The Thesis Committee for Peiyu Tu
Certifies that this is the approved version of the following Thesis:

New calix[4]pyrrole derivatives for ionic and neutral guests

APPROVED BY
SUPERVISING COMMITTEE:

Jonathan L. Sessler, Supervisor

Eric V. Anslyn

New calix[4]pyrrole derivatives for ionic and neutral guests

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Peiyu Tu

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Dedication

I delicate this thesis to my mother for her kind love and support.

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I would like to thank my supervisor Jonathan L. Sessler for his mentorship and support. I also want to thank all Sessler group members for their help. Specially thanks to Qing for helping me with crystals and all the discussions.

Abstract

New calix[4]pyrrole derivatives for ionic and neutral guests

Peiyu Tu, M.A.

The University of Texas at Austin, 2018

Supervisor: Jonathan L. Sessler

The first chapter is a review of fluorescent sensors for explosives detection and ion pair receptors. In the second chapter, two novel pyrene-appended calix[4]pyrroles are reported. Their binding properties to various guests including aromatic explosives and anions are discussed. The third chapter describes the design and synthetic attempts of two calix[4]arene-strapped calix[4]pyrroles to serve as ion pair receptor in order to be selective for potassium salts and sodium salts, respectively.

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Chapter 1: Introduction

1.1 Introduction to aromatic explosives detection

The detection of explosives is crucial to global security, human health and environmental stability.[1] Chemical explosives include a variety of compounds such as nitroaromatics, nitramines, nitrate esters and peroxides (Table 1). Among them, nitroamomatics such as 2,4,6-nitrotoluene (TNT), 2,4-dinitrotoluene (DNT), are the primary components in the landmines and principal military explosives. They can form strong π-π interactions with electron-rich compounds such as polycyclic aromatic hydrocarbons. Nitramines like cyclotrimethylenetrinitramine (RDX) and nitrate esters like pentaerythritol tetranitrate (PETN) are of interest because they are the major components in highly energetic explosives, such as C-4 (91% RDX).[2] Peroxide-based explosives, such as triacetone triperoxide (TATP), can be synthesized relatively easily from low-cost materials thus becoming a main source of homemade explosives. Apart from bomb detection, health concerns are also related to nitroaromatics. Exposure to TNT can cause abnormal liver function and anemia.[3] The Environmental Protection Agency has established a technical guide for authorities for TNT contaminated drinking water.[4] Thus, the demand for rapid, less expensive and sensitive detection is increasing.

Detection of explosives often requires a chemical response (such as the binding of analyte or an occurrence of a reaction) leading to a signal output (such as fluorescence quenching or color change). However, each class of chemical explosives present different physical properties and broad-class detection is very challenging. To diminish cost, professional training as well as enhancing sensitivity and portability, a large number of sensors and some technologies have been developed and explored for explosives detection at fixed sites and in the field.

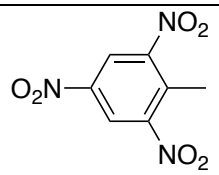
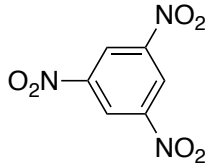
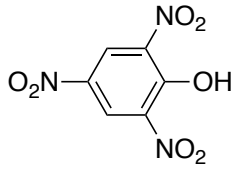
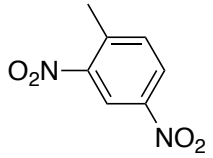
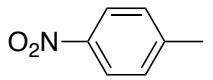
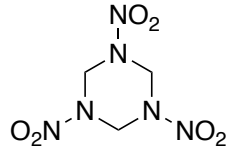
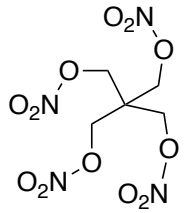
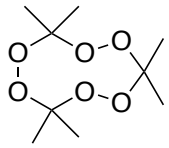
Structure	Name	Abbreviation	Class
	2,4,6-Trinitrotoluene	TNT	Nitroaromatic
	2,4,6-benzene	TNB	Nitroaromatic
	Picric acid	PA	Nitroaromatic
	2,4-Dinitrotoluene	DNT	Nitroaromatic
	4-Nitrotoluene	NT	Nitroaromatic
	Cyclotrimethylenetrinitramine	RDX	Nitramine
	Pentaerythritol tetranitrate	PETN	Nitrate ester
	Triacetone triperoxide	TATP	Peroxide

Table 1. Examples of compounds of interest for explosives detection

1.2 CURRENT METHODOLOGIES

Currently, the commercially available methodologies for portable and fixed site detection, such as screenings at airport including canine teams, metal detectors, X-ray dispersion and ionization mass-spectrometry (IMS), are effective but unwieldy.

Canine teams with professional training have been widely used to detect and identify different explosives. However, the training of canine teams is expensive and not suitable for long-term detection as dogs can easily get tired.[5] IMS, commonly used in airports for explosive detection, has very high sensitivity for common explosives since it analyzes the molecular mass. However, the calibration for IMS is sophisticated and time-consuming. A library of standard compounds and residues has to be established first in order to identify explosives successfully.[6] IMS instruments are expensive and limited by poor portability. Metal detectors are efficient in detecting weapons packaged in metals but cannot identify the chemical properties of the explosives, limiting their broader use in the field and at transportation sites. X-ray dispersion can provide high resolution images for baggage and clothing. Therefore, the instruments are widely used at transportation sites to detect any concealed devices. However, as true for metal detectors, these instruments cannot detect the chemical components and are not easily portable. Optical sensing, on the other hand, offer many advantages over current detection techniques, including low cost, high sensitivity and easy portability.

1.3 FLUORESCENCE SENSING

Fluorescent detection is an indirect method to employ fluorescent materials that undergo fluorescence changes (turn-on or quenching) upon interactions with target molecules. Fluorescent sensors for the detection of explosives include organic and inorganic conjugated polymers, small organic and inorganic molecules, and other

supramolecular systems. Many efforts have been devoted to fluorescence quenching, in which the fluorescence intensity is decreased in the presence of the analyte. There are a number of mechanisms responsible for fluorescence quenching, including photo-induced electron transfer (PET), intermolecular charge transfer (ICT), resonance energy transfer and electron exchange.[7]

The drawbacks for fluorescence sensing are photodegradation and photobleaching of the indicator, as well as potentially non-specific responses. On the other hand, fluorescence detection methods are typically characterized by lower cost and increased portability compared to commercially available methods. Fluorescence sensing may also offer the best sensitivity because the interference from the background is very low.

1.3.1 Conjugated polymers: organic and inorganic

Fluorescent conjugated polymers have been extensively developed for the detection of nitrated explosives.[8] Since conjugated polymers are good electron donors, the electrostatic interaction between the analyte (the electron-deficient nitroaromatic explosives) and the conjugated polymer is enhanced. The efficient exciton migration and communication between the analyte and the polymer lead to the high sensitivity in fluorescence quenching.[9-10] Typically, conjugated polymers can be classified into organic and inorganic polymers based on their backbone structures (Figure 1.1).

The most widely used organic conjugated poly(phenyleneethynylene) (PPEs) and poly(phenylenevinylene) (PPVs). PPEs and PPVs are composed of electron-rich aryl rings, which can interact with electron-deficient nitroaromatics. The sensitivity of PPEs and PPVs toward TNT is high due to the fast exciton migration within the backbone.

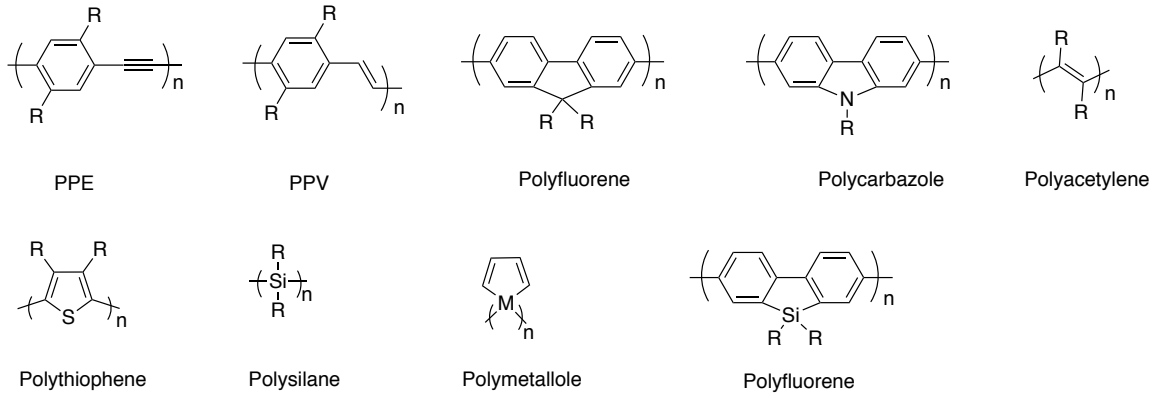


Figure 1.1 Types of organic and inorganic conjugated polymers for explosives detection

Polysilanes and polymetalloles are representatives conjugated inorganic polymers used for explosives detection. Polysilanes have Si-Si backbones and permit exciton migration in analogy to the organic conjugated polymers. One example is poly(3,3,3-trifluoropropylmethylsilane), reported in 2005, which exhibits high quenching efficiencies in the presence of TNB, and picric acid.[11] Polymetalloles are composed of silicon or germanium cyclopentadienes with high quantum yield. The Trogler group reported that thin films of certain polysiloles have high sensitivity toward nitroaromatics. The limits of detection for TNT and picric acid are 50 ppb and 6 ppb, respectively.[12-13]

1.3.2 Small molecules: organic and inorganic

Small molecules present many benefits, such as simple synthesis, different pathways of fluorescence quenching and an ability to detect various analyte of interest. The principle difference between polymer-based sensors and small molecule fluorophores lies in the absence of excitonic migration in small molecules and the associated mechanism of quenching.[5] Polymeric systems commonly detect explosives by static quenching while small molecules fluorophores are quenched by collision. Furthermore, small molecules are quenched stoichiometrically by analytes while

fluorescent conjugated polymers have high quenching efficiencies once one molecule of analyte is bound to the polymer. Small molecules fluorophores can be divided to organic molecules and inorganic ones.

