HYDROGEN BOND BASED NONCOVALENT ASSOCIATION IN THE SEMI-FLUOROUS SOLVENT PERFLUOROBUTYL-METHYL ETHER: HOST-HOST AND HOST-GUEST ASSOCIATION OF THE HOST 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-HEPTADECAFLUORO-DECYL)-3-PYRIDIN-2-YL-UREA

by

Candace McGowan

BS, Florida State University, 2010

Submitted to the Graduate Faculty of

The Dietrich School of Arts and Sciences

in partial fulfillment

of the requirements for the degree of Master of Science

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Candace McGowan

It was defended on

August 15, 2013

and approved by

Dr. Dennis Curran, Professor, Department of Chemistry

Dr. Shigeru Amemiya, Professor, Department of Chemistry

Thesis Director: Dr. Stephen G. Weber, Professor, Department of Chemistry

HYDROGEN BOND BASED NONCOVALENT ASSOCIATION IN THE SEMI-FLUOROUS SOLVENT PERFLUOROBUTYL-METHYL ETHER: HOST-HOST AND HOST-GUEST ASSOCIATION OF THE HOST 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-HEPTADECAFLUORO-DECYL)-3-PYRIDIN-2-YL-UREA

Candace McGowan, M.S.

University of Pittsburgh 2013

A fluorous pyridyl-urea, 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-3-pyridin-2-yl-urea, was prepared to act as a host and analyzed by ^{1}H NMR inCD$_2$Cl$_2$ and perfluorobutyl-methyl ether (HFE7100). Crystals were analyzed by X-ray diffraction. The host molecules were found to form pillar-like structures in the crystal. There is an intramolecular bond between the pyridyl nitrogen and one urea hydrogen. ^{1}H NMR spectra demonstrated that the urea hydrogens' positions shift as the concentration of the host changes. The dependence of the shifts on concentration are consistent with the formation of a trimer of hosts with a logK$_{eq}$ for formation of trimer from monomer approximately 6. Association of the host with guests octanoic acid, ethyl acetate, *N*-ethylacetamide, *N,N*-dimethylacetamide, and acetone, was analyzed by titration of the host with individual guests in HFE7100 solvent. Downfield or upfield shifts of the urea hydrogens were used to indicate hydrogen bond formation with the guest. Acetone and ethyl acetate were unable to overcome the self-association of the host and form host-guest complexes. Octanoic acid binding caused shifts in the ^{1}H NMR spectra of one hydrogen of the urea group. *N*-ethylacetamide and *N,N*-dimethylacetamide induced shifts in both urea hydrogens. The

results indicate that the host monomer's favored conformation contains an intramolecular hydrogen bond. This bond is not broken upon association with octanoic acid, but it is broken upon association with the two acetamides.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF EQUATIONS

PREFACE

I would like to thank my advisor, Dr. Weber, and my family for their support throughout the years.

Nomenclature

HFE7100 - perfluorobutyl-methyl ether

Fluorous pyridyl-urea - 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-3-pyridin-2-yl-urea

1.0   INTRODUCTION

1.1   SELECTIVE EXTRACTION AND MOLECULAR RECOGNITION

Selective extraction has long been an area of interest for analytical researchers. The notion of aiding the solubility of an analyte of interest with a host molecule in an otherwise poor solvent has manifested itself in many different areas of chemistry. Since the early days of work with cyclodextrin and crown ethers[1], metal ion chelators have been used to aid extraction of metals into organic and fluorous solvents[2-4] and artificial receptors have been constructed to aid extraction of barbiturates[5,6]. Though the host/guest concept is the same for all these techniques, the forces used to create the bond between host and guest can differ greatly. Hydrogen bonding is extremely important in nonpolar solvents and, along with π-stacking forces[7], is one of the two most commonly used forces used in molecular recognition. Because of this, hydrogen bonding shall be the main focus of this paper.

