mu\text{M}$ for the H_2PO_4^- observed.⁵⁹² In a final example of anion detection, **67** (Figure 4.30), responded to the presence of HSO_4^- with an increase in fluorescence, even in the presence of competing anions.⁵⁹⁸ The observed fluorescence increases were due to the hydrolysis of **67** by the anion, which led to a detection limit of $0.98 \mu\text{M}$.

Figure 4.30. Calixarenes that have been used for the detection of anions⁵⁹⁴⁻⁵⁹⁸

Many dual-detection calixarene systems that detect both cations and anions have been developed in recent years. The premise of these systems is that a macrocyclic host is initially used for the detection of a cation, and the resulting host-cation species is subsequently used for the detection of an anion that sequesters the cation, allowing for

the regeneration of the initial emission profile of the system. Many of these systems have been shown to have good reusability. Due to the high affinity of phosphates for zinc, several techniques for the detection of phosphate and zinc have been developed by Rao and coworkers using salicylyl-imine bearing calixarenes.⁵⁹⁹⁻⁶⁰⁴ In 2010, the group synthesized **68** (Figure 4.31), and the addition of three equivalents of Zn^{2+} to this host promoted a 30-fold increase in emission, due to the analyte-induced disruption of PET between the phenolic oxygen and imine nitrogen, allowing for a minimum detection level of 192 ppb.⁵⁹⁹ A Benesi-Hildebrand binding constant of $2.7 \times 10^4 \text{ M}^{-1}$ was calculated, and competition experiments revealed that Fe^{2+} , Cu^{2+} , and Hg^{2+} all completely negated the Zn^{2+} -promoted fluorescence enhancement, leading to no fluorescence changes compared to the uncomplexed macrocycle host, while Mn^{2+} , Na^+ , K^+ , Ca^{2+} , and Mg^{2+} had moderate deleterious effects. The titration of Zn-**68** with various anions revealed that the zinc was successfully sequestered by inorganic phosphate anions H_2PO_4^- , HPO_4^{2-} , and PO_4^{3-} ; as well as by biologically relevant analytes: AMP, ADP, ATP, cysteine, and aspartic acid. A minimum detectable concentration of HPO_4^{2-} was established to be 426 ppb. The same group then developed host **69**, which could detect Zn^{2+} at levels as low as 45 ppb, with only the presence of Fe^{2+} and Cu^{2+} leading to significant changes in the detection ability of **69** (Figure 4.31) toward Zn^{2+} .⁶⁰⁰ A relatively high Benesi-Hildebrand constant of $4.93 \times 10^5 \text{ M}^{-1}$ was calculated for this interaction. In a similar fashion to the Zn-**68** association complex, the Zn-**69** association complex was disrupted by the addition of inorganic phosphates, H_2PO_4^- , HPO_4^{2-} , and $\text{P}_2\text{O}_7^{4-}$; with the sequestration of Zn^{2+} leading to regeneration of the fluorescence

emission of **69**. The minimum detectable concentration of HPO_4^{2-} was found to be 247 ppb.

Rao and coworkers then modified their salicyl-imine containing hosts by inserting triazole moieties into the pendant arms, forming **70** (Figure 4.31).⁶⁰¹ The detection limit for zinc using **70** was 47 ppm, which was similar to the limit found when using **69**. The addition of thiols to the Zn^{2+} -**70** complex led to fluorescence quenching, due to interference of the thiols with PET, with the greatest degree of fluorescence quenching observed in the presence of the thiol-containing small molecules cysteine, dithiothreitol, and glutathione monosulfide. Of note, mercaptopropionic acid led to minimal quenching of the system; and homocysteine, mercaptoethanol, and cysteamine led to no fluorescence quenching. Reversibility of the system via the release of Zn^{2+} from the thiol was achieved by either oxidizing the thiol with H_2O_2 or by sequestering the thiol with Cd^{2+} or Hg^{2+} , allowing the zinc to rebind to **70**. This same Zn^{2+} -host adduct was used for the detection of pyrophosphate anion, with a reported detection limit of 340 ppb.⁶⁰² Unlike **68** and **69**, this host was selective for pyrophosphate, with H_2PO_4^- , ATP, ADP, and AMP leading to very minimal quenching of the Zn^{2+} -**70** emission. In another report, the emission of Zn^{2+} -**70** was also found to be quenched by histidine and cysteine.⁶⁰³ Upon treatment of HeLa cells with **70**, zinc and pyrophosphate could be detected *in vitro*. However, no study was conducted comparing the affinity of Zn^{2+} -**70** to pyrophosphate, histidine, and the aforementioned thiols. In a later publication, Rao and coworkers ascertained that pyrophosphate could be detected selectively by zinc-bound-**71** (Figure 4.31).⁶⁰⁴ The unassociated **71** could detect Zn^{2+} with a limit of 112 ppb and a Benesi-Hildebrand constant of $7.2 \times 10^4 \text{ M}^{-1}$, while the subsequent association

complex could detect pyrophosphate with a limit of 278 ppb. While ATP was also found to sequester zinc, quenching was much less effective with ATP than with pyrophosphate. Successive additions of Zn^{2+} and pyrophosphate to **71** allowed for moderate reversibility.

Figure 4.31. Calixarenes employed in the dual detection of zinc and phosphates⁵⁹⁹⁻⁶⁰⁴

Rao and coworkers developed other salicylyl-imino-bearing calixarenes that were selective for metals other than Zn^{2+} . In one example, a 1:2 host-guest complex of **72** (Figure 4.32) with cadmium was employed for the detection of phosphate-containing species by fluorescence quenching.⁶⁰⁵ H_2PO_4^- was the most effective at quenching the emission of the association complex, which allowed for a detection limit of 20 ppb. HPO_4^- , ATP, ADP, AMP, and $\text{P}_2\text{O}_7^{4-}$ also quenched the emission, with reported

detection limits between 50 and 580 ppb. Salicyl-yl-imine-containing calix[6]arene **73** (Figure 4.32), with a larger cavity size than calix[4]arene (7.6 Å vs. 3.0 Å cavity diameters),⁶⁰⁶ was able to bind La^{3+} , a cation with a relatively large atomic radius.⁶⁰⁷ The binding of La^{3+} to **73** was selective over other lanthanide metals and led to a ca. 70-fold increase in fluorescence emission upon the addition of eight equivalents of the analyte, translating into a 65 ppb minimal detectable La^{3+} concentration. Upon the addition of F^- to the La^{3+} -**73** association complex, a quenching of emission was observed. No other halide was found to promote the same behavior, and successive additions of La^{3+} and F^- led to excellent reversibility of the fluorescence emission signal. Although Zn^{2+} also bound to **73**, leading to observable fluorescence enhancements, the addition of F^- had no effect on the Zn-based association complex. Leray, Reinaud and coworkers also developed a calix[6]arene that has potential as a dual-sensing platform for multiple analytes.⁶⁰⁸ The macrocycle, **74** (Figure 4.32), bound to Zn^{2+} to form a complex that was responsive to the presence of primary alkylamines.

Rao and coworkers developed an extensive multiple sensor array system, using **75** (Figure 4.32), for the detection of a variety of metal cations and amino acids.⁵⁷³ **75** bound to Zn^{2+} , Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , forming 1:2 host-metal complexes and resulting in a hypsochromic shift in the fluorescence emission peak. Response limits for these metal ions were found to be 0.76 μM , 1.8 μM , 1.0 μM , 1.99 μM , 1.99 μM , and 1.05 μM , respectively. All of the complexes formed had unique responses to amino acids, which enabled the creation of an array-based detection scheme. Mn^{2+} -**75** was able to sense aspartic acid and glutamic acid with detection limits of 20.2 μM and 19.0 μM , respectively; whereas complexes of **75** with Cu^{2+} and Zn^{2+} could detect cysteine at limits

of 3.45 μM and 2.15 μM , respectively. Co^{2+} -**75** could detect 5.65 μM of cysteine, 3.44 μM of histidine, and 2.50 μM of aspartic acid. Ni^{2+} -**75** was found sensitive to 3.00 μM of histidine and 7.90 μM of aspartic acid. While all 20 natural amino acids were examined, only aspartic acid, glutamic acid, histidine, and cysteine effected a change in the emission profile of the metal-**75** complexes.

Figure 4.32. Calixarenes used as dual detection scaffolds^{573,605,606,608}

Erdemir and coworkers developed perylene-linked bis-calix[4]arene **76** (Figure 4.33) for the dual detection of Hg^{2+} and I^- .⁶⁰⁹ Upon binding of Hg^{2+} to the macrocycle, a 1:2 host-guest complex formed with a Benesi-Hildebrand binding constant of 1.66 x

10^9 M^{-2} , resulting in an order of magnitude increase in quantum yield due to the disruption of PET between the pseudo-azacrown ether and perylene diimide fluorophore. The system could detect mercury at concentrations as low as 556 nM, and the addition of potentially interfering cations had little effect on this detection ability. Of a variety of anions examined, only I^- was able to effectively sequester Hg^{2+} from the system. Human colon cancer cells were incubated with Hg^{2+} and the host sequentially, leading to the detection of mercury in live cells. A detection limit of the system for I^- was not reported, and a relatively narrow optimal pH range of 5.5 to 7.5 was determined. Erdemir and coworkers also established that previously mentioned **67** (Figure 4.30) was a selective sensor for the detection of Cu^{2+} through fluorescence quenching, with a limit of $1.05 \text{ }\mu\text{M}$, and that other cations did not interfere with the detection capabilities of the system.⁵⁹⁸ The authors found, via Job's plot analysis, that a 1:2 host-guest association complex was formed between **67** and Cu^{2+} . The resulting Cu^{2+} -**67** complex was used for the detection of S^{2-} , with the anion effectively sequestering Cu^{2+} and promoting fluorescence enhancement. No other anion sequestered the copper, and a detection limit of $1.54 \text{ }\mu\text{M}$ for sulfide was achieved.

A copper-cyanide dual detection scheme using **77** (Figure 4.33) was created by Chawla and coworkers.⁶¹⁰ In this scheme, a 1:1 host-guest complex of Cu^{2+} and **77** was formed, resulting in an emission decrease compared to the free calixarene. Upon the addition of CN^- , the fluorescence of the host was restored as the copper selectively bound to the anion and was removed from proximity to the host. Other cations and anions had little effect on this system, and detection limits of $0.4 \text{ }\mu\text{M}$ and $1.26 \text{ }\mu\text{M}$ were determined for Cu^{2+} and CN^- , respectively. The Stern-Volmer constant for binding of

77 with Cu^{2+} was reported to be $1.472 \times 10^5 \text{ M}^{-1}$. Zhang et al. were able to selectively sense Ag^+ in aqueous media using **78** (Figure 4.33), through the generation of a new, bathochromically-shifted emission peak for the Ag^+ -**78** complex.⁶¹¹ This analyte could be detected with high sensitivity (detection limit of $0.62 \mu\text{M}$) and selectivity (no other cations induced analogous fluorescence responses). Of note, the addition of formaldehyde, a toxicant widely used in industrial processes, to the system sequestered the silver cation, leading to the regeneration of the emission spectrum of free **78**. A detection limit for formaldehyde was calculated to be $0.66 \mu\text{M}$ in THF, and successful formaldehyde detection was demonstrated in doped tap water samples. In a final example of dual-detection schemes, Qazi et al. found that the addition of Pb^{2+} to **79** (Figure 4.33) led to a six-fold increase in emission, while other cations only led to moderate fluorescence changes.⁶¹² Subsequent addition of chromate caused a significant decrease in the fluorescence emission due to the sequestration of lead, in a phenomenon that other anions did not replicate.

Figure 4.33. Calixarenes exploited for dual-detection systems⁶⁰⁹⁻⁶¹²

The sensing of organic molecules by calixarenes has been pursued by several groups in recent years, especially for the detection of nitroaromatics. Each of these nitroaromatic detection schemes involved a fluorescent, electron rich calixarene donor transferring energy to a non-fluorescent, electron-deficient nitroaromatic guest. Thus, the fluorescence response of all such calixarenes upon complexation of the analyte was an emission quench. For example, Boonkitpatarakul et al. developed phenylethynylene calixarene **80** (Figure 4.34) for the detection of TNT in both solution and in the vapor phase.⁶¹³ The addition of one equivalent of TNT to **80** led to a 7.5-fold emission quench, though this technique was not fully selective, as the same amount of DNT led to a 4-fold emission quench. As little as 0.3 μM of TNT could be detected in aqueous solution over a wide pH range of 3 to 10. A solid-state device was fabricated for the detection of TNT in the vapor phase by dipping filter paper in a solution of the **80** and allowing it to

dry in open air, and then using the functionalized paper for effective vapor-phase detection. Additionally, Rao and coworkers were able to detect TNT with **81** (Figure 4.34).⁶¹⁴ A fluorescence quench of the macrocycle was also seen with the addition of similar nitroaromatic species dinitrobenzene and *m*- and *p*-nitrotoluene. Of note, in solution phase, concentrations as low as 3.03 μM of TNT could be detected.

Rao and coworkers also found that trinitrophenol (TNP) was selectively detected using **82** (Figure 4.34) with a detection limit of 300 nM and a Stern-Volmer quenching constant of $4.51 \times 10^5 \text{ M}^{-1}$.³¹ No other analogous electron-deficient analytes led to comparable quenching efficiencies nor did they interfere with TNP detection. Filter paper was soaked with a solution of the macrocycle to create a solid-state device, allowing for the naked eye detection of as low as 10 nM TNP under a UV-light irradiation. In another example, calix[4]arene **83** (Figure 4.34) was found by Lee et al. to be strongly quenched by the presence of trinitrobenzene and trinitrotoluene and moderately quenched by dinitrotoluene, dinitrobenzene, and nitrobenzene.⁶¹⁵ Concentrations as low as 1.1 ppb TNT could be detected by this method. The authors propose that the emission quench observed was due to charge-transfer complexes forming between the electron rich pyrene units of **83** and the electron deficient nitroaromatic analyte. Several reports of calixarenes used for the detection of nitroaromatics have been published by Li and coworkers in recent years. In one example, the emission of **84** (Figure 4.34) was significantly quenched by the presence of *p*-nitrophenol, with other nitroaromatics leading to only minimal quenching.⁶¹⁶ **85** (Figure 4.34) was used for the detection of trinitrophenol where dinitro- and mononitroaromatics had minimal effect on the emission of **85**.⁶¹⁷ The group was also able to detect

p-nitroaniline over other nitroaromatic species using **86** (Figure 4.34).⁶¹⁸ A final example of nitroaromatic detection was reported by Teixeira et al. using **87** (Figure 4.34) for the detection of nitroanilines.⁶¹⁹

Figure 4.34. Calixarenes used for the detection of electron-deficient nitroaromatics^{31,613-619}

Choline, an essential nutrient, and acetylcholine, a neurotransmitter, have been detected by two different schemes in recent years. Acetylcholine was found by Jin to displace Rhodamine 800 that was encapsulated in the cavity of thiacalix[8]arene **88** (Figure 4.35).⁶²⁰ Using this method, acetylcholine could be detected in concentrations as low as 0.5 mM. Structurally similar neurotransmitters, dopamine and γ -aminobutyric acid, led to no change in the emission of **88**, yet choline was found to enhance the emission to a lesser extent than acetylcholine, reflecting a lower degree of fluorophore displacement from the cavity. Guo et al. developed a system using calixarenes **89-91**

(Figure 4.35) for the detection of acetylcholine via an indicator displacement assay, which was used for the real-time monitoring of acetylcholinesterase.⁶²¹ As acetylcholine was converted to choline by the enzyme, lower concentrations of acetylcholine were available for binding in the macrocycle and inducing fluorophore displacement, which provided more opportunities for association of the host with lucigenin, a fluorescent dye. Although encapsulated lucigenin displayed only weak fluorescence, displacement of the dye by acetylcholine led to a pronounced increase in emission. Thus, the conversion of acetylcholine to choline resulted in a marked emission decrease. In two final examples, Xu et al. found that the emission of **92** (Figure 4.35) was quenched in the presence of acidic amino acids⁶²² and enhanced in the presence of basic amino acids, and Han et al. used BODIPY-tethered **93** (Figure 4.35) for the monitoring of intracellular pH between 6.3 and 7.9.⁶²³

Figure 4.35. Calixarenes used for the detection of biomolecules in recent years⁶²⁰⁻⁶²³

4.5.6. Resorcin[n]arenes

Resorcin[n]arenes are a class of calixarenes that bear upper-rim hydroxyl groups and substitution at the methylene bridges. Other calixarenes, by contrast, are characterized by lower-rim hydroxyl groups and unfunctionalized methylene linkers.

