11-23-2005

Spectroscopic, electrochemical and mass spectrometric investigation of anion binding by tripodal molecular receptors

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DOI: 10.25148/etd.FI14061574

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SPECTROSCOPIC, ELECTROCHEMICAL AND MASS SPECTROMETRIC INVESTIGATION OF ANION BINDING BY TRIPODAL MOLECULAR RECEPTORS

A thesis submitted in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

in

CHEMISTRY

by

Richild Alecia Currie

2005

To: Interim Dean Mark Szuchman
College of Arts and Sciences

This thesis, written by Richild Alecia Currie, and entitled Spectroscopic, Electrochemical and Mass Spectrometric Investigation of Anion Binding by Tripodal Molecular Receptors, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this thesis and recommend that it be approved.

Kenneth G. Furton

Watson J. Lees

Konstantinos Kavallieratos, Major Professor

Date of Defense: November 23, 2005

The thesis of Richild Alecia Currie is approved.

Interim Dean Mark Szuchman
College of Arts and Sciences

Dean Douglas Wartzok
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Florida International University, 2005

ACKNOWLEDGMENTS

I would like to thank Dr. Konstantinos Kavallieratos for his continued support and assistance in the completion of this project. I would like to thank my committee members, Dr. Kenneth G. Furton and Dr. Watson J. Lees, for their support. I would like to thank Dr. Robert J. Alvarado for his assistance with the electrochemistry studies. I also would like to thank Mr. Myron Georgiadis for his assistance with the mass spectrometry part of this project.

I would like to thank Ms. Amanda Pau for her assistance with the NMR and fluorescence studies. I would also like to thank the other members of my research group, past and present, Dr. Ivy Sweeney, Michael Lago, Aileen Andreu, Patty Galarza, Patricia Nuñez, Pablo Valdes, Thalia Lopez, Gabrielle Berlinski, and Peta-Gaye Samuda.

I would also like to thank my parents, Anson and Joyce Currie, for their encouragement and support throughout my studies.

ABSTRACT OF THE THESIS

SPECTROSCOPIC, ELECTROCHEMICAL AND MASS SPECTROMETRIC

INVESTIGATION OF

ANION BINDING BY TRIPODAL MOLECULAR RECEPTORS

by

Richild Alecia Currie

Florida International University, 2005

Miami, Florida

Professor Konstantinos Kavallieratos, Major Professor

The synthesis and anion binding properties of a fluorescent tripodal *n*-dansylamide (**2**) and a redox active tripodal quinone-based (**3**) receptor derived from 1,3,5-tris-(aminomethyl)-2,4,6-triethylbenzene. Herein the investigation of anion binding by these receptors via ^{1}H-NMR, FT-IR, UV-Visible, and (APCI-MS) is reported. Fluorescence and electrochemical studies determined the ability of these receptors to sense anions. The downfield chemical shift changes in the ^{1}H-NMR spectra and the low energy shifts of the $\nu_{N\text{-}H}$ stretching frequency in the FT-IR spectra indicated anion binding via hydrogen bonding. The binding constants for anion-receptor complex formation were determined and indicate a preference of receptor **2** for the binding of nitrate over chloride, bromide and iodide, while receptor **3** was also found to be selective for binding nitrate over chloride. For receptor **2**, the 1:1 anion-receptor binding stoichiometry was confirmed by fluorescence Job plots and the 1:1 anion-receptor supramolecular complexes were identified by APCI-MS.

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LIST OF ABBREVIATIONS

APCI-MS	Atmospheric Pressure Chemical Ionization Mass Spectrometry
CV	Cyclic Voltammetry
Dansyl	N-(5-dimethylamino)-naphthalene sulfonyl
DCE	Dichloroethane
DCM	Dichloromethane
DNS	see dansyl
EtOAc	ethyl acetate
EtOH	ethanol
FT-IR	Fourier-Transform Infrared Spectroscopy
LOD	limit of detection
M	molarity (moles per liter)
mM	millimolar (1×10^{-3} moles/liter)
$(n\text{-Bu})_4NX$	tetrabutylammonium salts with $X = Cl^-$, Br^-, I^- or NO_3^-
nM	nanomolar (1×10^{-9} moles/liter)
NMR	Nuclear Magnetic Resonance Spectroscopy
OSWV	Osteryoung Square Wave Voltammetry
PVC	poly(vinyl chloride)
RBOE	Rhodamine B octadecylester perchlorate
SBS	polystyrene-*block*-polybutadiene-*block*-polystryrene polymer
TDMACl	tridodecylmethylammonium chloride
tren	tris(2-aminoethyl)amine

μL	microliter
UV-Vis	Ultraviolet Visible Spectroscopy

Specific Aims

The aims of the project described in this thesis are:

1) To synthesize tripodal sensors having pendant fluorophore and redox active groups that are sensitive and selective for nitrate.
2) To characterize the anion-binding and sensing properties of the receptors by ^{1}H-NMR, FT-IR, UV-Vis, fluorescence and electrochemical techniques.
3) To characterize the anion-receptor complexes formed by Atmospheric Pressure Chemical Ionization Mass Spectrometry (APCI-MS).

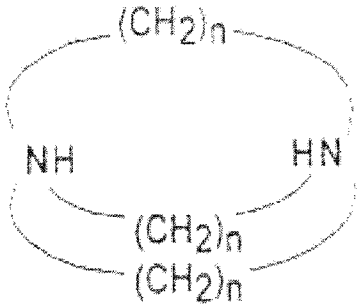
Chapter 1: Anion Recognition and Sensing: Principles and Historical Development

1.1 Introduction

Anions are important in a wide range of biological and chemical processes. In addition to their importance in the areas of medicine and catalysis, many environmental pollutants are anionic, such as phosphate, nitrate, and pertechnetate. The development of receptors for anions has been the focus of increasing attention over the past years. The design and synthesis of anion binding hosts has been relatively slow to develop, in contrast to the analogous chemistry of cation receptors due to a number of inherent difficulties associated with anion recognition.[1-3] Anions are more difficult to sense via electrostatic interactions than cations because of their lower charge to size ratio; the majority of neutral anion receptors thus utilize hydrogen bonding as the predominant binding force. Anions also have a wide range of geometries and require a high degree of complementarity in receptor design in order to achieve selectivity. In comparison to cations of similar size, anions have high free energies of solvation, and hence, anion hosts must compete more effectively with the surrounding medium. Anions are very strongly solvated, and the free energy gained upon binding must exceed the free energy lost as the result of anion dehydration. This can make binding in protic or hydroxylic solvents particularly challenging. Currently, there are two general classes of synthetic anion receptors: i) positively charged and ii) neutral. The major advantage of neutral hosts is that the absence of a positive charge generally provides for more selective binding for the simple reason that positive charges are non-directional and lead to electrostatic attractions that cannot by definition be selective for a particular anion. Another advantage of neutral

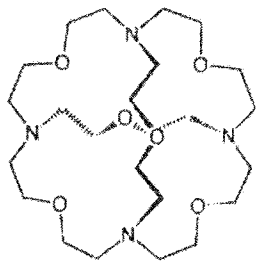
hosts is that there is no inherent competition with the receptor-associated counterion, which can often result in a weaker affinity for the intended guest.

The first report of designed anion hosts, the bicyclic *katapinands* (**1.1**), was published in 1968.[4] In 1975 the hypothesis that these materials encapsulated halide anions was confirmed by X-ray crystallography.



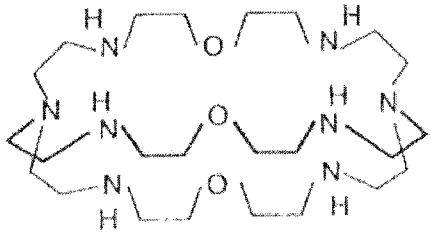
1.1 n = 7-10

However, progress in the field lagged until the mid-1970s, at which time a crystal structure appeared in which the chloride ion is encapsulated in a macrotricyclic ligand, which became known as the "soccer ball" ligand (**1.2**).[5]



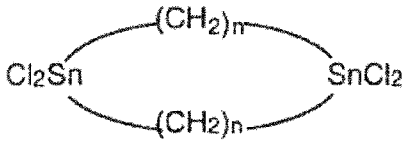
1.2

Lehn and co-workers reported the structures of four anion cryptates X^-·**BT**·$6H^+$ (**BT** = *bis*-tren, **1.3**), in which the structural complementarity between the hexaprotonated **BT**·$6H^+$ and, N_3^-, was linked to the high association constant for binding of *bis*-tren to this anion.[6]

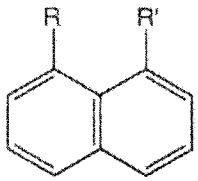


1.3

During the past decade a new class of neutral receptors such as compounds **1.4-1.6** were introduced; that contain Lewis acids as binding sites. The distannamacrobicycles **1.4** were shown to bind only one halide anion.[7] The class of boron-containing ligands **1.5** has been described by Beer et al. and anion complexation has been established.[8] Silicon has also been incorporated into macrocylic receptors. Compounds such as silacrown **1.6** have been shown to transport chloride and bromide anions from water to an organic phase.[9]

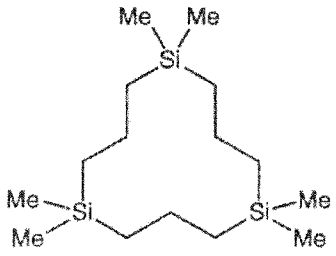


1.4



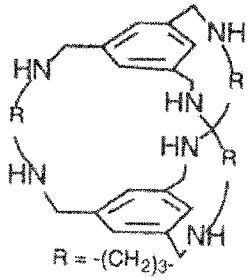
a) R = R' = BMe_2
b) R = R' = BCl_2
c) R = BMe_2, R' = $SiMe_3$

1.5

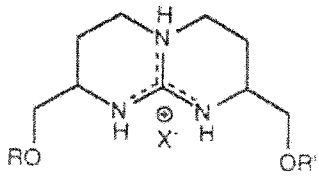


1.6

In 1986, a more elaborate and suitable receptor for the nitrate anion was reported (**1.7**). The X-ray analysis revealed that in the solid state the anion was not exactly located within the cavity of the receptor.[10]

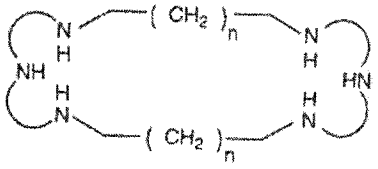


1.7

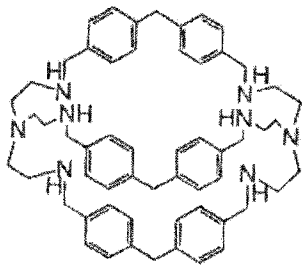


1.8

Guanidinium-containing receptors, such as **1.8**, based on rigid framework have been largely used for carboxylate complexation. Recognition of dicarboxylate anions was achieved using ditopic hexaazamacrocycles such as **1.9**.[11]



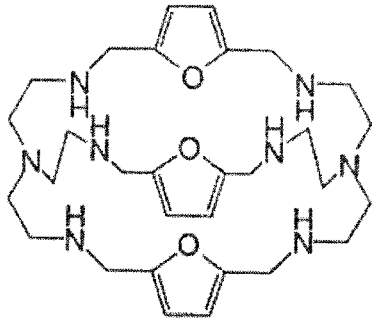
1.9



1.10

A more elaborate receptor, for dicarboxylate dianions, has been reported (**1.10**). The inclusion of the terephthalate dianion within the cavity of the protonated **1.10** in the solid state was established by X-ray crystallography.[11]

The structure of the complex of **1.11**-$6H^+$ with ClO_4^- was established by an X-ray study, which revealed that the anion was enclosed in the center of the ligand's cavity.[12]



1.11

The recognition of anions by synthetic receptor molecules still remains a rapidly developing field. Although over the past 20 years only a rather small number of groups have investigated the coordination of anions using diverse approaches, it appears that over the past decade many other groups are taking up this challenge, and are focusing into investigating applications of anion recognition to areas of practical importance.

1.2. Sensing Mechanisms

1.2.1 General Background

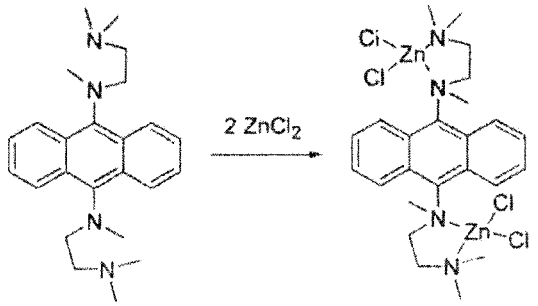
Anionic species are known to play numerous fundamental roles in biological and chemical processes and the detrimental effects of many anions as environmental pollutants are of growing concern.[13] Therefore there is intense current research interest in the design and synthesis of receptors and sensors that are effective at detecting anions in

solution.[14] By incorporating redox and photo-active signaling probes into various ligand frameworks, a series of selective optical and electrochemical anion sensors have been synthesized. In some cases a receptor having a reasonable affinity and high selectivity for a guest can be used in an optical or electrochemical sensing application for quantification of a target guest in a competitive medium.[15] A receptor, which is also a sensor is termed a chemosensor. As defined by Czarnik,[16] a chemosensor is comprised of a binding site and a moiety containing a signaling element, so that when a guest reversibly binds to the binding site, there is communication with the signaling element, which results in an electrochemical, colorimetric or fluorescent signal change. With regard to detection assays, there are two main categories of ion-sensors: electrochemical and optical. The transformation of a host to a chemosensor often entails the introduction of a chromophore or a fluorophore. One solution is to append an optically active moiety through covalent attachment. This is advantageous, because any spectroscopic modulation is directly correlated to the interaction with the guest. The sensors based on anion-induced changes in fluorescence appear particularly attractive because they offer the potential for high sensitivity at low analyte concentration and an ease with which the quantitative information is communicated to the investigator. However, the disadvantage lies in the introduction of additional steps to the synthetic route of the host molecule. Additionally, the appended fluorophore often occupies a position on the host scaffold that could interfere with the binding site.

The mechanisms by which this signal may be transferred optically are numerous, including charge transfer excited states, photoinduced electron transfer, and electronic energy transfer.[14b] Through this signal transduction mechanism, a sensor reports the

presence of the analyte. One such example reported by Czarnik is the anthracene-based receptor **1.12**, which upon binding two equivalents of Zn(II) results in fluorescence enhancement.[17] The lone pairs on the N-centers quench the anthracene fluorescence, but upon binding of the metal through the nitrogen lone pairs, the fluorescence is reestablished. In essence receptor **1.12** is a chemosensor for Zn(II). This concept has had great utility in the field of fluorescent sensing.

1.12



The majority of anion sensors have been designed to affect a change in the electrochemical properties of the host upon the binding of the guest.[18-21] Such examples include the cobaltocenium and ferrocenyl-based receptors shown in Figure 1.1.[18]

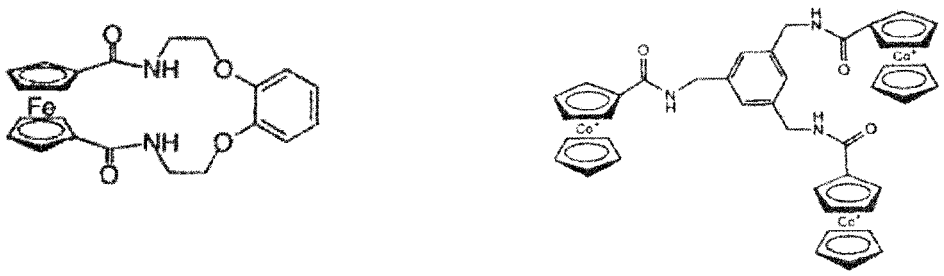


Figure 1.1. Electrochemical anion sensors reported by Beer.[18]

The choice of developing an electrochemical vs. an optical sensor depends on the desired sensitivity, selectivity, and instrumental availability within each laboratory.