Organic small molecules including polycyclic aromatic hydrocarbons, porphyrins and others have been studied and utilized in explosives detection.

Polycyclic aromatic hydrocarbons are similar to compounds with fused aromatic rings like pyrene, naphthalene, anthracene, perylene and the like. They often have high quantum yields and are excellent electron donors. This facilitates π-π interactions with nitrated explosives especially nitroaromatic explosives. In particular, pyrene and its derivatives have been widely used in the detection of nitrated organics. The fluorescence spectra of pyrene have monomer emission below 400 nm at dilute concentrations (e.g. < 10^{-3} M in solution).[14] When the concentration increases, the fluorescence peak shifts from the UV range into the visible range as the result of excimer formation. Strong π-π interactions can be formed between electron-rich pyrene and electron deficient nitroaromatics resulting in quenching of both pyrene monomer and excimer emission.

1.4 General Introduction to Ion Pair Receptors

A great deal of effort has been devoted to developing cation receptors, including acyclic and macrocyclic compounds over the past several decades. Numerous anion receptors have also been constructed in recent years and their ability to bind anions have been evaluated.[15-16] However, these classic systems contain either a cation binding site or an anion binding site but not both. To implement a higher-level of control over ion recognition, ion pair receptors, bearing both cation and anion binding sites, are being prepared. Such systems may display higher affinity and/or better selectivity over simple ion receptors.

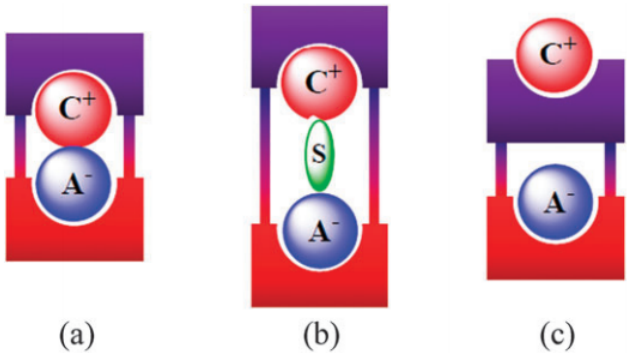
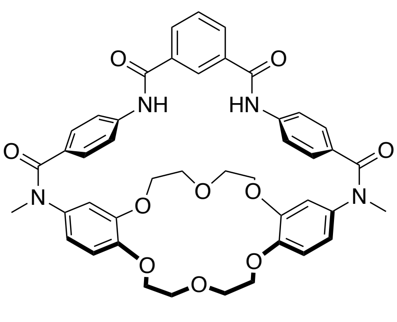


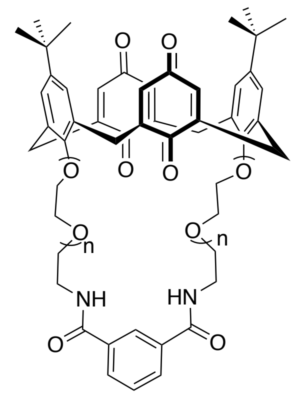
Figure 1.2 Three limiting modes for ion-pair interactions. C^+: cation. A^-: anion. S: solvent. Adapted with permission from ref. 17. Copyright 2010 the Royal Society of Chemistry.

There are three limiting modes of ion-pair interactions as shown in Figure 1.2. The first one is a contact ion pair within the host molecule. In this case, the cation and the anion are close to each other and are essentially in a direct contact (Figure 1.2 a). The second one is the solvent-bridged mode. One or more solvent molecules also exist in the receptor and serve as a bridge between the cation and the anion (Figure 1.2 b). The third

one is termed as host-separated ion pair, where the cation and the anion are separated far from one another and separated by the host molecule (Figure 1.2 c).[17]



1.1



1.2 n=1
1.3 n=2
1.4 n=8

Figure 1.3 Structures of **1.1 – 1.4**

Nevertheless, the potential importance of this field is leading to ongoing efforts to construct new ion pair receptors. One of the earliest example was from Smith's group in 2000.[18] Smith and coworkers synthesized a preorganized bicyclic receptor **1.1** (Figure1.3) where the cation and anion binding sites were held close to each other. This team evaluated the ability of receptor **1.1** to extract KCl into DMSO solution and found that it was a superior salt extractant. In 2008, the same group reported the calix[4]diquinone receptors **1.2 – 1.4** (Figure 1.3). These systems displayed cooperative ion-pair recognition whereas the receptor displayed no affinity for individual cation or anion.[19] The strong contact ion-pair interactions occur through the preorganization of the receptor so that the cation and anion binding sites are in close proximity. By manipulating the length of the glycol linkage, these receptors show different selectivity and affinity for alkali halides. This offers the potential use for ion pair receptors as transporters to selectively induce transmembrane potential, which has attracted attention as a possible cancer treatment.

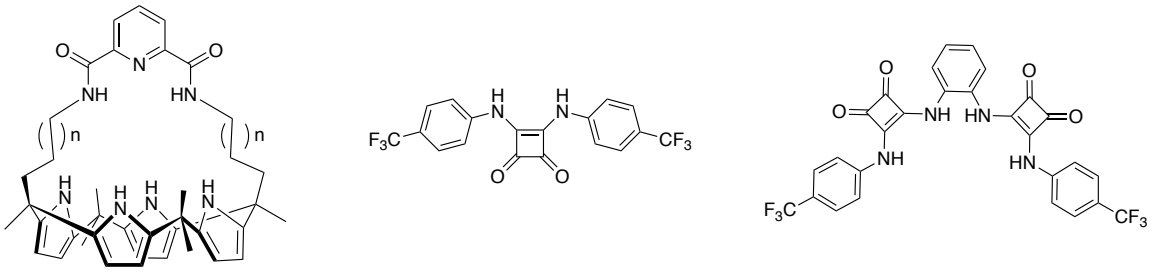
Not only are ion pair receptor able to recognized various ions, they also show promise in recognizing amino acids and small molecules. Additionally, by incorporating chiral binding sites and modifying the scaffold, enantioselective receptors can be created. For example, the enantioselective recognition of N-protected amino acid derivatives was achieved by using acyclic thiourea receptors in 2001 by Kilburn group.[20]

In spite of the potential use in ion extraction, membrane transport and sensing, the number of ion pair receptors remains limited. There are several reasons for this. First, the molecular design of new ion pair receptors is challenging because the binding sites have to be in close proximity but not too close within the scaffold. Moreover, most reported systems are not easy to prepare. Furthermore, tracking various ions in the host is often an experimental challenge.

1.5 ION TRANSPORTER FOR ANTICANCER TREATMENT

Maintaining the ion homeostasis through transmembrane ion transporters and ion channels is vital for cells to survive. The disruption of ion homeostasis may influence proliferation, differentiation and eventually lead to apoptosis and cell death. For chloride anion, the extracellular concentration is 115 mM, which is much higher than the intracellular concentration (~6 mM) in healthy cells.[21] However, abnormal intracellular chloride anion concentration may lead to various diseases, such as cystic fibrosis, Dent's disease, etc.[22-23] In these diseased cells, chloride anion concentration is usually higher. Typically, this is due to the functional failures in ion channels.

In 2014, our group and collaborators reported a strapped calixpyrrole system (**1.5** – **1.6**) that could function as a Na^+/Cl^- cotransporter and induce apoptosis in cancer cells.[24] Later on, several squaramide derivatives (**1.7** – **1.8**) were reported to also have an ability to mediate autophagy by promoting chloride transport.[25]



1.5 n = 1
1.6 n = 2

1.7

1.8

Figure 1.4 Structures of **1.5** – **1.8**

While those simple ion receptors exhibit good binding properties, ion pair receptors are still needed. If both cation and anion binding could be enhanced, it might be possible to create synthetic ion transporters capable of carrying Na^+ and Cl^- together. Presumably, this would promote chloride transport and increase the intracellular Cl^- concentrations by taking advantage of the Na^+ gradient. This could allow for the preparation of improved drug leads.

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Chapter 2: Pyrene-appended calix[4]pyrroles for explosives and ion detection

2.1 INTRODUCTION

The demand for rapid, less expensive, and sensitive detection of aromatic explosives is increasing for the simple reason that explosives have deleterious effects on human health and the environment while providing a risk for global security.[1] Current sensing methodologies for detecting trace explosives include ion mobility spectrometry (IMS), canine teams and X-ray dispersion. However, these methodologies are time-consuming and require bulky and expensive instruments.[2] In contrast, fluorescence-based detection offers several advantages such as faster detection, real-time monitoring and high sensitivity.[3] Small molecules as well as polymers have been developed for explosives detection.

Calix[4]pyrrole was first synthesized by Baeyer in 1886.[4] After a century, it was discovered to selectively bind halide anions by the Sessler group.[5] Calix[4]pyrroles have four conformations as shown in Figure 2.1.[6] X-ray crystallographic analysis reveals that after anion binding, it changes its conformation from 1,3-alternate to cone conformation to facilitate the hydrogen bonding between the NH protons and anions. Based on this feature, it would be reasonable to assume that electron deficient substrates, such as those bearing nitro groups, can also form hydrogen bonds with the four NH protons.