Often, resorcinarenes have additional methylene linkages between the hydroxyl substituents on the aromatic rings, as shown in Figure 4.36.⁶²⁴ The condensation of resorcinol and aldehydes to form resorcinarenes was first reported in the literature in 1940⁶²⁵ and, like calixarenes, the four-membered resorcinarene macrocycle, termed resorcin[4]arene, is the thermodynamically favored product under most reaction conditions.⁶²⁶ The majority of publications that report the use of resorcinarene-containing fluorescent chemosensors use resorcinarenes in the context of resorcinarene-based coordination polymers (CPs) and metal-organic frameworks (MOFs). While both of these terms describe crystalline structures comprised of infinite arrays of metal nodes and organic linkers, the term coordination polymer is much broader, encompassing a wide range of these structures, while the term ‘metal-organic framework’ is used to describe three-dimensional networks.⁶²⁷ The research group of Jian-Fang Ma has reported the synthesis of a number of resorcinarene-based CPs and MOFs and their use as fluorescent chemosensors, noting that these structures benefit from high tunability, enhanced sensitivity, and unique photophysical properties compared to free macrocycles.⁶²⁸ Aside from their use as fluorescent chemosensors, resorcinarenes have shown promise as ligands for metal-based catalysis,⁶²⁶ in chemical separations,⁶²⁹ and in other, non-luminescent molecular recognition schemes.⁶³⁰

Figure 4.36. Typical core structures of calix[4]arenes and resorcin[4]arenes⁶²⁴

Ma and coworkers have described several MOFs formed from resorcin[4]arenes shown in Figure 4.37, for the detection of cations, anions, and small molecules.^{628,631-633} Luminescent zinc, europium, and terbium MOFs were created using **94** (Figure 4.37), whose emission was almost fully quenched by the presence of Fe^{3+} in aqueous solution.⁶³¹ Stern-Volmer quenching constants of $1.519 \times 10^3 \text{ M}^{-1}$, $3.81 \times 10^2 \text{ M}^{-1}$ and $4.749 \times 10^3 \text{ M}^{-1}$ were reported for the binding of Fe^{3+} with the Eu, Zn, and Tb MOFs, respectively, with a detection limit of 50 μM reported for the Tb-MOF sensor. While no other metal cations effected MOF luminescence, a number of polyoxometalates were also shown to quench emission. In a subsequent publication by the same research group, the ethyl groups of the resorcin[4]arene backbone were replaced with aromatic moieties to create **95** and **96** (Figure 4.37), which were used to form zinc MOFs.⁶³² In the presence of metal cations in aqueous solution, hypsochromic shifts of the fluorescence of the zinc MOF were observed along with various degrees of fluorescent enhancement or quenching, with Fe^{3+} , Fe^{2+} , and Cu^{2+} leading to the most significant quenching. The addition of small amounts of acetone to aqueous solutions of **95** and **96** also quenched the emission, and acetone concentrations as low as 0.5 % and 10 % by volume could be detected, respectively. Additionally, fluorescence quenching was reported in the

presence of vapor phase amines. Cadmium and zinc MOFs made from **97** (Figure 4.37), were also used for the detection of amine vapors, and comparison plots of quenching efficiency vs. wavelength shift allowed for nearly complete differentiation of seven different primary, secondary, and tertiary amines.⁶²⁸ Aldehyde vapors also led to fluorescence quenching of the supramolecular sensor, with the presence of benzaldehyde leading to approximately 80 % quenching of both MOFs after 10 minutes. Finally, the emission of a fluorescent cadmium-**98** MOF, (Figure 4.37), was completely quenched in the presence of Fe^{3+} and chromate anion, with Stern-Volmer constants for these analytes of $2.67 \times 10^5 \text{ M}^{-1}$ and $9.19 \times 10^5 \text{ M}^{-1}$, respectively.⁶³³

Figure 4.37. Resorcin[4]arenes used in metal-organic frameworks for the detection of cations, anions, and small molecules^{628,631-633}

The Ma group also developed a series of coordination polymers based on resorcin[4]arenes, some of which are shown in Figure 4.38.⁶³⁴⁻⁶³⁶ Zinc and cadmium CPs of **99** (Figure 4.38) were treated with aqueous solutions of chromate, and significant

fluorescence quenching was observed, as well as a bathochromic emission shift of the cadmium-**99** CP.⁶³⁴ Fe^{3+} was also able to quench the emission of both CPs with minimal interference from other cations. The Stern-Volmer quenching constants for the interaction of chromate and Fe^{3+} with the Zn-**99** CP were found to be $5.98 \times 10^4 \text{ M}^{-1}$ and $2.048 \times 10^5 \text{ M}^{-1}$, respectively. The fluorescence emission of zinc CPs of **100** and **101** (Figure 4.38) was also quenched by chromate anion, with Stern-Volmer constants of $4.303 \times 10^4 \text{ M}^{-1}$ obtained using **100** and $3.879 \times 10^4 \text{ M}^{-1}$ obtained with **101**.⁶³⁵ Furthermore, the replacement of aqueous solution with nitrobenzene was found to quench both CPs by several orders of magnitude. The presence of nitrobenzene was also found to quench cadmium and zinc CPs of **102** (Figure 4.38).⁶³⁶

Figure 4.38. Resorcin[4]arenes used in coordination polymers for the fluorescent detection of cations, anions, and solvents⁶³⁴⁻⁶³⁶

Boron-based fluorescent appendages have been installed on the upper-rim of resorcin[4]arenes by Kubo et al. and used for the detection of alkyl ammonium cations.^{637,638} Ratiometric sensing of hexyltrimethylammonium, tetramethylammonium, and acetylcholine cations was achieved in 9:1 methylene chloride: dimethylsulfoxide solution using **103** (Figure 4.39), with high association constants of $3.8 \times 10^8 \text{ M}^{-1}$ and

$1.6 \times 10^7 \text{ M}^{-1}$ reported for the latter two, respectively.⁶³⁷ Interestingly, bulkier quaternary ammonium salts did not induce a fluorescence response. In a later publication, when resorcin[4]arene **104** (Figure 4.39) was treated with hexyltrimethylammonium hexafluorophosphate in methylene chloride solution, no changes in fluorescence were observed.⁶³⁷ However, with the addition of 5% dimethylsulfoxide, a fluorescence quench and hypsochromic shift of the fluorescence emission occurred. It was posited by the authors that in purely methylene chloride solution, the resorcin[4]arene exists in an open “kite-like” structure, whereas the presence of dimethylsulfoxide facilitates and stabilizes strong non-covalent binding between the arms of the cavitand, pulling the cavity closed into a “vase-like” structure. This more closed cavity shape is ideal for binding the long alkyl chain of hexyltrimethylammonium hexafluorophosphate, with the cation of the analyte held tightly in the electron-rich macrocycle center. Indeed, a high association constant of $1.44 \times 10^7 \text{ M}^{-1}$ was observed in a 95:5 methylene chloride: dimethylsulfoxide solvent mixture. Mettra et al. functionalized the upper rim of phosphonate resorcin[4]arenes with fluorene appendages to form structures including **105** and **106** (Figure 4.39).⁶³⁹ In the presence of acetylcholine, a neurotransmitter, in chloroform solvent, dramatic quenching of the host’s fluorescence was observed. Notably, the binding of acetylcholine and *cis*-fluorene-bearing host **106** had a higher association constant, $9.28 \times 10^7 \text{ M}^{-1}$ than the *trans*-fluorene-bearing host **105** and species containing one and four fluorene substituents, whose association constants fell in the range of $1.07\text{-}1.82 \times 10^7 \text{ M}^{-1}$.

Figure 4.39. Resorcin[4]arenes bearing fluorescent tags that have been used for the detection of quaternary ammonium cations⁶³⁷⁻⁶³⁹

4.5.7. Calix[n]pyrroles

Calixpyrroles, also known as *meso*-octamethylporphyrinogens, are macrocycles which are formed from the condensation of pyrrole with acetone in acidic media, with the acetone forming covalent bonds to the alpha positions of the pyrrole.⁶⁴⁰⁻⁶⁴² While first synthesized by Baeyer in 1886,⁶⁴³ the utility of these species as supramolecular hosts was not realized until over a century later in 1996 by Sessler and coworkers.⁶⁴⁴

Sessler showed that in the uncomplexed state, methyl- and cyclohexyl-*meso*-substituted calix[4]pyrroles exist in a 1,3-alternate conformation, yet when complexed with a chloride or fluoride anion, the hosts adopted “cone-like” structures with all pyrrole units oriented in the same direction and with the nitrogen atoms non-covalently bound to the halide. Substitution at the *meso*-position of calixpyrroles prevents the spontaneous oxidation of these species to form porphyrins, and while methyl-substitution at this position is ubiquitous, more highly functionalized moieties including fluorescent groups^{645,646} and highly polar solubility-enhancing groups⁶⁴⁷ are also common.⁶⁴¹ Additionally, calixpyrroles with substitution at the pyrrole carbon backbone, or carbon-rim, have also been reported.^{648,649} Functionalized at the nitrogen atoms of the calixpyrroles has also been described, although such substituted variants are rarely used as chemosensors due to disruption of the main binding site of the compounds.⁶⁴¹ Hybrid calixpyrroles that have one or two pyrrole units replaced with other units, such as pyrene^{650,651} or phenol⁶⁵² have been reported, as well as extended calixpyrroles in which other units are interspersed between the four pyrrole units to form larger cavity sizes.⁶⁵³ Strapped or capped calixpyrroles contain a strap over the main binding pocket that aid in the preorganization of the binding pocket and can be tuned to enhance selectivity of the host system for target guests.⁶⁴² These straps often contain additional handles for analyte binding and fluorescent units for chemosensing purposes.^{654,655} Like calixarenes and resorcinarenes, the 4-membered calixpyrrole macrocycle, termed calix[4]pyrrole, is the most thermodynamically favored product under the vast majority of reaction conditions.⁶⁴²

Calix[4]pyrroles show preferential binding toward halides in general, and fluoride in particular, due to its small size and hydrogen-bonding capabilities. Of note, several BODIPY-tagged calix[4]pyrroles have been developed for fluoride binding and concomitant fluoride detection.^{645,656,657} For example, **107** (Figure 4.40) was found to be a selective F⁻ sensor as binding of the fluoride to **107** resulted in a ratiometric change in fluorescence emission.⁶⁴⁵ A high Stern-Volmer constant of $5.48 \times 10^7 \text{ M}^{-1}$ was established. Similar species **108** (Figure 4.40) was found to be less selective for F⁻ based on changes in the host's fluorescence properties, with fluorescence quenching observed upon binding of OAc⁻, Cl⁻, and H₂SO₄⁻ in addition to quenching in the presence of F⁻.⁶⁵⁶ However, fluoride was the only species that also produced a colorimetric change, and coupling these signal outputs led to a dual-responsive sensor that was selective for fluoride. Job's plot analysis indicated a 1:1 stoichiometry for all anions, with a Stern-Volmer constant for fluoride of $7.34 \times 10^4 \text{ M}^{-1}$ reported. All of the fluorescence studies were conducted in acetonitrile and adding water to these systems was found to release the guest from the calixpyrrole cavity. The fluorescence emission of BODIPY-tagged dicalix[4]pyrrole species **109** (Figure 4.40) was quenched by the presence of F⁻, Cl⁻, Br⁻, OAc⁻, and H₂PO₄⁻, with F⁻ providing the greatest amount of quenching with a ca. 10 nm hypsochromic shift reported.⁶⁵⁷ Job's plot analysis indicated a 1:1 binding stoichiometry with all anions, indicating that a sandwich-like complex forms with the anion bound to both macrocyclic moieties.

Figure 4.40. BODIPY-tagged calix[4]pyrroles used for the detection of fluoride anion^{645,656,657}

Coumarin-tagged calix[4]pyrrole **110** (Figure 4.41), was found, in the deprotonated form, to exist with the coumarin appendage bound inside the calix[4]pyrrole cavity, with the binding resulting in effective quenching of the coumarin fluorescence.⁶⁴⁶ With the addition of fluoride, which binds more strongly to the **110** cavity than the coumarin appendage the coumarin was released, leading to notable fluorescence increases. The presence of other anions did not affect the fluorescence of the host, but the introduction of lithium cation sequestered fluoride, prevented the fluoride from displacing the coumarin moiety, and led to quenching of the system fluorescence. Of note, a sensitive detection limit of 0.4 nM for fluoride was reported. Similarly, anthracene-bearing dicalix[4]pyrrole **111** (Figure 4.41) was found to be weakly emissive in acetonitrile until the addition of fluoride, which enhanced the emission significantly.⁶⁵⁸ High selectivity for fluoride was observed in this system, with a variety of other inorganic and organic mono- and multi-anionic species having no effect on the fluorescence emission. 1:2 host-guest stoichiometry was confirmed by Job's Plot analysis and isothermal titration

calorimetry, and fluorescence titration showed association constants of $1.91 \times 10^5 \text{ M}^{-1}$ for the first binding event and $5.95 \times 10^7 \text{ M}^{-1}$ for the second.

One way to achieve selectivity is through the use of steric differences between the target analyte and related structures. For example, Samanta et al. developed a series of strapped calix[4]pyrroles with very short straps, including **112-114** (Figure 4.41), with the goal of creating a binding pocket small enough to bind fluoride and no other anions.⁶⁵⁹ As expected, only fluoride was found to bind inside the cavities of the hosts, with no other anions causing notable spectral changes. Despite this high selectivity, **112-114** did not bind fluoride as well as other, larger homologues, with association constants generally an order of magnitude lower for the new hosts, suggesting that larger cavities are preferential for fluoride binding.

In contrast to the systems described above, the strong binding of fluoride to **115** (Figure 4.41) was used to modulate the response of the host to other analytes.⁶⁵⁰ The cone-shaped cavity created through binding of **115** with fluoride created an electron-rich binding pocket that was used by Lee and coworkers to bind the electron-deficient, sphere-shaped fullerene species C_{70} and C_{60} , resulting in fluorescence quenching of the host. With fluoride present, a 1:1 host-guest stoichiometry was formed between the host and either guest, and association constants were found to be $9.4 \times 10^5 \text{ M}^{-1}$ for C_{60} binding and $5.4 \times 10^6 \text{ M}^{-1}$ for C_{70} binding. In the absence of fluoride to modulate the cavity shape, 2:1 host-guest stoichiometries were observed with slightly lower association constants of $2.7 \times 10^5 \text{ M}^{-1}$ for C_{60} and $2.0 \times 10^6 \text{ M}^{-1}$ for C_{70} . Of note, the detection limit for C_{70} was found to be in the nanomolar range.

Figure 4.41. Calix[4]pyrrole hosts for the fluorescent detection of fluoride (**110-114**) or the fluoride-modulated detection of fullerenes(**115**)^{646,650,658,659}

Strapped calix[4]pyrroles with pyrene fluorescent tags, **116** and **117** (Figure 4.42), were developed by Lee and coworkers. Upon titrating these macrocycles with anions in a 5% acetonitrile in toluene solvent system, fluorescence quenching was observed.⁶⁵⁴ In this instance, chloride, rather than fluoride, exhibited the strongest binding, with chloride binding to **116** and **117** with association constants of $4.9 \times 10^6 \text{ M}^{-1}$ and $4.6 \times 10^6 \text{ M}^{-1}$, respectively, and fluoride binding to the hosts with association constants of $3.0 \times 10^6 \text{ M}^{-1}$ with **116** and $2.7 \times 10^6 \text{ M}^{-1}$ with **117**. Competition studies were not conducted to determine whether fluoride or other anions had an effect on chloride binding and the subsequent emission quench. Naphthalene-strapped **118** and **119** (Figure 4.42) also bound most strongly to chloride, with association constants similar to those of **116** and **117**.⁶⁵⁵

Figure 4.42. Fluorescent, strapped calix[4]pyrroles used for the recognition of chloride and other anions^{654,655}

Calix[4]pyrrole **120** (Figure 4.43), bearing fluorescent pyrene appendages, was found to form 1:1 host-guest complexes with halides, which resulted in fluorescence quenching.⁶⁶⁰ Chloride bound to **120** with an association constant of $3.2 \times 10^5 \text{ M}^{-1}$, which was only slightly higher than that of fluoride, $1.1 \times 10^5 \text{ M}^{-1}$. Hosts **121** and **122** (Figure 4.43) underwent a fluorescence quench in the presence of several halides and oxoanions.⁶⁶¹ Iodide was found to quench the system most effectively compared to bromide and chloride, although the effect of fluoride was not examined. Stern-Volmer constants for iodide, bromide, and chloride with **121** were found to be $3.36 \times 10^2 \text{ M}^{-1}$, $2.28 \times 10^2 \text{ M}^{-1}$, and $1.92 \times 10^2 \text{ M}^{-1}$, respectively. A dye displacement assay for the detection of pyrophosphate, a biologically relevant anion, was accomplished using supramolecular complex **123** (Figure 4.43).⁶⁴⁷ The fluorescent dye, 7-hydroxy-4-(trifluoromethyl) coumarin, was quenched when held inside the calix[4]pyrrole cavity using a combination of hydrogen-bonding and cation- π interactions. Upon addition of pyrophosphate anion, the dye was released from the cavity and replaced with pyrophosphate, resulting in significant fluorescence enhancements. Good selectivity

over fluoride, phosphate and other anions was found, with each of those species binding at least two orders of magnitude weaker than pyrophosphate, which had an extremely strong binding constant of $2.55 \times 10^7 \text{ M}^{-1}$ in acetonitrile. The authors hypothesize that this strong binding is facilitated through a combination of several intermolecular forces: hydrogen-bonding between the oxygen atoms of pyrophosphate and the pyrrole hydrogens; electrostatic interactions between the anion guest and pyridinium cation components of the host; and anion-pi interactions between the anionic guest and the aromatic core of the calix[4]pyrrole. Using this system, a nanomolar detection limit for pyrophosphate was obtained.

Figure 4.43. Calix[4]pyrroles used for the fluorescent detection of a variety of anions^{647,660,661}

A variety of carboxylate species, including non-steroidal anti-inflammatory drugs (NSAIDs) have been detected using calix[4]pyrroles.^{648,649,653,662} A number of fluorophore-tagged calix[4]pyrroles, shown in Figure 4.44a, were developed by Anzenbacher and coworkers for the fluorimetric and colorimetric differentiation of 14 analytes, including six NSAIDs, several other drugs, and other biologically relevant compounds.⁶⁴⁹ Using the fluorescent and colorimetric responses of eight sensors to the analytes, an array-based detection scheme was developed. Principal component analysis

(PCA) of the response patterns led to 95 % discrimination of analytes and linear discriminant analysis (LDA) enabled 89.4 % discrimination. When a cross-validation LDA method was used, however, 100% correct classification of the 14 analytes was achieved in both pure water and in human urine. PCA also allowed for quantitative detection of the six NSAIDs, with detection limits near 0.1 ppm and full discrimination at concentrations between 0.5 and 100 ppm, which includes typical NSAID urinary concentrations. In a later publication by the same authors, a series of fluorophore-tagged calix[4]pyrroles and hybrid, extended calixpyrroles, including those shown in Figure 4.44b, were used for the fluorescent detection of 18 analytes, including halides, oxoanions, carboxylates, and NSAIDs.⁶⁵³ LDA utilizing five fluorescent calixpyrroles allowed for 100 % correct classification of all analytes. Accurate quantitative recognition of oxalate, malonate, glutamate, aspartate, and phthalate was also achieved. In addition, Anzenbacher and coworkers have reported the use of poly(ether-urethane) hydrogel-encapsulated **124** (Figure 4.44a) for the array-based detection of several different anionic guests.⁶⁶² Rather than using a variety of fluorescent hosts, the authors used ten different polymer matrices for the encapsulation of **124**. These matrices varied by comonomer ratio, which resulted in differences in matrix hydrophilicity, and also varied based on the environmental polarity of the hydrogel probe. LDA analysis using these hydrogels allowed for 100% correct classification of the eight anions examined and the quantitative detection of the NSAIDs ibuprofen and diclofenac, both in water and in human saliva with detection limits of 0.1 ppm obtained. Additionally, different concentrations of mixtures of chloride and phosphate were accurately quantified in human urine. A final dicarboxylate fluorescent detection scheme was reported by Gotor

et al., in which BODIPY-tagged mono- and di-calix[4]pyrroles, similar to **108** and **109** (Figure 4.40) yet without bromine substitution on the BODIPY tag, were used for the sensing of aliphatic and aromatic carboxylates via fluorescence quenching and/or fluorescence modulation.⁶⁴⁸

Figure 4.44. Calix[4]pyrroles and hybrid, extended calixpyrroles used for the array-based detection of carboxylates and NSAIDs^{649,653,662}

Sensing of metal cations can also be achieved using calix[4]arenes, such as those shown in Figure 4.45.^{663,664,665} Dansyl-tagged calix[4]pyrrole, **125** (Figure 4.45), was found to undergo fluorescence quenching in the presence of uranium(IV), thorium(IV) and iron(III) cations in methanol solution.⁶⁶³ Additional metal cations, including alkali metals, alkaline earth metals, and other heavy metals, had no effect on the fluorescence of **125**. The authors propose that the mechanism of fluorescence quenching by cation inclusion is the disruption of ICT from the dimethylamino nitrogen to the naphthalene moiety by the presence of a metal cation. All three cations were found to bind in a 1:1 stoichiometry with binding constants of $1.90 \times 10^4 \text{ M}^{-1}$ for U^{4+} , $1.50 \times 10^4 \text{ M}^{-1}$ for Th^{4+} ,

and $1.40 \times 10^4 \text{ M}^{-1}$ for Fe^{3+} . Quinoline-bearing **126** (Figure 4.45) has been shown to bind to Cu^{2+} and Pb^{2+} with association constants of $2.42 \times 10^4 \text{ M}^{-1}$ and $2.91 \times 10^4 \text{ M}^{-1}$, respectively.⁶⁶⁴ The significant fluorescence quenching observed is also hypothesized to be a result of ICT disruption of the fluorescent appendages. Despite the known affinity of calix[4]pyrroles toward anions, neither of these hosts were evaluated for anion detection applications. **127** (Figure 4.45), however, was found to undergo fluorescence enhancement in the presence of Cu^{2+} and Pb^{2+} with no interference from anions that were added after the initial complexation event.⁶⁶⁵ Association constants of the host with these species were found to be $6.6 \times 10^5 \text{ M}^{-1}$ for Cu^{2+} and $5.90 \times 10^5 \text{ M}^{-1}$ for Pb^{2+} . 1:2 host-guest binding stoichiometries identified by Job's plot analyses indicated that the metal cations were likely binding to the carbonyl groups of the fluorescent appendages, leaving the central calix[4]pyrrole cavity open to anion binding. However, addition of chloride or bromide to Pb-complexed or uncomplexed **127** resulted in no changes in fluorescence. Conversely, treatment of **127** with Cl^- before the addition of Pb^{2+} prevented the binding of Pb^{2+} , likely due to a chloride-mediated conformational change in the host.