1.2.2. Electrochemical Sensors

Redox-based sensors containing ruthenium, cobalt, and iron have been in development over the past years. As a result of the redox-active metal center and the guest communicating with one another, a change in the redox potential of the metal center can occur in the presence of a guest. This communication can take place via a variety of interactions, including through-space, through-bond, or direct coordination between the metal center and the guest. Induced conformational changes of the redox center upon guest binding guest, and interruption in the interaction between two redox centers are other ways whereby anion binding can induce a measurable change.[22] In the case of redox-based receptors this change is often manifested in terms of the electrochemical properties of the system. An ideal electrochemical sensor will retain the reversibility of the redox couple in the presence of an anion, causing the potential of the metal center to shift cathodically. This is because the close proximity of an electron density, due to the presence of the anion, lowers the oxidation potential of the metal center. It is possible to correlate the magnitude of the cathodic shift to the strength of anion binding in the two redox states of the receptor. With the caveat that the affinity to one redox state is known, it becomes possible to calculate the enhancement in the binding affinity due to the oxidation of the metal center (referred to as reaction coupling efficiency, or RCE).[23]

1.2.2.1 Cobaltocenium-Based Electrochemical Anion Sensors

The positively charged, pH-independent dicobaltocenium ester-type receptor (Figure 1.2) was found to bind anions through electrostatic interactions and to induce a cathodic shift in the redox potential.[24]

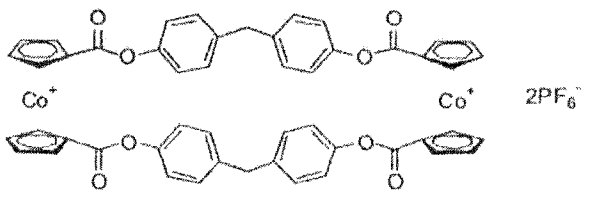
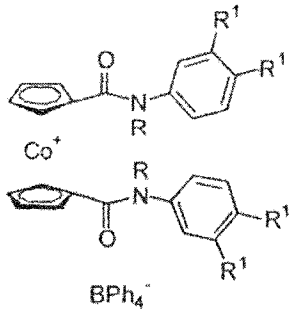


Figure 1.2. A dicobaltocenium receptor reported by Beer.[24]

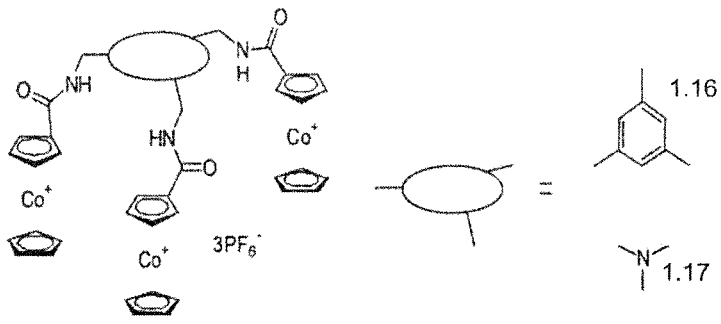
Compounds **1.13**, **1.14** and **1.15**[25] were the first examples of a wider range of amide-type sensors. In these cases the sensors use of amide linkage introduces an additional hydrogen-bonding anion recognition motif that complements those arising from the positively charged colbaltocenium center. It has been demonstrated structurally and spectroscopically that the amide functionalities participate in the anion binding process.



1.13 R = R^1 = H

1.14 R = H; R^1 = OMe **1.15** R = Me; R^1 = H

Other receptors reported by the Beer group include the tripodal systems **1.16** and **1.17**, which provided the first true indication that metallocene systems could function as effective anion-binding sensors.



Cobaltocenium-substituted calixarene systems[26] (Fig.1.3) demonstrate that remarkable versatility and sensitivity can be achieved through the careful design of electrochemical anion sensors.

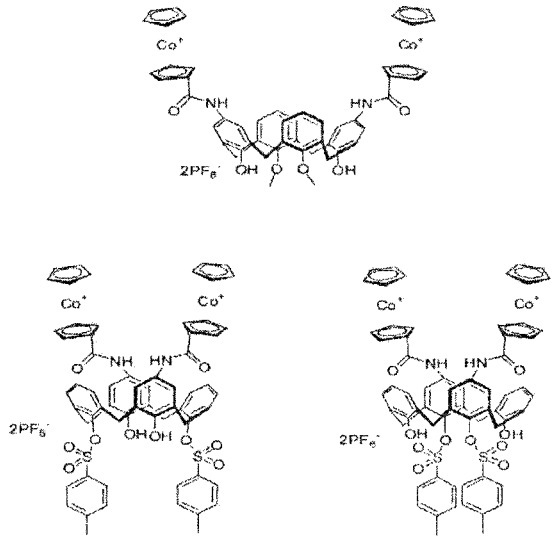
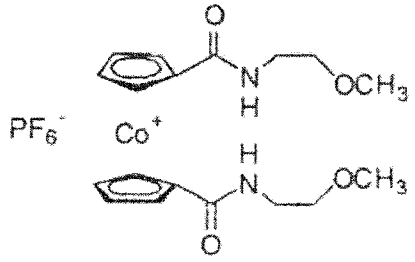
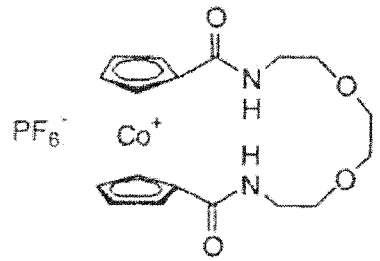


Figure 1.3 Cobaltocenium-substituted calixarene-type electrochemical sensors.[26]

In addition to topology, the importance of rigidity was illustrated through a comparison of systems **1.18** and **1.19**. The acyclic cobaltocenium receptor **1.18** displays a binding constant lower than the cyclic analog **1.19**, when bound to the same anion.



1.18



1.19

This "macrocyclic effect" is presumably due to the greater preorganization induced by the cyclic system, leading to more entropically favorable anion binding. These examples provide the solid foundation upon which the utility and versatility of redox-active anion binding systems was initially set and is currently sustained.[27]

1.2.2.2. Ferrocene-Based Electrochemical Anion Sensors

Shortly after the development of cobaltocenium anion sensors, attention was turned to analogous ferrocene-based systems.[18, 23, 27, 28] In contrast to cobaltocenium systems, in the case of these neutral receptors, anion binding is thought to occur solely as a result of hydrogen bonding. Although the absence of a positive charge results in a lower intrinsic binding affinity compared to cobaltocenium systems these

ferrocene-based systems are attractive because their electrostatic interaction with the anion can be switched on by oxidation of the Fe(II) ferrocene to the corresponding Fe(III) ferrocenium form. Consequently, these kinds of molecular receptors exhibit considerable potential for use as amperometric sensors. The first indication that ferrocene-based systems could be used to sense anions electrochemically came from studying the electrochemical properties of a multi-metallocene sensor (Figure 1.4).[26]

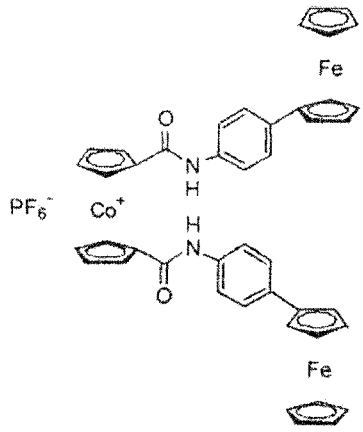
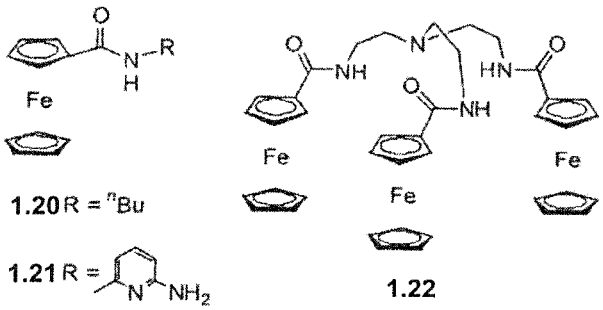


Figure 1.4. A ferrocene-based anion sensor reported by Beer.[26]

Inspired by the results of these studies, the first ferrocene-containing amide derivatives were prepared (**1.20-1.22**).[26, 29]



As in the case of cobaltocenium systems, receptor topology is known to play an important role in determining anion-binding selectivity. In addition to the systems already discussed, a wide variety of other ferrocene-based anion sensors have been developed. These include an extensive series of amide-substituted ferrocenes,[29-35] ferrocene-substituted porphyrins,[18, 36] calixarenes,[37, 38] and dendrimers. A number of systems capable of sensing anions in aqueous solution have also been developed. [34, 39-45]

1.2.2.3. Quinone-Based Electrochemical Anion Sensors

Calix-quinones have received considerable attention as an interesting class of ionic and molecular binding hosts. Calix-quinones have been studied extensively for their electrochemistry and binding of anions.[46] The amide moieties of calix[4]diquinones (Figure 1.5) act mainly as the binding site for anions, and the quinone moieties of the calix[4]diquinone constitute the redox active center as well as the binding site.

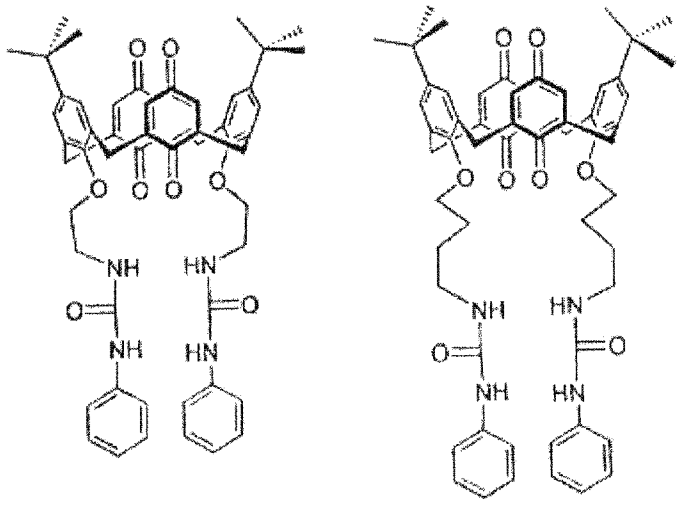


Figure 1.5. Calix[4]diquinone anion sensors reported by Jeong et al.[46]

The anion recognition properties of these receptors have been studied by electrochemical methods. When stoichiometric equivalents of anion guests are added to the solutions of calix[4]diquinones, substantial negative shifts of the redox potential are observed.

1.2.3. Fluorescent Sensors

The development of supramolecular fluorescent sensors presents another set of potential challenges that must be addressed by the synthetic chemist. There are several considerations that arise with fluorescent sensing. The type of fluorophore needs to be chosen in such a way that a reproducable and quantitative change in the fluorescence properties will be induced upon ion binding. This effect could be achieved through a charge-transfer process, a photoinduced electron transfer (PET) process, or an electronic energy transfer (EET) process.[14b] There are different types of charge transfer processes: all-organic internal charge transfer (ICT); metal-to-ligand charge transfer (MLCT); twisted internal charge transfer (TICT); and through-bond charge transfer.[14b] ICT and TICT processes involve non-hydrocarbon π-electron systems where the ground state has a very different dipole moment compared to the lowest energy singlet excited state.[14b] In these cases, the solvent used can be very influential on the fluorescent state of the system. Polar solvents can often cause interference in the signal due to hydrogen-bonding induced effects. This solvent interference changes may be minimal. This is often due to the longer lifetime of the emission signal. The main difference between ICT and TICT (Figure 1.6) processes is that full charge separation is achieved in TICT systems by twisting the donor and acceptor components of the system 90°.[14b]

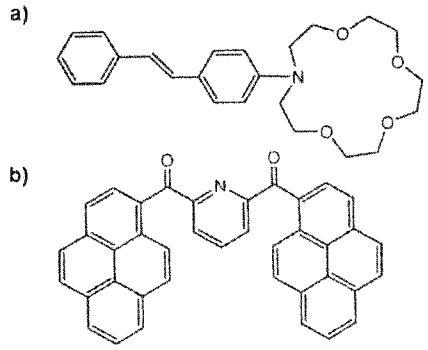


Figure 1.6. a) ICT- and b) TICT-based fluorescent sensors.[14b]

MLCT processes (Fig. 1.7) are most commonly found in organometallic systems. Ru(II) complexes dominate this area of research, through Re(I), Au(III) and Pt(II) complexes have also been investigated. In these cases, binding of a guest species induces significant changes in the luminescence properties of the receptor.[14b]

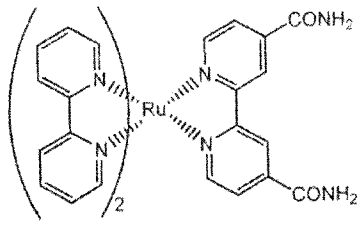


Figure 1.7. MLCT-based fluorescent sensor.[14b]

Widely studied PET processes were first introduced in the study of plant photosynthetic pathways. In these cases, a fluorophore acts as the site of both excitation and emission photonic transactions.[14b] An organic spacer links the fluorophore to a guest binding site. These systems can be designed as either "off-on" or "on-off" fluorescence switches (Fig. 1.8). As the names suggest, guest binding will open the fluorescence pathways in "off-on" switches, leading to fluorescence enhancement. On the other hand,

binding will close fluorescence pathways in "on-off" switches, leading to fluorescence quenching.[14b]

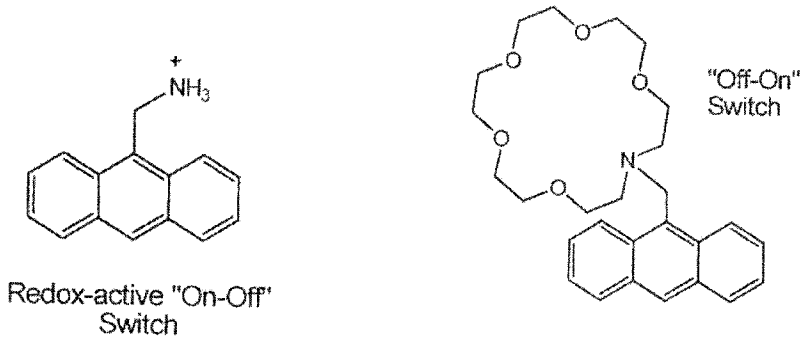


Figure 1.8. PET-based fluorescent sensors.[14b]

Redox-active host species can also act as PET "on-off" switches. EET process (Fig. 1.9) involves systems with multiple fluorophores. These systems frequently depend on guest recognition-induced conformational changes in the host molecule for the EET process to work efficiently.[14b]

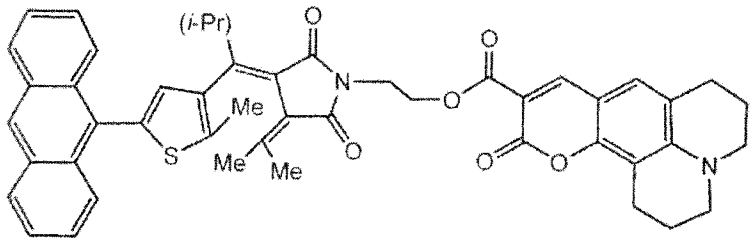


Figure 1.9. EET-based fluorescent sensor.[14b]

1.3. Forces involved in Anion Binding.

The weak interactions that enable molecules in solution to associate with a specific orientation and strength are representative of binding forces. Such forces are often

described as electrostatic interactions or hydrophobic interactions. Electrostatic binding forces include hydrogen bonding, ion-pairing, dipole-dipole, cation-π, charge-dipole, π-π interactions, H-π, and Van der Waals interactions. Each one of these interactions differs in the modes of strength, geometry, and nature of driving force.