Pyrene is a sensitive fluorescent dye. When a pyrene molecule in ground state is brought close with an excited-state pyrene moiety, an excimer is formed. The emission of an excimer is shifted from 375 nm (for the monomer) to 475 nm which two bands appear on the fluorescence spectrum.[7] This unique property has led to the wide use of pyrene in sensing ions and small molecules.[8]

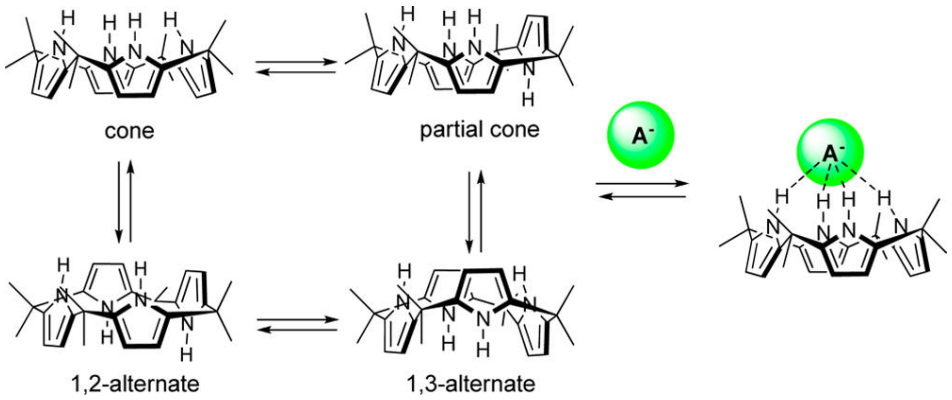
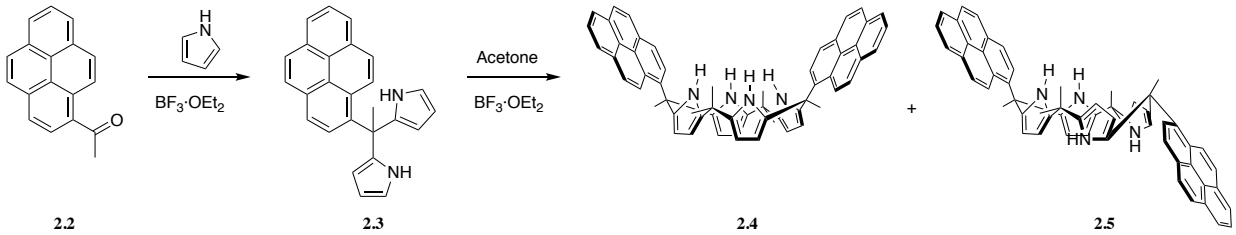


Figure 2.1 Four conformations of calix[4]pyrrole. The cone conformation dominates upon anion binding. Aadapted with permission from ref 6. Copyright 2014 American Chemical Society.

The goal of this chapter is to develop novel fluorescent-based sensors by incorporating two pyrene moieties onto calix[4]pyrrole. By donor-acceptor interaction between pyrene and aromatic explosives, the fluorescence of pyrene is expected to be quenched and high binding affinity may be achieved because of the hydrogen bonding between NH protons and nitro groups.

2.2 RESULTS AND DISCUSSION

The syntheses of **2.4** and **2.5** are shown in Scheme 2.1. Acid-catalyzed condensation of pyrrole and 1-acetopyrene **2.2** gave the corresponding dipyrromethane derivative **2.3** with 82% yield. Precursor **2.3** was further reacted with acetone in the presence of $BF_3 \cdot OEt_2$. This generated the cis-form pyrene-calix[4]pyrrole **2.4** and the trans-form pyrene-calix[4]pyrrole **2.5**, which could be purified by column chromatography (18% yield). Receptors **2.4** and **2.5** were characterized by standard spectroscopy means and single crystal X-ray diffraction analysis.



Scheme 2.1 Synthetic route of **2.4** and **2.5**

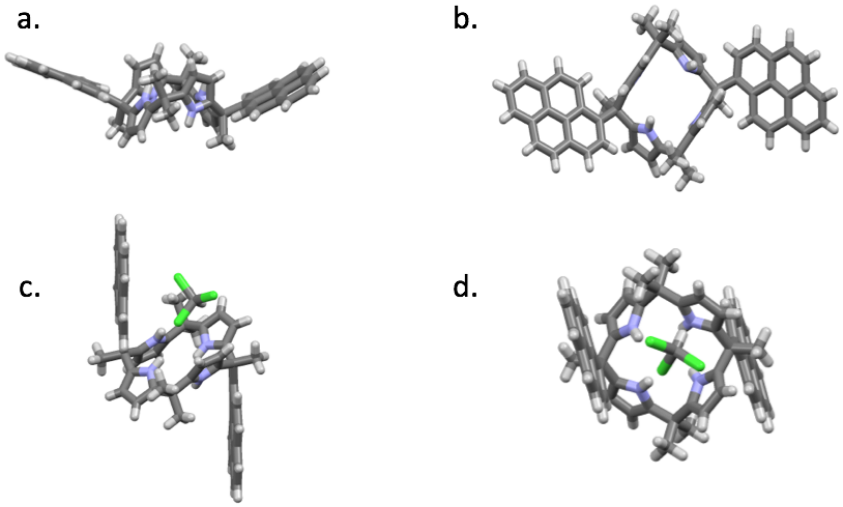


Figure 2.2 Crystal structures of **2.4** (a. side view, b. top view) and **2.5** (c. side view, d. top view).

The crystals were obtained by subjecting **2.4** and **2.5** in guest-free form to slow evaporation from chloroform. The resulting structure revealed that, in solid state, **2.4** adopts 1,3-alternate conformation (Figure 2.2 a) as expected while **2.5** is in 1,2-alternate conformation with two chloroform molecules bound to the pyrrolic NH protons (Figure 2.2 b). In the crystal structure of **2.4**, the distance between two pyrene units is about 3.68 Å, confirming the intermolecular π-π interaction between the two pyrene moieties. Similar intermolecular π-π interactions (d = 4.02 Å) was also observed in the crystal of **2.5**.

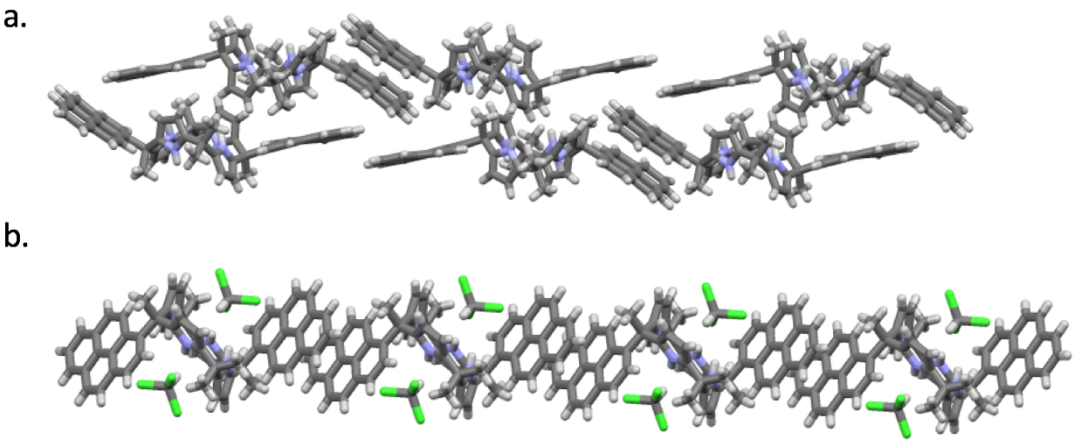


Figure 2.3 Packing mode of **2.4** (a) and **2.5** (b).

Prior to testing whether the receptors **2.4** and **2.5** could be used to detect nitroaromatic targets, a UV-vis study was conducted to determine whether self-aggregation existed. A series solutions of **2.4** and **2.5** in chloroform were made up at various concentrations ranging from 10^{-4} to 10^{-6} M. The relationship between concentration and absorbance at different wavelengths served to confirm that no appreciable self-aggregation was occurring at low concentration (Figures 4.1 and 4.2).

The interaction between pyrene to TNB were then carried out by means of spectroscopic titrations in chloroform. However, no significant fluorescence quenching was observed (Figure 4.5). Fluorescence spectral titration involving different guests were then carried out. Both aromatic explosives and anions were tested. Compound **2.4** displays both monomer and excimer emissions when irradiated at 345 nm in chloroform as illustrated in Figure 2.4. These emission features were quenched after adding TNB. This fluorescence intensity quenching is ascribed to the charge-transfer between two pyrene moieties (donor) and one TNB molecule (acceptor). A Job plot reveals a 2:1 binding mode. After fitting, K_{11} and K_{21} were calculated to be 770 M^{-1} and 6.10×10^{7} M^{-1}

respectively. The monomer is not quenched as efficiently as the excimer band, which may be explained from the solid-state structure that revealed that only one of the two pyrenes within a given molecule benefits from π-π interactions with another molecule.