Figure 4.45. Calix[4]pyrroles used for the fluorescent detection of metal cations⁶⁶³⁻⁶⁶⁵

Like with **127**, while the central cavity of a calixpyrrole is generally used for anion binding, appendages can be installed on a calixpyrrole rim that allow for cation binding, resulting in multi-functional hosts for ion pair detection.^{3,666} For example, **128** (Figure 4.46) underwent fluorescence enhancement with the addition of iron difluoride in aqueous solution, as a result of dual binding of the cation and anions.³ Upon addition of an Fe^{2+} source with a non-coordinating counteranion, no fluorescence enhancement was observed; similarly, no change in fluorescence occurred with the addition of F^- with a non-coordinating countercation. Thus, **128** is an efficient host for the selective detection of the FeF_2 ion pair upon the coordination of F^- to the central calix[4]pyrrole cavity and Fe^{2+} to the triazole moiety of the fluorescent appendages. Gotor et al. synthesized **129** (Figure 4.46), in which a calix[4]pyrrole anion-binding unit and a azo-crown ether cation-binding unit were linked together by a BODIPY fluorophore.⁶⁶⁶ Hypsochromic fluorescence emission shifts were observed with the addition of cations, with NH_4^+ and K^+ leading to the most significant shifts; while bathochromic shifts and quenches of

fluorescence emission were observed in the presence of anions, with F^- leading to the most significant change. A three-dimensional comparison of emission intensity, emission wavelength, and the ratio of absorbance at 680 nm and 625 nm allowed for the discrimination of nine different salts comprised of K^+ , Li^+ , Na^+ , Cl^- , Br^- , and F^- ions. Seven zwitterionic amino acids were also examined, all of which were successfully differentiated using the same analysis. Notably, γ -butyric acid showed the most significant fluorescence response, indicating optimal matching of the distance between the host cavities with the size of the analyte.

Figure 4.46. Calix[4]pyrroles used for the fluorescent detection of ion pairs^{3,666}

Certain calixpyrroles, shown in Figure 4.47, have been used for the detection of electron-deficient nitroaromatic analytes.^{651,667,668} Supramolecular complex **130** (Figure 4.47), comprised of a cholesterol-functionalized calix[4]pyrrole and a perylene bisimide diacid fluorophore was formed in solution, after treatment with ammonia resulted in diacid deprotonation.⁶⁶⁷ Once formed, this complex was shown to be efficient for the detection of TNT in ethanol, with a detection limit of 80 nM. The mechanism of

this detection was via analyte-induced fluorescence quenching, due to the disruption of the supramolecular complex that occurred through TNT-calix[4]pyrrole association. Although some nitroaromatic species, specifically nitrobenzene and 2,5-dinitrobenzene, had no effect on the system's fluorescence, 2,4-dinitrotoluene exhibited some fluorescence quenching. Additionally, the fluorescence of a **130** film was quenched by phenol vapor, with a 1 ppb detection limit for phenol obtained. More substituted phenols were also shown to quench the system fluorescence, albeit with lower efficiencies. The fluorescence emission of hybrid calixpyrrole **131** (Figure 4.47) was also quenched in the presence of nitroaromatics, with 8000 equivalents of nitrobenzene and 3000 equivalents of TNT leading to a 5-fold and 10-fold quenching, respectively.⁶⁵¹ A 1:1 binding stoichiometry was determined by Job's plot analysis, and the binding constant of **131** with TNT was found to be $1.1 \times 10^6 \text{ M}^{-1}$. In a final example, oligomeric supramolecular complexes formed from calix[4]pyrrole **132** and fluorophore **133** (Figure 4.47) were used to detect trinitrobenzene.⁶⁶⁸ Upon oligomer formation, the fluorescence of **133** was quenched; subsequent addition of trinitrobenzene disrupted the supramolecular aggregates, resulting in restoration of the **133** fluorescence emission. Because aggregation is highly dependent on the concentration of the aggregating species, significant fluorescence enhancement was only seen with high concentrations of **132** and **133** that formed effective aggregates.

Figure 4.47. Calixpyrroles used for the fluorescent detection of nitroaromatics^{651,667,668}

4.5.8. Pillar[n]arenes

Pillar[n]arenes are a recently developed class of macrocycles, first reported by Ogoshi and coworkers in 2008,⁶⁶⁹ which are generally formed through the facile and versatile condensation of phenols with paraformaldehyde.⁶⁷⁰ Pillararenes are structurally similar to calixarenes, with both composed of aromatic repeating units, with the former having methylene bridges at the 2 and 5 positions of the repeat unit, and the latter bound at the 1 and 3 positions of the aromatic rings. Thus, whereas calixarenes are characterized by a wide upper rim and narrow lower rim, leading to a basket-like shape, the rims of traditional pillararenes are identical, allowing for a rigid, pillar-shaped

cavity.⁴⁸ Pillararenes have been employed as supramolecular hosts for the encapsulation of a variety of guests, with such binding promoted by charge-transfer interactions, cation- π interactions, hydrophobic/hydrophilic interactions, electrostatic interactions or hydrogen bonding.⁶⁷⁰ More complex architectures have been formed from pillararenes, including self-inclusion complexes,^{671,672} rotaxanes,⁶⁷³⁻⁶⁷⁵ polyrotaxanes,^{676,677} catenanes,^{678,679} micelles,⁶⁸⁰ microtubes,⁶⁸¹ liquid crystals,^{682,683} and metal organic frameworks (MOFs).⁶⁸⁴

Metal cations are common analytes for pillararene-based detection, and a number of modified pillararenes have been employed in such schemes in recent years. In one example, Yao et al. encapsulated a fluorescent dye, perylene diimide, in the cavity of **134** (Figure 4.48), leading to quenching of the dye emission through a PET mechanism.⁶⁸⁵ The PET was disrupted by the addition of Fe^{3+} , which led to an almost 100-fold increase in emission. Among all cations investigated, only Fe^{3+} was found to enhance the fluorescence emission of the system, leading to a detection limit of 0.21 μM . Although researchers reported that sodium pyrophosphate could sequester Fe^{3+} and “turn-off” the fluorescent probe, comparative behaviors of other anions were not reported, and competition experiments with other metal cations were not conducted.

Zhang, Wei, and coworkers provided two additional schemes for the detection of Fe^{3+} by pillararene complexation. In the first example, fluorescent pillararene **135** (Figure 4.48) was synthesized, which displayed strong fluorescence in the absence of guest due to binding of the covalently appended benzothiazole unit in its own hydrophobic cavity.⁶⁸⁶ Introduction of Fe^{3+} led to its binding inside the cavity of **135**, displacing the benzothiazole moiety and quenching the macrocycle’s fluorescence. A

detection limit of 0.90 μM was found, and of all other metal cations examined, only Hg^{2+} also led to fluorescence quenching. Competition experiments showed little effect on the quenching ability of Fe^{3+} in the presence of 1 equivalent of a second metal cation. The addition of F^- regenerates the emission profile of **135**, with a fluoride detection limit of 26 nM. Other anions led to moderate fluorescence enhancement, and competition experiments revealed that the effect of F^- was altered somewhat in the presence of other species. Similarly, **136** (Figure 4.48) was found to complex both Fe^{3+} and Cu^{2+} with a detection limit for iron of 0.14 μM .⁶⁸⁷ The Fe^{3+} -**136** adduct was then used to detect F^- at concentrations as low as 0.25 μM . Other transition metal-**136** complexes did not have a pronounced affinity for F^- , and the iron complex was only moderately selective for fluoride over other anions.

Thorium was detected using **137** (Figure 4.48), with selectivity over a variety of other metals, including lanthanides, actinides, transition metals, and base metals, as reported by Fang et al.⁶⁸⁸ Upon the addition of one equivalent of Th^{4+} to **137**, the emission of the macrocycle was almost completely quenched. In the presence of 10 equivalents of potentially interfering metal cations, no disruption of the quenching was observed. Similar to previously discussed systems, the addition of fluoride sequestered the heavy metal, allowing the fluorescence of **137** to be regenerated, even in the presence of 100 equivalents of competing anion. Detection limits of 0.54 μM and 3.0 μM were observed for Th^{4+} and F^- , respectively.

Figure 4.48. A series of pillararenes that have been reported for the detection of metal cations⁶⁸⁵⁻

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A 1:2 supramolecular complex of **138** (Figure 4.48) and fluorophore **140** (Figure 4.49) was employed by Wei and coworkers for the sequential detection of Al^{3+} and CN^- in aqueous media.⁶⁸⁹ Fluorescence enhancement unique to Al^{3+} was seen, with a detection limit of 99 nM. Notably, the addition of CN^- to the **138-140- Al^{3+}** system did not sequester the Al^{3+} and decrease the fluorescence, as with the aforementioned dual-detection systems, but instead led to another significant emission enhancement. The authors attribute emission enhancement to the formation of a highly fluorescent 1:2:1:1 **138-140- Al^{3+} - CN^-** quaternary complex. The further addition of Al^{3+} equivalents, however, re-formed the **138-140- Al^{3+}** complex, thus regenerating its emission profile, allowing for reversible switching between the moderately and highly fluorescence states. No other anion was found to produce a response similar to that of CN^- , nor were any found to quench the emission of the **138-140- Al^{3+}** complex. Furthermore, a detection limit of 2.3 μM was found for CN^- . The group also discovered that **139** could

be used for the detection of CN^- ,⁶⁹⁰ where the addition of CN^- to the macrocycle led to a significant fluorescence enhancement along with a bathochromic shift that was unique to the presence of CN^- . Although no other anion caused enhancement of the fluorescence of **139** (Figure 4.48), a variety of anions, including F^- , AcO^- , H_2PO_4^- , HSO_4^- , as well as Ca^{2+} , interfered with the enhancement ability of CN^- and led to less fluorescence enhancement. A CN^- detection limit of 10.8 nM was observed, and the system maintained detection efficacy in a complex system, namely the detection of CN^- in sprouting potatoes. Compound **134** (Figure 4.48) was also used for both the detection of cyanide and of paraquat, an herbicide, as reported by Wang et al.⁶⁹¹ At pH 7.4, paraquat was found to displace *N*-methylacridinium iodide, a fluorophore, from the cavity of **134**, leading to significant emission enhancement. Of note, other substrates were not examined and so the detection selectivity could not be determined. When the solution was acidified to pH 6.0, protonation of the carboxylic acid pendant arms of the macrocycle led to the displacement of the acridinium dye. In this uncomplexed form, the dye readily reacted with CN^- and water, leading to oxidation in the 9-position of the molecule and a consequent fluorescence quench and hypsochromic shift in emission, allowing for the detection of CN^- .

Figure 4.49. Novel fluorophores that have been used in pillararene-based detection schemes^{689,695}

Wang et al. synthesized a dissymmetric pillararene that spontaneously formed fluorescent daisy chains in solution, leading to the application of the material as a fluorescent chemosensor for temperature, pH, solvent, and the presence of certain anions (Figure 4.50).⁶⁹² Cation- π interactions between the ammonium and anthracene moiety governed the formation of the fluorescent daisy chains, thus changes in pH and subsequent deprotonation of the ammonium to form an amine led to decomplexation and fluorescence quenching. Moreover, because cation- π interactions are much weaker in polar solvents than in non-polar solvents, daisy chain formation was also solvent dependent. Anions were hypothesized to form ion pairs with the ammonium cation, blocking the cation from interactions with the anthracene and providing a mechanism for anion detection. Finally, heat was found to lead to decomplexation of the daisy chain and fluorescence quenching, by reducing the binding affinities of the macrocycles to one another. Of note, all of these supramolecular interactions were found to be reversible.

Figure 4.50. A pillararene daisy chain and its responses to temperature, solvent, pH, and the presence of anions. Adapted with permission from Ref. 692. Copyright 2014 Royal Society of Chemistry.

Certain biologically relevant molecules have also been sensed by pillararene constructs in recent years. For example, L-tryptophan⁶⁹³ and L-methionine⁶⁹⁴ were detected by Wei and coworkers with hosts **142** (Figure 4.51) and **138** (Figure 4.48), respectively. In the former case, all 20 naturally-occurring amino acids were investigated, and only L-tryptophan successfully quenched the emission of **142**.⁶⁹³ A limit of detection of 0.28 μM was found, and competition experiments showed that the system was highly selective for L-tryptophan. Additionally, glass slides were dip-coated in a solution of **142**, and treatment of the dried slide with a solution of the analyte led to a noticeable quenching of fluorescence under a UV lamp. The detection of L-methionine with **138** was less selective than with **142**, with only 0.20 equivalents of interfering

amino acids leading to significant decreases in the emission enhancement induced by L-methionine.⁶⁹⁴ The detection limit of L-methionine was 0.55 μM when no interfering species were present, and increased to 2.0 μM in the presence of 10 equivalents of histidine.

Host **143** (Figure 4.51) was found to be selective for the detection of ATP via the ATP-induced displacement of fluorophore **141** (Figure 4.49).⁶⁹⁵ ATP bound strongly to **143**, with an association constant an order of magnitude higher than GTP, ADP, and AMP, allowing for a much greater fluorescence quenching by the target analyte compared to other structurally similar substances. While these reported results were promising, competition experiments were not conducted, and a detection limit was not calculated. In another example, Hua et al. realized the ability of **134** (Figure 4.48) as a probe of enzymatic activity.⁶⁹⁶ In this system, choline bound strongly in the cavity of **134**, displacing a previously encapsulated fluorophore, acridine orange, which resulted in an increased emission. By monitoring this fluorescence, the activity of the enzyme choline oxidase was measured via the enzymatic-induced transformation of the choline reactant into a betaine product, which does not bind in the **134** cavity.

144 (Figure 4.51) was shown by Hua et al. to encapsulate salicylaldehyde, promoting deprotonation of the guest and leading to a highly fluorescent supramolecular complex.⁶⁹⁷ Salicylaldehyde could then be displaced by chlorophenols, which are ubiquitous, toxic environmental contaminants. While mono- and di-chlorophenols were found to decrease the emission of the complex somewhat by binding in the cavity and displacing salicylaldehyde, 2,4,6-trichlorophenol quenched the emission of the host-dye complex to the largest extent, most likely due to a binding constant two orders of

magnitude higher than salicylaldehyde and the other guests. A final report by Strutt et al. described the synthesis of **145** (Figure 4.51) and its application in the detection of moderately toxic alkyldiamines via fluorescence quenching.⁶⁷³

Figure 4.51. A series of pillararenes that have been used as scaffolds for detection schemes^{673,693,695,697}

4.5.9. Cucurbiturils

Cucurbiturils, or CBs,^{698,699} are pumpkin-shaped structures (cucurbituril is derived from the Latin word for “pumpkin”), and three of the most common cucurbituril architectures are shown in Figure 4.52, below.^{700,701} Unlike cyclodextrins, cucurbiturils are not naturally occurring, and their syntheses can involve relatively harsh conditions,³⁹⁷ typically involving a condensation reaction between glycouril and formaldehyde.⁷⁰² The interior cavities of cucurbiturils are hydrophobic, much like the cyclodextrin hydrophobic cavities, but there are two main differences when comparing these classes of macrocycles: First, cucurbiturils are much more rigid structures, and their binding affinities for small molecule guests are much stronger.⁷⁰³ Cyclodextrin binding affinities for small molecule guests usually have binding constants between 100 and 1000 M^{-1} . Cucurbiturils, by contrast, can have binding affinities as high as 10^{14} or

$10^{15} \text{ M}^{-1,704,705}$ which rivals the binding of avidin and biotin, which is among the strongest interactions known.^{706,707} Secondly, cucurbiturils have a ring of carbonyls pointed at each entrance to the cavity.⁷⁰⁸⁻⁷¹⁰ These carbonyls are polarized to have negative electron charge density, and therefore cucurbiturils are much stronger cation binders than are cyclodextrins. Cucurbiturils show the strongest binding affinities in cases where they can bind molecules that are both cationic (in one portion),⁷¹¹ and hydrophobic (in a different portion),⁷¹² such as biogenic amines,⁷¹³ which take full advantage of the structural features of the cucurbiturils.

Figure 4.52. The most common cucurbituril architectures, CB6, CB7, and CB8. Reproduced from Ref. 700. Copyright 2011 American Chemical Society.

Applications of cucurbiturils as chemosensors have emerged in recent years, with many examples of cucurbiturils used for the detection of over-the-counter (OTC) or prescription drugs, pesticides and toxicants. One example by Anzenbacher and coworkers used CB derivative **146** and acyclic analogue **147** (Figure 4.53) for the detection of addictive OTC drugs, such as doxylamine, pseudoephedrine, and phenylephrine, that are found in common cold and flu medications such as NyQuil and Sudafed.⁷¹⁴ Each analyte provided a unique fluorescence quench or enhancement, with the enhanced fluorescence a result of rigidification of the photophysically active moieties and elimination of undesired non-radiative decay pathways. Linear

discriminant analyses (LDA) of the response patterns allowed for the 100% correct classification of individual analytes as well as three component mixtures of doxylamine, pseudoephedrine, and phenylephrine at a variety of concentrations. The calculated detection limits of doxylamine, pseudoephedrine, and phenylephrine were 1.0 ppm, 0.7 ppm, and 0.8 ppm, respectively, and doxylamine was accurately detected in undoped and doped human urine samples. Notably, fluctuations of electrolyte levels in solution had no effect on the detection ability of the system.

Figure 4.53. CB6 derivative **146** and acyclic derivative **147** used by Anzenbacher for the detection of over-the-counter drugs. Adapted from Ref. 714. Copyright 2013 American Chemical Society.