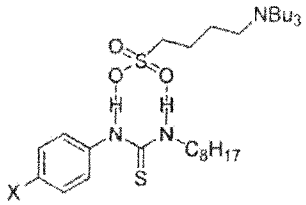
1.3.1. Hydrogen Bonding

Hydrogen bonding occurs through the sharing of a hydrogen atom between a hydrogen bond donor and a hydrogen bond acceptor. Both the donor and the acceptor are generally highly electronegative atoms such as nitrogen or oxygen. The strength of the bond is dependent on the pK_a values of both the donor and the acceptor. In general, the hydrogen bond strength increases as the acceptor becomes more basic and the donor more acidic. A unique feature of the hydrogen bond is the directionality, which arises from the presence of a dipole between interacting donor and acceptor atoms and their geometries; the optimum arrangement for hydrogen bond is linear. The linear arrangement allows for the best dipole alignment between the donor and acceptor. The strength of a single hydrogen bonding interaction averages between 3 and 9 kcal/mol for charged hydrogen bond partners and 0.5-1.5 kcal/mol for uncharged partners in natural systems.[47] The thermodynamics of hydrogen bond formation relies on the participating donor and acceptor atoms, as well as the solvent.

1.3.2 Hydrogen Bonding in Anion Binding

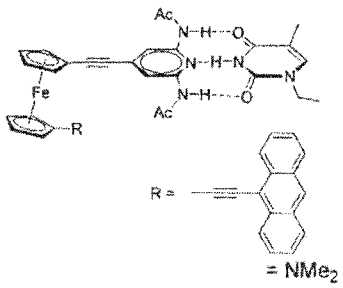
Supramolecular chemists have been successful in modulating the properties of synthetic hosts as a means of effecting the complexation of a guest through hydrogen

bonds.[48] Substituent effects and host preorganization are the primary means by which this has been accomplished. Wilcox has shown that the difference in binding energy between nitro-substituted host **1.24** and dimethylamine substituted host **1.25** with a sulfonate guest is 3.8 kcal/mol ($CDCl_3$).[49] The electron-withdrawing ability of the nitro group on **1.24** renders the host a better hydrogen bond donor, thereby increasing the binding affinity to the guest relative to **1.25**.



1.24 X = NO_2
1.25 X = NMe_2

Another approach to modulating hydrogen bonded complexes involves the use of different intermolecular interactions to complement and promote hydrogen bonded arrays. An example of this comes from the work of Inoue[50] in which π-stacking interactions were used to appropriately organize the donor and acceptor groups for effective hydrogen bond formation with 1-butylthymine (**1.26**).



1.26

1.3.3. Ion-Pairing

Ion-pairing is another example of an electrostatic interaction that can participate in complex formation. In the case of ion-pairing, oppositely charged functional groups approach through space to form non-bonded contacts (Figure 1.10). The simplest example is found in salts such as sodium chloride, potassium sulfate, or magnesium sulfate.

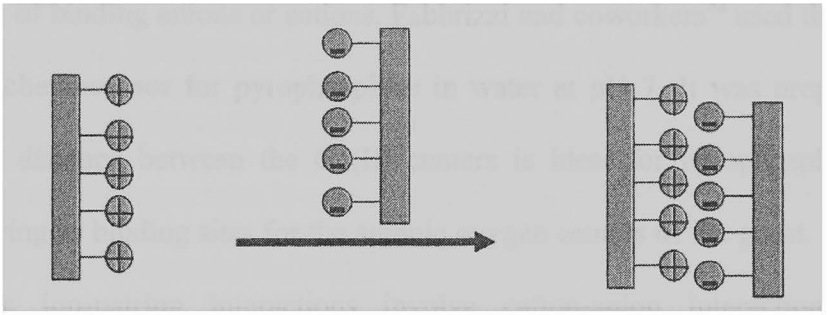


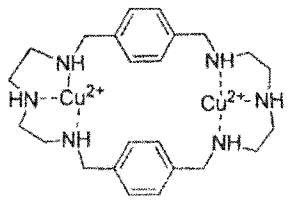
Figure 1.10. Schematic Representation of Ion-Pairing: A molecule with positively charged groups on the surface will approach another having negatively charged groups to form a complex through non-bonded interactions.

In general, larger cations on ion-exchange resins form tighter ion pairs with larger monoatomic anions. The large anions are poorly solvated, therefore they shed their hydration shell more easily to form ion-pairs. In contrast, the smaller ions have a more tightly held solvation shell, and therefore form weaker contacts with cations. This is also true for poly-atomic anions, such as perchlorate, which forms tighter ion pairs with an ion-exchange resin than does phosphate, due to a diffuse charge density.[51] The energies of ion-pairing interactions are dependent on the solvent, the size of the ions, and the charge

density of the ions. Ion-pair formation has favorable enthalpy change as the charged moieties interact to attain a state of neutral charge.

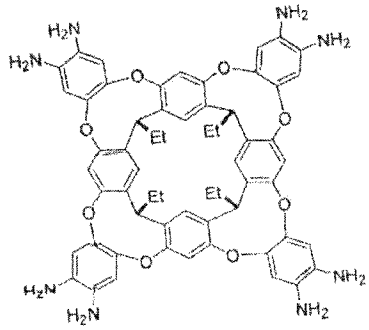
1.3.3.1. Ion-Pairing in Molecular Recognition

The utility of ion-pairing interactions in molecular recognition chemistry has been demonstrated by the design of synthetic receptors bearing charged functional groups for the purpose of binding anions or cations. Fabbrizzi and coworkers[52] used the dicopper(II) host **1.27** chemosensor for pyrophosphate in water at pH 7. It was proposed that the interatomic distance between the Cu(II) centers is ideal for pyrophosphate, with the centers serving as binding sites for the anionic oxygen centers of the guest. In the strictest sense these ion-pairing interactions involve cation-anion interactions, but other ion-pairing interactions are often utilized in molecular recognition as well. These include cation-π[53, 54] π-π[55-57], dipole-dipole and metal-anion interactions.



1.27

Rebek[58] reports studies on a 'vase shaped' cavity (**1.28**), which binds tetramethylammonium chloride in d_6-DMSO with an affinity of 2.2 x 10^4 M^{-1} as a result of cation- π interactions.



1.28

Electrostatic interactions cannot be fully characterized without recognizing the role of van der Waals forces that are present for each one of these interactions. As atoms approach another in space there is an attractive force involved, but at a distance less than a specific interatomic distance the atoms repell each other. These are described as van der Waals forces. These, too, are weak interactions, contributing a maximum of 2.0 kcal/mol per interaction.

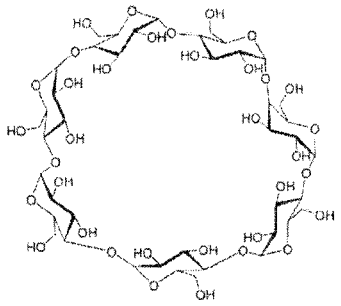
1.3.4. Hydrophobic Interactions

The individual electrostatic interactions described above are weak, yet if combined together they are partially responsible for the high affinities and selectivities seen in natural and synthetic systems. The apparent driving forces for the formation of salt bridges or hydrogen bonds between binding partners are not as dominant in aqueous media, indicating that there are other binding forces that contribute to the high-affinity complexes observed in nature. This additional binding arises from hydrophobic interactions. Hydrophobic interactions describe the tendency of non-polar molecules, such as hydrocarbons to interact with other non-polar molecules in water. The driving

force is derived from the strong hydrogen-bonding interaction between water molecules. This contributes to the binding of molecules as the hydrophobic portions of a binding partner transfer to the hydrophobic interior of a binding cavity.

1.3.4.1. Hydrophobic Interactions in Molecular Recognition

Hydrophobic interactions have been incorporated into the design of synthetic host-guest systems. The interior of these receptors is hydrophobic, and in aqueous solvent encapsulates hydrophobic guests as a result of hydrophobic binding.[59, 60] Inoue et. al. have studied the binding of several napthalenesulfonates to β-cyclodextrins (**1.29**) in water. The binding proceeds through hydrophobic interactions between the naphthalene ring of the guest and the hydrophobic interior of the cyclodextrin cavity. Several of these host-guest systems were characterized by favorable entropy changes and positive enthalpy changes. The favorable entropy is thought to arise from displacement of water molecules from the cavity upon binding of the guest.[61]



1.29

Although each of the predominant binding forces has been addressed individually, in reality they all operate in various levels, each influencing the strength of the other. In

general the individual binding forces are relatively weak, yet substrate-enzyme and host-guest complexes can be rather robust. Some or all of the binding forces identified above act simultaneously in the enzyme-substrate or host-guest binding with, and their combined strengths are responsible for the high affinity of complexes observed. With some knowledge of the binding forces at work in a binding event, the supramolecular chemist seeks to appropriately match binding partners and combine them in such a way so that tight associations of molecules such as those found in nature can be engineered.

1.3.5. Solvent Effects

The strengths and thermodynamic profiles of binding interactions are highly dependent upon the properties of the medium in which they occur (dielectric constant, protic, or aprotic medium). In any molecular recognition study the solvent choice can significantly alter the energetics of host-guest binding. Solvent effects on hydrophobic binding interactions has been extensively studied by Diederich and co-workers.[623] The properties of various solvents can have marked effects on the binding propensities of host-guest complexes promoted by hydrophobic or electrostatic interactions. The role of the solvent does indeed add another consideration to the design of effective host-guest systems.

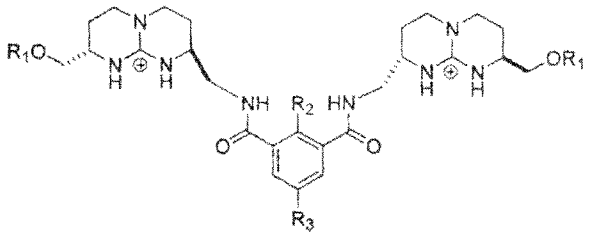
1.4. Thermodynamics

The formation of a host-guest complex is a dynamic process that is not just restricted to the host and the guest, but is also relevant to the solvent and the counterions involved. Complex formation between a host and a guest with displacement of counterions and changes in the solvation shells is quite analogous to a reaction in which

bonds are broken and formed. Just as a reaction has associated thermodynamic parameters, so does complex formation between two entities in solution. A more comprehensive understanding of a binding system can be sought through quantification of the thermodynamic parameters such as the enthalpy changes and entropy changes of binding. Direct heat measurement of a binding event using isothermal titration calorimetry (ITC) permits such parameters to be quantified and has been shown to be amenable to host-guest chemistry.[63] Thermodynamic investigations of host-guest binding have provided insights into the fundamental energetics of molecular associations.

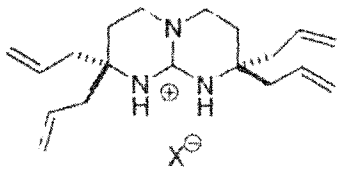
1.4.1. Energetics of Binding

Calorimetric investigations by both Schmitdchen and Hamilton[64] serve to highlight the power of using $\Delta H°$ and $\Delta S°$ values to decipher the roles of various participants in host-guest systems. Schmidtchen reports the study of the binding of sulfate to ditopic host **1.30** in methanol. Binding of this guest to the host has an unfavorable enthalpy change (+7.71 kcal/mol) and a highly favorable entropy change (+17.18 kcal/mol). The authors propose that the guanidinium groups on the host and the charged sulfate guest are well solvated in methanol, so that upon binding the solvent reorganization is endothermic. Additionally, the host-guest complex is not as well solvated as the individual components, thereby accounting for positive entropy change as solvent is released into solution.



1.30

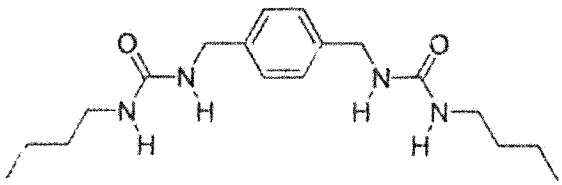
The counterion to a charged host molecule often influences the binding ability of the host to a guest. Schmidtchen recently reported a thermodynamic investigation to probe the effect of the counterion (Cl^-, Br^-, I^-, BF_3^-, PF_6^-) to bicyclic guanidinium **1.31** on the binding of tetraethylammonium benzoate in acetonitrile.[65] The data indicate that a strongly bound chloride anion has the lowest exothermic value (-2.93 kcal/mol) upon exchange for benzoate. In contrast, the exchange of weakly bound hexafluorophosphate counterion for benzoate is more exothermic (-5.21 kcal/mol). Survey of the $\Delta G°$ values (-6.35 *vs.* -7.73 kcal/mol) reveal a more subtle difference. In all cases the $T\Delta S°$ term was positive, reflecting the release of solvent and counter ions solvating the binding sites.



1.31

Binding that proceeds through the formation of multiple hydrogen bonds between host and guest functional groups can be influenced by the solvent. While this is reflected in the binding affinities, the enthalpic and entropic contributions offer a more complete understanding of binding. This is exemplified in work by Hamilton[64] on the binding of dicarboxylates to a series of bis-functional hydrogen bonding receptors. Receptor **1.32**

binds glutarate with an affinity of 1.3 x 10^3 M^{-1} in DMSO, a $\Delta H°$ value of -2.5 kcal/mol and a $\Delta S°$ value of +5.9 cal/mol K. Upon moving to a more competitive solvent such as methanol, the binding of glutarate to a similar host becomes 2.7 x 10^3 M^{-1} with a $\Delta H°$ of +3.7 kcal/mol and a $\Delta S°$ of 28 cal/mol K. Although the values are not directly comparable, the authors postulate that competitive solvation of the host and the guest in methanol results in endothermic enthalpy changes, and the complexation is driven by entropic factors.



1.32

The investigations discussed above serve to exemplify the utility of thermodynamic parameters to identify differences or trends in host-guest binding that would otherwise appear rather subtle, if the binding strength alone was used as the only criterion.

1.5. Host Design

Selective anion binding found within natural systems, provides the inspiration for the rational design of synthetic hosts. Just as the molecular complexes in nature are "exact fits" as a result of molecular evolution, the design of a synthetic host is fundamental to the function of the host in binding the intended guest. The implication here is that the guest often dictates the size, shape, and charge of the binding cavity. The

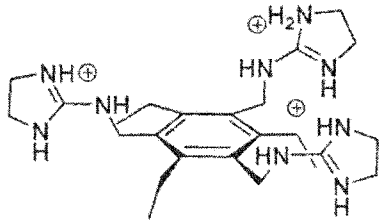
first set of guidelines used in the design of a synthetic receptors originate in a review article by Cram.[66] Through the decades receptor design has become more elaborate, yet supramolecular chemists still apply the well established fundamental principles.

1.5.1. Design Principles

In using synthetic receptors for the purpose of binding guests in solution it is desirable to maximize the number and the strength of non-bonded interactions between the host and the guest. In molecular recognition this is achieved by incorporating the notions of the "lock and key" and preorganization into the receptor design. The "lock and key" design approach is an adaptation of "lock and key" model of enzyme-substrate binding first proposed by Emil Fischer in 1894.[67] The host (lock) is engineered to match the guest (key) such that the binding cavity of the host compliments the guest in terms of size, shape, and charge. In the idealized host design the matched size, shape, and pairwise interactions of the host and guest should lead to a tight contact pair. Energetically, the unfavorable entropy change that may arise from conformational changes in the host as the guest binds can be minimized by incorporating the concept of preorganization.[66, 68-71] This design feature involves the use of a rigid molecular scaffold which serves to lock the positions of the functional groups into a conformation and orientation suitable to guest binding. The incorporation of functional groups for the purpose of forming non-bonded interactions with the guest is often used to create an enthalpic advantage to the binding process.