1.1.1   Hydrogen Bonding

Intermolecular hydrogen bonds between host and guest compete in solution with solute-solvent and solvent-solvent interactions[8]. Generally speaking, the equilibria having a more favorable ΔG value will be the dominant interaction. A general method to describe the solute and solvent of

1

interest has been well-documented. First, a description of the solute or solvent must be determined by assigning values for its ability to act as a hydrogen bond donor (α) and as a hydrogen bond acceptor (β)[8,9]. By using the values for α and β, it is possible to estimate the $\Delta\Delta G_{\text{H-Bond}}$ for this system and determine which interactions will prevail. It should be noted that this profile was constructed under the assumption of neutral functional groups.
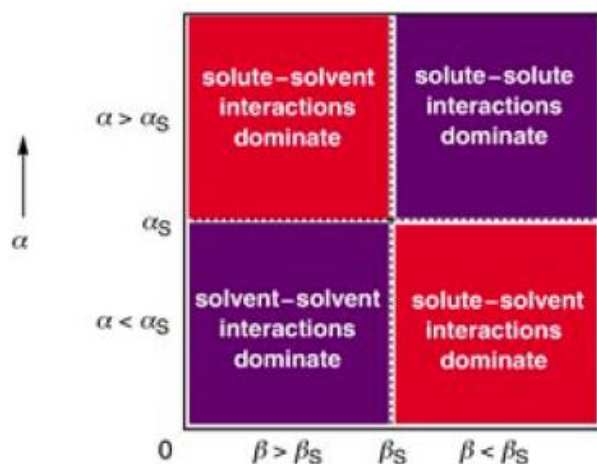
Figure 1-1 – Guide to hydrogen bond interactions in solution.[8] Figure reproduced with permission from Angewandte Chemie

A convenient way to ascertain which interactions (solute-solvent, solvent-solvent, or solute-solute) will dominate a given system is to use a chart similar to the one shown in Figure 1-1 from Hunter[8]. Favorable (-$\Delta\Delta G_{\text{H-Bond}}$) interactions are displayed in the two blue quadrants, while the red quadrants indicate unfavorable (+$\Delta\Delta G_{\text{H-Bond}}$) interactions. Using this guide and a table of α and β values, it is possible to extend this general idea to what functional groups will provide favorable host-guest H-bond interactions. Because α and β are zero or slightly negative (in the case of β) in perfluorinated solvents[9], hydrogen bond interactions should prove favorable in these solvents.

1.1.2 The Urea Group and Pyridyl-Ureas

Of particular interest to host-guest interaction research has been the urea group. According to Hunter's table, urea functions as both a hydrogen bond donor ($\alpha = 3.0$) and a strong hydrogen bond acceptor ($\beta = 8.3$). This makes urea an extremely versatile host[10-14] or guest[15,16]. Ureas have also been utilized in stereoselective reactions[17].

Because of the dual hydrogen bond donor-acceptor characteristic of the urea group, it tends to self-assemble. This tendency can prove very useful in the construction of crystals[18-22] and gelators[23]. Having crystals available for analysis via X-ray diffraction provides urea group-containing hosts or guests the unique opportunity to truly "see" the hydrogen bond network involved in the crystal structure. X-ray studies have shown the formation of pillar-like structures when aromatic rings contain urea substitutents.[20,24] When the aromatic ring is pyridine, the urea groups can form a hydrogen bond with either the pyridyl nitrogen or the urea oxygen. . Because of this, pyridyl-ureas have a documented history of intramolecular bonding between the urea group and the pyridyl-nitrogen[23,25]. Figure 1-2 uses X-ray diffraction to show this unique network of intermolecular and intramolecular hydrogen bonding possible in pyridyl-ureas.
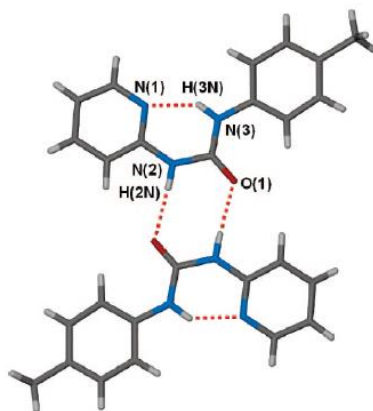
Figure 1-2 - X-ray crystal structure of inter and intramolecular hydrogen bonding in pyridyl-ureas.[25] Figure reproduced with permission from ACS

Observing Figure 1-2, it is clear that H_{3N} from the urea group and N_1 of the pyridine form an intramolecular hydrogen bond. This leaves H_{2N} and the oxygen from the urea group free to form an intermolecular hydrogen bond. Despite the tendency of pyridyl-ureas to form intramolecular bonds and self-associate, they have been shown to be effective hosts for carboxylic acids[13], hydrogen bond donors[20], oxo-anions[26], and metals[27].