Amantadine, a drug for the treatment of Parkinson's disease, was successfully detected by del Pozo et al.⁷¹⁵ and Yang et al.⁷¹⁶ In the former report, fluorescent dye thionine was displaced from the cavity of CB7 or CB8 by adamantadine, leading to a decrease in fluorescence for the CB7 host and an increase in fluorescence for the CB8 host.⁷¹⁵ Structurally similar drugs rimantadine, ribavirine, and acyclovir, were examined, and only rimantadine was found to lead to perturbations of the CB/dye emission spectra; allowable concentrations of the potential interferents were found to be 4.5 nM, 36 μM , and 3.6 μM , respectively. A detection limit of 0.16 μM was found and the system was then applied to doped human serum samples and pharmaceutical

capsules containing adamantadine with high accuracy. Notably, the binding studies occurred in a flow reactor with the analyte and host mixing in flow before being analyzed by the detector, which facilitated quick and automated results. The report by Yang et al. utilized CB7 with a different fluorophore, 1,1'-butane(1,4-diyl)bis(2-aminopyridine)bromide (DPAD), for the detection of adamantadine by fluorescence quenching.⁷¹⁶ A very high binding constant of $4.23 \times 10^{12} \text{ M}^{-1}$ was reported,⁷¹⁷ which allowed for the low analyte detection limit, 1.3 μM , and moderate selectivity observed.

An assay of CB7 with three fluorophores, palmatine, berberine, and coptisine, was used by Li and coworkers for the detection of both labetalol hydrochloride,⁷¹⁸ a performance-enhancing drug, and dibucaine,⁷¹⁹ a cocaine-related local anesthetic. Labetalol hydrochloride was detected with limits ranging from 4.9 nM to 12.0 nM,⁷¹⁸ and dibucaine was detected with limits of 6.0 nM to 25.0 nM.⁷¹⁹ In both instances, common components of urine were analyzed as potential system interferents, and it was found that only the amino acids cysteine, alanine, phenylalanine, and valine led to any quenching of the system. Of note, although the same system was used to test both dibucaine and labetalol hydrochloride, the analytes were not compared against one another.

Aryal and coworkers found that certain therapeutic drugs were able to displace a naphthalimide-derived dye from the cavity of CB7 leading to an observed quench in the fluorescence emission signal.⁷²⁰ The therapeutic drugs *N*-(aminophenyl)-piperidine, doxorubicin, and adamantyl-carboxamido-benzenesulfonamide all exhibited high affinity for CB7, with association constants of $1.0 \times 10^7 \text{ M}^{-1}$, $2.5 \times 10^6 \text{ M}^{-1}$, and $1.3 \times 10^9 \text{ M}^{-1}$, respectively. Competition studies between the wide array of analytes were not

conducted, and no method was employed for the discrimination of one analyte from another. In a report by Lazer et al., displacement of a fluorescent dye (perylene diimide, berberine chloride, or methylene blue) from the cavity of CB8 was caused by a number of steroids, allowing for effective steroid detection.⁷²¹ Strong binding constants between 10^5 and 10^9 M^{-1} were found for the steroid analytes, and the steroids could be detected at low micromolar concentrations. LDA analysis enabled the successful differentiation of 10 of the 12 steroids examined, and the assay was used to monitor the activity of steroid-producing enzymes.

Two reports of the detection of pesticides and fungicides by CB encapsulation were reported by Huang and coworkers in recent years. In the first report, three different cucurbiturils, CB6, CB7, and tetramethyl-CB6 were screened as potential sensors for the fungicide thiabendazole.⁷²² Upon encapsulation of thiabendazole by a cucurbituril, its fluorescence was enhanced, enabling low nanomolar limits of detection for this toxic pesticide. In 2018, the group published the use of a pyronine Y-CB8 supramolecular complex for the detection of thiabendazole, fuberidazole, and carbendazim.⁷²³ Initially, a weakly fluorescent 1:2 host-dye complex formed, from which one of the two pyronine Y molecules was displaced upon introduction of the analyte. A ternary complex between the host, dye, and analyte was formed that exhibited a large increase in fluorescence emission along with a slight bathochromic shift. Detection limits of approximately 100 nM were calculated, and it was found that other pesticides, including paraquat and tritconazole, did not show the same fluorescence-increasing behavior. The host-dye complex had low cytotoxicity, and was used to detect exogenous thiabendazole, fuberidazole, and carbendazim in PC3 cells. A similar report by del Pozo et al. also

described the detection of carbendazim by encapsulation with CB7.⁷²⁴ Detection and quantification limits of 5.0 nM and 26 nM were observed, and the technique was applied to the sensing of carbendazim in orange peels.

Compounds **146** and **147** (Figure 4.53) were again used by Anzenbacher and coworkers, this time for the detection of the toxic nitrosamines *N*-nitrosonornicotine and (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone, along with a range of other toxicants.⁷²⁵ In this report, the cyclic and acyclic analogues were first complexed with metal cations, including Zn^{2+} , Eu^{3+} , Yb^{3+} , and Hg^{2+} , which were subsequently displaced by the analytes of interest, resulting in appreciable changes in fluorescence emission. The authors use statistical analyses of the differences in the signal responses of **146**, heavy metal-containing **146**, and acyclic analogue **147** to each analyte to create array-based detection schemes. LDA allowed for 100% classification of all 12 guests, and a support vector machine (SVM) regression method allowed for quantification of analytes, even in the presence of nicotine, which was a strong interferent. Detection limits of *N*-nitrosonornicotine and (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone were found to be 0.05 ppm and 0.27 ppm, respectively.

Cucurbiturils have been employed for the detection of biologically relevant molecules, including the detection of cadaverine, a naturally occurring toxic diamine, by Wang et al.⁷²⁶ In this system, the addition of cadaverine to a highly fluorescent supramolecular complex of CB7 with acridine orange led to the displacement of the dye and a subsequent decrease in fluorescence. The activity of lysine decarboxylase, which converts lysine into cadaverine, was monitored by observing the differential fluorescence responses of the enzymatic reactant and its product. The presence of lysine

did not affect the fluorescence intensity of the system as lysine cannot displace the fluorophore from the host cavity. As lysine was converted to cadaverine, the system fluorescence decreased accordingly as acridine orange was displaced. The inhibition of the enzyme by several organophosphate esters was examined using this system. Enzyme inhibition was monitored in a similar manner by Biedermann et al. where a fluorophore, either MDAP⁺ or perylene diimide, was displaced from the cavity of CB8 by an analyte that was either a substrate or product of an enzymatic reaction.⁷²⁷ The key for this detection to be successful was that the substrate and product need to have complementary association constants, meaning that one species will bind preferentially to the macrocyclic cavity whereas the other species will not, resulting in differential response signals.

Ye et al. synthesized a modified bipyridinium fluorene, **148** (Figure 4.54), which acted as a fluorescent guest for CB8 encapsulation and enabled ATP detection.⁷²⁸ The long chain fluorophore threaded through the CB8 cavity, and the authors hypothesize that electrostatic interactions between the positively charged fluorophore and negatively charged ATP induced aggregation of the supramolecular complex, which led to a decrease in fluorescence emission. ADP, AMP, and carbonate were also found to quench the emission of the supramolecular host, and all other anions led to negligible changes in emission.

Figure 4.54. Novel fluorophores that have been involved in cucurbituril-based detection schemes^{728,729}

Synthetically accessible twisted CB14⁷³⁰ (Figure 4.55) was used by Zhang et al. for the detection of metal cations.⁷³¹ In this scheme, thiazole orange was encapsulated in CB14, and the additions of Ba²⁺ and Pb²⁺ led to a decrease in the fluorescence and hypsochromic shift of emission signal. Conversely, the addition of one equivalent of Hg²⁺ led to an increase in emission, and further Hg²⁺ aliquots led to fluorescence quenching. The authors hypothesized that in the presence of one equivalent or less of mercury, a highly fluorescent ternary complex was formed, whereas at higher concentrations of the analyte, binary Hg-CB14 and Hg-thiazole orange complexes were formed, both of which are minimally fluorescent. The detection limit of Hg²⁺ at neutral pH was found to be 78 nM, with only Ba²⁺ and Pb²⁺ disturbing the emission profile. Notably, in acidic media, Hg²⁺ does not increase emission, and only Ba²⁺ and Pb²⁺ were shown to affect the CB14-thiazole orange complex, again leading to decreases and hypsochromic shifts in emission. Under these conditions, the detection limits of Ba²⁺ and Pb²⁺ were found to be 0.46 μ M and 3.6 μ M, respectively.

Figure 4.55. Side (left) and top (right) view of twisted CB14 that was used by Zhang et al. for the detection of metal cations.⁷³¹ Reproduced with permission from Ref. 730. Copyright 2013 Wiley.

Sinha et al. were able to sense copper ions via displacement of 4-aminobipyridine from the cavity of CB6.⁷³² The fluorescence quenching observed was readily reversed by the addition of EDTA to sequester the metal cation. CB6 was also used to monitor enzymatic reactions in which 4-aminobipyridine was produced, due to the significant fluorescence of the 4-aminobipyridine-CB6 complex. A final notable example of the applicability of CB sensors was the detection of hydrocarbon gases encapsulated by CB6, published by Florea et al. (Figure 4.56).⁷²⁹ Volatile hydrocarbons, such as isobutane and cyclopentane, bound strongly to CB6, with association constants on the order of 10^6 M^{-1} . In acidic aqueous solution with hydrocarbon gas bubbled through, fluorescent dye **149** (Figure 4.54) was displaced from the cavity of CB6 by the hydrocarbon, leading to a drastic decrease in the dye emission. Upon bubbling air into the solution, the hydrocarbon was released, and the dye reentered the CB6 cavity, allowing the restoration of fluorescence. This cycle could be repeated several times without a loss of efficiency. Notably, non-hydrocarbon gases Ar, Kr, and N₂ did not bind in CB6.

Figure 4.56. Illustration of the ability of CB6 to capture hydrocarbon gases and provide an emission response via analyte-induced dye displacement. Reproduced with permission from Ref. 729. Copyright 2011 Wiley.

4.6. Conclusions and Outlook

This review article covers a broad variety of macrocycle-based supramolecular luminescent sensors that have been developed for an extremely diverse range of analytes based on supramolecular associations. These sensors are based on supramolecular macrocycle architectures and respond to the presence of the target analyte with a measurable change in their luminescence signal, including a change in luminescence intensity or a shift in the spectral position of the luminescence read-out signal. Low limits of detection have been reported in numerous cases, including pM level sensitivities,⁷³³ and high levels of selectivity for the target analyte have been demonstrated, even in the presence of large numbers of potentially interfering analytes.

Despite these significant advances and the enormity of the intellectual effort that has been spent in this field, unsolved problems in the area of chemical detection remain. Many of these problems relate to detection in complex systems, such as in the remediation of large-scale environmental disasters (i.e. oil spills,⁷³⁴ industrial chemical contamination,⁷³⁵ etc). In such cases, a priori knowledge of the main chemical contaminant(s) is still necessary in order to accomplish practical detection/screening, especially of large numbers of potentially contaminated samples in a rapid time frame. This knowledge is necessary because state-of-the-art detection methods still rely overwhelmingly on mass spectral-based detection, which generates a signal for every one of the uniquely massed species in the complex environment. In order to screen for a particular compound with a particular mass, therefore, a priori knowledge is required.

While such knowledge is usually available, there are multiple reported cases in which inaccurate or incomplete knowledge delayed accurate detection and was responsible for inadvertent toxicant exposure. In the 2014 Elk River chemical spill in West Virginia, for example, first responders were initially unaware of the presence of a secondary contaminant in addition to the primary 4-methylcyclohexylmethanol (4-MCHM) contaminant.⁷³⁶ The first responders in this case relied on the chemical company responsible for the spill to accurately disclose the nature of the contamination, and then screened large numbers of samples only for the reported contaminant. When accurate information was not forthcoming until several days after the initial contamination event, residents were inadvertently exposed to additional contaminants, first responders were unable to develop effective remediation strategies, and the development of an effective containment response was delayed.⁷³⁷ Similar gaps in

current state-of-the art detection methods explain why consumers were initially unaware of the presence of bisphenol A (BPA) analogues, including bisphenol S (BPS) and bisphenol F (BPF), in the presence of products labeled “BPA-free,” and were inadvertently exposed to these BPA derivatives.⁷³⁸ Detection methods for BPA relied on mass spectral methods;⁷³⁹ because the BPA analogues have slightly different molar masses, they remained undetected in the products for an as-yet undetermined amount of time.

Array-based luminescent sensors that are not specific for a single analyte but display patterns of interactions with broader varieties of analytes can provide some knowledge of the nature of an unknown contaminant, especially if the statistical analyses of such signals can be tuned to identify certain structural features of the analyte. Rotello discusses some of the challenges of unknown analyte identification in his 2015 review article on selectivity vs. specificity in chemical sensors,³⁴ and highlights the potential of luminescent chemical sensors to address these challenges. Currently used commercial sensors still do not have the ability to accomplish completely unguided analyte identification, however, and numerous practical and technical challenges remain before such powerful commercial devices become a reality. In the interim, the large numbers of chemists working in this extremely active research area are developing and reporting significant research advances in luminescent chemical sensors, and numerous practical applications of such sensors in airport security screening, fluorescence-guided surgery, cancer diagnostics, and other areas have been, and continue to be, reported. There is great need for stand-alone luminescence-based sensors that encompass selectivity, sensitivity, and applicability that overcome the aforementioned challenges, and the

chemistry described herein exemplifies the significant advances that have been taken toward that goal from numerous research groups in recent years.

Supramolecular luminescent sensors have solved significant problems in a broad variety of research areas, including in biological imaging,⁷⁴⁰ medical diagnostics,⁷⁴¹ national security,³⁴⁷ and food and agricultural safety.⁷⁴² Despite the significant advances that have been made in solving sensor-related problems, a number of unsolved challenges still remain. Such challenges include:

(a) Achieving selectivity in anion detection in aqueous environments: The high degree of solvation of anions means that anion-specific binders often are binding a highly solvated anionic analyte.⁷⁴³ Such solvated anions often have less structural differences than the unsolvated anions, and as a result, achieving selectivity in the detection of solvated anions remains challenging.⁷⁴⁴ Efforts to address this lack of selectivity including the use of array-based analysis to generate unique response patterns,⁷⁴⁵ the development of methods to desolvate anions prior to binding,⁷⁴⁶ and the ability to generate sensors that can accurately distinguish between solvated anions, despite their small structural differences.⁷⁴⁷

(b) Demonstrating robust performance in biological environments: Chemical sensing in biological environments is inherently complex, due to the large numbers of potentially interfering analytes as well as the highly polar aqueous environment.⁷⁴⁸ Although significant progress has been made in this area, there is still a significant need for sensors that operate with high sensitivity, selectivity, and robust performance within the complex biological milieu.⁷⁴⁹

(c) Accomplishing unguided chemical detection: Although the chemistry community has made significant progress in detecting an analyte when the identity of the analyte is known, detecting analytes whose identity is unknown remains a largely unsolved challenge. The need for such unguided detection occurs in a number of real-world scenarios, including in the 2014 Elk River chemical spill in West Virginia, in which the identity of the contaminants was not initially disclosed;⁷⁵⁰ when an unconscious patient comes into the emergency room as a result of a chemical exposure event that is unknown to the physician; and when food is contaminated with an unknown pathogen that needs to be detected accurately. Progress in achieving such unguided detection has been reported, although significantly more work remains to be accomplished before this problem is solved.³⁴

4.7. References

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CHAPTER 5 PREFACE

A Polycationic Pillar[5]arene for the Binding and Removal of Organic Toxicants from Aqueous Media describes research that was conducted in collaboration with the group of Dr. Brenton DeBoef from the Chemistry Department at the University of Rhode Island, and was published in the peer-reviewed journal *Supramolecular Chemistry* in 2019. Contributing authors from the Levine group are Adelaide Levenson and Joan Racicot, who conducted fluorescence measurements. Contributing authors from the DeBoef group are Dr. Ashvin Fernando, Paul Cesana, and Adriana Mendieta, who conducted pillar[5]arene syntheses, nuclear magnetic resonance analyses, and computational analyses. T. Mako conducted fluorescence measurements, analyzed fluorescence data, developed cation exchange resin protocol, produced and applied the pillararene-resin, and conducted thermogravimetric analyses. Equal contribution to the manuscript with Dr. Ashvin Fernando is recognized.

CHAPTER 5

A Polycationic Pillar[5]arene for the Binding and Removal of Organic Toxicants from Aqueous Media

5.1. Introduction

The development of methods for the selective removal of highly toxic organic pollutants from aqueous environments is a pressing research need with significant implications in public health,¹ environmental legislation,² and biological sciences.^{3,4} Many existing methods for such removal suffer from significant drawbacks, including lack of selectivity in toxicant removal,⁵ introduction of toxic removal agents in order to remove the targeted pollutants,⁶ inefficient toxicant removal performance,⁷ and lack of recyclability of the removal agents.⁸ These drawbacks are particularly significant for pollutants that are highly environmentally persistent, which means that such compounds will remain in the environment for several years after an initial contamination event unless actively removed, as well as for compounds that lack straightforward detectable signatures,⁹ including visible colour and/or high luminescence, which means that their continued presence in the environment is challenging to detect.

Previous work from our research groups has reported extensive results using cyclodextrin-based systems for highly effective toxicant detection and medical imaging applications.^{10,11,12} Some work in synthetically-modified cyclodextrins,¹³⁻¹⁵ modified cucurbiturils,¹⁶ and fully synthetic all-organic macrocycles^{17,18} has also been reported, but the utility of such materials in small molecule binding and sequestration has not been fully explored. The highly efficient removal of micropollutants using insoluble cyclodextrin polymers cross-linked with rigid aromatic groups has been reported by

Dichtel and co-workers.^{19,20} While this material was effective at pollutant capture in both air and water,²¹ it required anhydrous conditions and a multi-day reaction time to synthesize the porous polymer in a 45% isolated yield. Moreover, the use of an insoluble material for pollutant removal rather than the soluble macrocycle reported herein comes with some additional trade-offs as well.

Compared to cyclodextrin-based supramolecular systems which have been known for more than 50 years, pillararenes are relatively new, with the first reported pillararene synthesized by Ogoshi and co-workers in 2008.²² These macrocycles, which are formed from the condensation reaction of a 1,4-dialkoxybenzene with paraformaldehyde, generally form the thermodynamically favored 5-membered cyclic oligomer, termed a pillar[5]arene,²³ with symmetrical, rigid, pillar-like cavities.²⁴ The electronic and steric properties of pillararenes can be tuned via judicious choice of dialkylhydroquinone starting material, although overall highly electron-rich structures are obtained.²⁵ As a result, pillar[5]arenes are well-suited to bind electron-deficient small molecule guests in their interior cavities,²⁶ with binding constants between 10^3 and 10^5 M⁻¹ generally obtained.²⁷ Examples of small molecule guests include biologically relevant analytes such as methionine,²⁸ tryptophan,²⁹ and adenosine triphosphate (ATP),³⁰ with the pillararene hosts in those cases bearing cationic groups that facilitate aqueous solubility.