Preliminary host design is often modeled with the aid of space filling molecular models to approximate a first guess at the desired cavity. Numerous preorganized

molecular scaffolds have been used for molecular recognition purposes. One such scaffold relevant to our studies, first used by the Anslyn group is the 1,3,5-substituted-2,4,6-triethylbenzene (**1.33**).



1.33

The alternating ethyl groups impart a steric bias of the functional groups to the one face of the benzene ring, positioning them to participate in guest binding with little conformational change. The placement of the binding functionalities rendered the host selective for citrate binding in D_2O with an affinity of 6.9×10^3 M^{-1}.[72] A crystal structure of **1.33** with tricarballate bound to the cavity was reported and verified the orientation of the guanidinium groups to one face of the plane. Binding of citrate to a host lacking the ethyl groups resulted in a reduced affinity (K_a = 2.4×10^3 M^{-1}), documenting the effectiveness of preorganization.

1.6. Binding Studies

The ability of a host to associate with a guest is commonly evaluated through the determination of a binding constant (K_a) and the binding stoichiometry (n). The analytical techniques that are often used in molecular recognition to determine a binding affinity are

absorption spectroscopy, nuclear magnetic resonance spectroscopy, and potentiometry. Solubility measurements, liquid-liquid partitioning, chromatography, and dialysis are also used, but less frequently.[73] The utility of thermal methods in the study of host-guest binding has recently become more prevalent in the literature. Each of the techniques above permit the monitoring of an experimental observable, as aliquots of a guest solution are added to a solution of the host. The data obtained from such changes in the observable, as the host and guest associate, can be used to generate a binding isotherm which can then be fit with a curve, from which K_a and n may be determined.[73-74] Nuclear magnetic resonance (NMR) can be used to monitor the proton (and in some instances the phosphorous) signal of the host or the guest or the host-guest complex. One can follow the changes in the chemical shift and plot these changes vs. the mole ratio of host to guest in order to produce a mole ratio plot. This raw data may then be fit with a curve generated from the binding equation in order to obtain the K_a value, and the binding stoichiometry. In a very similar fashion Ultraviolet-visible spectroscopy (UV-Vis) or fluorescence spectroscopy data can be used to monitor a change in the absorbance or emission of the host, or the guest as it participates in the formation of a host-guest complex. Thermal methods can also be used to measure the heat absorbed or released upon host-guest complex formation. The heat change can be used in order to generate a mol ratio plot for curve fitting. The equations used to fit the binding isotherm from the raw data are derived for the experimental observable unique to the technique. ^{1}H NMR has been extensively used in the research discussed in the following chapters.

1.7. Molecular Complex Stability in Solution[73]

Equilibrium processes in which non-covalent interactions take place to form supramolecular complexes occur widely in chemical and biological systems. The measurement of the equilibrium constants is therefore of crucial importance in understanding these processes. Methods for K_a determination include but are not limited to optical absorption spectroscopy, magnetic resonance spectroscopy, fluorimetry, potentiometry, chromatography, dialysis and kinetic methods. The general problem is to accurately determine a property (variable) of the supramolecular complex and its components that shows a regular variation upon binding, and measure it as a function of the total concentration of the one of the components. Examining the simple case of a 1:1 equilibrium in which receptor S is complexing the ligand L resulting in the 1:1 supramolecular complex SL, we have

$$S + L \leftrightarrow SL \qquad (2)$$

From the expression for the equilibrium constant we can directly derive the 1:1 binding isotherm expression :

$$f_{11} = \frac{K_a[L]}{1 + K_a[L]} \qquad (3)$$

where f_{11} is the fraction of the receptor that has been complexed:

$$f_{11} = \frac{[SL]}{[S]_t} = \frac{[L]_t - [L]}{[S]_t} \qquad (4)$$

Substituting L from equation (4) to equation (3) and solving for f_{11} we get expression (5) that contains as a variable only the total ligand concentration $[L]_t$, if under the experimental conditions $[S]_t$ is kept stable:

$$f_{11} = \frac{[S]_t+[L]_t+K_a^{-1}-((([S]_t+[L]_t+K_a^{-1})^2-4[L]_t[S]_t)^{1/2})}{2[S]_t} \qquad (5)$$

The f_{11} value is directly related to the measured property, and therefore non-linear fitting of the expression $f_{11} = f([L]_t)$ via equation (5) allows direct determination of the association constant.

For example, consider an NMR titration experiment in which the complex and the components are in fast exchange. In that case the observed chemical shift c is the weighted average of the chemical shifts of the components. Let a be the chemical shift of a specific resonance at the start of the titration when $[L]_t = 0$ and therefore $[S] = [S]_t$ or $f_{11} = 0$, and b be the chemical shift of the same resonance at the end of the titration when $[L]_t = \infty$ and therefore $[S] = 0$ or $f_{11} = 1$. If we define $\Delta\delta_{max} = b - a$ and define $\Delta\delta = c - a$, then the f_{11} can be substituted in equation (5) via the expression (6) resulting in the final expression (7). Then (7) can be used directly to fit the data, thus allowing the determination of the values of K_a as well as of $\Delta\delta_{max}$:

$$f_{11} = \Delta\delta / \Delta\delta_{max} = (c-a) /(b-a) \qquad (6)$$

$$\Delta\delta = \frac{([S]_t + [L]_t + K_a^{-1} - ((([S]_t + [L]_t + K_a^{-1})^2 - 4[L]_t [S]_t)^{1/2}))\,\Delta\delta_{max}}{(2[S]_t)} \qquad (7)$$

Similar expressions with more parameters can be obtained for more complicated equilibria involving multiple complexation steps.[73] In many cases the analysis is carried out using assumptions that reduce the number of free parameters and simplify the fit.

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Chapter 2: Spectroscopic and Mass Spectrometric Investigation of the Anion Binding Properties of a Dansylamide Derivative of 1,3,5-Tris(2-aminomethyl)-2,4,6-triethylbenzene.

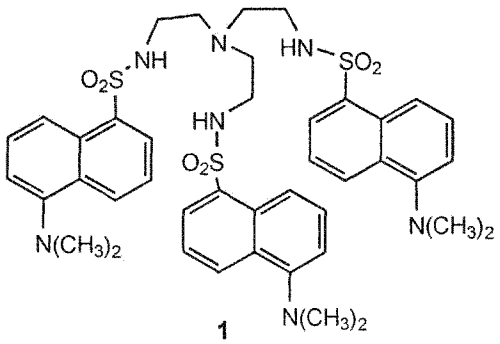
2.1. Overview of Nitrate Sensors

The use of supramolecular chemistry principles for ion sensor design has been largely driven by biologically and environmentally related applications.[1-5] Anions have received relatively less attention than cations as potential recognition targets. However, in recent years several researchers have turned their attention to the development and characterization of artificial receptors for anions.[6-12] One anion of particular importance is nitrate, due to its widespread presence in the environment as a fertilizer and in nuclear waste streams. Few nitrate receptors have been designed thus far, and only a small portion of these have been neutral lipophilic hosts, which would be appropriate for a nitrate extraction system.[13-15] Considerations for the design of nitrate-specific hosts are similar to those for general anion-binding hosts, including strong, selective, and preferably reversible binding. In addition to these considerations discussed in detail in Chapter 1, a nitrate-specific host should contain hydrogen bond donor sites specifically arranged so that all three oxygen atoms of the nitrate ion will be bound. Bisson et al. have reported an amide-linked C_3-symmetric bicyclic neutral cyclophane capable of recognizing nitrate exclusively through hydrogen bonding.[16] Hydrogen bonding between the geometrically matched host and nitrate led to enhanced binding, overcoming the weak coordinative ability of this anion.

In the past, most nitrate sensor research has focused on nitrate-responsive membrane development[17,18] and other nitrate-selective optical sensors.[14,19] A nitrate-responsive optical membrane has been developed using a combination of the highly fluorescent Rhodamine B octadecylester perchlorate (RBOE) as a dye, and tridodecylmethylammonium chloride (TDMACl) as an anion exchanger incorporated into PVC or a PVC co-polymer.[17] This combination works very well for lipophilic matrices, with a limit of detection (LOD) of 1 ppm for nitrate. The selectivity factor for nitrate over chloride is 200 in such matrices. The use of various betaine salts in polystyrene-*block*-polybutadiene-*block*-polystyrene (SBS) polymeric membranes as nitrate-selective electrodes has also been investigated.[18] The most effective of these membranes worked over a pH range of 2-8, with an LOD of 0.02 ppm for nitrate. The selectivity coefficient ($K^{pot}_{NO_3^-,Cl^-}$) for nitrate over chloride was 3.4×10^{-3}. Fluorescent fiber-optic sensors for nitrate have been developed based on the fluorescence quenching induced by the irreversible nitration of fluorescein upon exposure to nitrates.[19] A system has also been reported which contains a cationic potential-sensitive fluorescent dye incorporated into a hydrogel-plasticizer matrix.[14] This system showed strong fluorescence enhancement upon nitrate exposure and was effective in sensing nitrate in the 0.1-50 mM range, while showing no response to the presence of chloride, even at 200 mM. These receptors have a collective effectiveness in the mM range and considerable selectivity over chloride. However, there are still no practical nitrate sensors reported giving a fluorescent response at the nM level.

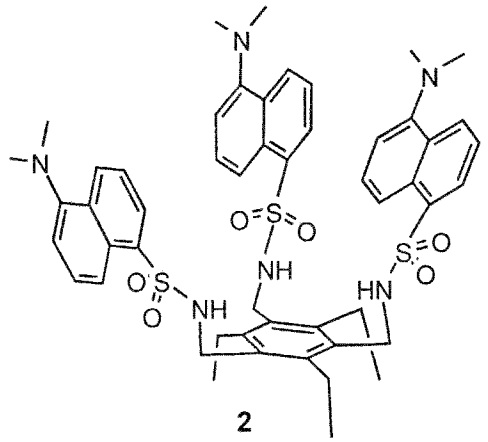
As part of our efforts to develop a fluorescent nitrate sensor, we previously focused our attention on the tris(2-aminoethyl)amine (tren) framework, which has been

used in the past for anion binding and extraction.[12,20] In order to incorporate an anion sensing capability to the tren framework, we had investigated in the past the anion-binding properties to the N-dansylamide derivative of tren previously synthesized by Prodi et al (**1**).[21]



1

This dansylated tren derivative **1** was found to bind anions, however it was shown to bind Cl^- (K_a = 640 ± 34 M^{-1}) stronger than NO_3^- (K_a = 83 ± 2 M^{-1}). This selectivity pattern is not unexpected considering the relative hydrophilicity of the anions, as expressed by their hydration energies.[22] Therefore, building selectivity for nitrate solely through the orientation of the hydrogen bonding groups appeared to be a challenging task. The lower selectivity for NO_3^- *vs.* Cl^- binding for **1** prompted us to attempt similar studies with the more rigid 1,3,5-tris(aminomethyl)benzene framework (**2**). In this chapter the synthesis and spectroscopic study of the anion binding properties of **2** by NMR, FT-IR, and fluorescence spectroscopy is reported. Along with an APCI-MS investigation of the receptor and anion-receptor complexes.



2

2.2. Results and Discussion

2.2.1 Synthesis

Compound **2** (Figure 2.1) was synthesized in good yields from the commercially available dansyl chloride and 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene[23]. The compound was purified by column chromatography, recrystallized from CH_2Cl_2/hexanes, and dried under vacuum at 40-50 °C. It was characterized by FT-IR, and ^{1}H-NMR and gave satisfactory elemental analysis.

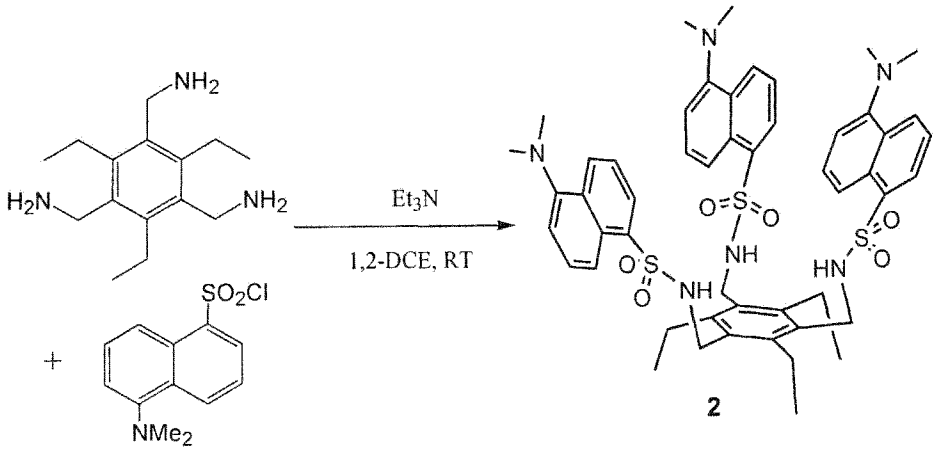


Figure 2.1. Pathway for synthesis of receptor **2**.

2.2.2. ^{1}H-NMR Titrations

The anion binding properties of receptor **2** were determined in $CDCl_3$ by ^{1}H-NMR titration experiments. Tetrabutylammonium salts of the chloride, nitrate, bromide and iodide anions were used as the anion sources. Significant downfield shifts of the N-H proton resonance were observed, suggesting anion binding via hydrogen bonding. (Figure 2.2)

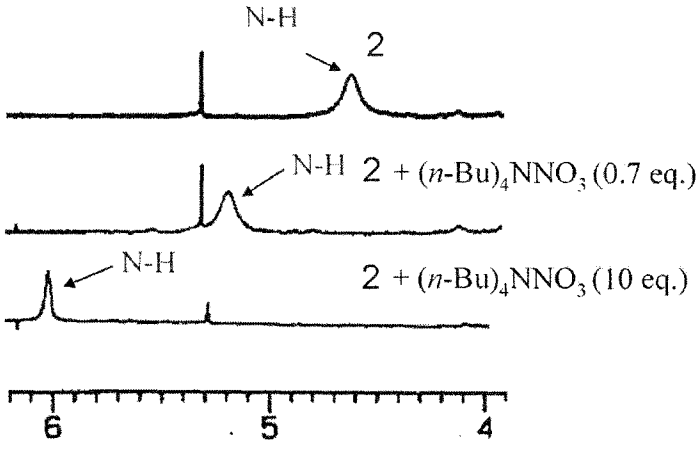


Figure 2.2. ^{1}H-NMR spectra (N-H resonance region) of i) **2** in $CDCl_3$ (top), ii) after titration with 0.7 eq. of *n*-Bu_4NNO_3 (middle), and iii) after titration with 10 eq. of *n*-Bu_4NNO_3 (bottom).

In all experiments only a single N-H resonance was observed, suggesting the participation of all three N-H protons in anion binding. This could occur in one of two ways: either with all three N-H protons of receptor **2** binding simultaneously, or with a fast exchange occurring between different modes of complexation involving all three protons.