1.1.3   NMR Investigation of Complex Formation

Even more information can be obtained about ureas and pyridyl-ureas through NMR study. ^{1}H NMR has been successfully applied in the investigation of hydrogen bonding in studies as intricate as amino acids and nucleotides[28-30]. ^{1}H NMR has also been a mainstay in the study of complex formation in both self-associating[31-40] and hetero-associating[41-43] molecules. Depending on the structure of the host/guest, self-association and hetero-association can occur simultaneously[15,44-47], leading to difficulties in obtaining equilibrium constants for the system.

NMR has also been used in the investigation of urea compounds[48-50] and urea complexes.[12-15,48] ^{1}H NMR is an incredibly useful tool which can provide valuable knowledge of the chemical environment in which a given urea hydrogen resides. Even knowledge of the structure of the molecule surrounding the urea hydrogen is sometimes possible through ^{1}H NMR. Typically, ^{1}H NMR is used in the study of complex formation to elucidate the stoichiometry and provide the binding constant of the complex in solution. This is usually accomplished by plotting the chemical shift (ppm) versus the equivalents of guest added (M). The binding constant is then obtained by linear or non-linear regression fitting of the line or curve.[32,44,51,52] This process is demonstrated in Figure 1-3.
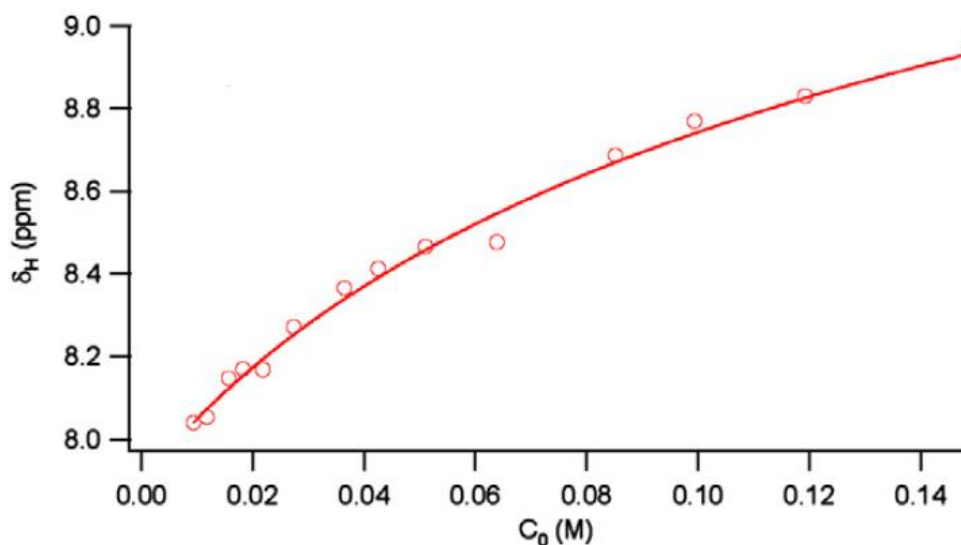
Figure 1-3 - Determination of binding constant by curve-fitting.[31] Figure reproduced with permission of Elsevier

For simple systems, the curve-fitting process works very well in the determination of binding constants. However, in more complex systems involving both self-association and hetero-association, this technique becomes less accurate[44,52].

1.2 FLUOROUS MEDIA

The term "fluorous" was first coined in 1994 by Horvath in his seminal paper detailing the usage of an organic phase and an immiscible fluorous phase in catalysis[53,54]. Since then, these highly non-polar solvents[55] have become increasingly popular[56-58] for many different purposes. Catalysis[59-63], synthesis[27,64-70], chiral separation[71-74] and selective extractions[6,64,75-78] have all found uses for the fluorous phase. However, the mere appearance of fluorine does not make a molecule "fluorous"

Many studies have been done to determine how to predict the partitioning of solutes into the fluorous phase, or in other words, how to predict "fluorophilicity."[56,57,79] Several general rules for prediction of fluorophilicity exist, such as a minimum fluorine content of 60% or the presence of one or more fluorous "ponytails."[57,59] One might postulate from this that simply adding $-CF_2-$ groups will automatically cause a molecule to partition into the fluorous phase, rather than the organic phase. However, as detailed by O'Neal[76] and Huque,[56] if the solubility parameter for a particular solute (δ_b) is greater than the solubility parameter for the organic solvent (δ_o), then the addition of $-CF_2-$ shall cause the solute to further partition into the organic phase. However, if the solubility parameter of the solute (δ_b) is between that of the organic

solvent (δ_o) and that of the fluorous solvent (δ_F), then the addition of –CF$_2$- shall cause partitioning into the fluorous phase. Hence, the mere addition of –CF$_2$- does not intrinsically guarantee partitioning into fluorous media.