Despite the significant advances in pillararene syntheses and applications that have been reported in recent years, the use of pillararenes for environmental remediation applications such as the purification of contaminated water has been only rarely reported.^{31,32} This is true despite the fact that pillararene-induced binding of environmentally relevant analytes has strong potential to facilitate such environmental

remediation, provided that there is a mechanism to remove the analytes of interest after binding in the pillararene is achieved. Such environmentally-relevant analytes include polycyclic aromatic hydrocarbons (PAHs),³³ perfluorooctanoic acid (PFOA),³⁴ aromatic pesticides,³⁵ pharmaceutical drugs such as Tylenol and Advil,³⁶ and plasticizers such as phthalate esters,³⁷ all of which have been found in aqueous environments and have the potential to induce deleterious health effects.³⁸

Reported herein is the use of a cationic pillar[5]arene to bind a broad variety of small molecule organic analytes, including several of the analytes listed above, with binding constants up to 10^{10} M^{-1} observed. This macrocyclic host demonstrates good generality for a range of analytes as well as high aqueous solubility due to its cationic pendant groups, which facilitates its usage in water purification efforts. Moreover, the ability to use cationic exchange resins to remove the cationic pillar[5]arene after binding the analyte is also demonstrated, as are comparisons to a neutral pillar[5]arene host that highlight the advantage of the cationic macrocycle. Computational efforts are invoked to explain the observed experimental data and overall trends.

5.2. Results and Discussion

The water-soluble pillar[5]arene host **3** was synthesized with an 80% overall yield over three steps. The first step of the synthesis consisted of bromination of *para*-hydroquinone to form the dialkoxyether monomer **1**, followed by cyclization using boron trifluoride etherate as a Lewis acid to promote the desired cyclization in a solution of 1,2-dichloroethane, which serves as both the bulk solvent and as the molecular template for the macrocyclization to form pillar[5]arene **2**. A subsequent substitution

using *N*-methylimidazole provided the decacationic pillar[5]arene **3** in an 81% yield over two steps.³⁹

Figure 5.1. Illustration of the synthesis of pillar[5]arene **3** via cyclization of monomer **1** in the presence of dichloroethane solvent, followed by nucleophilic substitution of the terminal alkyl bromides on compound **2**. Three-dimensional structures underneath the reaction scheme show energy-minimized molecular conformations

Figure 5.2. Example of host-guest inclusion complex formed from host **3** and guest toxicant anthracene, **15**

Molecular mechanics calculations predicted that compound **3** has a unique structure with a readily-accessible central cavity (Figure 5.1), which is attributed to the charge-

charge repulsion created by the ten positive charges on the ethylene arms. The hydrophobic core, flexible aperture, and high water solubility of **3** provide features needed to bind a wide variety of small organic molecules in aqueous media. Furthermore, the imidazolium cations that are present at the termini have the potential to participate in π - π ⁴⁰ or cation- π ⁴¹ interactions. Consequently, we predicted that **3** could accommodate different types of toxicants with a broad variety of sizes, electronics, and other structural components, as shown in Figure 5.2. The toxicant analytes chosen along with their calculated stabilization energies are shown in Figure 5.3.

Figure 5.3. Array of toxicants and small molecules that were used in the binding study with supramolecular host **3**, with calculated stabilization energies of the toxicants upon binding in host **3** (obtained via Spartan 16) shown. The values given represents the stabilization energy for the final complex formation between the toxicant and **3**. The equation used is: $\Delta\Delta H(\text{stabilization energy}) = \Delta H(\mathbf{3} + \text{guest}) - \Delta H(\mathbf{3}) - \Delta H(\text{guest})$

5.3. Computational Investigations

Pillararene **3** has a calculated internal diameter of 9 Å and an outer diameter of 11 Å. The diameters of toxicants **4-15** in this study ranged from 7 Å to 11.5 Å, which means that most of them should be able to fit in the cavity of the supramolecular host. Furthermore, docking studies performed using supramolecular host **3** and toxicants **4-15** resulted in calculated stabilization energies and docking scores that highlight the favourability of supramolecular complexation.

The most favourable stabilization energy (largest negative value) corresponds to the binding of naproxen (analyte **10**), a pharmaceutical drug with some associated toxicity, with this high favourability likely due to the strong fit between the analyte and the supramolecular cavity (Figure 5.4A). This is also true for other molecules such as PFOA (Figure 5.4B), cyclophosphamide (Figure 5.4C), and 1,10-phenanthroline (Figure 5.4D), all of which appear to be using the majority of the interior space and all of which have favourable intermolecular interactions. More generally, the uniformly negative stabilization energies obtained for all toxicants in the supramolecular host **3** indicate that all complexes should spontaneously form in aqueous media. Of note, toxicants such as 1,10-phenanthroline were bound more towards the outer portal of the host (Figure 5.4D), and such toxicants generally displayed weaker binding compared to binding that was deeper in the interior cavity.

Figure 5.4. Computed images of analytes docked in pillararene **3**. (A) naproxen; (B) PFOA; (C) cyclophosphamide; and (D) 1,10-phenanthroline

5.4. Fluorescence Spectroscopy of Inclusion Complexes

Fluorescence studies were undertaken to elucidate the binding stoichiometries and affinities of the small molecule toxicants shown in Figure 5.3. The results of analyte binding inside cationic pillararene **3** are summarized in

Table 5.1, with selected results highlighted in Figure 5.5 and Figure 5.6. These studies showed that most of the analytes formed 1:1 association complexes both in phosphate buffered saline (PBS) as well as in DMSO. The compounds that formed 1:2 complexes in PBS were clofibric acid and myclobutanil. Of note, both clofibric acid and myclobutanil contain a chlorine-substituted benzene ring with the chlorine in the *para*-position relative to the rest of the structure. *Para*-chlorobenzene structures have been shown in the literature to bind strongly in pillararene structures,⁴² and the relatively small size of this structure allows for the inclusion of two small molecule guests simultaneously. Myclobutanil also forms a 1:2 complex with **3** in DMSO, albeit with an overall lower binding constant. Both 1,10-phenanthroline and simazine formed 2:1 complexes in PBS, with 1,10-phenanthroline also forming a 2:1 complex with **3** in DMSO and simazine forming a 1:1 complex with **3** in DMSO. The 2:1 binding nature of simazine to **3** in PBS is likely due to the ability of the amine substituents to associate with two different pillararene hosts simultaneously. The fact that phenanthroline formed a 2:1 complex is likely due to the ability of the heterocyclic aromatic architecture to form strong π -stacked association complexes, in accordance with literature precedent.^{43,44}

Table 5.1. Association constants of various analytes with pillararene 3 obtained from fluorescence titrations^a

Guest	H:G ^b	Association constant in PBS (M ⁻¹)	Association constant in DMSO (M ⁻¹)
Anthracene	1:1	7.18 (0.0001) x 10 ⁵	ND ^c
Carbamazepine	1:1	1.06 (0.12) x 10 ⁵	ND ^c
Clofibric acid	1:2	K _{a1} = 6.34 (1.27) x 10 ⁶ K _{a2} = 4.77 (0.32) x 10 ⁵	ND ^c
Cyclophosphamide	1:1	1.33 (0.19) x 10 ⁶	2.46 (0.94) x 10 ⁵
Dibutylphthalate	1:1	5.67 (0.95) x 10 ⁵	3.32 (0.45) x 10 ⁶
Myclobutanil	1:2	K _{a1} = 5.10 (0.92) K _{a2} = 2.62 (0.0044) x 10 ¹⁰	ND ^c
<i>N,N,N',N'</i> -tetramethylbenzidine	1:1	1.62 (0.12) x 10 ⁶	ND ^c
Naproxen	1:1	6.51 (0.911) x 10 ³	ND ^c
Perfluorooctanoic acid	1:1	1.13 (0.13) x 10 ⁶	2.44 (0.17) x 10 ⁴
Phenanthrene	1:1	2.32 (0.02) x 10 ⁴	8.10 (1.80) x 10 ³

1,10-Phenanthroline	2:1	$K_{a1} = 2.43 (0.32) \times 10^6$ $K_{a2} = 4.72 (0.21) \times 10^4$	$K_{a1} = 4.40 (0.027) \times 10^5$ $K_{a2} = 2.67 (0.24) \times 10^4$
Simazine	2:1	$K_{a1} = 1.37 (0.22) \times 10^{10}$ $K_{a2} = 6.47 (1.42) \times 10^9$	$1.00 (0.13) \times 10^7$

^a Methods for obtaining binding constants and stoichiometries via fluorescence spectroscopy can be found in the ESI; ^b host-guest stoichiometry; ^c binding constants were not calculated for this combination; PBS = phosphate buffered saline; DMSO = dimethylsulfoxide.

Figure 5.5. 1:1 binding of phenanthrene with cationic host 3 in PBS solution analyzed by (A) fluorescence titration and (B) Job's plot analysis. Detailed procedures for the calculation of these binding constants can be found in the experimental section

Figure 5.6. 1:2 binding of 1,10-phenanthroline with cationic host 3 in DMSO solution analyzed by (A) fluorescence titration and (B) Job's plot analysis. Detailed procedures for the calculation of these binding constants can be found in the experimental section

Table 5.2. Association constants of various analytes with a neutral propargyl pillararene obtained from fluorescence titrations^a

Guest	H:G ^b	Association constant in PBS (M ⁻¹)	Association constant in DMSO (M ⁻¹)
Anthracene	2:1	$K_{a1} = 7.34 (0.39)$ $K_{a2} = 1.13 (0.0097) \times 10^9$	ND ^c
Carbamazepine	1:2	$K_{a1} = 2.43 (0.00036) \times 10^{12}$ $K_{a2} = 1.06 (0.12) \times 10^5$	ND ^c
Clofibric acid	1:2	$K_{a1} = 2.47 (0.15) \times 10^2$ $K_{a2} = 1.32 (0.26) \times 10^6$	ND ^c
Cyclophosphamide	1:2	$K_{a1} = 8.85 (0.12)$ $K_{a2} = 3.21 (0.13) \times 10^9$	$9.44 (0.59) \times 10^4$
Dibutylphthalate	1:2	$K_{a1} = 6.05 (0.0011) \times 10^{10}$ $K_{a2} = 7.14 (2.52) \times 10^4$	$K_{a1} = 6.73 (0.72)$ $K_{a2} = 9.10 (0.78) \times 10^9$

Myclobutanil	1:2	$K_{a2} = 1.26 (0.069) \times 10^5$ $K_{a2} = 1.13 (0.95) \times 10^1$	ND ^c
N,N,N,N-tetramethylbenzidine	1:1	$1.13 (0.19) \times 10^5$	ND ^c
PFOA	1:2	$K_{a1} = 4.69 (0.18)$ $K_{a2} = 9.07 (0.000001) \times 10^3$	$2.45 (0.21) \times 10^5$
Phenanthrene	1:1	$1.10 (0.011) \times 10^5$	$5.04 (0.81) \times 10^4$
1,10-Phenanthroline	2:1	$K_{a1} = 4.19 (0.46)$ $K_{a2} = 1.18 (0.052) \times 10^9$	$K_{a1} = 3.08 (0.041) \times 10^2$ $K_{a2} = 2.89 (0.12) \times 10^7$
Simazine	1:2	$K_{a1} = 7.52 (0.000065) \times 10^{11}$ $K_{a2} = 5.80 (0.42) \times 10^4$	$1.37 (0.15) \times 10^6$

^a Methods for obtaining binding constants and stoichiometries via fluorescence spectroscopy can be found in the ESI; ^b binding constants were not calculated for this combination; PBS = phosphate buffered saline; DMSO = dimethylsulfoxide.

In comparison, we synthesized a neutral pillar[5]arene that contains ten propargyl groups as a control to compare with the cationic structure of supramolecular host **3**.⁴⁵ In the control case, most of the toxicants formed 1:2 complexes with the propargyl-substituted host, likely as a result of the fact that the alkynes extend the size of the hydrophobic cavity and facilitate the binding of multiple guest molecules.⁴⁶ These association constants can be found in Table 5.2. Moreover, cationic host **3** likely suffers from charge repulsion, either via self-repulsion or via repulsion with cationic small molecule guests.⁴⁷ This charge repulsion, in turn, leads to more 1:1 complexation compared to any other binding stoichiometry.

Of note, pillararene **3** showed the strongest binding to simazine in aqueous solution, with a 10^{10} M^{-1} binding constant observed (for binding the first equivalent of toxicant), and myclobutanil, with a 10^{10} M^{-1} binding constant observed (for binding a second

equivalent of the toxicant). These binding constants are four orders of magnitude higher than the next highest strength constants, seen for clofibric acid, cyclophosphamide, *N,N,N',N'*-tetramethylbenzidine, perfluorooctanoic acid, and 1,10-phenanthroline, all of which displayed association constants on the order of 10^6 M^{-1} . A structural comparison between the two strongest binding guests indicates high levels of electron deficiency for both simazine and myclobutanil. Although other analytes also show moderate to significant electron deficiencies, the highly aminated structures of myclobutanil and simazine provide additional benefits for association with a cationic supramolecular host, with the nitrogen atoms able to associate with the cationic charge. The weakest binding guests, phenanthrene (10^4 M^{-1}) and naproxen (10^3 M^{-1}), have much higher electron density, which disfavours binding inside the pillararene host.

Switching the solvent to DMSO generally resulted in decreases in host: guest association complexes, with a reduction in binding affinity of up to three orders of magnitude observed (simazine in PBS = 10^{10} M^{-1} ; in DMSO = 10^7 M^{-1}). The decreased binding affinity in non-aqueous environments means that the likely mechanism of binding is via hydrophobic association and that switching to non-aqueous solvents results in decreasing the energetic favorability of such association. Of the species studied in DMSO, only the complexation of dibutylphthalate with **3** was found to have a higher association constant than what was seen in PBS, the reasons for which are currently under investigation in our laboratories. Literature precedent strongly supports the notion of hydrophobically-driven binding in pillararene architectures,⁴⁸ as well as the fact that switching to non-aqueous solvents reduces the favorability of hydrophobically-driven inclusion.⁴⁹

Finally, we have shown that pillararene host **3** can be removed by a cation exchange resin after it binds the toxicant small molecule guests (Figure 5.7). Several different cation exchange resins were studied in the attempt to remove pillararene **3** from solution, and Dowex 50WX2 was found to remove up to 91 % of the host from a 0.2 mM solution with 89 mg of the resin as seen by fluorescence spectroscopy.

Figure 5.7. Quantitative assessment of the amount of pillararene that was removed from ultrapure water by different cation resin types

In a subsequent study, pillararene **3** was bound to the surface of Dowex 50WX2 via electrostatic interactions following similar methods for affinity binding of macrocyclic hosts to charged resins.⁵⁰ This created a solid-supported pillararene **3** which was investigated for the removal of fluorescent analytes anthracene, naproxen, phenanthrene, 1,10-phenanthroline, and *N,N,N,N*-tetramethylbenzidine from both ultrapure water and PBS solution. Thermogravimetric analysis of the resin-bound **3** (Figure 5.8, black line) in comparison to measurements of **3** (Figure 5.8, blue line) and

Dowex 50WX2 (Figure 5.8, green line) as well as a physical mixture of **3** and Dowex 50WX2 (Figure 5.8, red line) indicated that the pillararene was truly bound to the resin, as evidenced by a unique degradation peak at 560 °C shown in Figure 5.8.

Figure 5.8. Normalized first derivative of the thermogravimetric analysis of resin-bound pillararene **3** (“3-resin”, black line) in comparison to: a physical mixture of **3** and Dowex 50WX2 (“3 + resin”, red line), pillararene **3** (“3”, blue line), and Dowex 50WX2 (“resin”, green line). Details of thermogravimetric analysis can be found in the ESI

Naproxen and phenanthrene could both be removed from ultrapure water, with removal efficiencies of 60% and 83%, respectively, and PBS solution, with removal efficiencies of 74% and 59%, respectively. The removal of naproxen from PBS solution and the removal of phenanthrene from ultrapure water are shown in Figure 5.9. Notably, while 34% of anthracene could be removed from PBS solution, anthracene could not be removed from ultrapure water using the same method. The removal of both 1,10-

phenanthroline and *N,N,N',N'*-tetramethylbenzidine from either matrix was inefficient, and in all instances, a minimal amount of pillararene **3** is released into solution.

Figure 5.9. (A) The removal of naproxen from PBS solution using cation resin-bound pillararene **3** as shown by fluorescence spectroscopy, (B) the comparison of the normalized fluorescence integration of naproxen in PBS solution with increasing amounts of pillararene **3** resin, (C) the removal of phenanthrene from ultrapure water using cation resin-bound pillararene **3** as shown by fluorescence spectroscopy, and (D) the comparison of the normalized fluorescence integration of phenanthrene in ultrapure water with increasing amounts of pillararene **3** resin

5.5. NMR Spectroscopy

^1H NMR spectroscopy investigations provided additional structural insights into the host:guest complex, with upfield shifts observed in the peaks that correspond to the methylene bridge protons of **3** that are numbered as 2, the methylene protons numbered as **3** on the imidazolium-terminated side chains and methylene linkers arms of **3** numbered as 5 and 6 (Figure 5.10). Similarly, ^{19}F NMR spectroscopy (Figure 5.11) demonstrated broadening of the fluorine signal that corresponds to the PFOA analyte **4** in the presence of the pillararene host, indicating restricted conformational freedom of the guest as a result of host-guest inclusion.

Figure 5.10. ¹H NMR spectra of: (A) 10 mM macrocycle **3**; and (B) 10 mM macrocycle **3** and 10 mM naproxen **10**

Figure 5.11. Fluorine NMR spectra of: (A) perfluorooctanoic acid (PFOA); and (B) the association complex formed between PFOA and supramolecular host **3**

5.6. Conclusions

The ability to use rationally designed supramolecular hosts such as pillararene **3** for the removal of toxic compounds from contaminated aqueous environments has significant potential advantages, provided that the removal can occur with high efficacy for toxic compounds and broad relevance for a variety of potential contaminants, and that the contaminants can be removed from the aqueous solution following binding. The results reported herein constitute significant progress towards achieving this goal, through the development of polycationic pillararene host **3**, using computational and experimental results to understand its binding to a variety of small molecule toxicants, and then demonstrating the practical relevance of such systems via the use of cationic exchange resins to remove the complex after toxicant binding. Current efforts in our laboratory are focused on the development of practical environmental remediation systems based on such technology, and on developing other effective supramolecular systems based on the progress reported herein. The results of these and other investigations will be reported in due course.

5.7. Experimental

5.7.1. Materials and Methods

Chemicals, including carbon tetrabromide, anhydrous acetonitrile, anhydrous 1,2-dichloroethane, boron trifluoride ethane, triphenylphosphine, and *N*-methylimidazole were purchased from Sigma-Aldrich, Fisher Scientific, or TCI chemicals. All reagents were stored under an inert atmosphere before use. Unless otherwise noted, all reactions were performed under N₂.

NMR spectra were obtained using Bruker Avance 300 MHz and 400 MHz spectrometers. Low resolution mass spectrometry was performed using a Shimadzu LRMS-2020. High resolution mass spectrometry was performed using a Thermo Scientific LTQ Orbitrap XL™ instrument. Fluorescence spectra were obtained using a Shimadzu RF-6000 spectro fluorophotometer. All column chromatography was performed by automated column chromatography using a Teledyne isco combiflashRf instrument. All thermogravimetric measurements were collected using a Shimadzu TGA-50 thermogravimetric analyzer stabilized by an Accurion Halcyonics-i4 active vibration isolation system.

5.7.2. Synthetic Details

Figure 5.12. Overall synthetic route for the synthesis of supramolecular host **3**

Supramolecular host **3** (Figure 5.12) was synthesized according to the literature procedures,⁵¹ with further optimizations and better yields. All NMR spectra are in agreement with literature reported spectra.