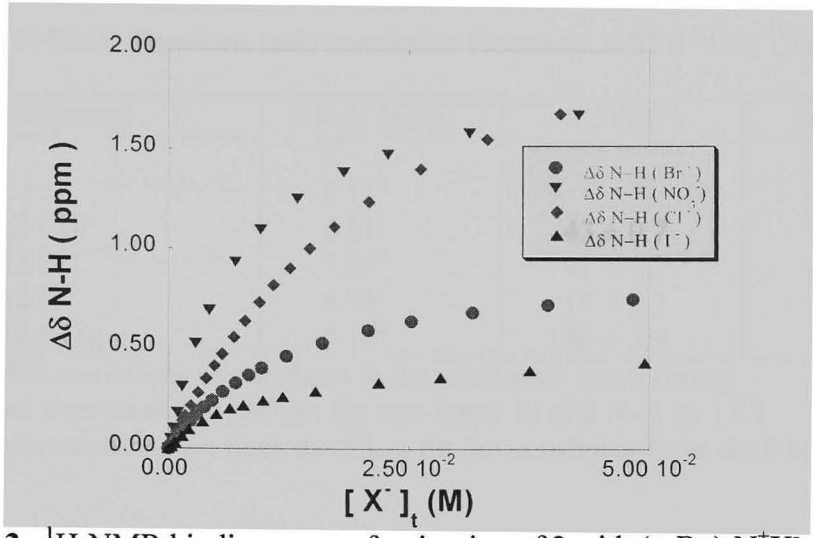


Figure 2.3. ^{1}H-NMR binding curves for titration of **2** with $(n\text{-Bu})_4N^+X^-$ ($X^- = Cl^-, Br^-, I^-, NO_3^-$).

Association constants (Table 2) for the formation of a 1:1 complex, K_a, were determined from the 1:1 binding isotherm (Eq. 2), where $\Delta\delta$ is the change in the chemical shift of the N-H resonance, δ_{obs} is the observed N-H resonance, δ_2 is the actual change N-H resonance for receptor **2**, $[\mathbf{2}]_t$ is the total concentration of **2**, $[X^-]_t$ is the total concentration of $(n\text{-Bu})_4NX$, K_a is the association constant, and $\Delta\delta_{max}$ is the maximum chemical shift change for the N-H resonance.

$$\Delta\delta = \delta_{obs} - \delta_2$$

$$= ([\mathbf{2}]_t + [X^-]_t + K_a^{-1} - ((([\mathbf{2}]_t + [X^-]_t + K_a^{-1})^2 - 4[X^-]_t\,[\mathbf{2}]_t)^{1/2}\,\Delta\delta_{max}) / (2[\mathbf{2}]_t) \quad \text{(Eq. 2)}$$

Table 2 ^{1}H-NMR Titrations and Association Constants at 22.0 °C in $CDCl_3$

Compound	δ N-H (ppm)	K_a[b] (M^{-1})	ΔG° (kJ/mol)
2	4.14[a]		
[**2**·Cl]$^-$	6.81[c]	43 ± 0.7	- 9.2
[**2**·Br]$^-$	5.06[c]	91 ± 1.2	-11.1
[**2**·I]$^-$	4.94[c]	15 ± 2.7	- 6.6
[**2**·NO_3]$^-$	6.12[c]	146 ± 3.9	-12.2

[a] Values that were input as constants in the non-linear curve fitting.
[b] K_a values were determined from the non-linear fit of δ N-H vs. [X^-].
[c] Values were determined from the $\Delta\delta_{max}$ for the non-linear fit of the δ N-H vs. [X^-].

The formation constant values (Table 2) clearly show a preference of receptor **2** for binding of NO_3^- over Cl^-, Br^- and I^-. This selectivity pattern indicating preference of nitrate over other anions is unexpected based on the relative hydrophilicities and inherent hydrogen-bond acceptor capabilities for each anion. It is suggested that binding for nitrate is favored because in contrast to receptor **1** the introduction of the aromatic ring makes the receptor structure more rigid and preorganized for NO_3^- binding. Figure 2.4 summarizes the results of Table 2 in a form that makes the observed relative trends more obvious. Comparison of the standard free enthalpies of formation and the free enthalpies of hydration[22] (Figure 2.4) shows that the less rigid receptor **1** follows the same trend as the hydration energies, while the more rigid receptor **2** does not, suggesting that the added rigidity is responsible for the nitrate selectivity.

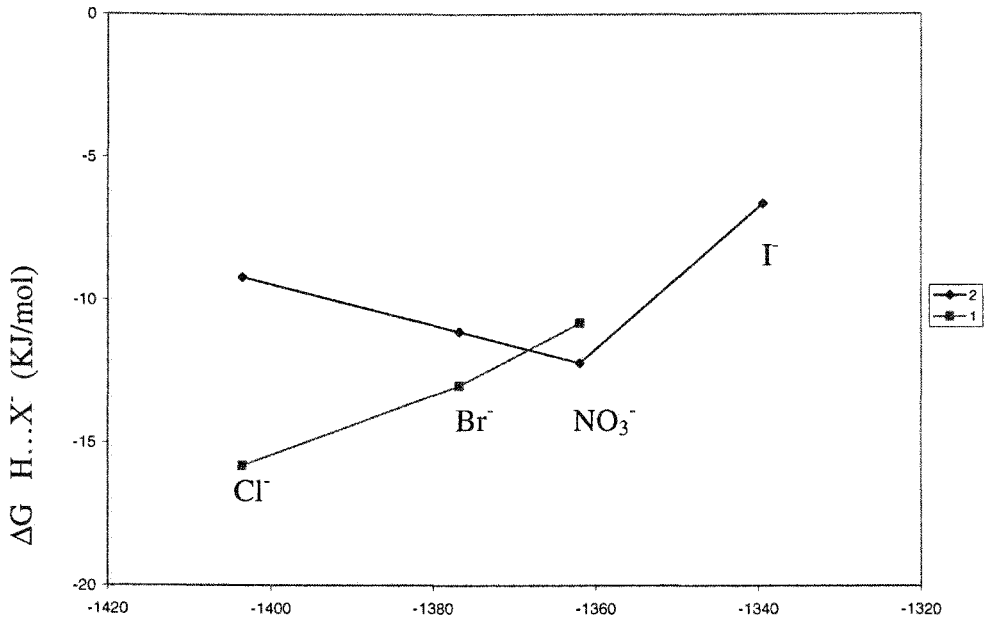


Figure 2.4. Plot of ΔG° of binding vs. hydration energy. Experimental hydration free enthalpies are taken from ref. 22.

2.2.3. Fluorescence Spectroscopy

The presence of the dansyl fluorophore in the structure of **2** allows characterization of the fluorescence effects in the system upon ion binding. Fluorescence titration studies of **2** with $(n\text{-Bu})_4N^+X^-$(X^- = Cl^-, Br^-, I^-, NO_3^-) in CH_2Cl_2 were carried out in order to observe if there is a change in the fluorescence of the dansyl groups at 505.5 nm upon anion binding. However the change observed (enhancement) was small and inconsistent presumably because of the high quantum yield of the dansyl group.

Since the fluorescence titrations were not yielding useful results, we set up a set of continuous variation experiments in order to generate a Job plot.[24] This set of experiments does not rely on the continuous addition of the anion solution to the ligand solution. Instead, ten independent solutions of variable anion and receptor concentration ratios were prepared, and the fluorescence emission spectra were collected for each

ratios were prepared, and the fluorescence emission spectra were collected for each solution. A control experiment, using a set of solutions combining receptors with dichloromethane instead of $(n\text{-Bu})_4N^+X^-$(X^- = NO_3^-, Cl^-, Br^-, and I^-) was run in order to determine the true emission intensity (I_o) of **2** at the concentrations used. These intensities were found by a linear regression of the control data. The observed emission intensities (I) were subtracted from the calculated I_o for each point, and these differences were plotted against the variable x, which is defined by Eq.2.1, where X^- is anion.

$$X = [\mathbf{2}]_f / ([\mathbf{2}]_f + [X^-]_f) \qquad \text{(Eq. 2.1)}$$

The results of the continuous variation experiment (Figure 2.4) did provide strong evidence for the formation of 1:1 anion-receptor complex upon addition of nitrate to **2**, as seen by the maximum of the bell-shaped Job plot falling at x = 0.50 for **2**. 1:1 anion-receptor complexation was also observed with chloride x = 0.51, bromide x = 0.50 and iodide x = 0.50.

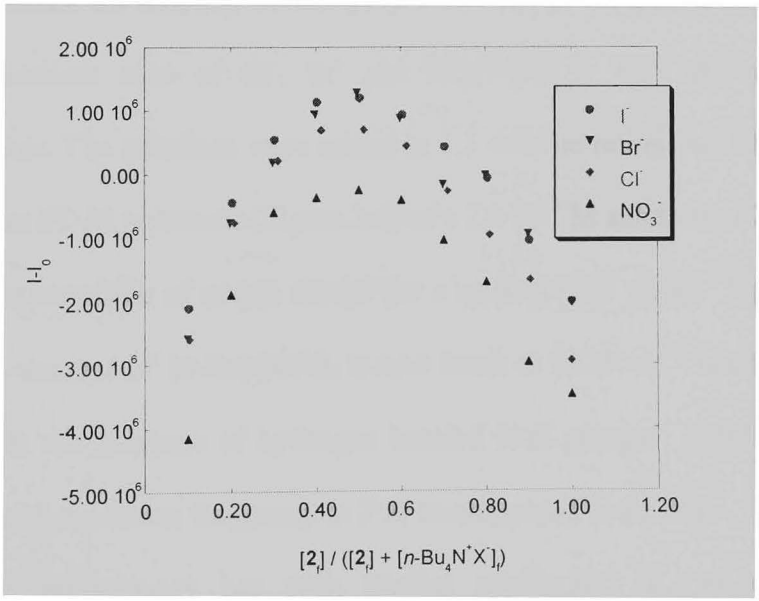


Figure 2.5. Fluorescence Job plot of **2** with $(n\text{-Bu})_4N^+X^-$ (X^- = NO_3^-, Cl^-, Br^-, and I^-) in CH_2Cl_2.

2.2.4. UV-Visible Spectroscopy

A UV-Visible titration was performed in order to determine the effect, on absorbance by adding $(n\text{-Bu})_4NNO_3$ (1×10^{-3} M) to a solution of **2** (1×10^{-5} M). If there was a shift in the absorbance peak of the dansyl moiety in **2**, this could have caused non-specific changes in the fluorescence emission spectra, which are independent of any anion binding effects. In this case, the emission spectra would have to be collected at a different excitation, and possibly emission wavelengths, making titrations complicated and time-consuming. Fortunately, while a new peak was observed, which corresponds to the tetrabutylammonium nitrate absorbance, appearing and growing in intensity, there were no major changes in the absorbance peak of the dansyl fluorophore at 345 nm.

2.2.5. FT-IR Spectroscopy

The solution FT-IR spectra of **2** in CH_2Cl_2 before and after anion addition provide additional evidence for binding. Solutions (2×10^{-3} M) of receptor **2** and solutions of the tetrabutylammonium salts of Cl^-, Br^- and NO_3^- (7.5×10^{-3} M) were prepared in dichloromethane. The solutions were mixed in 1:1 volume ratios and FT-IR spectra were collected. The FT-IR spectrum (Figure 2.6) of a 2×10^{-3} M solution of **2** shows a band at 3355 cm^{-1}, characteristic of a $\nu_{N\text{-}H}$ stretch for a sulfonamide group. Upon addition of a stochiometric amount of $(n\text{-Bu})_4NNO_3$ a new band at 3170 cm^{-1} is observed, which is consistent with the presence of hydrogen bonded N-H groups. Solution FT-IR specta observed formed at a lower frequency in $\mathbf{2}\cdot X^-$ as compared to **2** alone.

FT-IR spectroscopy has seen limited application in molecular recognition studies[24] but it provides a fast and versatile method for comparison of hydrogen bonds in

solution and in the solid state. FT-IR spectra (Table 2.1) for **2**·X^- (X^- = Cl^-, Br^-, and NO_3^-) were therefore measured both in dilute CH_2Cl_2 solutions and in thin films, formed by evaporation of CH_2Cl_2 solutions. The FT-IR spectra for pure **2** are slightly different moving from solution to thin film, showing only a non hydrogen bonded ν_{N-H} band at 3355 cm^{-1} in solution, but only a hydrogen bonded ν_{N-H} band at 3279 cm^{-1} in thin film, characteristic of a self-associated sulfonamide. The N-H band at 3279 cm^{-1} indicates self-association of the sulfonamide ligand in thin film, presumably due to N-H...O=S hydrogen bonding that is typical of sulfonamides in the solid state. Thin film FT-IR of **2** shows a band at 3279 cm^{-1} and a new band at 3168 cm^{-1} upon complexation with nitrate. Similar effects were observed with bromide and chloride complexes (Table 2.1). This observation, in combination with broadening, is indicative of anion binding to **2** via hydrogen bonding.

Table 2.1. N-H Stretching frequencies for receptor **2** and its anionic adducts.

Compound	ν (solution) (cm^{-1})	ν (thin film) (cm^{-1})
2	3355	3279
2·NO_3^-	3170	3168
2·Cl^-	3190	3184
2·Br^-	3190	3180

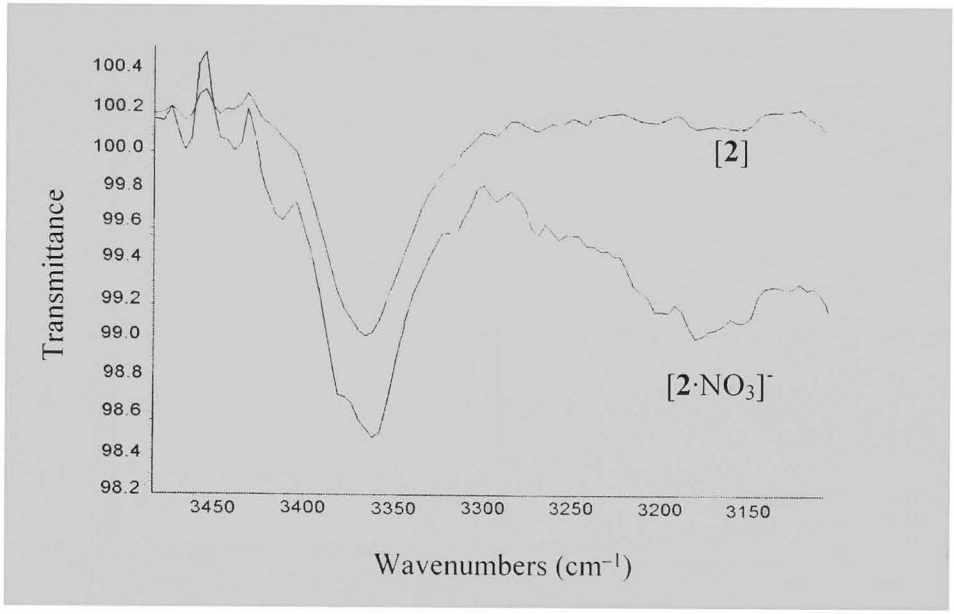


Figure 2.6. Solution FT-IR spectra of **2** and **2**·NO_3^-

2.2.6. Atmospheric Pressure Chemical Ionization Mass Spectrometry (APCI-MS).

Anion complexation of **2** with Cl^-, Br^-, I^- and NO_3^- was observed by APCI-MS in anion detection mode. Additionally, the APCI of spectra [**2**·Br]$^-$ and [**2**· NO_3]$^-$ gave peaks at m/z = 947 and 983, corresponding to the deprotonated ligand [**2**-H]$^-$ and the chloride adduct resulting from the ionization of the dichloromethane. For Cl^-, Br^-, I^- and NO_3^- intense peaks for the [**2**·Cl]$^-$, [**2**·Br]$^-$, [**2**·I]$^-$ and the [**2**·NO_3]$^-$ 1:1 anion-receptor complexes at m/z = 983, 1029, 1074 and 1010, respectively (Figures 2.7-2.10).