As with organic solvents, there are decisions to be made when choosing a fluorous solvent. Although there are considerably fewer choices with regards to fluorous media, there are still many differences between fluorous solvents. Table 1 below provides a summary of several different fluorous and semi-fluorous solvents and their characteristics. Although many other fluorous and semi-fluorous solvents exist, the table below provides an overview of some of the physical properties that can be achieved with fluorinated solvents.

Table 1-1 - Summary of fluorous solvent properties.[53] Table reproduced with permission from Elsevier

	FC-72	HFE7100	HFE7500	HFE7200	F-626
Formula	C_6F_{14}	$C_4F_9OCH_3$	$C_3F_7CF(OC_2H_5)$-$CF(CF_3)_2$	$C_4F_9OC_2H_2$	$CF_3(CF_2)_5CH_2CH_2O$-$CH(CH_3)CH_2CH(CH_3)_2$
F-Content (%)	78.3	68.4	66.3	64.7	55.1
Mp (°C)	-90	-138	-110	-135	<-78
Bp (°C)	56	61	128	76	214
Density (g/mL)	1.68	1.42	1.61	1.51	1.35
Dipole Moment (D)	0	2.4	2.7	2.5	2.3
Dielectric Constant	1.8	7.4	5.8	7.4	-

Examining the table above, it is clear that a range of physical properties are available among fluorous and semi-fluorous solvents, and that these properties are not governed by fluorine content alone. Therefore, it can be concluded that fluorous solvents must be carefully chosen for a specific purpose. In some cases, more fluorous character may be desired to obtain a more selective extraction with little interference. For another application, a higher boiling point may be desired. Fluorous solvents can even be used to coordinate with metals, as demonstrated by the work of the Bühlmann group, which has produced some of the first quantitative data on coordination of perfluoroethers and perfluoroalkylamines with monocations.[80] The properties of some fluorous solvents may also be controlled by mixing with other organic or fluorous solvents, called solvent tuning, to achieve intermediate properties[53,54]. For example, FC-72 may be mixed with HFE7100 in varying ratios with either wet or dry DMF to obtain higher partitioning into either the organic or fluorous phases (increasing fluorous). This notion of solvent tuning proves to be very useful, by opening up access to different partitioning behaviors with only small modifications.

1.2.1 Molecular Recognition and Selective Extraction in Fluorous Media

Being extremely non-polar, fluorous solvents have a reputation for being very poor at solvating non-fluorous solutes[55]. This characteristic makes fluorous solvents the ideal matrix for selective extractions. In fact, selective extractions into fluorous media have proved to be

successful.[5,64,75,77,78] Hydrogen bonding and proton transfer can also occur in fluorous solvent.[81] Coupling these concepts with the idea of solvent tuning opens many opportunities for molecular recognition in fluorous solvent.

The work of El Bakkari under Jean-Marc Vincent delves deeper into the concept of molecular recognition and selective extractions in the fluorous phase. El Bakkari has successfully demonstrated molecular recognition and extraction of histamine,[82,83] ethanol,[84] and porphyrins/fullerenes.[85] El Bakkari has also been successful at switching the partitioning of pyridyl-tagged substrates and products between the organic and fluorous phase.[83]

Palomo also had very important work in the realm of fluorous molecular recognition. Palomo utilized a fluorinated urea to recognize a fluorinated carboxylic acid in the fluorous phase.[65] O'Neal from the Weber group also used fluorous carboxylic acid, Krytox 157 FSH, this time as the host to aid extraction of pyridines into fluorous solvents.[77] A speculative structure of Krytox 157 FSH and pyridine, which includes proton transfer, is shown below. It should be noted that while the stoichiometry and occurance of proton transfer are known, the exact structure is not.