Figure 5.13. Synthesis of brominated monomer 1

Procedure: A solution of 1,4-bis(2-hydroxyethyl)benzene (10.0 g, 50.4 mmol, 1 eq.) and triphenylphosphine (31.5 g, 120 mmol, 2.4 eq.) in anhydrous acetonitrile (250 mL) was cooled in an ice bath to 0°C . Under vigorous stirring, carbon tetrabromide (39.8 g, 120 mmol, 2.4 eq.) was slowly added in four portions. After every addition, the solution immediately turned bright yellow, and with stirring returned to a colorless solution, although after the final (fourth) addition, the solution remained cloudy. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for four hours and twenty minutes. After that, the reaction mixture was quenched with the addition of cold water (200 mL) to yield a white precipitate. The precipitate was collected and washed with another 200 mL of cold water followed by three methanol/water washes (3:2 methanol: water (vol/vol), 100 mL each wash, 3 washes total). The collected white solids were dried under vacuum for 24 hours and used without further purification. (14.5 g, 97% yield). ^1H NMR and ^{13}C NMR was performed using CDCl_3 . ^1H NMR (400 MHz, Chloroform-*d*) δ 6.89 (s, 4 H), 4.27 (t, $J = 6.3$ Hz, 4 H), 3.64 (t, $J = 6.3$ Hz, 4 H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.5, 117.2, 68.6, 29.6.

Figure 5.14. Synthesis of deca-brominated pillar[5]arene **2**

Procedure: A solution of brominated monomer **1** (3.37 g, 11.5 mmol, 1 eq.) and paraformaldehyde (0.349 g, 11.5 mmol, 1 eq.) in 1,2-dichloroethane (50 mL) was cooled with an ice bath. Boron trifluoride etherate (3.26 g, 23.0 mmol, 2 eq.) was added to the solution, and the mixture was stirred at room temperature for one hour. During that time, the reaction underwent various color changes from slight yellow, sea green, dark sea green and end up being dark green. After one hour, the reaction mixture was washed with deionized water (2 × 50 mL), saturated sodium bicarbonate (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried with anhydrous Na₂SO₄, followed by solvent evaporation to provide the crude product, which was sufficiently pure for the next phase of the reaction sequence (92% yield). ¹H NMR and ¹³C NMR were performed using CDCl₃. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.91 (s, 10 H), 4.23 (t, *J* = 6.3, 5.1 Hz, 20 H), 3.84 (s, 10 H), 3.63 (t, *J* = 5.6 Hz, 20 H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 149.7, 129.1, 116.1, 68.9, 30.7, 29.4.

Figure 5.15. Synthesis of deca-methyl imidazolium pillar[5]arene **3**

Procedure: A mixture of brominated pillar[5]arene **2** (1.68 g, 1.00 mmol, 1 eq.) and *N*-methylimidazole (1.64 g, 20.0 mmol, 20 eq.) in anhydrous toluene (25 mL) was stirred in a 40 mL pressure tube at 120 °C for 24 hours. After 24 hours, the reaction mixture was cooled to room temperature and the solvent was removed via rotary evaporation. The crude residue was then dissolved in ethanol and diethyl ether was added, which resulted in the formation of a white precipitate. This mixture was further cooled for 24 hours and then the off-white product was filtered and collected (2.1 g, 87% yield). ^1H NMR and ^{13}C NMR were performed using DMSO- d_6 . ^1H NMR (300 MHz, DMSO- d_6) δ 9.17 (br, 10 H), 8.11 (s, 10 H), 7.44 (br, 11 H), 6.72 (br, 10 H), 4.72 (br, 21 H), 4.45 (br, 20 H), 3.74 (br, 31 H), 3.51 (br, 10 H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 148.1, 136.3, 127.2, 122.7, 122.1, 113.6 65.8, 48.4, 44.0, 35.3, 27.9

Figure 5.16. Overall synthetic route to neutral propargyl-substituted pillar[5]arene host

Figure 5.17. Synthesis of propargyl-substituted monomer⁴⁵

Procedure: Hydroquinone (5.0g, 45 mmol, 1.0 eq) and anhydrous potassium carbonate (18.8g, 136 mmol, 3 eq.) were added into a solution of anhydrous acetonitrile in a round-bottomed flask, followed by cooling to 0 °C. Propargyl bromide (16.2 g, 136 mmol, 3 eq.) was added dropwise, and the reaction mixture was heated to 60 °C and stirred for 20 hours. After 20 hours, the reaction mixture was cooled to room temperature and the solvent was removed via rotary evaporation. Dichloromethane (100 mL) was added to the round-bottomed flask, and the resulting mixture was transferred into a separatory funnel for further washes. Washing steps were conducted using 2.5 M NaOH (3 x 100 mL) followed by deionized water (3 x 100 mL) and brine (2 x 100 mL). Then the dichloromethane layer was collected and dried over anhydrous sodium sulfate. The final mixture was subjected to dry-loaded automated flash chromatography (silica, *n*-hexane/ethyl acetate = 10/1 v/v) and the purified product was collected (86%). ¹H

NMR and ^{13}C NMR were performed using CDCl_3 . ^1H NMR (400 MHz, CDCl_3) δ 6.95 (s, 4 H), 4.74 (d, $J = 2.5$ Hz, 4 H), 3.53 (t, $J = 2.4$ Hz, 2 H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.6, 111.3, 74.1, 70.6, 51.7.

Figure 5.18. Synthesis of propargyl-substituted pillar[5]arene

Procedure: The propargyl-substituted monomer (3.0 g, 16.1 mmol, 1 eq.) and paraformaldehyde (1.45 g, 48.3 mmol, 3 eq.) were added into an anhydrous solution of dichloromethane, followed by the addition of iron (III) trichloride (0.78 g, 4.83 mmol, 0.3 eq.). The reaction mixture was stirred for three hours at room temperature, followed by the addition of 200 mL of deionized water. The layers were separated, and the organic layer was washed with 200 mL of brine, then dried of anhydrous sodium sulfate, filtered, and concentrated. The resulting crude product was adsorbed onto silica and dry-loaded onto automated flash chromatography instrument (silica, *n*-hexane/dichloromethane = 2/3 v/v), resulting in a light brown final product (60%). ^1H NMR and ^{13}C NMR were performed using CDCl_3 . ^1H NMR (400 MHz, Chloroform-*d*) δ 6.76 (s, 10H), 4.47 (d, $J = 2.4$ Hz, 21H), 3.74 (s, 10H), 2.21 (t, $J = 2.4$ Hz, 10H).

5.7.3. ^1H and ^{13}C NMR Characterizations of Pillar[5]arene Hosts:

Figure 5.19. ^1H NMR spectrum in CDCl₃ of brominated monomer **1**

Figure 5.20. ^{13}C NMR spectrum in CDCl_3 of brominated monomer **1**

Figure 5.21. ¹H NMR spectrum in CDCl₃ of deca-brominated pillar[5]arene **2**

AIF-09-BP5A.10.fid
LabGroup DeBoef
C13CPD CDCl3 {C:\Bruker\TopSpin3.5pl5} nmr 5

Figure 5.22. ^{13}C NMR spectrum in CDCl_3 of deca-brominated pillar[5]arene **2**

Figure 5.23. ^1H NMR spectrum in DMSO-d_6 of deca-imidazolium pillar[5]arene **3**

Figure 5.24. ^{13}C NMR spectrum in DMSO- d_6 of deca-imidazolium pillar[5]arene **3**

Figure 5.25. ^1H NMR spectrum in DMSO-d_6 of propargyl-substituted monomer

Figure 5.26. ^1H NMR spectrum in DMSO-d_6 of propargyl-substituted pillar[5]arene

5.7.4. Methods for Job's Plot Analysis

Methods were developed following a previous report.¹⁵ A 0.5 mM solution of the host (**3** or propargyl-substituted pillar[5]arene) and a 0.5 mM solution of the guest (toxicant) were created in THF (for phosphate buffered saline (PBS) conditions) or DMSO (for DMSO conditions). The fluorescence spectra of varying concentrations of the host-guest solution (increasing guest and decreasing host according to Table S1 below) were collected, with four measurements taken for each solution, according to the parameters listed in Section 4. All fluorescence spectra were integrated vs. wavenumber on the X-axis using OriginPro 2018. Normalized fluorescence intensity [$f = (F - F_0)/F_0$; where F is the fluorescence intensity at a particular host concentration and F_0 is the intensity at initial concentration] were calculated for each solution. The product of mole fraction of the guest (γ) and difference in normalized fluorescence intensity (Δf) was plotted against mole fraction of the guest to produce the Job's plot. The mole fraction at which $\gamma \cdot \Delta f$ reaches a maximum ($\gamma_{\max}$) corresponds to the host-guest stoichiometry, with $\gamma_{\max} \sim 0.5$ indicating a 1:1 host-guest stoichiometry, $\gamma_{\max} \sim 0.3$ suggesting a 2:1 host-guest stoichiometry, and $\gamma_{\max} \sim 0.6$ indicating a likely 1:2 host-guest stoichiometry. It is important to note that Job's plot analyses do not account for the possible presence of multiple binding modes.

Table 5.3. Amounts of phosphate buffered saline (PBS), host solution, and guest solution used to make solutions with varying host-guest ratios (with total H+G concentration remaining constant) used for Job's plot analyses.

Amount PBS (mL)	Amount host solution (μL)	Amount guest solution (μL)
2.5	16	0
2.5	14	2.0
2.5	12.5	3.5
2.5	11	5.0
2.5	9.5	6.5
2.5	8.0	8.0
2.5	6.5	9.5
2.5	5.0	11
2.5	3.5	12.5
2.5	2.0	14
2.5	0	16

5.7.5. Methods for Fluorescence Titrations

Methods were developed following a previous report.¹⁵ A solution of pillararene (DI water for **3** – 2 mg/mL, DMSO for propargyl pillar[5]arene – 1 mg/mL), and a 0.4 mg/mL solution of toxicant molecule (in THF for PBS studies or in DMSO for DMSO studies) were created. 5 – 20 μ L of host molecule (most fluorescent species) was added to a cuvette containing 2.5 mL of PBS (for PBS studies) or DMSO (for DMSO studies) to reach a solution concentration of 6 μ M. The fluorescence spectra of this solution were measured after titration with solution of the guest molecule (least fluorescent species) at the following addition volumes: 0.0, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, 13.5, 15.0, 20.0, 30.0, 40.0 and 50.0 μ L guest solutions. Each measurement was repeated for four trials. The concentration range scanned for each guest vs. host concentration was further refined based on the association constant values of the host-guest combination (i.e. for association constant values greater than 10^6 M^{-1} , the guest concentration was reduced to a sub-stoichiometric range with respect to the host) and the appearance of the fluorescence spectra (i.e. if a large change in fluorescence was observed between 0.0 and 1.5 μ L addition volumes, the guest concentration was reduced to a sub-stoichiometric range with respect to the host, and if minimal change was seen between 0.0 and 50.0 μ L addition volumes, the guest concentration was increased to a super-stoichiometric range with respect to the host). All modifications of technique were achieved by diluting or concentrating the guest stock solutions to concentrations of 0.04 mg/mL or 4 mg/mL, respectively, and adjusting the addition volume accordingly.

All fluorescence spectra were integrated vs. wavenumber on the X-axis using OriginPro 2018. All fluorescence titration data fits were done with Solver.xlam using

“GRG-Nonlinear” method in Excel 2017. A nonlinear curve fitting method was employed to compare against standard 1:1 and 1:2 host-guest interaction models, using Equations (1) and Equation (2),⁵² respectively:

$$(1) \quad \Delta F = \Delta F_{HG} (K_1 [G_0] / (1 + K_1 [G_0]))$$

$$(2) \quad \Delta F = (\Delta F_{HG} K_1 [G_0] + \Delta F_{HG2} K_1 K_2 [G_0]^2) / (1 + K_1 [G_0] + K_1 K_2 [G_0]^2)$$

Where ΔF is the observed change in the normalized fluorescence intensity ($\Delta F = F/F_0 - 1$) of the host H; ΔF_{HG} is the change in the normalized fluorescence intensity of host H at the first binding event; ΔF_{HG2} is the overall change in the normalized fluorescence intensity of the host, H, at the second binding event; K_1 is the association constant value for the first binding event of guest G to the host H; K_2 is the association constant value for the second binding event of guest G to HG; and $[G_0]$ is the concentration of guest G.

5.7.6. Anthracene Fluorescence Analyses

Table 5.4. Summary of anthracene association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed.

Host	Solvent	<i>a</i>	K_{a1} (M⁻¹)	K_{a2} (M⁻¹)	Sum(χ^2)
3	PBS	1:1	7.18 (0.0001) x 10 ⁵	-	0.0014
<i>b</i>	PBS	2:1	7.34 (0.39)	1.13 (0.0097) x 10 ⁹	0.0012

Figure 5.27. Job's plot analysis of anthracene and **3** in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 anthracene – **3** binding mode ($\gamma_{\max} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.5. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with anthracene in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{anthracene})$	$\gamma(\text{anthracene}) * \Delta F$
1	0
0.88	106699
0.78	159832
0.68	170877
0.59	193647
0.50	203499
0.41	200956
0.31	147395
0.22	117708
0.13	81313
0	0

Figure 5.28. Fluorescence titration of anthracene with **3** in PBS fit to a 1:1 anthracene – **3** stoichiometry. $K_a = 7.18 (0.000076) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0014$.

Figure 5.29. Job's plot of anthracene and propargyl-substituted pillar[5]arene in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 anthracene – pillararene binding mode ($\gamma_{\text{max}} = 0.37$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.6. Tabulated data of the Job's plot analysis of the host-guest binding of anthracene with propargyl-substituted pillar[5]arene in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{anthracene})$	$\gamma(\text{anthracene}) * \Delta F$
1	0
0.90	53301
0.74	111496
0.57	173350
0.47	186621
0.37	189407
0.27	152836
0.16	112304
0	0

Figure 5.30. Fluorescence titration of anthracene with propargyl-substituted pillar[5]arene in PBS fit to a 1:2 anthracene - pillararene stoichiometry. $K_{a1} = 7.34 (0.39) \text{ M}^{-1}$; $K_{a2} = 1.13 (0.0097) \times 10^9 \text{ M}^{-1}$; $\text{Sum}(\chi_2) = 0.0012$.

5.7.7. Carbamazepine Fluorescence Analyses

Table 5.7. Summary of carbamazepine association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed.

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	1:1	$1.06 (0.12) \times 10^5$	-	0.0017
<i>b</i>	PBS	1:2	$2.43 (0.000000036) \times 10^{12}$	$1.06 (0.12) \times 10^5$	0.00066

Figure 5.31. Job's plot analysis of **3** and carbamazepine in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** – carbamazepine binding mode ($\gamma_{\text{max}} = 0.55$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.8. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with carbamazepine in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{carbamazepine})$	$\gamma(\text{carbamazepine}) * \Delta F$
1	0
0.85	37711
0.75	46093
0.64	51796
0.55	59416
0.45	51421
0.36	53709
0.27	45268
0.19	34796
0.11	23555
0	0

Figure 5.32. Fluorescence titration of **3** with carbamazepine in PBS fit to a 1:1 **3** – carbamazepine stoichiometry. $K_a = 1.06 (0.12) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0017$

Figure 5.33. Job's plot analysis of propargyl-substituted pillar[5]arene and carbamazepine in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene – carbamazepine binding mode ($\gamma_{\text{max}} = 0.68$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.9. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with carbamazepine in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{carbamazepine})$	$\gamma(\text{carbamazepine}) * \Delta F$
1	0
0.88	3961738
0.78	5517031
0.68	7427062
0.59	5385966
0.50	3994950
0.41	3293916
0.31	726594
0.22	75622
0.13	461213
0	0

Figure 5.34. Fluorescence titration of propargyl-substituted pillar[5]arene with carbamazepine in PBS fit to a 1:2 pillararene – carbamazepine stoichiometry. $K_{a1} = 2.43 (0.000000036) \times 10^{12} \text{ M}^{-1}$; $K_{a2} = 1.06 (0.12) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00066$

5.7.8. Clofibric Acid Fluorescence Analyses

Table 5.10. Summary of clofibric acid association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (\text{M}^{-1})$	$K_{a2} (\text{M}^{-1})$	$\text{Sum}(\chi^2)$
3	PBS	1:2	$6.34 (1.27) \times 10^6$	$4.77 (0.32) \times 10^5$	0.016
<i>b</i>	PBS	1:2	$2.47 (0.15) \times 10^2$	$1.32 (0.26) \times 10^6$	0.004

Figure 5.35. Job's plot analysis of **3** and clofibric acid in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 **3** – clofibric acid binding mode ($\gamma_{\max} = 0.41$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.11. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with clofibric acid in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(3)$	$\gamma(3) \cdot \Delta F$
1	0
0.88	33833
0.78	53375
0.68	59388
0.59	70251
0.50	74500
0.41	74551
0.31	50703
0.22	34149
0.13	21777
0	0

Figure 5.36. Fluorescence titration of **3** with clofibric acid in PBS fit to a 1:2 **3** – clofibric acid stoichiometry. $K_{a1} = 6.34 (1.27) \times 10^6 \text{ M}^{-1}$; $K_{a2} = 4.77 (0.32) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi_2) = 0.016$

Figure 5.37. Job's plot analysis of propargyl-substituted pillar[5]arene and clofibric acid in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene – clofibric acid stoichiometry ($\gamma_{\text{max}} = 0.59$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.12. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with clofibric acid in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{clofibric acid})$	$\gamma(\text{clofibric acid}) * \Delta F$
1	0
0.88	15575963
0.78	29432344
0.69	26494806
0.59	31606916
0.50	27499900
0.41	22343669
0.31	18761594
0.22	13098444
0.13	7790588
0	0

Figure 5.38. Fluorescence titration of propargyl-substituted pillar[5]arene with clofibric acid in PBS fit to a 1:2 pillararene – clofibric acid stoichiometry. $K_{a1} = 2.47 (0.15) \times 10^2 \text{ M}^{-1}$; $K_{a2} = 1.32 (0.26) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi_2) = 0.004$

5.7.9. Cyclophosphamide Fluorescence Analyses

Table 5.13. Summary of cyclophosphamide association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	1:1	$1.33 (0.19) \times 10^6$	-	0.000040
3	DMSO	1:1	$2.46 (0.94) \times 10^5$	-	0.00197
<i>b</i>	PBS	1:2	8.85 (0.12)	$3.21 (0.13) \times 10^9$	0.0046
<i>b</i>	DMSO	1:1	$9.44 (0.59) \times 10^4$	-	0.0080

Figure 5.39. Job's plot analysis of **3** and cyclophosphamide in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** – cyclophosphamide stoichiometry ($\gamma_{\text{max}} = 0.55$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.14. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with cyclophosphamide in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{cyclophosphamide})$	$\gamma(\text{cyclophosphamide}) * \Delta F$
1	0
0.85	38244
0.75	49068
0.64	64809
0.55	67066
0.45	57459
0.36	59221
0.27	45382
0.19	35006
0	0

Figure 5.40. Fluorescence titration of **3** with cyclophosphamide in PBS fit to a 1:1 **3** – cyclophosphamide stoichiometry. $K_a = 1.33 (0.19) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.000040$