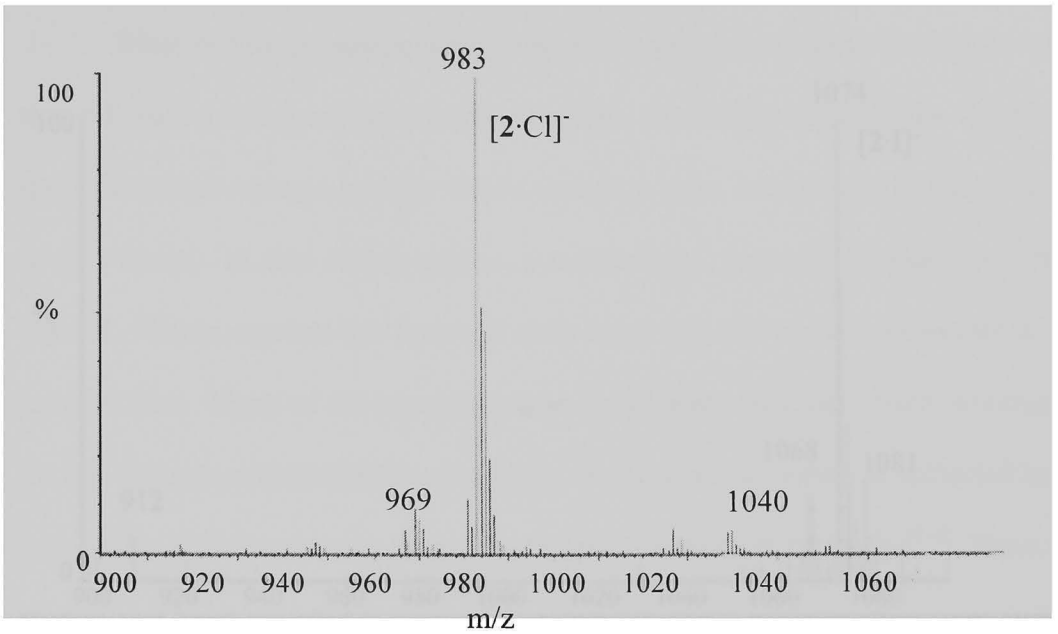


Figure 2.7. APCI-MS spectrum of a solution of **2** (2.0 x 10^{-3} M) and (n-Bu)$_4$NCl (4.0 x 10^{-3} M) in CH_2Cl_2, Cone voltage: –15V, probe temperature ramp: 25°C to 375°C, ionization energy (corona pin): 4.5kV.

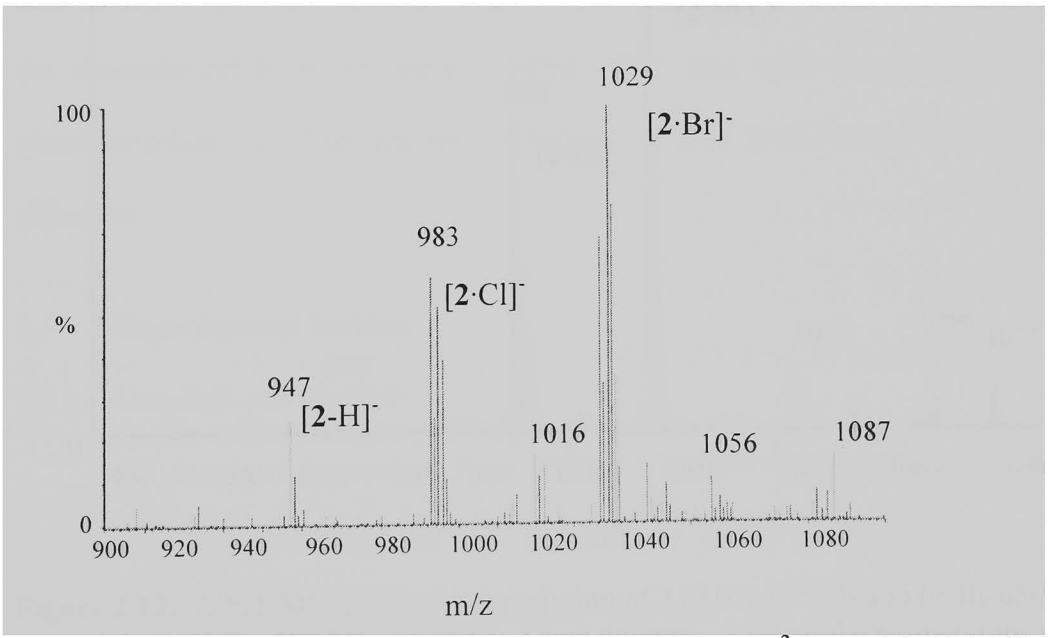


Figure 2.8. APCI-MS spectrum of a solution of **2** (2.0 x 10^{-3} M) and (n-Bu)$_4$NBr (4.0 x 10^{-3} M) in CH_2Cl_2, Cone voltage: –15V, probe temperature ramp: 25°C to 375°C, ionization energy (corona pin): 4.5kV.

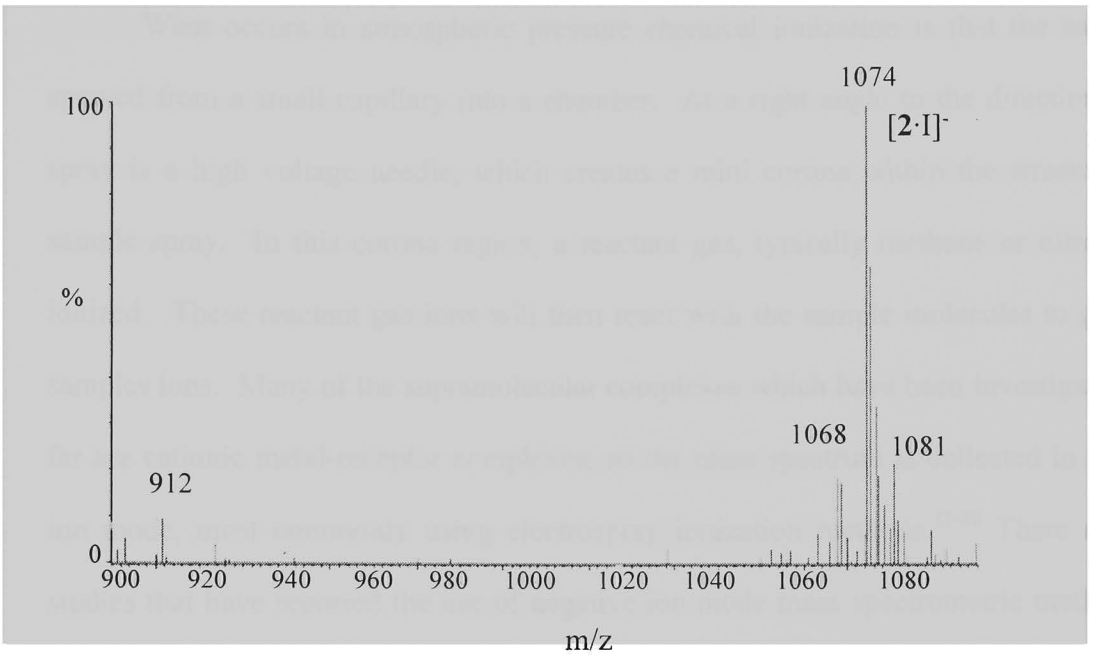


Figure 2.9. APCI-MS spectrum of a solution of **2** (2.0×10^{-3} M) and $(n\text{-Bu})_4\text{NI}$ (4.0×10^{-3} M) in CH_2Cl_2, Cone voltage: –15V, probe temperature ramp: 25°C to 375°C, ionization energy (corona pin): 4.5kV.

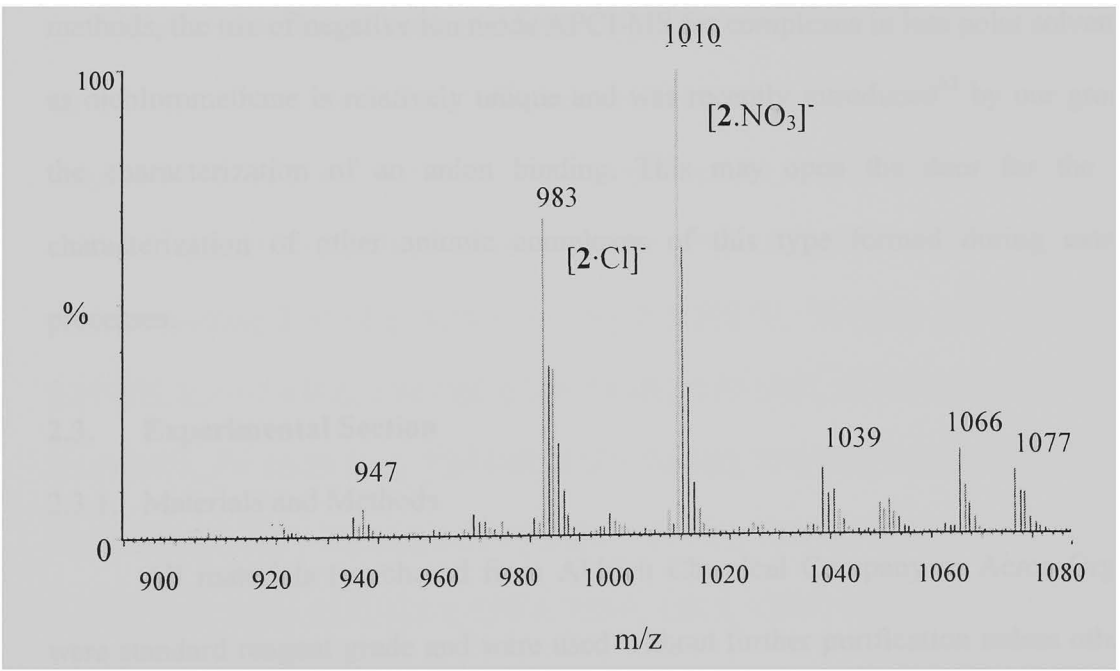


Figure 2.10. APCI-MS spectrum of a solution of **2** (2.0×10^{-3} M) and $(n\text{-Bu})_4\text{NNO}_3$ (4.0×10^{-3} M) in CH_2Cl_2, Cone voltage: –15V, probe temperature ramp: 25°C to 375°C, ionization energy (corona pin): 4.5kV.

What occurs in atmospheric pressure chemical ionization is that the sample is sprayed from a small capillary into a chamber. At a right angle to the direction of the spray is a high voltage needle, which creates a mini corona within the stream of the sample spray. In this corona region, a reactant gas, typically methane or nitrogen, is ionized. These reactant gas ions will then react with the sample molecules to generate samples ions. Many of the supramolecular complexes which have been investigated thus far are cationic metal-receptor complexes, so the mass spectrum is collected in positive ion mode, most commonly using electrospray ionization methods.[25-28] There are also studies that have reported the use of negative ion mode mass spectrometric methods for complex characterization.[29-32] These studies typically use polar solvents with high dielectric constants, such as water, acetonitrile, methanol. In comparison to existing methods, the use of negative ion mode APCI-MS for complexes in less polar solvent such as dichloromethane is relatively unique and was recently introduced[33] by our group for the characterization of an anion binding. This may open the door for the future characterization of other anionic complexes of this type formed during extraction processes.

2.3. Experimental Section

2.3.1. Materials and Methods

All materials (purchased from Aldrich Chemical Company or Acros Organics) were standard reagent grade and were used without further purification unless otherwise noted. 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene was synthesized as previously reported[23]. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker NMR

spectrometer and were referenced to the residual solvent resonance. All chemical shifts, δ, are reported in ppm. FT-IR spectra were recorded on a Nicolet Magna-IR 560 spectrometer. Fluorescence spectra were recorded on a Jobin-Yvon Horiba Fluoromax-3 instrument. APCI mass spectra were obtained on a Finnigan ThermoQuest Navigator aQa single-quadrupole LC-MS instrument.

2.3.2 Synthesis of Tris[2-(5-dimethylamino-1-naphthalenesulfonamido)ethyl]amine.

To a stirring solution of dansyl chloride (0.12 g, 0.46 mmol) dissolved in 6 mL of 1,2-DCE, a solution of 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene[23] (0.039 g, 0.155 mmol) and triethylamine (0.062 mL, 0.465 mmol) in 2 mL of anhydrous 1,2-DCE was slowly added. After stirring for 4 h, 15 mL ethyl acetate (0.1 M in water) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined CH_2Cl_2 layers were dried by pouring through an anhydrous sodium sulfate column and evaporated to ca. 5 mL. Hexanes was added dropwise and the yellow precipitate was collected, purified by column chromatography (70:30 CH_2Cl_2/EtOAc) and dried under vacuum yielding **2** (0.12 g, 85% yield): mp 218-220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), 0.45 (9H, t, J = 7.4 Hz), 1.86 (6H, q, J = 7.4 Hz), 2.93 (18H, s), 3.66 (6H, d, J = 5.2 Hz), 4.14 (3H, t, J = 10.29 Hz), 7.24 (3H, d, J = 7.6 Hz), 7.56 (6H, m) 8.22 (3H, d, J = 8.6 Hz), 8.26 (3H, d, J = 7.2 Hz), 8.58 (3H, d, J = 8.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz) δ 15.6, 21.8, 40.8, 45.4, 115.4, 118.4, 123.0, 128.5, 129.6, 129.7, 129.8, 130.2, 130.7, 133.4, 144.3, 152.0; FT-IR (CH_2Cl_2, thin film-cm^{-1}) 3282. Elemental anal. Calcd for $C_{51}H_{60}N_6O_6S_3 \cdot 3CH_2Cl_2$: C, 61.1; H, 6.6; N, 8.4. Found: C, 60.9; H, 6.3; N, 8.3. APCI

Mass Spectrometry: Calculated for $(M-H)^-$: 947.3. Found: 947.3. *Note*: **2** was kept stored in the dark.

2.3.3 ^{1}H NMR Titrations

The association constants for the formation of anion-receptor complexes were determined by titration of **2** (2×10^{-3} M) in $CDCl_3$ (solution A) with 0.1 - 0.7 M solutions of $(n\text{-}Bu)_4N^+X^-$ (X^- = Cl^-, Br^-, I^-, and NO_3^-), prepared by dilutions with solutions A, thus keeping a constant concentration of **2** (Solution B). In a typical experiment, solution A (0.700 mL) was placed in an NMR tube. Solution B was added in increments ranging from 1.0 μL to 50.0 μL at a time. The chemical shift changes for the N-H proton were monitored, with the results plotted and fitted to the 1:1 binding isotherm (Eq.2)[34] using non-linear regression analysis:

$$\Delta\delta = \delta_{obs} - \delta_2$$
$$= ([\mathbf{2}]_t + [X^-]_t + K_a^{-1} - ((([\mathbf{2}]_t + [X^-]_t + K_a^{-1})^2 - 4[X^-]_t\,[\mathbf{2}]_t)^{1/2}))\Delta\delta_{max}) / (2[\mathbf{2}]_t) \quad \text{(Eq.2)}$$

2.3.4. Fluorescence Spectroscopy

Fluorescence titrations were run using solutions of **2** (1×10^{-6} M) in CH_2Cl_2 (solution A), which were titrated, with solutions of $(n\text{-}Bu)_4N^+NO_3^-$ (1×10^{-3} M) and **2** (1×10^{-6} M) in CH_2Cl_2 (solution B). Fluorescence emission was measured using an excitation wavelength of 352 nm, a measurement increment of 0.5 nm, and integration time of 0.1 s, excitation slit width of 10 nm, emission slit width of 5 nm, and an emission wavelength of 505.5 nm. The intensity of the dansyl fluorescence at 505.5 nm was monitored and recorded. 2.5 mL of solution A was added to the fluorescence cuvette and solution B was added up to 240 equivalents of anion, in increments between 0.5 to 200 μL.