$$CF_3 - CF_2 - CF_2 - O - [CF(CF_3)CF_2 - O-]_n CF(CF_3)COOH$$
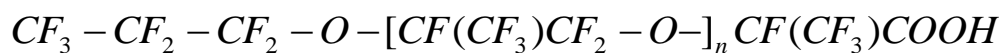
Scheme 1-1 - Structure of Krytox 157 FSH (n≈3)[77]. Figure reproduced with permission from ACS
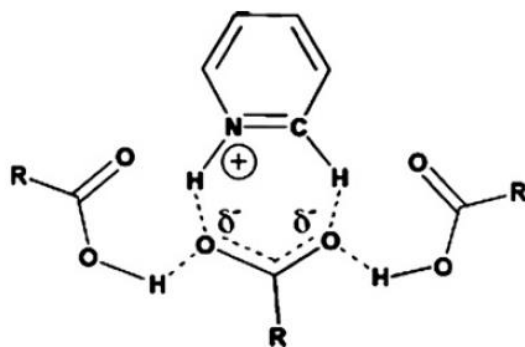
Figure 1-4 – Proposed structure of Krytox 157 FSH-pyridine complex in fluorous phase post-extraction with proton transfer.[77] Figure reproduced with permission from ACS

Additionally, the Weber group has demonstrated the use of perfluorinated carboxylic acids as plasticizers to increase transport of organic solutes through amorphous Teflon AF films.[86]

1.3   OBJECTIVE AND RESEARCH PLAN

Given the strong evidence that pyridyl ureas can function as effective hosts, a pyridyl-urea host shall be synthesized, purified and analyzed. Because ureas are known for self-association, ^{1}H NMR experiments will first be performed which investigate and quantify the stoichiometry and binding constant of the complex formed. As crystals should form with the urea group, X-ray diffraction experiments will be performed to elucidate the hydrogen bond network formed by intermolecular bonding of the fluorous pyridyl-urea and verify the presence of intramolecular

bonds. To aid in future work of selective molecular recognition, a fluorous tag will be added to the pyridyl-urea and all work will be performed in the fluorous phase.

Section two will focus on the effectiveness of the fluorous pyridyl-urea as a host for different titrants. ^{1}H NMR will again be used to verify complexation of the fluorous pyridyl-urea host with different guests. Again, this work will be performed in the fluorous phase to verify the host's effectiveness in fluorous media.

2.0   SYNTHESIS AND SELF-ASSOCIATION OF FLUOROUS PYRIDYL-UREA

2.1   INTRODUCTION

Ureas have long been recognized in the world of molecular recognition as a key source of hydrogen bond donor and acceptor sites. As a key source of hydrogen bond donor and acceptor sites, ureas are a key functional group in hydrogen bond based molecular recognition. Ureas have often been accompanied by pyridine groups to help add an additional hydrogen bond acceptor site and create a rich network of hydrogen bond interactions. Pyridyl-ureas have appeared solo,[13,20,23,26,27,48] or acting as a guest[16] or host[12,14,15] in molecular recognition and hydrogen bond literature.

Because of the convenient source of both hydrogen bond donor and acceptor sites in pyridyl-ureas, molecules containing these groups tend to self-associate and form crystals.[18,20-23,25] Not only are intermolecular bonds common between pyridyl-ureas, but intramolecular bonds can also occur between the pyridyl nitrogen and one of the hydrogen atoms belonging to the urea group.[23,25]   This network of inter- and intra-molecular hydrogen bonds can be easily seen by

analyzing pyridyl-urea crystals using X-ray diffraction.[23,25] This study will also use X-ray diffraction to study the hydrogen bond network of the pyridyl-urea host in the solid state.

Fluorous media have become increasingly popular since Horvath's seminal paper in 1994 detailing the use of an immiscible fluorous solvent with an organic solvent.[62] The size differential created by substituting a fluorine atom for a hydrogen atom, as in hydrocarbons, leads to an increased free-energy penalty for hydration[87]. Because of this increased energy cost to create a cavity for hydration, fluorous molecules and solvents are considered incredibly nonpolar and are immiscible with organic and aqueous phases; though there are exceptions.[53] Because of this, fluorous solvents provide an almost ideal matrix for selective extractions, as most organic molecules will not partition into fluorous phases. Molecular recognition has had some documented success in the fluorous phase, including the work of El Bakkari,[82-85] Palomo[65] and O'Neal.[81] In particular, O'Neal was able to induce pyridine to partition from chloroform into fluorous solvent using perfluorinated carboxylic acids.[77] Using the work of O'Neal it would be useful to demonstrate the ability of a pyridyl-urea to function as a host in fluorous solvent.