Figure 5.41. Job's plot analysis of **3** and cyclophosphamide in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** – cyclophosphamide stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.15. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with cyclophosphamide in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{cyclophosphamide})$	$\gamma(\text{cyclophosphamide}) * \Delta F$
1	0
0.88	62124
0.78	102147
0.68	153695
0.59	147183
0.50	170640
0.41	168674
0.31	144671
0.22	105211
0.13	75557
0	0

Figure 5.42. Fluorescence titration of **3** with cyclophosphamide in DMSO fit to a 1:1 **3** – cyclophosphamide stoichiometry. $K_a = 2.46 (0.94) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00197$

Figure 5.43. Job's plot analysis of propargyl-substituted pillar[5]arene and cyclophosphamide in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene – cyclophosphamide stoichiometry ($\gamma_{\text{max}} = 0.66$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.16. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with cyclophosphamide in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{cyclophosphamide})$	$\gamma(\text{cyclophosphamide}) * \Delta F$
1	0
0.82	14634317
0.74	16411037
0.66	17024377
0.57	11629172
0.47	9717701
0.37	5065862
0.27	4761058
0.16	2835974
0	0

Figure 5.44. Fluorescence titration of propargyl-substituted pillar[5]arene with cyclophosphamide in PBS fit to a 1:2 pillararene - cyclophosphamide stoichiometry. $K_{a1} = 8.85$ (0.12) M^{-1} ; $K_{a2} = 3.21$ (0.13) $\times 10^9 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0046$

Figure 5.45. Job's plot analysis of propargyl-substituted pillar[5]arene and cyclophosphamide in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 pillararene – cyclophosphamide stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.17. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with cyclophosphamide in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{propargyl pillararene})$	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.88	1510
0.69	-52
0.59	54189
0.50	196183
0.41	32223
0.31	12854
0.22	-17608
0.13	-9020
0	0

Figure 5.46. Fluorescence titration of propargyl-substituted pillar[5]arene with cyclophosphamide in DMSO fit to a 1:1 pillararene – cyclophosphamide stoichiometry. $K_a = 9.44 (0.59) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0080$

5.7.10. Dibutylphthalate Fluorescence Analyses

Table 5.18. Summary of dibutylphthalate association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (\text{M}^{-1})$	$K_{a2} (\text{M}^{-1})$	$\text{Sum}(\chi^2)$
3	PBS	1:1	$5.67 (0.95) \times 10^5$	-	0.00028
3	DMSO	1:1	$3.32 (0.45) \times 10^5$	-	0.0014
<i>b</i>	PBS	1:2	$6.05 (0.0011) \times 10^{10}$	$7.14 (2.52) \times 10^4$	0.0016
<i>b</i>	DMSO	1:2	$6.73 (0.72)$	$9.10 (0.78) \times 10^9$	0.066

Figure 5.47. Job's plot analysis of **3** and dibutylphthalate in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** - dibutylphthalate stoichiometry ($\gamma_{\text{max}} = 0.55$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.19. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with dibutylphthalate in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{dibutylphthalate})$	$\gamma(\text{dibutylphthalate}) * \Delta F$
1	0
0.85	30345
0.75	49700
0.64	59034
0.55	67596
0.45	65952
0.36	56825
0.27	48619
0.19	27800
0.11	18541
0	0

Figure 5.48. Fluorescence titration of **3** with dibutylphthalate in PBS fit to a 1:1 **3** – dibutylphthalate stoichiometry. $K_a = 5.67 (0.95) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00028$.

Figure 5.49. Job's plot analysis of **3** and dibutylphthalate in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** – dibutylphthalate stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.20. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with dibutylphthalate in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{dibutylphthalate})$	$\gamma(\text{dibutylphthalate}) \cdot \Delta F$
1	0
0.88	45566
0.78	105280
0.69	153838
0.59	160320
0.50	197153
0.41	176401
0.31	143168
0.22	102695
0.13	71629
0	0

Figure 5.50. Fluorescence titration of **3** with dibutylphthalate in DMSO fit to a 1:1 **3** – dibutylphthalate stoichiometry. $K_a = 3.32 (0.45) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0014$

Figure 5.51. Job's plot analysis of propargyl-substituted pillar[5]arene and dibutylphthalate in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene - dibutylphthalate stoichiometry ($\gamma_{\text{max}} = 0.74$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.21. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with dibutylphthalate in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{dibutylphthalate})$	$\gamma(\text{dibutylphthalate}) * \Delta F$
1	0
0.90	26135622
0.82	32020707
0.74	35383755
0.66	34671733
0.57	30192845
0.47	26285783
0.37	17952059
0.27	13621627
0.16	8121965
0	0

Figure 5.52. Fluorescence titration of propargyl-substituted pillar[5]arene with dibutylphthalate in PBS fit to a 1:2 pillararene – dibutylphthalate stoichiometry. $K_{a1} = 6.05 (0.0011) \times 10^{10} \text{ M}^{-1}$; $K_{a2} = 7.14 (2.52) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0016$.

Figure 5.53. Job's plot analysis of propargyl-substituted pillar[5]arene and dibutylphthalate in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene - dibutylphthalate binding ($\gamma_{\text{max}} = 0.59$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.22. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with dibutylphthalate in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{dibutylphthalate})$	$\gamma(\text{dibutylphthalate}) * \Delta F$
1	0
0.88	81302
0.78	124959
0.69	153720
0.59	167295
0.50	123351
0.41	136498
0.31	110656
0.22	93099
0.13	68345
0	0

Figure 5.54. Fluorescence titration of propargyl-substituted pillar[5]arene with dibutylphthalate in DMSO fit to a 1:2 pillararene – dibutylphthalate stoichiometry. $K_{a1} = 6.73 (0.72) \text{ M}^{-1}$; $K_{a2} = 9.10 (0.78) \times 10^9 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.066$.

5.7.11. Myclobutanil Fluorescence Analyses

Table 5.23. Summary of myclobutanil association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	K_{a1} (M^{-1})	K_{a2} (M^{-1})	Sum(χ^2)
3	PBS	1:2	5.10 (0.92)	$2.62 (0.0044) \times 10^{10}$	0.00045
<i>b</i>	PBS	1:2	$1.26 (0.069) \times 10^5$	$1.13 (0.95) \times 10^1$	0.024

Figure 5.55. Job's plot analysis of **3** and myclobutanil in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 **3** – myclobutanil stoichiometry ($\gamma_{\max} = 0.64$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.24. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with myclobutanil in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{myclobutanil})$	$\gamma(\text{myclobutanil}) * \Delta F$
1	0
0.85	28701
0.75	47267
0.64	67439
0.55	51801
0.45	55205
0.36	50118
0.27	33720
0.19	31537
0.11	17782
0	0

Figure 5.56. Fluorescence titration of **3** with myclobutanil in PBS fit to a 1:2 **3** – myclobutanil stoichiometry. $K_{a1} = 5.10 (0.92) \text{ M}^{-1}$; $K_{a2} = 2.62 (0.0044) \times 10^{10} \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00045$.

Figure 5.57. Job's plot fluorescence analysis of propargyl-substituted pillar[5]arene and myclobutanil in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene – myclobutanil stoichiometry ($\gamma_{\text{max}} = 0.74$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.25. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with myclobutanil in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{myclobutanil})$	$\gamma(\text{myclobutanil}) * \Delta F$
1	0
0.90	10417838
0.82	13358125
0.74	14847663
0.66	13068972
0.57	11874350
0.47	8733928
0.37	6798844
0.27	4689125
0.16	3188900
0	0

Figure 5.58. Fluorescence titration of propargyl-substituted pillar[5]arene with myclobutanil in PBS fit to a 1:2 pillararene – myclobutanil stoichiometry. $K_{a1} = 1.26 (0.069) \times 10^5 \text{ M}^{-1}$; $K_{a2} = 1.13 (0.95) \times 10^1 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0024$

5.7.12. *N,N,N',N'*-Tetramethylbenzidine Fluorescence Analyses

Table 5.26. Summary of *N,N,N',N'*-tetramethylbenzidine association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (\text{M}^{-1})$	$K_{a2} (\text{M}^{-1})$	$\text{Sum}(\chi^2)$
3	PBS	1:1	$1.62 (0.12) \times 10^6$	-	0.00023
<i>b</i>	PBS	1:1	$1.13 (0.19) \times 10^5$	-	0.0043

Figure 5.59. Job's plot titration analysis of *N,N,N',N'*-tetramethylbenzidine (TMB) and **3** in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 TMB - **3** stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.27. Tabulated data of the Job's plot analysis of the host-guest binding of *N,N,N',N'*-tetramethylbenzidine (TMB) with **3** in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{TMB})$	$\gamma(\text{TMB}) \cdot \Delta F$
1	0
0.88	13122
0.78	36299
0.68	52250
0.59	47104
0.50	73686
0.41	66586
0.31	62296
0.22	50969
0.13	34710
0	0

Figure 5.60. Fluorescence titration of *N,N,N',N'*-tetramethylbenzidine (TMB) with **3** in PBS fit to a 1:1 TMB – **3** stoichiometry. $K_a = 1.62 (0.12) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00023$.

Figure 5.61. Job's plot analysis of *N,N,N',N'*-tetramethylbenzidine and propargyl-substituted pillar[5]arene in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 TMB – pillararene stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.28. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with *N,N,N',N'*-tetramethylbenzidine in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

γ (propargyl pillararene)	$\gamma(\text{propargyl pillararene}) \cdot \Delta F$
1	0
0.88	111850
0.78	147019
0.68	173736
0.59	181535
0.50	181265
0.41	164090
0.31	141234
0.22	120232
0.13	74424
0	0

Figure 5.62. Fluorescence titration of *N,N,N',N'*-tetramethylbenzidine (TMB) with propargyl-substituted pillar[5]arene in PBS fit to a 1:1 TMB – pillararene stoichiometry. $K_a = 1.13 (0.19) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0043$.

5.7.13. Naproxen Fluorescence Analyses

Table 5.29. Summary of naproxen association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	1:1	$6.51 (0.011) \times 10^3$	-	0.00051
<i>b</i>	PBS	1:1	<i>d</i>	-

Figure 5.63. Job's plot analysis of naproxen and **3** in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 naproxen – **3** stoichiometry ($\gamma_{\max} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.30. Tabulated data of the Job's plot analysis of the host-guest binding of naproxen with **3** in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

γ (3)	$\gamma(\mathbf{3}) \cdot \Delta F$
1	0
0.88	229185
0.78	360647
0.69	382989
0.59	479015
0.50	505076
0.41	486672
0.31	420426
0.22	330083
0.13	210427
0	0

Figure 5.64. Fluorescence titration of naproxen with **3** in PBS fit to a 1:1 naproxen – **3** stoichiometry. $K_a = 6.51 (0.011) \times 10^3 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00051$

Figure 5.65. Job's plot analysis of naproxen and propargyl-substituted pillar[5]arene in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 naproxen – pillararene stoichiometry ($\gamma_{\text{max}} = 0.47$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.31. Tabulated data of the Job's plot analysis of the host-guest binding of naproxen with propargyl-substituted pillar[5]arene in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

γ (propargyl pillararene)	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.90	225597
0.82	457604
0.74	472464
0.66	795250
0.57	705350
0.47	839436
0.37	792306
0.27	679991
0.16	439301
0	0

5.7.14. Perfluorooctanoic Acid Fluorescence Analyses

Table 5.32. Summary of naproxen association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	1:1	$1.13 (0.13) \times 10^6$	-	0.0039
3	DMSO	1:1	$2.44 (0.17) \times 10^4$	-	0.0018
3^c	DMSO- <i>d</i> ₆		$1.88 (0.30) \times 10^5$	-	0.00000033
<i>b</i>	PBS	1:2	4.69 (0.18)	$9.07 (0.000001) \times 10^3$	0.0027
<i>b</i>	DMSO	1:1	$2.45 (0.21) \times 10^5$	-	0.0477

Figure 5.66. Job's plot analysis of **3** and perfluorooctanoic acid (PFOA) in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** – PFOA stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.33. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with perfluorooctanoic acid in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

γ (PFOA)	$\gamma(\text{PFOA}) \cdot \Delta F$
1	0
0.88	34780
0.69	61746
0.59	66160
0.50	82911
0.41	64181
0.31	50905
0.22	41278
0.13	24741
0	0

Figure 5.67. Fluorescence titration of **3** with perfluorooctanoic acid (PFOA) in PBS fit to a 1:1 **3** – PFOA stoichiometry. $K_a = 1.13 (0.13) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0039$

Figure 5.68. Job's plot fluorescence analysis of **3** and perfluorooctanoic acid (PFOA) in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 **3** - PFOA ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.34. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with perfluorooctanoic acid (PFOA) in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{PFOA})$	$\gamma(\text{PFOA}) * \Delta F$
1	0
0.88	83617
0.78	154573
0.69	177051
0.59	207423
0.50	225409
0.41	200726
0.31	178312
0.22	130962
0.13	81501
0	0

Figure 5.69. Fluorescence titration of **3** with perfluorooctanoic acid (PFOA) in DMSO fit to a 1:1 **3** – PFOA stoichiometry. $K_a = 2.44 (0.17) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0018$

Figure 5.70. ^1H NMR titration of **3** with perfluorooctanoic acid (PFOA) in $\text{DMSO-}d_6$ fit to a 1:1 **3** – PFOA stoichiometry. $K_a = 1.88 (0.30) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00000033$

Figure 5.71. Job's plot fluorescence analysis of propargyl-substituted pillar[5]arene and PFOA in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene - PFOA stoichiometry ($\gamma_{\text{max}} = 0.69$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.35. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with PFOA in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{PFOA})$	$\gamma(\text{PFOA}) * \Delta F$
1	0
0.88	2302738
0.69	4095988
0.50	2579400
0.31	1856125
0.22	1061441
0.13	673388
0	0

Figure 5.72. Fluorescence titration of propargyl-substituted pillar[5]arene with perfluorooctanoic acid (PFOA) in PBS fit to a 1:2 pillararene – PFOA stoichiometry. $K_{a1} = 4.69$ $(0.18) \text{ M}^{-1}$; $K_{a2} = 9.07 (0.000001) \times 10^3 \text{ M}^{-1}$ $\text{Sum}(\chi_2) = 0.0027$

Figure 5.73. Job's plot fluorescence analysis of propargyl-substituted pillar[5]arene and PFOA in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 pillararene - PFOA stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.36. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with PFOA in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{PFOA})$	$\gamma(\text{PFOA}) * \Delta F$
1	0
0.78	64301
0.68	83734
0.59	92254
0.50	93619
0.41	92091
0.31	83827
0.22	61046
0.13	34855
0	0

Figure 5.74. Fluorescence titration of propargyl-substituted pillar[5]arene with perfluorooctanoic acid (PFOA) in DMSO fit to a 1:1 pillararene – PFOA stoichiometry. $K_a = 2.45 (0.21) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0477$.

5.7.15. Phenanthrene Fluorescence Analysis

Table 5.37. Summary of phenanthrene association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	1:1	$2.32 (0.020) \times 10^4$	-	0.0016
3	DMSO	1:1	$8.1 (1.8) \times 10^3$	-	0.0029
<i>b</i>	PBS	1:1	$1.10 (0.011) \times 10^5$	-	0.0032
<i>b</i>	DMSO	1:1	$5.04 (0.81) \times 10^4$	-	0.00060

Figure 5.75. Job's plot analysis of phenanthrene and **3** in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 phenanthrene – **3** stoichiometry ($\gamma_{\max} = 0.54$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.38. Tabulated data of the Job's plot analysis of the host-guest binding of phenanthrene with **3** in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\mathbf{3})$	$\gamma(\mathbf{3}) \cdot \Delta F$
1	0
0.85	173914
0.75	296923
0.64	337636
0.54	389595
0.45	385205
0.36	356463
0.27	319288
0.19	240142
0.11	147872
0	0

Figure 5.76. Fluorescence titration of phenanthrene with **3** in PBS fit to a 1:1 phenanthrene – **3** stoichiometry. $K_a = 2.32 (0.020) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0016$

Figure 5.77. Job's plot fluorescence analysis of phenanthrene and **3** in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:1 phenanthrene – **3** stoichiometry ($\gamma_{\max} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.39. Tabulated data of the Job's plot analysis of the host-guest binding of phenanthrene with **3** in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(3)$	$\gamma(3) \cdot \Delta F$
1	0
0.88	295283
0.78	439789
0.69	487040
0.59	555977
0.50	578021
0.41	548629
0.31	490763
0.22	381914
0.13	243145
0	0

Figure 5.78. Fluorescence titration of phenanthrene with **3** in DMSO fit to a 1:1 phenanthrene – **3** stoichiometry. $K_a = 8.1 (1.8) \times 10^3 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0029$

Figure 5.79. Job's plot fluorescence analysis of phenanthrene and propargyl-substituted pillar[5]arene in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:1 phenanthrene – pillararene stoichiometry ($\gamma_{\text{max}} = 0.47$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.40. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with phenanthrene in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{propargyl pillararene})$	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.90	201867
0.82	404914
0.74	494296
0.66	696249
0.57	659322
0.47	738206
0.37	672005
0.27	581950
0.16	412505
0	0

Figure 5.80. Fluorescence titration of phenanthrene and propargyl-substituted pillar[5]arene in PBS fit to a 1:1 phenanthrene – pillararene stoichiometry. $K_a = 1.10 (0.011) \times 10^5 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0032$

Figure 5.81. Job's plot analysis of phenanthrene and propargyl-substituted pillar[5]arene in DMSO obtained by fluorescence spectroscopy, indicating a likely 1:1 phenanthrene – pillararene stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.41. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with phenanthrene in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration

$\gamma(\text{propargyl pillararene})$	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.875	588263
0.69	1130353
0.59	1162188
0.5	1225575
0.41	1125203
0.31	1017866
0.22	796797
0.125	491291
0	0

Figure 5.82. Fluorescence titration of phenanthrene with propargyl-substituted pillar[5]arene in DMSO fit to a 1:1 phenanthrene – pillararene stoichiometry. $K_a = 5.04 (0.81) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00060$.