Fluorescence continuous variation experiments were run by varying the concentrations of both $(n\text{-Bu})_4N^+X^-$($X^- = NO_3^-$, Cl^-, Br^- and I^-) and **2**. Ten solutions were prepared by mixing solutions of $(n\text{-Bu})_4N^+X^-$($X^- = NO_3^-$, Cl^-, Br^- and I^-) and **2** (2×10^{-3} M) in variable volume ratios. The solutions were prepared in volume ratios of **2** to $(n\text{-Bu})_4N^+X^-$($X^- = NO_3^-$, Cl^-, Br^- and I^-) varying from 10:0 to 1:9 (10.0 mL total volume, from 10.0 mL of **2**, to 1.0 mL of **2** plus 9.0 mL of $(n\text{-Bu})_4N^+X^-$($X^- = NO_3^-$, Cl^-, Br^- and I^-). A set of control samples was also run, where CH_2Cl_2 was used in place of anion solutions. The Job plot was constructed by plotting $I - I_o$ *vs.* the property x, defined by Eq. 2.1, where L is **2** and X^- is anion.[24]

$$x = [L]_f / ([L]_f + [X^-]_f) \qquad \text{(Eq. 2.1)}$$

2.3.5. UV-Visible Spectroscopy

A 1×10^{-5} M solution of **2** in CH_2Cl_2 was prepared (solution A). A solution of $(n\text{-Bu})_4N^+NO_3^-$ (1×10^{-3} M) and **2** (1×10^{-5} M) was prepared by dilutions with solution A (solution B). After an initial UV-visible spectrum of solution A was collected, the solution A was titrated with solution B in increments ranging from 1.0 to 300.0 μL at a time. Spectra were collected in the 200 to 600 nm range.

2.3.6. FT-IR Spectroscopy

(2.5×10^{-3} M) solutions of the **2** and $(n\text{-Bu})_4N^+X^-$($X^- = NO_3^-$, Cl^-, Br^-, I^-) (7.5×10^{-3} M) were prepared in CH_2Cl_2. The two solutions were mixed in equal amounts, and the spectrum of the new solution was obtained in a NaCl, FT-IR solution cell. Right after the collection the same solution was layered on a NaCl plate in order to form a thin film (via slow evaporation), and the spectrum was obtained. The same procedure was applied

for the solution of the free receptor. A resolution of 4 cm^{-1} was used, and spectra were collected in the 4000 to 600 cm^{-1} range.

2.3.7. APCI-MS Experiments

The mass spectrometer was tuned within a range of 200 to 1100 atomic mass units and CH_2Cl_2 was run through the instrument before each analysis. 2.0 x 10^{-3} M solutions of **2** and 4.0 x 10^{-3} M of $(n\text{-}Bu)_4N^+X^-$ ($X^- = NO_3^-$, Cl^-, Br^-, I^-) were prepared in CH_2Cl_2. Spectra were obtained in APCI negative-ion detection mode after mixing the solutions in 1:1 volume ratios. The resulting solutions were introduced directly into the mass spectrometer by a thermal desorption technique (ramping the probe temperature). The following settings were utilized: Flow rate of sample infusion of 100 μL/min; cone voltage of –15 V; corona pin voltage of 4.5 kV; thermal desorption by ramping the probe temperature from 25°C to 375°C. After spectral collection, it was assured that the sample was fully desorbed before the next run was attempted, and CH_2Cl_2 was used to rinse the system between sample runs.

2.4. Conclusion

We have shown that selective nitrate binding can be achieved with a rigid and preorganized 1,3,5-tris(aminomethyl)benzene framework. Study of the binding properties may be useful in the design of further versatile, selective and widely applicable anion receptors. Trends in structure-binding relationships show receptor flexibility is an important factor in anion recognition. We expect that the anion binding properties of this

and other similar compounds available in large quantities will lead to future applications in separations and anion sensing devices.

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Chapter 3*: Spectroscopic and Electrochemical Investigation of the Anion Binding Properties of a Quinone Derivative of 1,3,5-Tris(2-aminomethyl)-2,4,6-triethylbenzene

3.1. Electrochemical Studies in Supramolecular Chemistry

Electroanalytical chemistry can play a very important role in the protection of our environment. In particular, electrochemical sensors and detectors can be used for on-site monitoring of priority pollutants, and satisfy many of the requirements for on-site environmental analysis. They are inherently sensitive and selective towards electroactive species, fast and accurate, compact, portable and inexpensive. Such capabilities have already made a significant impact on decentralized clinical analysis. Yet, despite their great potential for environmental monitoring, broad applications of electrochemical sensors for pollution control are still in their infancy.

Several electrochemical devices, such as pH- or oxygen electrodes, have been used routinely for years in environmental analysis. Recent advances in electrochemical sensor technology are expected to expand the scope of these devices towards a wide range of organic and inorganic contaminants. These advances include the introduction of modified- or ultra microelectrodes, selective chemical or biological recognition layers, molecular devices or sensor arrays, and developments in the areas of microfabrication, computerized instrumentation, and flow detectors.

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*The work was completed with the assistance of Dr. Robert J. Alvarado.

The purpose of a chemical sensor is to provide real-time reliable information about the chemical composition of its sample. Ideally, such a device is capable of responding continuously and reversibly and does not perturb the sample. Sensors normally consist of a transduction element covered with a biological or chemical recognition layer. In the case of electrochemical sensors, the analytical information is obtained from the electrical signal that results from the interaction of the target analyte and the recognition layer. Different electrochemical devices can be used for the task of environmental monitoring (depending on the nature of the analyte, the character of the sample matrix, and sensitivity or selectivity requirements). Most of these devices fall into two major categories (in accordance to the nature of the electrical signal): amperometric and potentiometric.

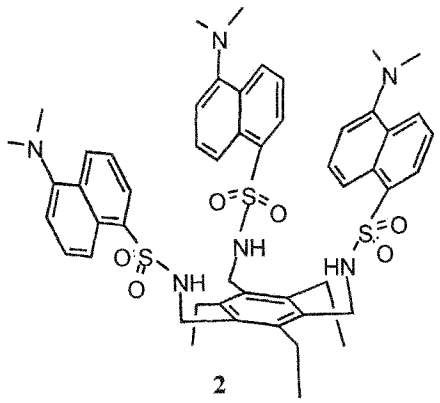
Amperometric sensors are based on the detection of electroactive species involved in the chemical or biological recognition processes. The signal transduction process is accomplished by controlling the potential of the working electrode at a fixed value (relative to a reference electrode) and monitoring the current as a function of time. The applied potential serves as the driving force for the electron transfer reaction of the electroactive species. The resulting current is a direct measure of the rate of the electron transfer reaction. It is thus reflecting the rate of the recognition event, and is proportional to the concentration of the target analyte.

In potentiometric sensors, the analytical information is obtained by converting the recognition process into a potential signal, which is proportional (in a logarithmic fashion) to the concentration (activity) of species generated or consumed in the recognition event. Such devices rely on the use of ion selective electrodes for obtaining

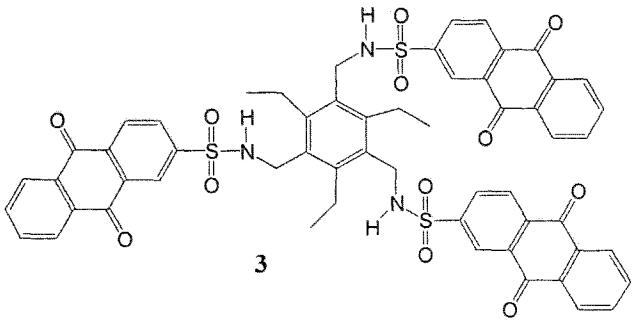
the potential signal. A permselective ion-conductive membrane (placed at the tip of the electrode) is designed to yield a potential signal that is primarily due to the target ion. Such response is measured under conditions of essentially zero current. Potentiometric sensors are very attractive for field operations because of their high selectivity, simplicity and low cost. They are, however, less sensitive and often slower than their amperometric counterparts. In the past, potentiometric devices have been more widely used, but the increasing amount of research on amperometric probes is expected to gradually shift this balance. Detailed theoretical discussion on amperometric and potentiometric measurements are available in many textbooks and reference works.[1-5]

Quinone-based sensors have received considerable attention as an interesting class of ionic and molecular binding hosts. It has been found that various derived calixquinones were selective host molecules for cations (alkali metal cations, alkylammonium ions).[6-8] Recently, calixquinones have been synthesized as redox-switchable calixarenes and studied for their electrochemistry and ionic binding[9-12]. A redox-switchable receptor is a compound capable of forming a complex with a given substrate in such as way that the thermodynamic stability of the complex is determined by the oxidation state of the receptor. The reduction of quinones in non-aqueous solvents is as an excellent example of a simple two-step cathodic reduction in which the quinone is first reduced to its radical anion and then to the dianion with the standard potential for insertion of the second electron falling a few tenths of a volt negative of that for the first electron. Because our studied trisulfonamide analog **2**, binds nitrate selectively in CH_2Cl_2, and as part of our efforts to develop an electrochemical sensor, we focused our attention on combining the sensing moiety antraquinone and the rigid

1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene framework, thus synthesizing a new potential selective tripodal sensor for the nitrate anion (**3**). In this chapter, a spectroscopic and electrochemical study of the anion binding properties of **3** is reported.



2



3

3.2. Results and Discussion

3.2.1 Synthesis

Compound **3** was synthesized in good yields from 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene[13] and Anthraquinone-2-sulfonyl chloride.[14] The compound was recrystallized from CH_2Cl_2/hexanes and dried under vacuum at 40 °C. **3** (Figure 3.1) was characterized by ^{1}H-NMR.

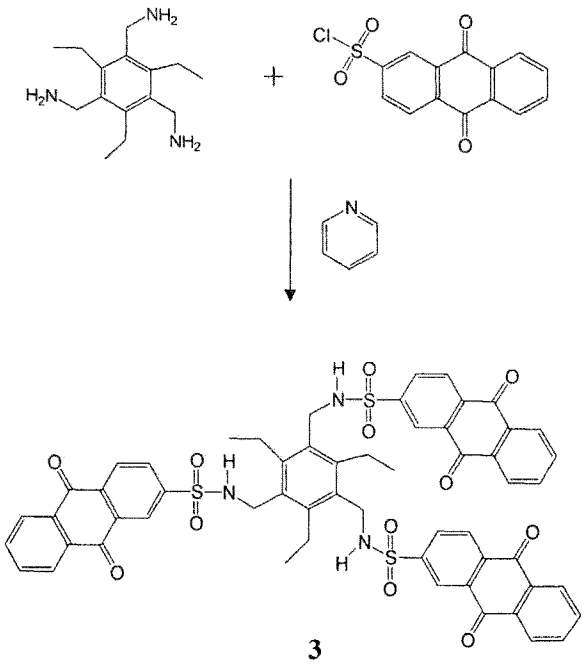


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Figure 3.1. Pathway for synthesis of compound **3**.

3.2.2. ^{1}H-NMR Titrations

The anion binding properties of compound **3** were determined in $CDCl_3$ by ^{1}H-NMR titration experiments. Tetrabutylammonium salts of the chloride and nitrate anions were used as the anion sources. Significant downfield shifts of the N-H proton resonance were observed, suggesting anion binding via hydrogen bonding (Figure 3.2). In all experiments only a single N-H resonance was observed, suggesting the participation of all three N-H protons in anion binding. This could occur in one of two ways: either with all three N-H protons of receptor **3** binding simultaneously, or with a fast exchange of different complex forms involving all three protons.

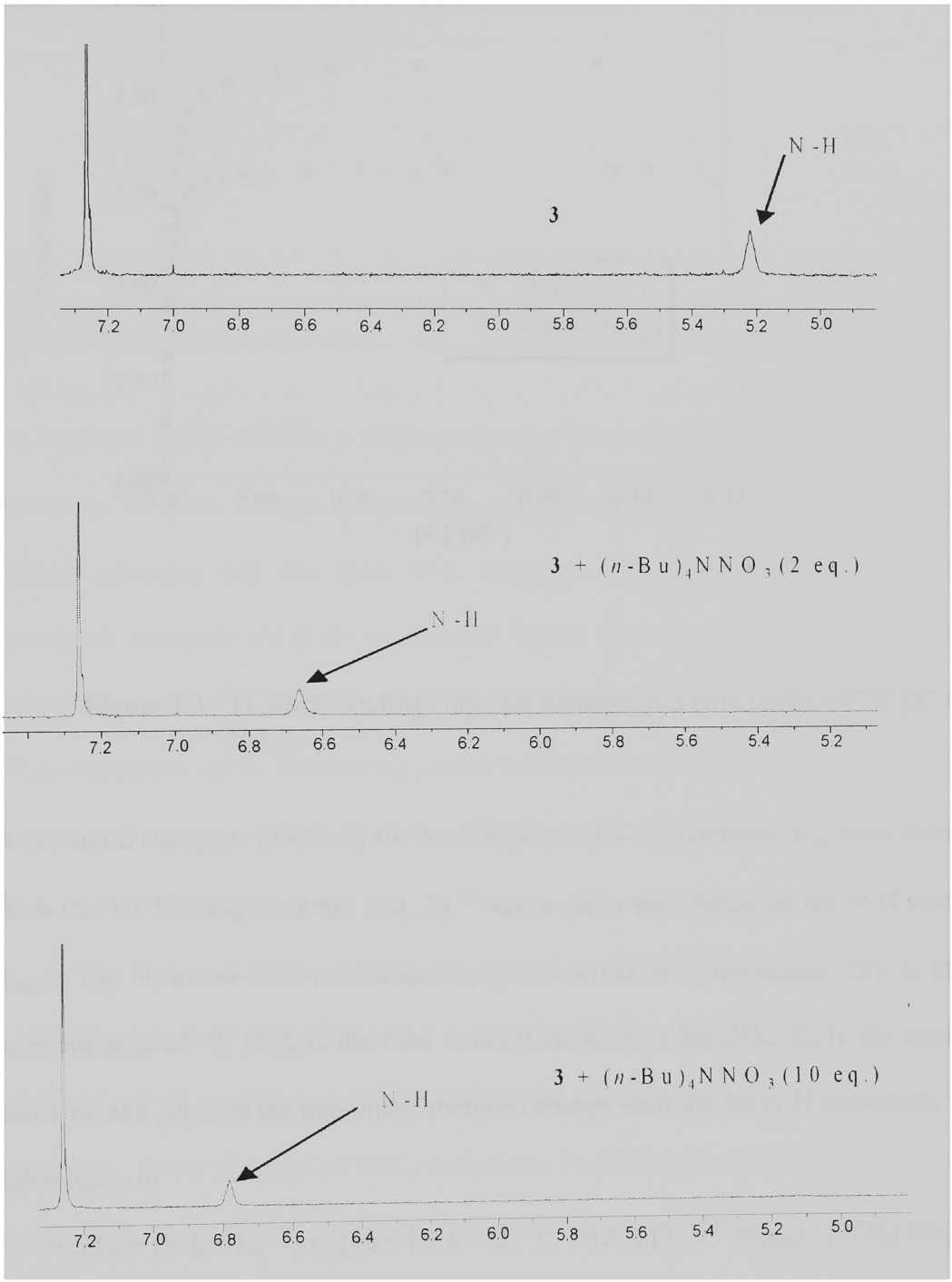

Figure 3.2. ^{1}H-NMR spectra (N-H resonance region) of i) **3** in $CDCl_3$ (top), ii) after titration with 2 eq. of n-Bu_4NNO_3 (middle), and iii) after titration with 10 eq. of $(n\text{-Bu})_4NNO_3$ (bottom).