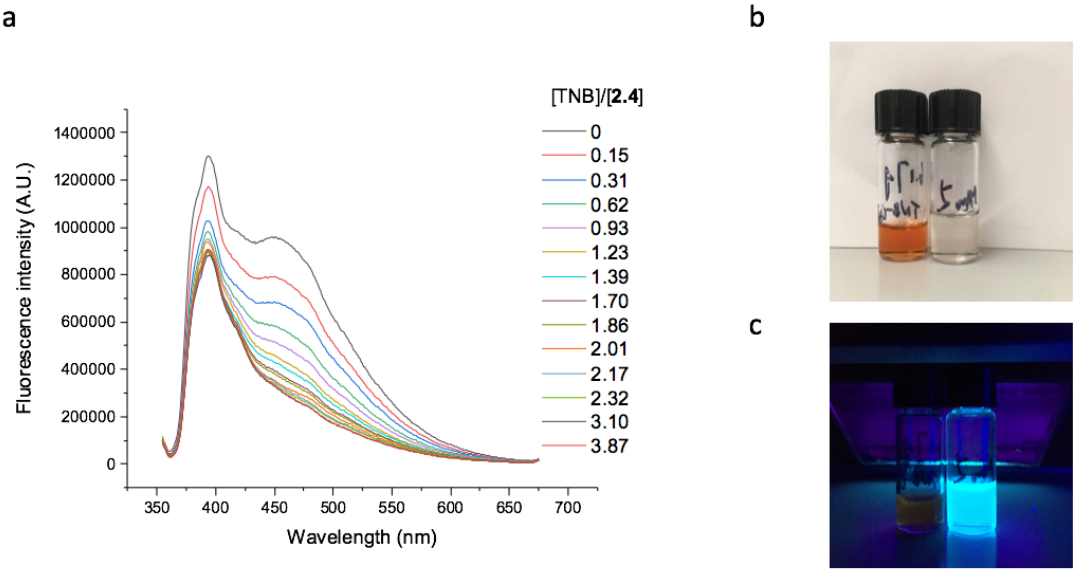


Figure 2.4 (a) Fluorescence spectral quenching seen upon subjecting a 5 μM solution of **2.4** in chloroform to titration with increasing quantities of TNB, λ_{ex} = 345 nm. (b) visual changes seen upon adding TNB to this same solution (c) fluorescent changes upon adding TNB to this initial solution. Left: **2.4** + TNB (10 equiv.). Right: **2.4** (5 mM in chloroform).

Fortunately, the crystal of **2.4** • TNB complex (Figure 2.5) was obtained by subjecting a solution of **2.4** in a mixture of chloroform and methanol containing 5 equiv amount of TNB to slow evaporation from chloroform and methanol mixture. The crystal structure reveals a 2:1 binding mode, confirming donor-acceptor interactions between the host and guest. Receptor **2.4** also exhibited dramatic fluorescence quenching upon the addition of TBAF. The binding constant for TBAF was determined to be 6×10^5 M^{-1}.

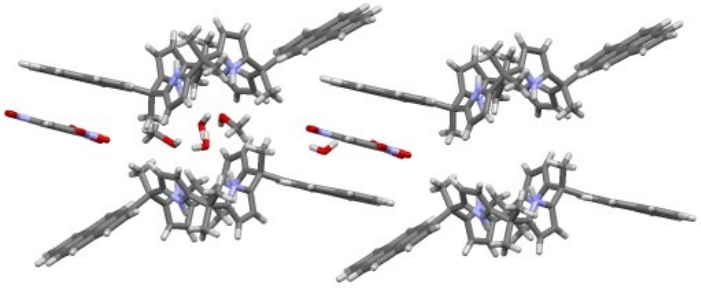


Figure 2.5 Crystal structure of **2.4** and TNB complex

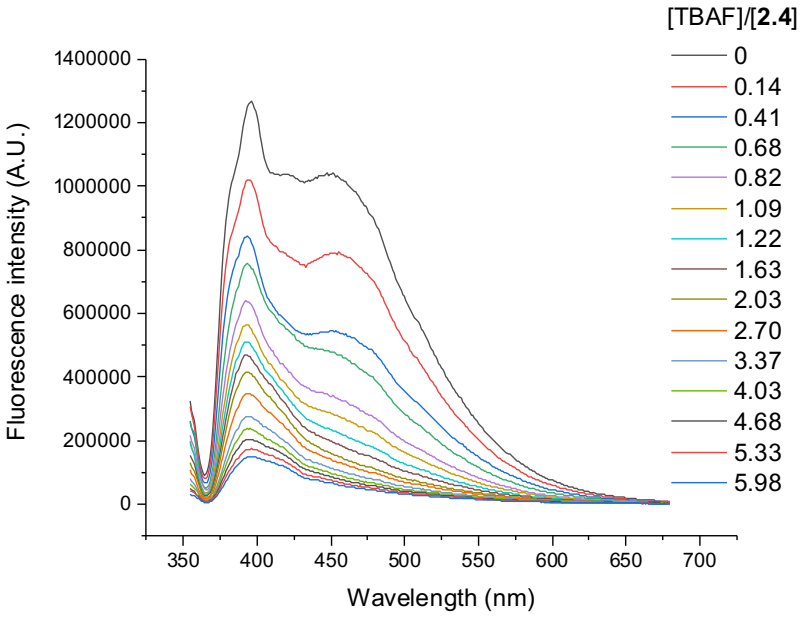


Figure 2.6 Fluorescence quenching upon subjecting a 5 μM solution of **2.4** in chloroform to titration with increasing quantities of TBAF, λ_{ex} = 345 nm

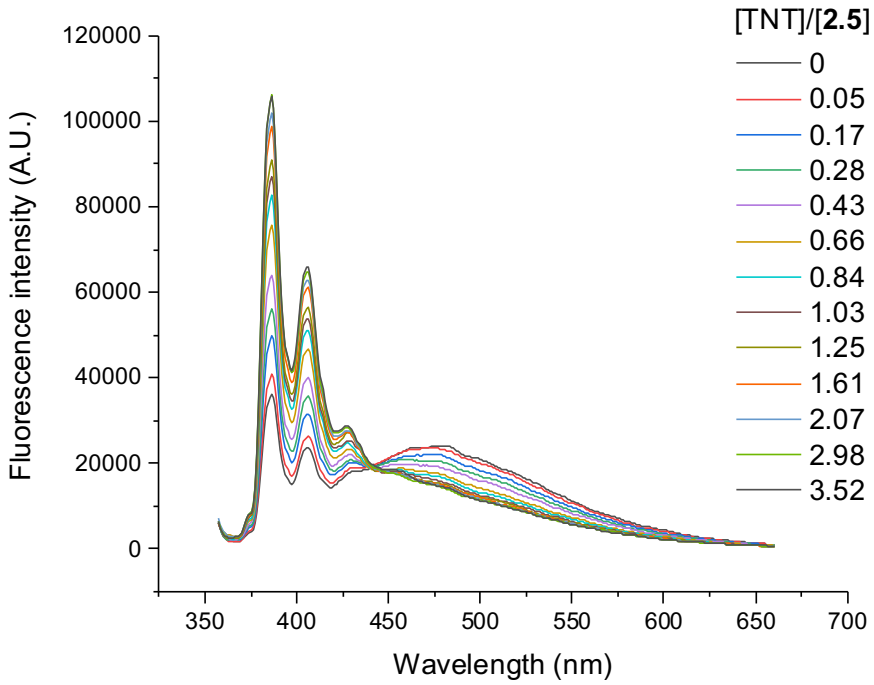


Figure 2.7 Fluorescence spectra of **2.5** (0.46 μM) in chloroform seen upon titration with TNT titration. λ_{ex} = 347 nm

Interestingly, receptor **2.5** in dichloromethane did not show significant fluorescence quenching with TNB titration (Figures 4.3 and 4.4). However, upon addition of TNT, the excimer band of **2.5** decreased while the monomer band increased. The Job plot reveals a 1:1 binding (Figure 4.7). The binding constant as determined by BindFit™ to be $1.5 \times 10^7\ M^{-1}$. Upon exposure to TBAF, the excimer emission of **2.5** in chloroform undergoes a red-shift from 485 nm to 535 nm upon binding with TBAF (Figure 2.8). The binding constant was determined to be $4 \times 10^4\ M^{-1}$.

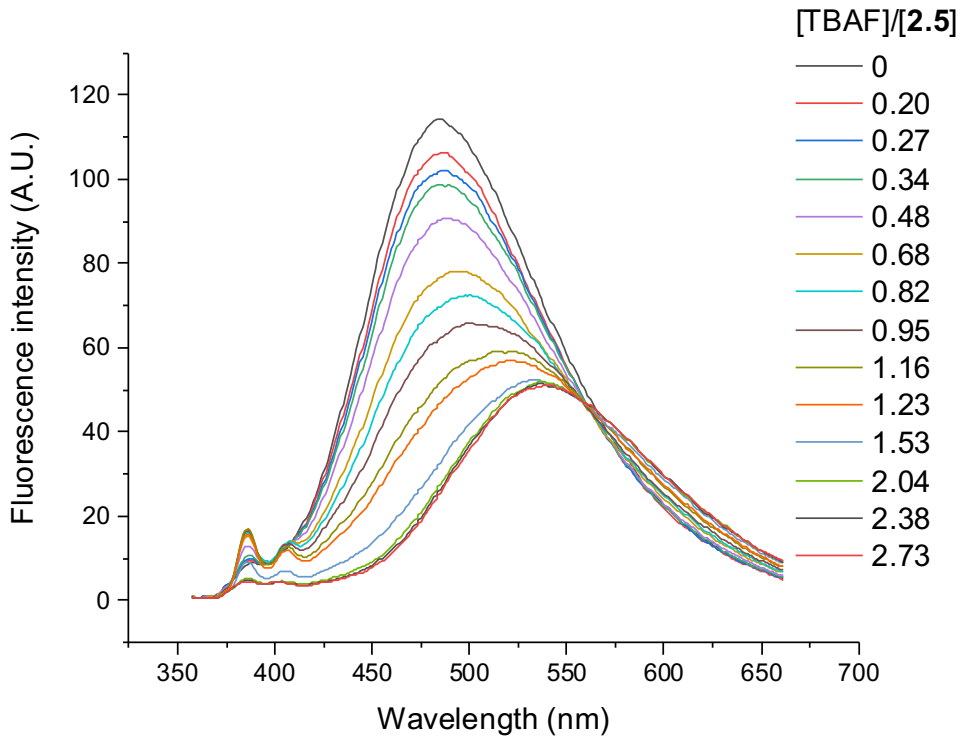


Figure 2.8 Fluorescence spectra of **2.5** (0.46 μM) with TBAF titration in dichloromethane. λ_{ex} = 347 nm