5.7.16. 1,10-Phenanthroline Fluorescence Analyses

Table 5.42. Summary of 1,10-phenanthroline association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (\text{M}^{-1})$	$K_{a2} (\text{M}^{-1})$	$\text{Sum}(\chi^2)$
3	PBS	2:1	$2.43 (0.32) \times 10^6$	$4.72 (0.21) \times 10^4$	0.000080
3	DMSO	2:1	$4.40 (0.027) \times 10^5$	$2.67 (0.24) \times 10^4$	0.17
<i>b</i>	PBS	2:1	4.19 (0.46)	$1.18 (0.52) \times 10^9$	0.029
<i>b</i>	DMSO	2:1	$3.08 (0.041) \times 10^2$	$2.89 (0.12) \times 10^7$	0.066

Figure 5.83. Job's plot analysis of 1,10-phenanthroline and **3** in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 1,10-phenanthroline – **3** stoichiometry ($\gamma_{\text{max}} = 0.64$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.43. Tabulated data of the Job's plot analysis of the host-guest binding of 1,10-phenanthroline with **3** in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(3)$	$\gamma(3)*\Delta F$
1	0
0.85	34489
0.75	41390
0.64	45145
0.55	27295
0.45	29287
0.36	17361
0.27	20137
0.19	16426
0.11	13523
0	0

Figure 5.84. Fluorescence titration of 1,10-phenanthroline with **3** in PBS fit to a 1:2 1,10-phenanthroline – **3** stoichiometry. $K_{a1} = 2.43 (0.32) \times 10^6 \text{ M}^{-1}$; $K_{a2} = 4.72 (0.21) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.000080$

Figure 5.85. Job's plot analysis of 1,10-phenanthroline and **3** in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:2 1,10-phenanthroline – **3** stoichiometry ($\gamma_{\text{max}} = 0.41$). γ is mole fraction of guest and ΔF is the change in fluorescence integration

Table 5.44. Tabulated data of the Job's plot analysis of the host-guest binding of 1,10-phenanthroline with **3** in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(1,10\text{-phenanthroline})$	$\gamma(1,10\text{-phenanthroline}) \cdot \Delta F$
1	0
0.88	33516
0.78	37239
0.59	91633
0.50	91983
0.41	103468
0.31	101743
0.22	85907
0.13	54375
0	0

Figure 5.86. Fluorescence titration of 1,10-phenanthroline with **3** in DMSO fit to a 1:2 1,10-phenanthroline – **3** stoichiometry. $K_{a1} = 4.40 (0.027) \times 10^5 \text{ M}^{-1}$; $K_{a2} = 2.67 (0.24) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.17$

Figure 5.87. Job's plot analysis of 1,10-phenanthroline and propargyl-substituted pillar[5]arene in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 1,10-phenanthroline - pillararene stoichiometry ($\gamma_{\text{max}} = 0.66$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.45. Tabulated data of the Job's plot analysis of the host-guest binding of 1,10-phenanthroline with propargyl-substituted pillar[5]arene in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{propargyl pillararene})$	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.90	12111
0.82	44767
0.74	71112
0.66	95513
0.47	80895
0.37	73608
0.27	64036
0.16	41138
0	0

Figure 5.88. Fluorescence titration of 1,10-phenanthroline with propargyl-substituted pillar[5]arene in PBS; fit to a 1:2 1,10-phenanthroline – pillararene stoichiometry. $K_{a1} = 4.19$ (0.46) M^{-1} ; $K_{a2} = 1.18$ (0.052) $\times 10^9 M^{-1}$; $\text{Sum}(\chi^2) = 0.029$

Figure 5.89. Job's plot analysis of 1,10-phenanthroline and propargyl-substituted pillar[5]arene in DMSO, obtained by fluorescence spectroscopy, indicating a likely 1:2 1,10-phenanthroline - pillararene stoichiometry ($\gamma_{\text{max}} = 0.59$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.46. Tabulated data of the Job's plot analysis of the host-guest binding of 1,10-phenanthroline with propargyl-substituted pillar[5]arene in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{propargyl pillararene})$	$\gamma(\text{propargyl pillararene}) * \Delta F$
1	0
0.6875	260453
0.59375	278432
0.5	270228
0.40625	218523
0.3125	188526
0.21875	123411
0.125	79875
0	0

Figure 5.90. Fluorescence titration of 1,10-phenanthroline with propargyl-substituted pillar[5]arene in DMSO fit to a 1:2 1,10-phenanthroline – pillararene stoichiometry. $K_{a1} = 3.08 (0.041) \times 10^2 \text{ M}^{-1}$; $K_{a2} = 2.89 (0.12) \times 10^7 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.066$.

5.7.17. Simazine Fluorescence Analyses

Table 5.47. Summary of simazine association constants and host:guest stoichiometries calculated from fluorescence titration data. a. Host-guest binding stoichiometry; b. propargyl-substituted pillar[5]arene; c. titration conducted by NMR spectroscopy; d. no binding observed

Host	Solvent	<i>a</i>	$K_{a1} (M^{-1})$	$K_{a2} (M^{-1})$	Sum(χ^2)
3	PBS	2:1	$1.37 (0.22) \times 10^{10}$	$6.47 (1.42) \times 10^9$	0.00073
3	DMSO	1:1	$1.00 (0.14) \times 10^7$	-	0.00055
<i>b</i>	PBS	1:2	$7.52 (0.000065) \times 10^{11}$	$5.80 (0.42) \times 10^4$	0.00073
<i>b</i>	DMSO	1:1	$1.37 (0.15) \times 10^6$	-	0.0034

Figure 5.91. Job's plot fluorescence analysis of **3** and simazine in PBS, obtained by fluorescence spectroscopy, indicating a likely 2:1 **3**-simazine stoichiometry ($\gamma_{\text{max}} = 0.36$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.48. Tabulated data of the Job's plot analysis of the host-guest binding of **3** with simazine in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{simazine})$	$\gamma(\text{simazine}) \cdot \Delta F$
1	0
0.85	41046
0.75	57559
0.64	60336
0.55	50067
0.45	55207
0.36	78168
0.27	50535
0.19	39151
0.11	18075
0	0

Figure 5.92. Fluorescence titration of **3** with dilute simazine in PBS fit to a 2:1 **3** – simazine stoichiometry. $K_{a1} = 1.37 (0.22) \times 10^{10} \text{ M}^{-1}$; $K_{a2} = 6.47 (1.42) \times 10^9 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00073$.

Figure 5.93. Job's plot analysis of simazine and **3** in DMSO, obtained by fluorescence spectroscopy, indicating a 1:1 **3** - simazine stoichiometry ($\gamma_{\text{max}} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.49. Tabulated data of the Job's plot analysis of the host-guest binding of simazine with **3** in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{simazine})$	$\gamma(\text{simazine}) * \Delta F$
1	0
0.88	37444
0.78	91458
0.69	119289
0.59	148709
0.50	157071
0.41	155606
0.31	137561
0.22	114808
0.13	73086
0	0

Figure 5.94. Fluorescence titration of **3** with simazine in DMSO fit to a 1:1 **3** – simazine stoichiometry. $K_a = 1.00 (0.137) \times 10^7 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00055$.

Figure 5.95. Job's plot analysis of propargyl-substituted pillar[5]arene and simazine in PBS, obtained by fluorescence spectroscopy, indicating a likely 1:2 pillararene - simazine stoichiometry ($\gamma_{\text{max}} = 0.59$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.50. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with simazine in PBS. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{simazine})$	$\gamma(\text{simazine}) * \Delta F$
1	0
0.78	1732188
0.69	2379919
0.59	3133136
0.50	2741055
0.41	2699600
0.31	2076616
0.22	1076141
0.13	780155
0	0

Figure 5.96. Fluorescence titration of propargyl-substituted pillar[5]arene with simazine in PBS fit to a 1:2 pillararene – simazine stoichiometry. $K_{a1} = 7.52 (0.000065) \times 10^{11} \text{ M}^{-1}$; $K_{a2} = 5.80 (0.42) \times 10^4 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.00073$.

Figure 5.97. Job's plot fluorescence analysis of propargyl-substituted pillar[5]arene and simazine in DMSO indicating a 1:1 pillararene – simazine stoichiometry ($\gamma_{\max} = 0.50$). γ is mole fraction of guest and ΔF is the change in fluorescence integration.

Table 5.51. Tabulated data of the Job's plot analysis of the host-guest binding of propargyl-substituted pillar[5]arene with simazine in DMSO. γ is mole fraction of guest and ΔF is the change in fluorescence integration.

$\gamma(\text{simazine})$	$\gamma(\text{simazine}) * \Delta F$
1	0
0.88	126139
0.78	145421
0.69	142554
0.59	155742
0.50	156445
0.41	136214
0.31	113451
0.22	91863
0.13	56678
0	0

Figure 5.98. Fluorescence titration of propargyl-substituted pillar[5]arene with simazine in DMSO fit to a 1:1 pillararene – simazine stoichiometry. $K_a = 1.37 (0.15) \times 10^6 \text{ M}^{-1}$; $\text{Sum}(\chi^2) = 0.0034$.

5.7.18. Removal of Cationic Pillararene from Deionized Water

A 2.0 mg/ mL (1.0 mM) solution of cationic pillararene in DI (de-ionized) water was created. A quartz cuvette was filled with 2.0 mL DI water and 0.5 mL of the cationic pillararene solution. Four fluorescence measurements were taken of this solution using the parameters: excitation: 295 nm; emission: 305-575 nm; slit widths: 3.0 nm, 3.0 nm; scan speed: 600 nm/min; data interval: 1.0 nm. 15 mg of a cation exchange resin were added, and the cuvette was capped and inverted for 60 seconds to mix. Four fluorescence measurements were taken using the same parameters as before. Further aliquots of the cation exchange resin were added until the fluorescence intensity stopped changing. All fluorescence spectra were integrated vs. wavenumber on the X-axis using OriginPro 2018.

Figure 5.99. Fluorescence analysis of the efficiency of cationic pillararene **3** removal from aqueous solution using the cation exchange resins Dowex Marathon, Dowex 50WX2, and Amberlite IRN150.

5.7.19. Fabrication of Pillararene **3** Resin

Procedure: Pillararene **3** (97.0 mg) was added to a 250 mL Erlenmeyer flask and dissolved, with the aid of sonication, in 50 mL of ultrapure water. 20 equivalents by mass of Dowex 50WX2, hydrogen form, was added and the solution was stirred gently (~100 rpm) for 30 minutes. A fluorescence measurement of the supernatant was taken to confirm saturation of the Dowex 50WX2 resin with **3**, as evidenced by the presence of fluorescence peaks attributed to **3** in the spectrum. If all of **3** has been removed from solution, more should be added until saturation is seen by fluorescence. The new beads of resin-bound-**3** were collected from solution by gravity filtration, washed well with ultrapure water, then allowed to dry in open air overnight. No mass analysis of the

product could be conducted due to the significant loss of water from the beads upon drying.

5.7.20. Thermogravimetric Analysis

All thermogravimetric analysis (TGA) measurements were conducted on an Shimadzu TGA-50 instrument using a TGA-50H detector with the following parameters: atmosphere: nitrogen, gas flow: 10 mL/min, pan type: aluminum; and the following program: initial temperature: 60 °C, hold for: 5 minutes, ramp rate: 10 °C/min; final temperature: 600 °C, hold for: 5 minutes.

Figure 5.100. Comparison of thermogravimetric analysis of the resin-bound pillar[5]arene (“3-resin”, black line), a physical mixture of pillar[5]arene 3 with DOWEX 50WX2 (“3 + resin”, red line), the pillar[5]arene (“3”, blue line), and DOWEX 50WX2 (“resin”, green line).

5.7.21. Toxicant Removal from Aqueous Solution

Fluorescence measurements were taken using the following parameters for all analytes - slit widths: 3.0 nm, 3.0 nm, scan speed: 600 nm/min, data interval: 1.0 nm, sensitivity: low; and the following parameters for specific analytes – phenanthrene: excitation: 270 nm and emission: 280-500 nm, 1,10-phenanthroline monohydrate: excitation: 290 nm and emission 300-475 nm, naproxen: excitation: 270 nm and emission: 280-500 nm, *N,N,N,N*-tetramethylbenzidine: 320 nm and emission: 330-550 nm, and anthracene: excitation: 360 nm and emission: 370-600 nm.

2.5 mL of a 6 μ M solution of analyte in ultrapure water or phosphate buffered saline (PBS) was added to a quartz cuvette and four fluorescence measurements were taken. 5 mg of pillararene resin were added to the solution and the cuvette was capped and inverted for 30 seconds to mix, then another set of four fluorescence measurements were taken. Further aliquots of the pillararene resin were added until the fluorescence intensity stopped changing. All fluorescence spectra were integrated vs. wavenumber on the X-axis using OriginPro 2018.

5.7.22. Fluorescence of Toxicant Removal from Aqueous Solution

Figure 5.101. Fluorescence spectra of anthracene in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water.

Figure 5.102. Normalized fluorescence integration (from 390 to 600 nm) of anthracene in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water. Indicates no removal of anthracene from ultrapure water.

Figure 5.103. Fluorescence spectra of anthracene in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.104. Normalized fluorescence integration (from 390 to 600 nm) of anthracene in the presence of increasing amounts of pillararene **3** exchange resin in PBS. Indicates minimal removal of anthracene from PBS with 50 mg of resin corresponding to 34% removal.

Figure 5.105. Fluorescence spectra of naproxen in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water.

Figure 5.106. Normalized fluorescence integration (from 340 to 420 nm) of naproxen in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water. Indicates removal of naproxen from ultrapure water with 50 mg of resin corresponding to 60% removal.

Figure 5.107. Fluorescence spectra of naproxen in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.108. Normalized fluorescence integration (from 340 to 420 nm) of naproxen in the presence of increasing amounts of pillararene **3** exchange resin in PBS. Indicates removal of naproxen from PBS with 50 mg of resin corresponding to 74% removal.

Figure 5.109. Fluorescence spectra of *N,N,N',N'*-tetramethylbenzidine in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water.

Figure 5.110. Normalized fluorescence integration (from 330 to 550 nm) of *N,N,N',N'*-tetramethylbenzidine in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water. Indicates that *N,N,N',N'*-tetramethylbenzidine is not removed from solution and might displace pillararene from the resin, leading to fluorescence enhancement via encapsulation.

Figure 5.111. Fluorescence spectra of *N,N,N',N'*-tetramethylbenzidine in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.112. Normalized fluorescence integration (from 330 to 550 nm) of *N,N,N,N'*-tetramethylbenzidine in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.113. Fluorescence spectra of phenanthrene in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water.

Figure 5.114. Normalized fluorescence integration (from 340 to 425 nm) of phenanthrene in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water. Indicates removal of phenanthrene from ultrapure water with 50 mg of resin corresponding to 83% removal.

Figure 5.115. Fluorescence spectra of phenanthrene in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.116. Normalized fluorescence integration (from 340 to 425 nm) of phenanthrene in the presence of increasing amounts of pillararene **3** exchange resin in PBS. Indicates removal of phenanthrene from PBS with 50 mg of resin corresponding to 59% removal.

Figure 5.117. Fluorescence spectra of 1,10-phenanthroline in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water.

Figure 5.118. Normalized fluorescence integration (from 340 to 400 nm) of 1,10-phenanthroline in the presence of increasing amounts of pillararene **3** exchange resin in ultrapure water. Indicates removal of 1,10-phenanthroline from ultrapure water with 20 mg of resin corresponding to ~50 % removal.

Figure 5.119. Fluorescence spectra of 1,10-phenanthroline in the presence of increasing amounts of pillararene **3** exchange resin in PBS.

Figure 5.120. Normalized fluorescence integration (from 340 to 400 nm) of 1,10-phenanthroline in the presence of increasing amounts of pillararene **3** exchange resin in PBS. Indicates removal of 1,10-phenanthroline from ultrapure water with 10 mg of resin corresponding to ~50 % removal.

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APPENDICES

6.1. Abbreviations

[G]	concentration of guest
[H]	concentration of host
[Q]	concentration of quencher
Å	angstrom
a.u.	arbitrary units
ADP	adenosine diphosphate
AIE	aggregation induced emission
AMP	adenosine monophosphate
ATP	adenosine triphosphate
ATR	attenuated total reflection
AVG _{blank}	average value of the blank
BPA	bisphenol A
BPF	bisphenol F
BPS	bisphenol S
CB	cucurbituril
CB14	cucurbituril 14
CB6	cucurbituril 6
CB7	cucurbituril 7
CB8	cucurbituril 8
CHEF	chelation enhanced fluorescence
CHEQ	chelation enhanced fluorescence quenching
CP	carbon paper
CP	coordination polymer
CRM	confocal Raman Microscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDT	dichlorodiphenyltrichloroethane
DI	deionized

DIBAL	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNT	dinitrotoluene
DPAD	1,1'-butane(1,4-diyl)bis(2-aminopyridine)bromide
EDTA	ethylenediaminetetraacetic acid
EE	Electron Exchange
EPA	Environmental Protection Agency
equiv	equivalents
<i>F</i>	fluorescence intensity in the presence of guest
<i>F</i> ₀	initial fluorescence intensity
FRET	Förester Resonance Energy Transfer
FT IR	Fourier Transform Infrared
G	guest
GTP	guanylyl imidodiphosphate
H	host
HEPES	(4-(2-hydroxyethyl)1-piperazineethanesulfonic acid
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
<i>I</i>	signal (absorbance, luminescence, fluorescence, phosphorescence) intensity in the presence of guest
ICP	inductively coupled plasma
ICT	internal (intermolecular) charge transfer
IFE	inner filter effect
IM-MS	ion mobility-mass spectrometry
<i>I</i> ₀	initial signal (absorbance, luminescence, fluorescence, phosphorescence) intensity
IR	infrared
IRMPD	infrared multiple photon dissociation
ITC	isothermal titration calorimetry

K (K_a)	association constant
K_D	dynamic quenching constant
k_q	diffusional quenching constant
K_S	static quenching constant
K_{SV}	Stern-Volmer Constant
LDA	linear discriminant analysis
LOD	limit of detection
LOQ	limit of quantitation
LUMO	lowest unoccupied molecular orbital
<i>m</i>	meta
M	molar
MCL	maximum contaminant level
mg	milligrams
MGV	Mean Grey Value
MHz	megahertz
min	minutes
mL	milliliters
MLCT	metal-ligand charge transfer
mM	millimolar
mm	millimeter
MOF	metal-organic framework
MS	mass spectrometry
ND	not determined
NED	<i>N</i> -(1-naphthyl)ethylenediamine
NGV	Normalized Green Value
nm	nanometers
nM	nanomolar
NMR	Nuclear Magnetic Resonance
NQS	1,2-naphthoquinone-4-sulfonate
NSAID	non-steroidal anti-inflammatory drug
<i>o</i>	ortho
OTC	over-the-counter

<i>p</i>	para
PAH	polycyclic aromatic hydrocarbon
PBS	phosphate buffered saline
PCA	principal component analysis
PCB	polychlorinated biphenyls
PET	photo-induced electron transfer
PFOA	perfluorooctanoic acid
pM	picomolar
ppb	parts per billion
ppm	parts per million
ppt	parts per thousand
PSD	pixel standard deviation
RET	resonance energy transfer
RGB	red-green-blue
RH	relative humidity
SGA	soybean agglutinin
STD	standard deviation
STD _{blank}	standard deviation of the blank value
TBAB	tetrabutylammonium bromide
Temp	temperature
THF	tetrahydrofuran
ThT	Thioflavin T
TICT	twisted internal (intermolecular) charge transfer
TMB	<i>N,N,N,N</i> -tetramethylbenzidine
TNP	trinitrophenol
TNT	trinitrotoluene
UV	ultraviolet
WGA	wheat germ agglutinin
α	alpha
β	beta
γ	gamma; mole fraction
δ	delta; chemical shift

ΔF	change in fluorescence
ΔH	change in enthalpy
ΔI	change in signal (absorbance, luminescence, fluorescence, phosphorescence) intensity
$\Delta\Delta H$	stabilization energy
κ^2	orientation factor
μg	micrograms
μL	microliters
μM	micromolar
π	pi
τ	luminescence lifetime in the presence of quencher
τ_0	initial luminescence lifetime
χ	mole fraction

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