Using isocyanates to quantitatively react with groups such as primary and secondary amines has been well-documented.[88-90] Using an isocyanate containing a heavy-fluorous tag to react with 2-aminopyridine should induce the resulting pyridyl-urea to partition into fluorous media.[54,56,57] Once this fluorous pyridyl-urea has demonstrated the ability to partition into fluorous solvent, it should be possible to utilize it as a potential host in molecular recognition.

2.2   EXPERIMENTAL SECTION

2.2.1   Materials

For the synthesis of the fluorous pyridyl-urea, 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-3-pyridin-2-yl-urea, *1H*,*1H*,*2H*,*2H*-perfluorodecyl isocyanate and 2-aminopyridine were purchased from Sigma-Aldrich (Milwaukee, WI). Wet THF was purchased from Fisher Scientific (Fair Lawn, NJ). Milli-Q water was obtained from a Millipore system. For crystallization studies, and verification of successful synthesis, CD_2Cl_2 and D_2O were purchased from Cambridge Isotope Labs (Andover, MA). Self-association studies were conducted in HFE7100, purchased from 3M (Minneapolis, MN).

2.2.2   Synthesis of 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-3-pyridin-2-yl-urea (Fluorous Pyridyl-Urea)

1H,*2H*,2H-perfluorodecyl isocyanate and a 1.5 molar excess of 2-aminopyridine were placed in a round bottom flask with minimal THF. The round bottom flask was placed in an oil bath and fitted with a condenser. The solution was allowed to stir and reflux at 80°C for at least eight hours to overnight. Excess solvent was allowed to evaporate after pouring the yellow solution into a Petri dish. The resulting white powder was purified by rinsing with Milli-Q water. Successful synthesis and purity were verified by ^{1}H NMR in CD_2Cl_2. ^{1}H NMR spectral references are versus TMS. The reaction scheme is shown below.

14
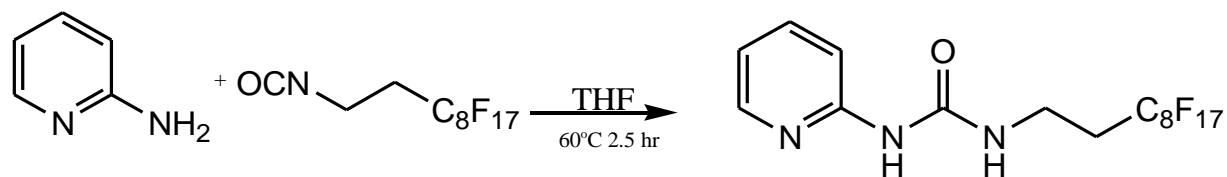
Scheme 2-1 - Synthesis of fluorous pyridyl-urea

2.2.3 Deuterium Oxide Kinetics Study

Kinetics of hydrogen-deuterium exchange for urea hydrogens in fluorous pyridyl-urea were investigated by addition of D_2O to a 0.005 M solution of fluorous pyridyl-urea in either CD_2Cl_2 or HFE7100. ^{1}H NMR data was collected over the course of several hours. A sealed capillary tube filled with D_2O was used in the NMR tube and served as both a locking solvent and as an internal reference. ^{1}H NMR spectral references are versus TMS in CD_2Cl_2 and HFE7100.

2.2.4 Crystallization of Fluorous Pyridyl-Urea

Crystals of fluorous pyridyl-urea were formed by preparing a saturated solution in CD_2Cl_2. No heating was required of the solution. The solution was allowed to sit, undisturbed, in a tightly capped vial for four weeks. Crystals were harvested and analyzed.

2.2.5 Self-association of Fluorous Pyridyl-Urea in HFE7100

The self-association of the fluorous pyridyl-urea was studied in HFE7100. Solutions from 0.001 to 0.01 M were prepared in HFE7100. ^{1}H NMR measurements were taken on either a 300 or 400 mHz Bruker NMR. A sealed capillary tube filled with D_2O was placed in the NMR tube with the

15

sample to serve as a locking solvent, and as an internal reference, during data collection. ^{1}H NMR spectral references are versus TMS.