2.3 Conclusion and Future Directions

Based on calix[4]pyrrole, two novel fluorescent-based chemosensors, **2.4** and **2.5**, have been synthesized and studied for the detection of aromatic explosives and anions. The X-ray structure of the complex **2.4** • TNB reveals a 2:1 binding mode. It also serves to confirm a donor-acceptor interaction between the host and guest. Furthermore, preliminary fluorescence spectral titrations reveal that receptor **2.4** has a high affinity for the anion F^- ($K_a \sim 10^6$ M^{-1}) as TBAF and TNB (K_{11} = 770 M^{-1}, $K_{21} = 6 \times 10^7$ M^{-1}). The changes in the fluorescence spectrum and the visual color change from colorless to red

are ascribed to a charge transfer effect and change in the π-π interactions between the guest and the two pyrene units. Receptor **2.5** has a high affinity for TNT ($K_a \sim 10^7$ M^{-1}) and F^- ($K_a \sim 10^4$ M^{-1}) as TBAF. Further binding studies, including those involving NMR spectroscopy and fluorescence titrations, will be performed using **2.4** and **2.5**. Density functional theory (DFT) calculations are also planned to support the proposed charge-transfer mechanism.

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Chapter 3: New Calix[4]arene strapped calix[4]pyrrole derivatives

3.1 INTRODUCTION

To improve chloride transport and implement a higher-level control over ion recognition, ion pair receptors, bearing both cation and anion binding sites, may display higher affinity and/or better selectivity over simple ion receptors.[1] A synthetic ion transporter which can carry Na^+ and Cl^- together would be able to take advantage of the Na^+ gradient and increase the intracellular Cl^- concentration.

Calix[4]pyrroles **3.1** are known as efficient anion receptors.[2] Strapped calix[4]pyrroles have been synthesized and reported to transport Cl^- for almost two decades.[1, 3] Derivatives of calix[4]arenes can serve as cation binding sites with different functional groups. For instance, the tetraester form of calix[4]arene **3.2** has high affinity toward sodium ion. As Beer group reported in 1997, receptor **3.3** displayed a high selectivity for the potassium ion.[4] By introducing functionalized calix[4]arenes as cation binding sites, new ion pair receptors **3.4** and **3.5** were designed. These systems were expected to be selective for potassium salts and sodium salts respectively.

The goal of this chapter is to develop new ion pair receptors and evaluate their ability to bind various ions, as well as small molecules, such as amino acids. In this respect, the author designed two new receptors **3.4** and **3.5** (Figure 3.1) that were expected to be selective for sodium and potassium salts and function as Na^+/ Cl^- and K^+/ Cl^- co-transporters, respectively.

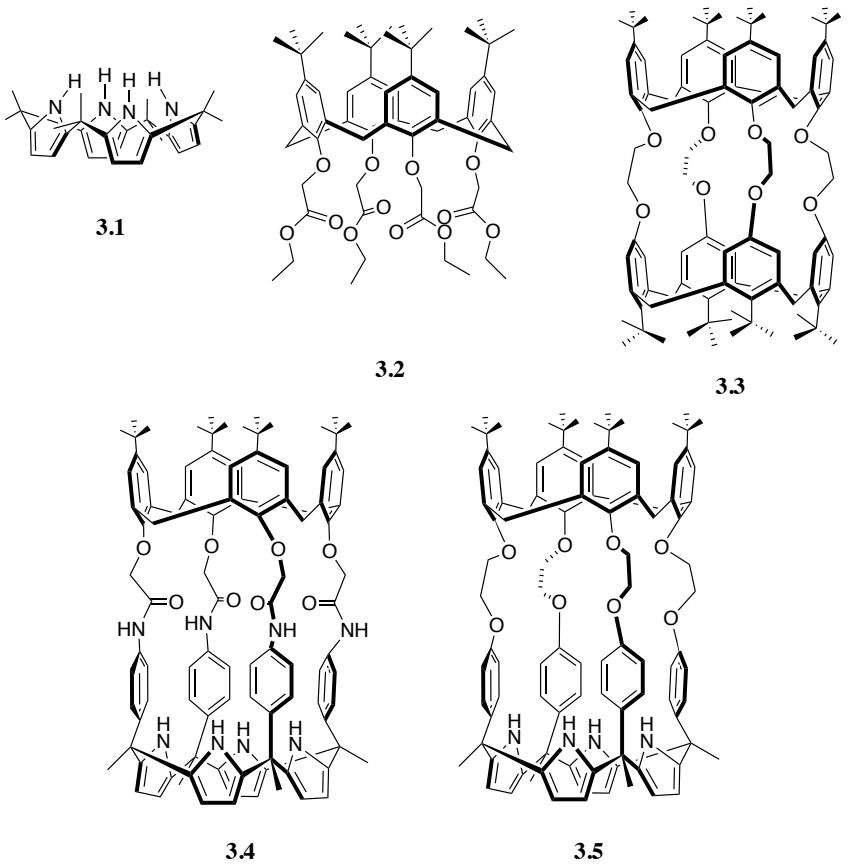
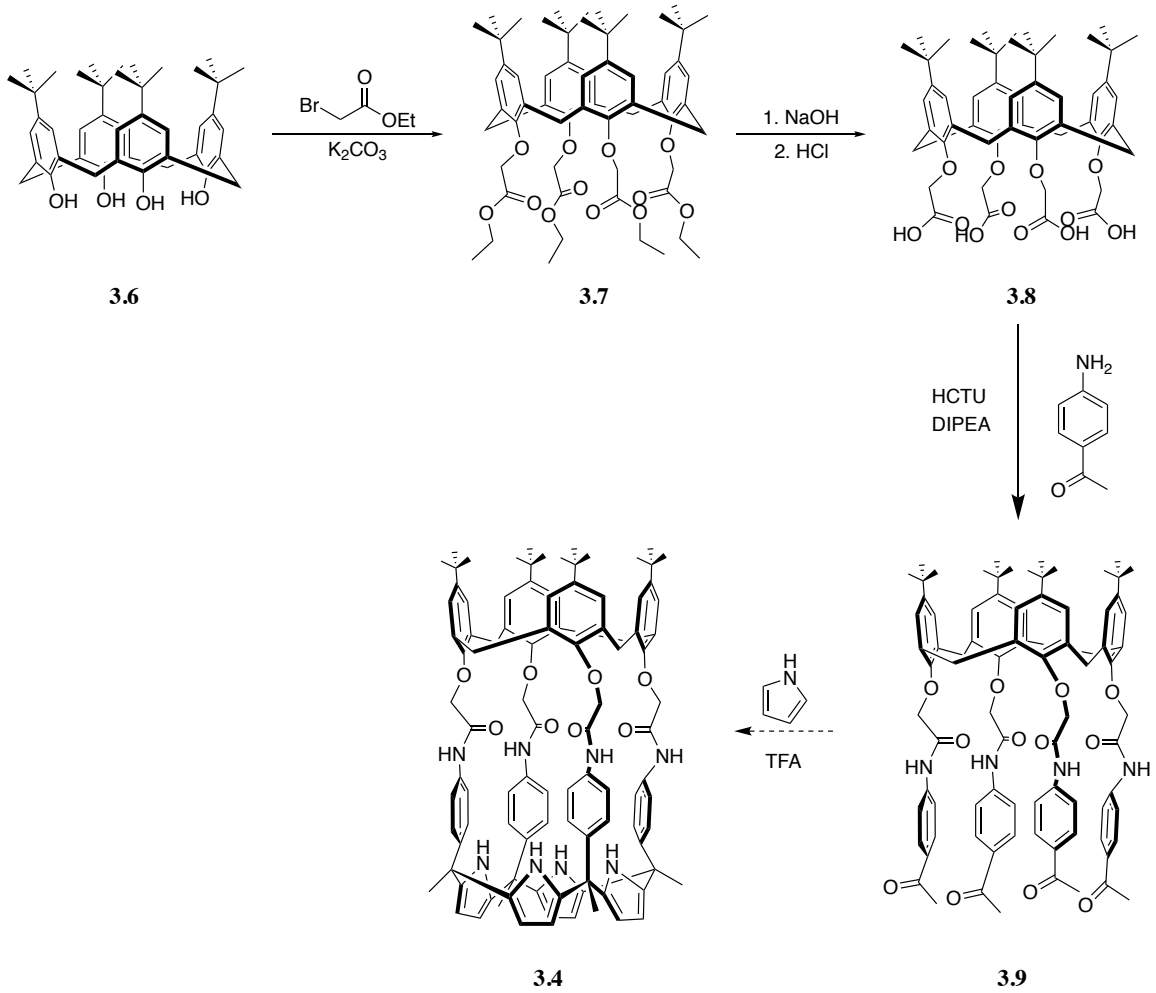