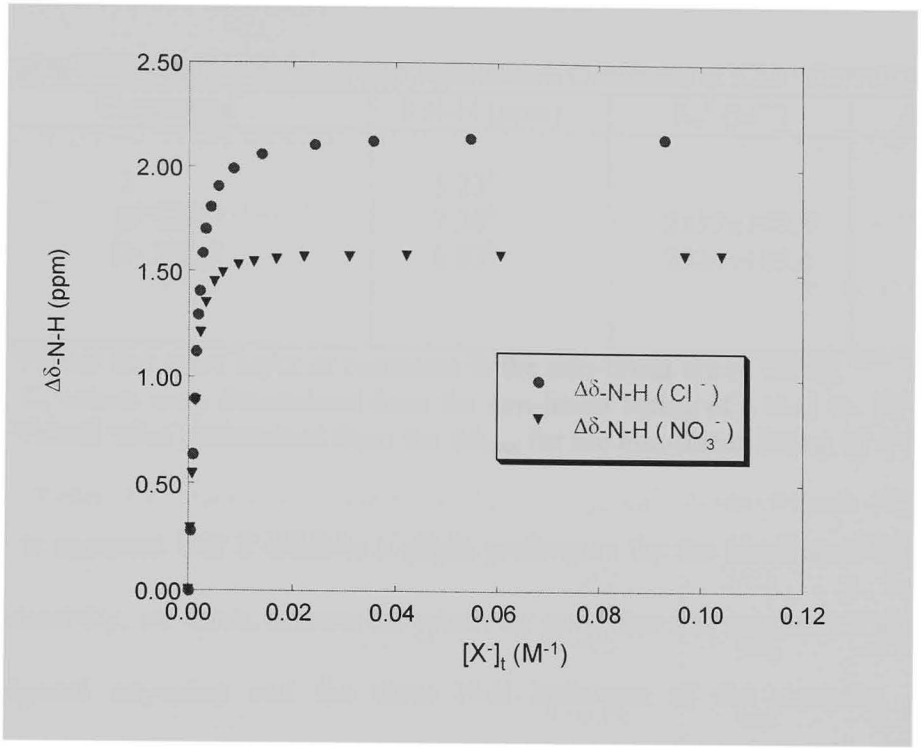

Figure 3.3. ^{1}H-NMR binding curve for titration of **3** with $(n\text{-Bu})_4N^+X^-$ ($X^- = Cl^-$, NO_3^-).

Association constants (Table 3) for the formation of a 1:1 complex, K_a, were determined from the 1:1 binding isotherm (Eq. 3),[15] where $\Delta\delta$ is the change in the N-H resonance, δ_{obs} is the observed N-H resonance, δ_3 is the actual N-H resonance, $[\mathbf{3}]_t$ is the total concentration of **3**, $[X^-]_t$ is the total concentration of $(n\text{-Bu})_4NX$, K_a is the association constant, and $\Delta\delta_{max}$ is the maximum chemical change shift for the N-H resonance.

$$\Delta\delta = \delta_{obs} - \delta_3$$

$$= ([\mathbf{3}]_t + [X^-]_t + K_a^{-1} - ((([\mathbf{3}]_t + [X^-]_t + K_a^{-1})^2 - 4[X^-]_t\,[\mathbf{3}]_t)^{1/2}\,\Delta\delta_{max}) / (2[\mathbf{3}]_t) \quad \text{(Eq. 3)}$$

Table 3 ^{1}H-NMR Titrations and Association Constants at 22.0 °C in $CDCl_3$

Compound	δ N-H (ppm)	K_a[b] (M^{-1})	ΔG° (kJ/mol)
3	5.23[a]		
[**3**· Cl]$^-$	7.38[b]	2137±147.9	-18.8
[**3**· NO_3]$^-$	6.83[b]	2524±105.6	-19.2

[a] Values that were input as constants in the non-linear curve fitting.
[b] K_a values were determined from the non-linear fitting of δ N-H vs. [X^-].
[c] Values were determined from the $\Delta\delta_{max}$ for the non-linear fitting of δ N-H vs. [X^-].

It is apparent that **3** exhibits a slight preference for the binding of NO_3^- over Cl^-. This selectivity, we think, reflects the relatively good size and geometry matching between the trigonal oxyanion and the three N-H hydrogen of the receptor. Additionally, the association constants for **3** are remarkably higher than those observed for receptor **2**, probably due to the fact that the quinone groups are electron withdrawing, making the NH protons more acidic thus having greater hydrogen bond donor capability.

3.2.3 Electrochemistry

The Cyclic Voltammograms and Osteryoung Square Wave Voltammograms of 2 x 10^{-4} M solution of disulfonamide **3** in CH_2Cl_2 were recorded before and after addition of 20, 40 and 80 equivalents of (n-Bu_4)NNO_3. 0.1 M (n-Bu_4)NPF_6 was used as an inert electrolyte. In the absence of NO_3^-, compound **3** exhibits five different redox processes as demonstrated by both Cyclic Voltammetry (CV) and Osteryoung Square Wave Voltammetry (OSWV). This behavior is unexpected and suggests that the three anthraquinone groups are interacting with each other. The first reduction process probably corresponds to the reduction of one of the three antraquinone groups to the

radical anion while the second reduction, which appears to be higher in current, possibly corresponds to the reduction of the other two groups to the radical anions. Consistently with this interpretation, the remaining redox process could correspond to the reduction of the quinone groups to the dianionic forms. The reversibility of these processes is difficult to access due to the fact that the peaks are overlapping. The reduction potentials of **3** are summarized in Table 3.1.

Table 3.1. Reduction Potentials of **3** (vs. Ag/Ag^+) in the absence of NO_3^- was determined by OSWV.

	E_1/V	E_2/V	E_3/V	E_4/V	E_5/V
3	-0.8208	-0.9480	-1.108	-1.400	-1.556
[**3**· NO_3]$^-$		-0.9480	-1.108	-1.400	

As demonstrated by both CV (Figure 3.4) and OSWV (Figure 3.5), addition of NO_3^- to a solution of **3** causes cathodic shifts in the potential of the first reduction. These shifts are attributed to the binding of NO_3^- by **3**. Clearly, there is a strong electrostatic interaction between the NO_3^- and at least one of the quinone groups causing the reduction of the quinone to the radical anion to become more difficult. Interestingly, no significant cathodic shifts were observed for the other redox processes. This is probably due to the expulsion of the NO_3^- upon the reduction of the first quinone unit. Analogous behavior has been observed in binding studies with tetrathiafulvalene modified cation receptors.[16]

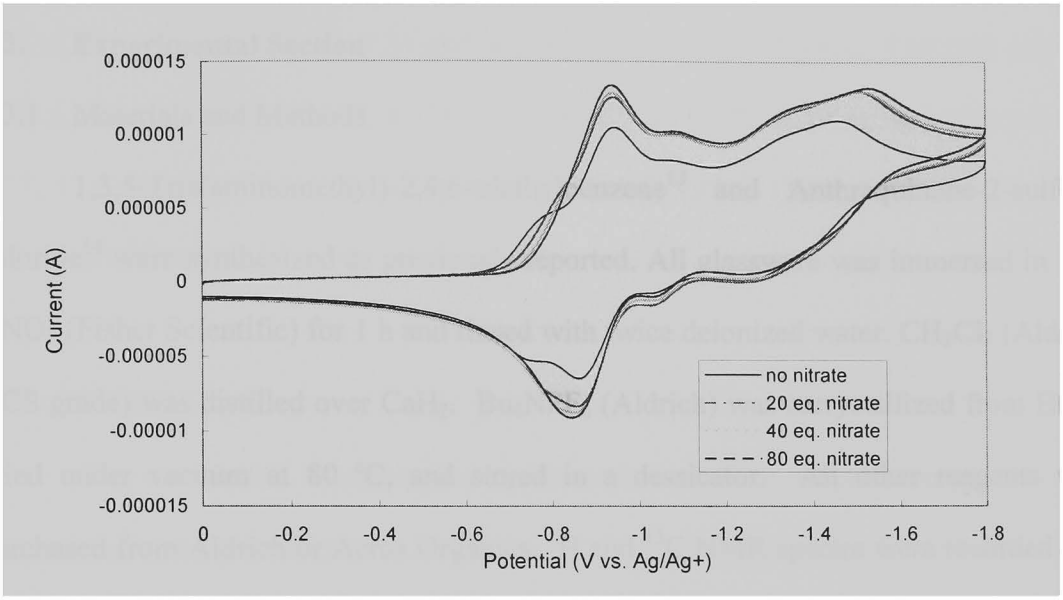

Figure 3.4. Cyclic Voltammetry of **3** in the absence and presence of 20, 40, and 80 equivalents of NO_3^-.

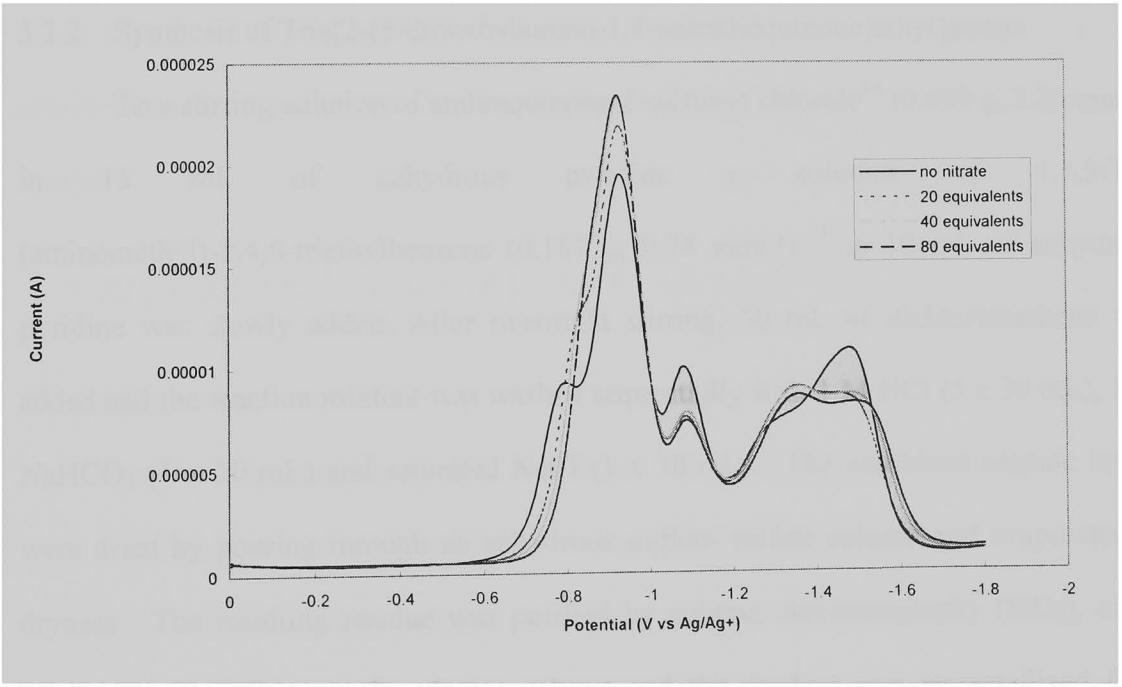

Figure 3.5. Osteryoung Square Wave Voltammetry of **3** in the absence and presence of 20, 40, and 80 equivalents of NO_3^-.

3.3. Experimental Section

3.3.1 Materials and Methods

1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene[13] and Anthraquinone-2-sulfonyl chloride[14] were synthesized as previously reported. All glassware was immersed in 50% HNO_3 (Fisher Scientific) for 1 h and rinsed with twice deionized water. CH_2Cl_2 (Aldrich, ACS grade) was distilled over CaH_2. Bu_4NPF_6 (Aldrich) was recrystallized from EtOH, dried under vacuum at 80 °C, and stored in a dessicator. All other reagents were purchased from Aldrich or Acros Organics. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer and were referenced to the residual solvent resonance. All chemical shifts, δ, are reported in ppm.

3.3.2. Synthesis of Tris[2-(5-dimethylamino-1,4-antrathoquinone)ethyl]amine

To a stirring solution of anthraquinone-2-sulfonyl chloride[14] (0.690 g, 2.25 mmol) in 15 mL of anhydrous pyridine a solution of 1,3,5-Tris (aminomethyl)-2,4,6-triethylbenzene (0.187 g, 0.74 mmol) [13] in 10 mL of anhydrous pyridine was slowly added. After overnight stirring, 50 mL of dichloromethane was added and the reaction mixture was washed sequentially with 1 M HCl (5 x 30 mL), 1 M $NaHCO_3$ (1 x 30 mL) and saturated NaCl (1 x 30 mL). The combined organic layers were dried by pouring through an anhydrous sodium sulfate column and evaporated to dryness. The resulting residue was purified by column chromatography (SiO_2), using 50:50 CH_2Cl_2/EtOAc as the eluting solvent and the product was recrystallized from CH_2Cl_2/hexanes, yielding **2** as a light green solid. (0.16g, 0.15 mmol, 20%): mp 208-210 °C; ^1H-NMR ($CDCl_3$, 400 MHz), 0.92 (9H, t, J = 7.4 Hz), 2.47 (6H, q, J = 7.4 Hz), 4.24

(6H, d, J = 4.3), 5.23 (3H, s), 7.85 (6H, m), 8.24 (3H, dd, J = 4.6 Hz), 8.30 (6H, m), 8.42 (3H, d, J = 8.1 Hz), 8.52 (3H, d, J = 1.7 Hz) $^{13}C\{^1H\}$ NMR ($CDCl_3$, 400 MHz) δ 16.2, 22.7, 41.0, 125.7, 127.6, 127.7, 128.5, 130.2, 131.9, 133.0, 133.2, 133.8, 134.7, 134.8, 135.8, 144.8, 144.9, 181.6, 181.8.

3.3.3. ^1H NMR Titrations

The association constants for the formation of anion-receptor complexes were determined by titration of **3** (2 x 10^{-3} M) in $CDCl_3$ (solution A) with 0.2 M $(n\text{-}Bu)_4N^+X^-$ (X^- = Cl^- and NO_3^-), prepared by dilutions with solution A, thus keeping a constant concentration of **3** (Solution B). In a typical experiment, solution A (0.700 mL) was placed in an NMR tube. Solution B was added in increments ranging from 1.0 μL to 50.0 μL at a time. The chemical shift changes for the N-H proton were monitored, with the results plotted and fitted to the 1:1 binding isotherm (Eq. 3)[17] using non-linear regression analysis:

$$\Delta\delta = \delta_{obs} - \delta_3$$
$$= ([\mathbf{3}]_t + [X^-]_t + K_a^{-1} - ((([\mathbf{3}]_t + [X^-]_t + K_a^{-1})^2 - 4[X^-]_t\,[\mathbf{3}]_t)^{1/2}))\Delta\delta_{max}) / (2[\mathbf{3}]_t) \quad \text{(Eq. 3)}$$

3.3.3. Electrochemistry

Prior to measurements, the salts were dried under vacuum at 80° C. All measurements were performed under N_2 in degassed CH_2Cl_2 containing 0.1 M Bu_4NPF_6, as the supporting electrolyte, using a three-electrode cell. Furthermore, the N_2 flow was saturated with vapors of the solvent. To saturate the atmosphere with these vapors, the N_2 was bubbled through a separate chamber containing the solvent. The saturation of the N_2 flow with solvent vapors helps to minimize evaporation effects. The concentration of

3 was 2.0 x 10^{-4} M. Tetrabutylammonium nitrate was dissolved in CH_2Cl_2 and added in microliter amounts. Electrochemical experiments were preformed with a CH Instrument (CHI) model 650B electrochemical workstation. A glassy carbon electrode (3.0 mm diameter) from CHI was used as a working electrode and a non-aqueous Ag/Ag^+ electrode from CHI was the reference electrode. A Pt wire served as the counter electrode. Solution resistance compensation was applied at all times.

3.4. Conclusion

In this work we reported the synthesis and binding properties of a new quinone-based receptor capable of anion binding and electrochemical sensing. The binding of NO_3^- to **3** is slightly stronger than of Cl^- presumably because of the relatively good size and geometry matching between this particular triangular anion and the receptor. Thus, this novel quinone-based receptor not only forms thermodynamically very stable complexes with NO_3^- but can also sense this anion guest electrochemically via substantial negative shifts of potential. The anion binding properties of this receptor could possibly have potential applications to areas such as anion sensing devices and ion-specific electrodes.

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