Figure 3.1 Structures of **3.1** - **3.5**

3.2 RESULTS AND DISCUSSION

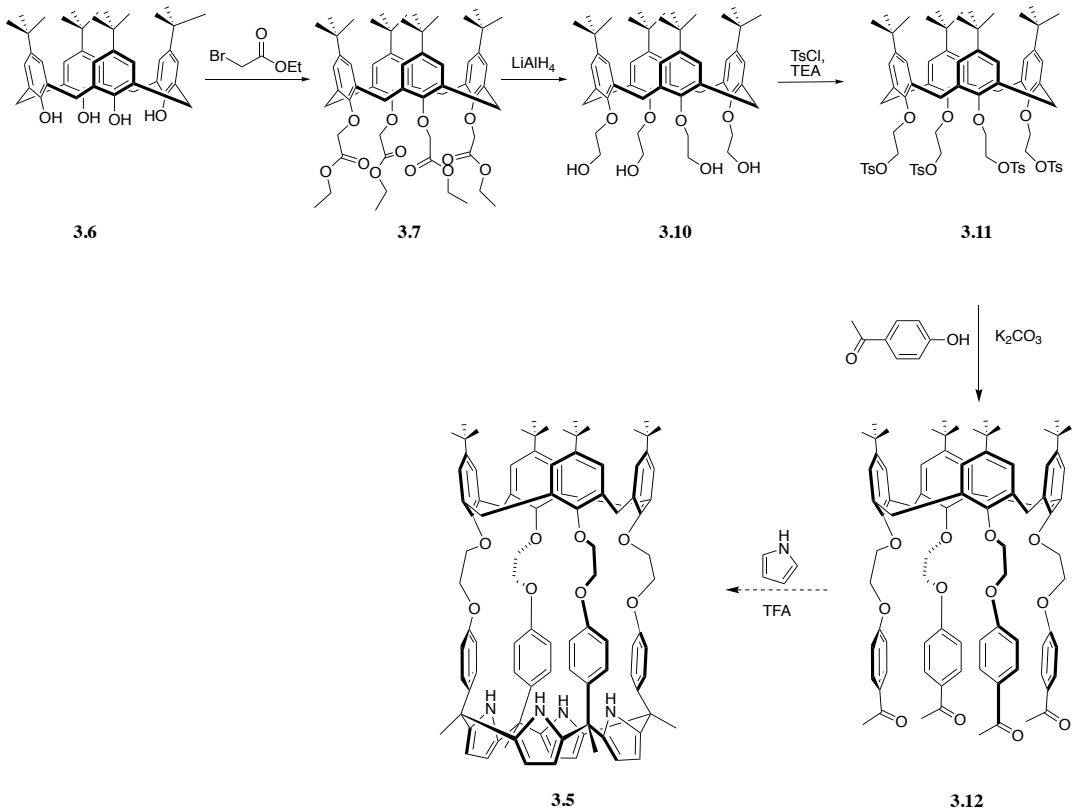
The synthesis of **3.5** is outlined in Scheme 3.1. First, the *p-tert*-butylcalix[4]arene **3.6** was reacted with bromoethylethatate and potassium carbonate to give the calix[4]arene tetraester **3.7** in 65% yield. Then, this latter calix[4]arene tetraester was hydrolyzed with NaOH in a mixed THF/H_2O medium and gave the calix[4]arene tetracarboxylic acid **3.8** as white powder in 87% yield. Next, **3.8** was reacted with 4'-aminoacetophenone using HCTU as the coupling reagent in the presence of excess DIPEA at room temperature. This gave the tetraketone **3.9** in 31% yield. After an acid-catalyzed condensation with pyrrole in CH_2Cl_2/acetonitrile over the course of three days,

the pseudo dimer **3.4** was expected to be obtained. Unfortunately, the key amidation reaction encountered challenges. Several reaction temperatures and coupling reagents were tried, but only low yields were obtained. Purification is also challenging since the four amide groups make **3.9** less soluble in organic solvents. Whereas **3.4** could be detected by LC-MS, purification via column chromatography and preparative TLC failed to give any isolated product.



Scheme 3.1 Proposed synthetic route leading to **3.4**

The synthesis of **3.5** is outlined in Scheme 3.2. The first step involves converting the calix[4]arene to the calix[4]arene tetraester. This tetraester was then reduced to give the calix[4]arene derivative **3.10** in 89% by treating with $LiAlH_4$ in diethylether followed acidic work-up. Compound **3.10** was reacted with TsCl to give **3.11** in 76% yield. The calix[4]arene tetratosylate was treated with excess 4'-hydroxyacetophenone in acetonitrile under reflux. This gave the tetraketone **3.12** in 70% yield. This precursor was treated with pyrrole in the presence of catalytic amount of $BF_3{\cdot}OEt_2$. This reaction failed to afford **3.5**. The author also tried to react the calix[4]arene tetratosylate with tetraphenol substituted calix[4]pyrrole. Unfortunately, this failed to give any final product, presumably reflecting the steric hindrance of the tosyl group.



Scheme 3.2 Proposed synthesis of **3.5**

3.3 FUTURE DIRECTION

The synthesis of neither **3.4** nor **3.5** was successful. If obtained, these systems will be studied as ion pair receptors by NMR spectroscopy.

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Chapter 4: Experimental Procedures

4.1 General Procedures

All chemicals and solvents were purchased from commercial sources (Arcros, Sigma Aldrich, TCI America, Fisher Sci. etc.) and used without further purification. Sorbent Technologies silica gel (200 μm, glass backed) sheets were used for thin layer chromatography (TLC) analyses. Preparative TLC was performed on silica gel (1000 μm, glass backed). Column chromatography was performed on Sorbent silica gel (40-63 μm). Nuclear magnetic resonance (NMR) spectra were recorded using a Varain 400/54/ASW spectrometers. All deuterated solvents were purchased from Cambridge Isotope Labrotories and Aldrich Chemical Co and used as received. Chemical shifts are reported in units of δ (ppm) and reference to the residual solvent and internal standard signals ($CDCl_3$: 7.26 ppm, $(CD_3)_2SO$: 2.50 ppm, D_2O: 4.79 ppm. UV-Vis spectroscopy was measured on a Shimadzu instrument and Agilent Cary 60 UV-Vis spectrophotometer. Fluorescence spectroscopic measurements were carried out using Photon Technology International and Agilent Cary Eclipse fluorescence spectrofluorimeter.

X-ray crystallographic data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα raduation source (λ = 1.5418 Å) with collimating mirror monochromators or a Rigaku AFC12 diffractometer with a Saturn 724+ CCD. Structures were solved by Dr. Qing He.

4.2 Synthetic Procedures and Characterization

Synthesis of **2.3**: 1-Acetylpyrene (2.46 g, 10 mmol) and pyrrole (15 mL, excess) were dissolved in ethanol (30 mL). Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) (46.5%, 1.5 mL) was added to the mixture dropwise and stirred overnight at room temperature (r.t.). Excess triethylamine was added to quench the reaction. After removing the solvent

in vacuo, the mixture was dissolved in dichloromethane and washed with NH_4Cl (aq.) twice (2 × 100 mL) and brine (2 × 100 mL). The organic phase was separated off and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: dichloromethane/hexanes = 1/2, v/v) to afford a white solid (2.95 g, 82% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-7.85 (m, 8H, Ar*H* (pyrene)), 7.47-7.45 (d, *J* = 8 Hz, 1H), 6.70-6.68 (m, 2H, Ar*H* (pyrrole)), 6.28-6.26 (m, 2H, Ar*H* (pyrrole)), 6.20-6.18 (m, 2H Ar*H* (pyrrole)), 2.42 (s, 3H, C*H*$_3$).

Synthesis of **2.4** and **2.5**: $BF_3{\cdot}OEt_2$ (46.5%, 1 mL) was added dropwise to a solution of **2.3** (1g, 2.8 mmol) in acetone (300 mL) at r.t. The reaction mixture was stirred for 24 hours at r.t. Then, excess triethylamine was added to quench the reaction. After removing the solvent under reduced pressure, the mixture was dissolved in DCM and washed with brine (2 × 100 mL). The organic phase was separated off and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: DCM/hexanes = 1/4, v/v) to obtain **2.5** (first fraction) and then **2.4** (second fraction) as white solids in 18% yield. **2.4** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-7.82 (m, 16H, Ar*H* (pyrene)), 7.17-7.15 (d, *J* = 8.2Hz, 2H, Ar*H* (pyrene), 5.99 (m, 2H, Ar*H* (pyrrole)), 5.91 (m, 2H Ar*H* (pyrrole)), 2.27 (s, 3H, C*H*$_3$), 1.83 (s, 3H, C*H*$_3$), 1.62 (s, 3H, C*H*$_3$).

2.5 ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-7.80 (m, 16H, Ar*H* (pyrene)), 7.41-7.39 (d, *J* = 8.3Hz, 2H, Ar*H* (pyrene)), 7.35 (br, 4H, N*H* (pyrrole)), 5.92-5.88 (m, 8H Ar*H* (pyrrole)), 2.27 (s, 6H, C*H*$_3$), 2.17 (s, 12H, C*H*$_3$).

Synthesis of **3.7**: To a suspension containing 900 mg tetrahydroxylcalix[4]arene **3.6** (1.4 mmol) and 1.6 g K_2CO_3 in acetone, 8 mL of bromoethylacetate (caution: this is a

very irritating reagent) was added with syringe. The reaction was stirred for 24 hours under reflux. After the reaction was deemed complete, the solvent was removed under reduced pressure. The mixture was washed with 1 N HCl (2 × 100 mL) and brine (2 × 100 mL) and the organic layer was separated off and collected. The solvent was removed from the organic phase under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: ethyl ehatate/hexanes = 1/5, v/v) to give a white solid (**3.7**) in 65% yield.

Synthesis of **3.8**: To a solution containing 1 g of **3.7** (1.0 mmol) in THF, 40 mL of 1M NaOH (aq.) was added. The reaction was stirred for 5 hours at 50 °C. The reaction was quenched by adding 6N HCl (aq.) until no precipitate was formed. The white solid after filtration was determined to be **3.8** in 87% yield.

Synthesis of **3.9**: To a mixture containing 881 mg of **3.8** (1.0 mmol) and 900 mg of 4'-aminoacetophenone (6.7 mmol) in DMF, were added 1.2 g HCTU and 5 mL DIPEA. The reaction was stirred for 3 days at room temperature. DMF was removed under reduced pressure. The mixture was dissolved in DCM and washed with 1 N HCl (2 × 50 mL) and brine (2 × 100 mL) and the organic layer was separated off and collected. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: methanol/dichloromethane = 1/10, v/v) to give a white solid (**3.9**) in 31% yield.

Synthesis of **3.10**: To a cool diethyl ether suspension containing 900 mg $LiAlH_4$ (23.7 mmol), 2.5 g of **3.7** (2.5 mmol) dissolved in diethyl ether was added dropwise. After stirring for 4 hours at r.t., the reaction was quenched with small amount of water and 60 mL 3N HCl (aq.). After separating the organic phase and removing the solvent, the crude material was subjected to ethanol for recrystallization to give white needles (**3.9**) in 89% yield.

Synthesis of **3.11**: To a solution containing 1.5 g of **3.9** (1.8 mmol) in dry DCM, 3 g TsCl (15.8 mmol) and 6 mL dry TEA were added. The mixture was stirred at r.t for 2 days. After the reaction was deemed complete, 50 mL 1N HCl (aq.) was added. The mixture was washed by brine (2 × 100 mL) and the organic layer was separated off and collected. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: ethyl acetate/hexanes = 1/4, v/v) to give a white solid (**3.11**) in 76% yield.

Synthesis of **3.12**: To a solution of 2.6 g **3.11** (1.8 mmol) and 2 g 4'-hydroxyacetophenone (14.8 mmol) mixture in acetonitrile, 5.1 g of solid K_2CO_3 was added. The reaction was stirred for 2 days under reflux. After the reaction was deemed complete, the excess K_2CO_3 was filtered off. The solvent was removed under reduced pressure. The mixture was washed with 1 N HCl (2 × 100 mL) and brine (2 × 100 mL) and the organic layer was separated off and collected. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography over silica gel (eluent: ethyl acetate/hexanes = 1/2, v/v) to give a white solid (**3.12)** in 70% yield.

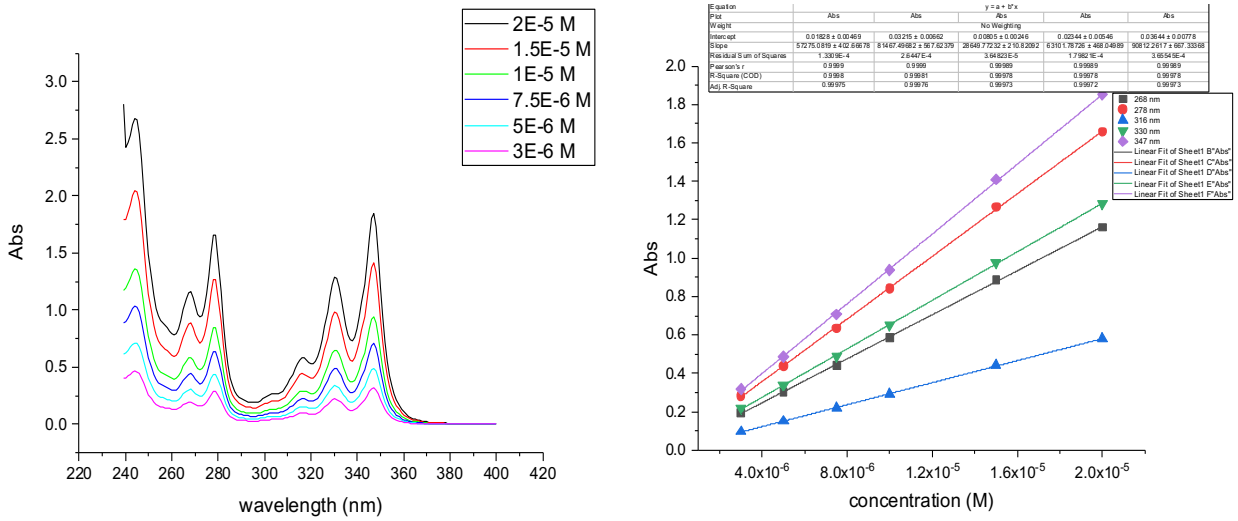

Figure 4.1 Left: UV-Vis spectra of **2.4** in chloroform recorded at 20 μ M, 15 μ M, 10 μ M, 7.5 μ M, 5 μ M, 3 μM. Right: Plots of absorption at 268 nm, 278 nm, 326 nm, 330 nm, and 347 nm vs concentraion.

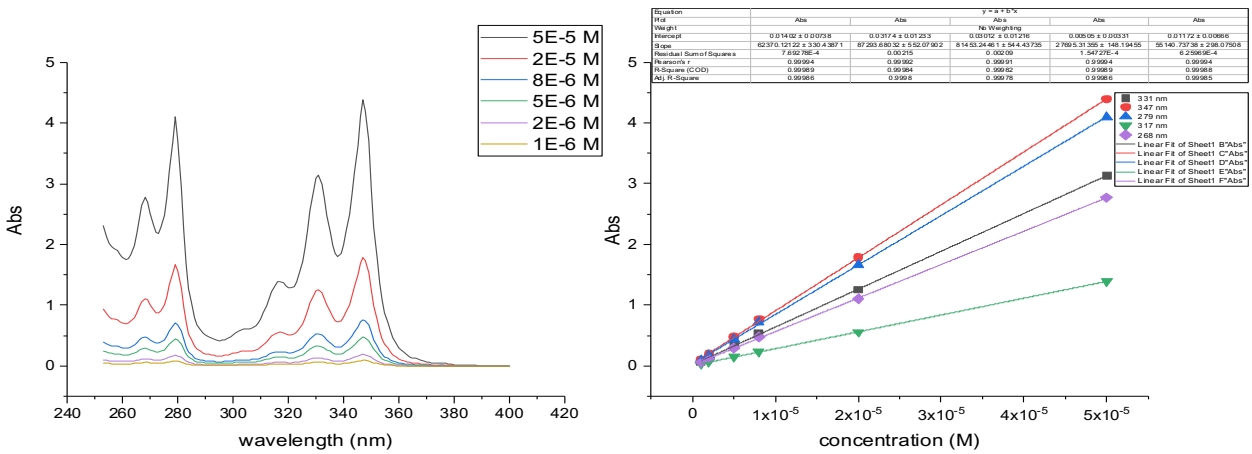

Figure 4.2 Left: UV-Vis spectra of **2.5** in chloroform recorded at 50 μ M, 20 μ M, 8 μ M, 5 μ M, 2 μ M, 1 μM. Right: Plots of absorption at 268 nm, 279 nm, 317 nm, 331 nm, and 347 nm vs concentration.

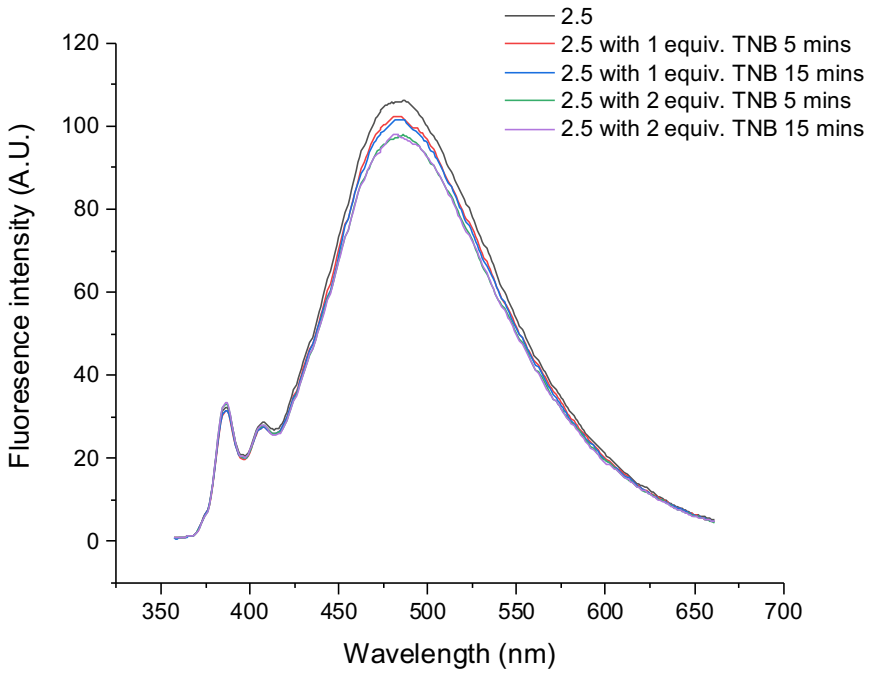

Figure 4.3 Change in the fluorescence spectral features of **2.5** (solvent: chloroform) seen in the presence of 1 and 2 equiv. TNB as a function of time.

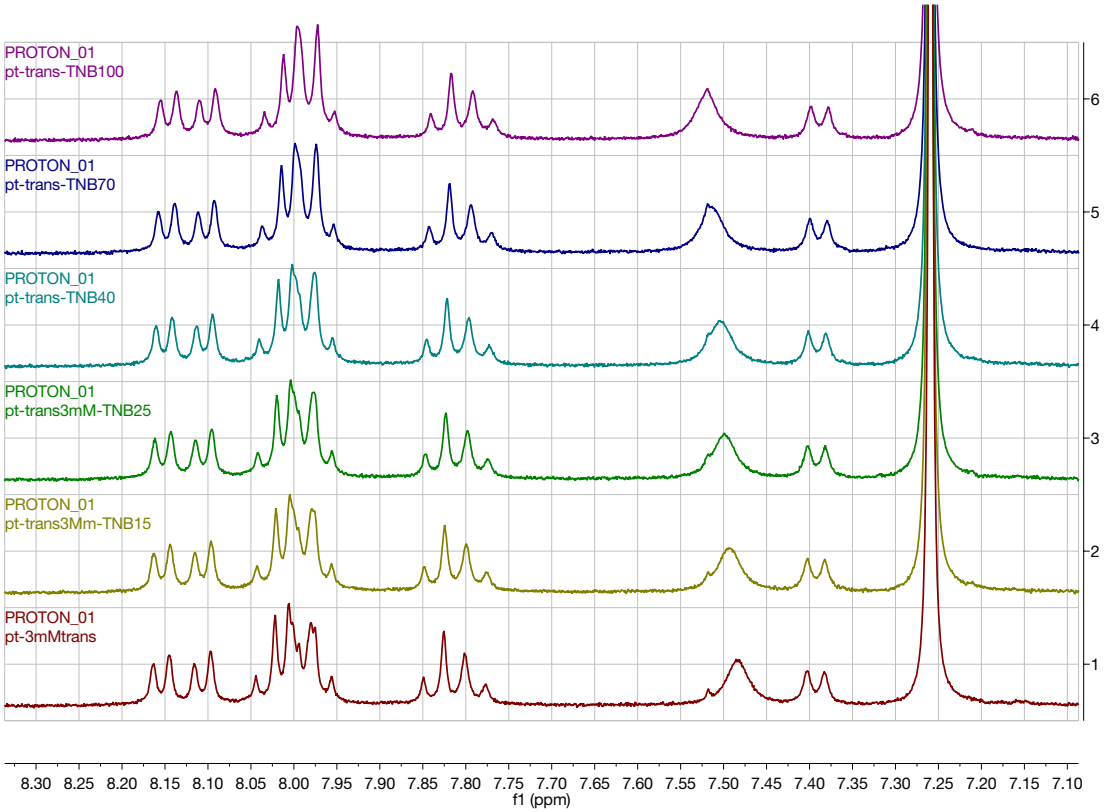

Figure 4.4 NMR spectral titration of **2.5** with TNB in $CDCl_3$

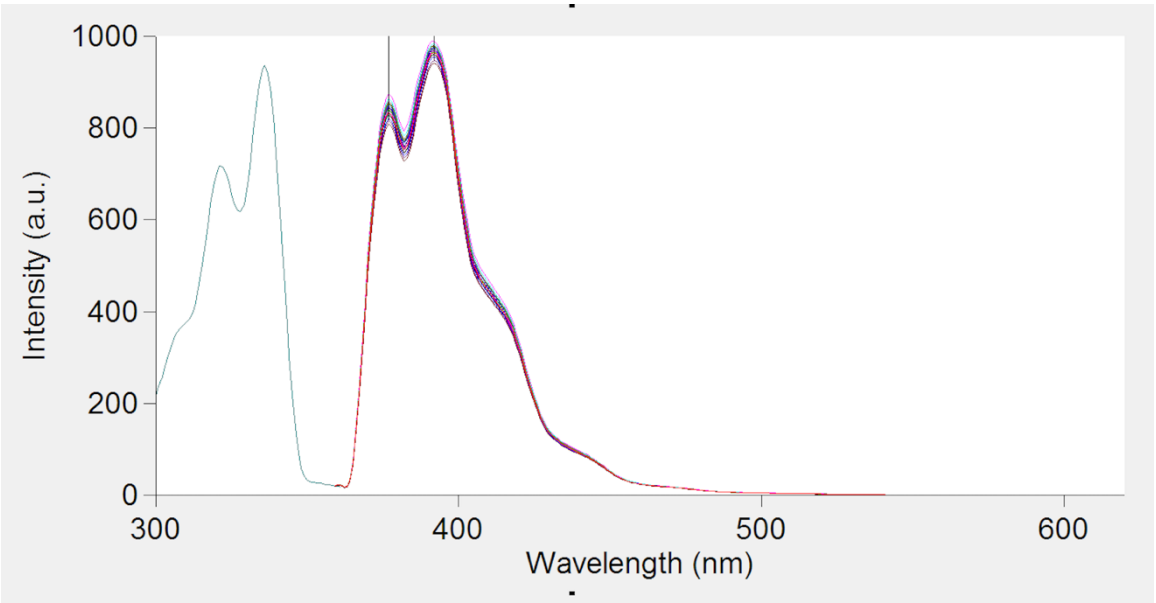

Figure 4.5 Fluorescence spectra of pyrene in chloroform recorded upon titration with TNB.

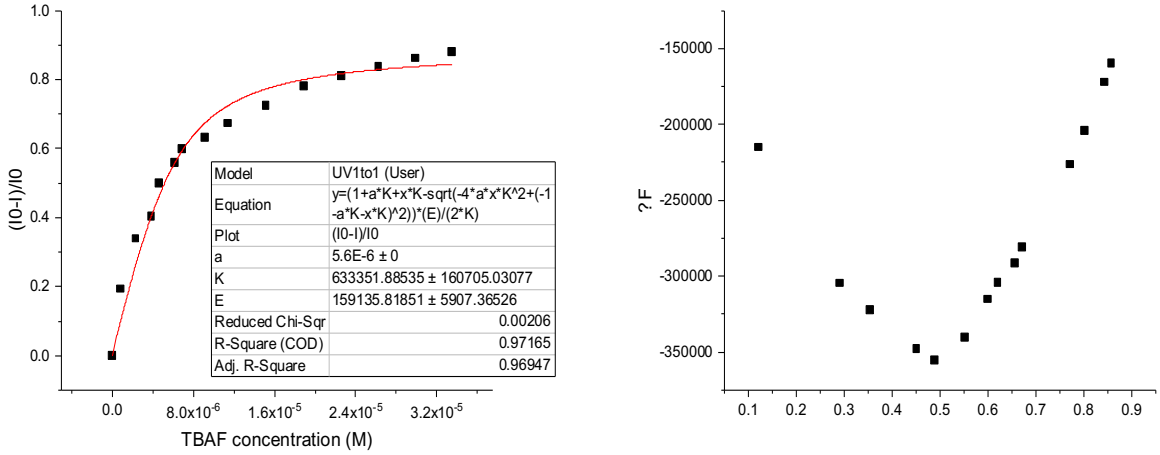

Figure 4.6 Left: Least-squares nonlinear fitting at 395 nm. Right: Job's plot of the complex of **2.4** and TBAF (solvent: chloroform).

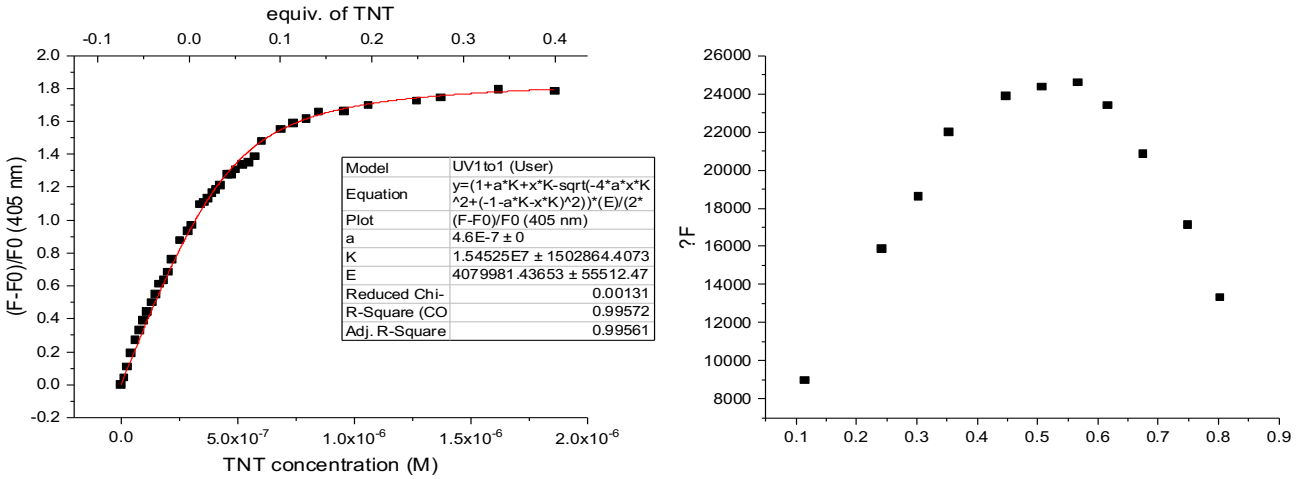

Figure 4.7 Left: Least-squares nonlinear fitting at 405 nm. Right: Job's plot of the complex of **2.5** and TNT (solvent: chloroform).

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CHAPTER 1

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