2.3 RESULTS AND DISCUSSION

2.3.1 Synthesis of Fluorous Pyridyl-Urea

Successful synthesis of the fluorous pyridyl-urea was verified by ^{1}H NMR in both CD_2Cl_2 and HFE7100. The final structure and relevant spectra are shown below.
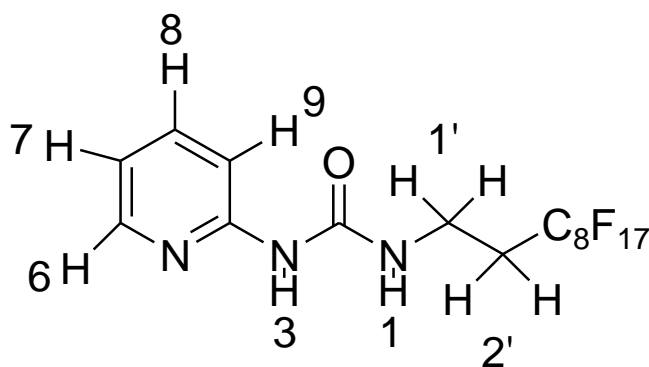
Figure 2-1 - Structure of flourous pyridyl-urea host
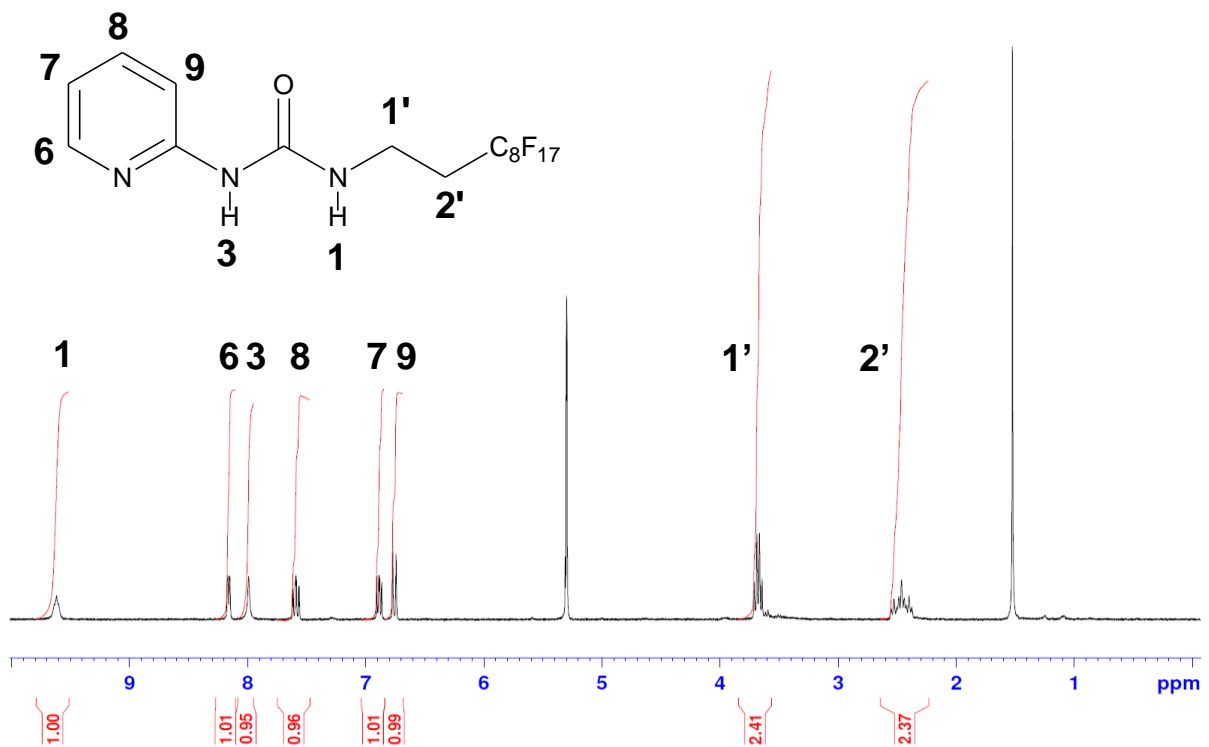
Figure 2-2 - ^{1}H NMR spectrum of fluorous pyridyl-urea in CD_2Cl_2[1]

---

[1] ^{1}H NMR spectra in CD_2Cl_2 are versus TMS reference
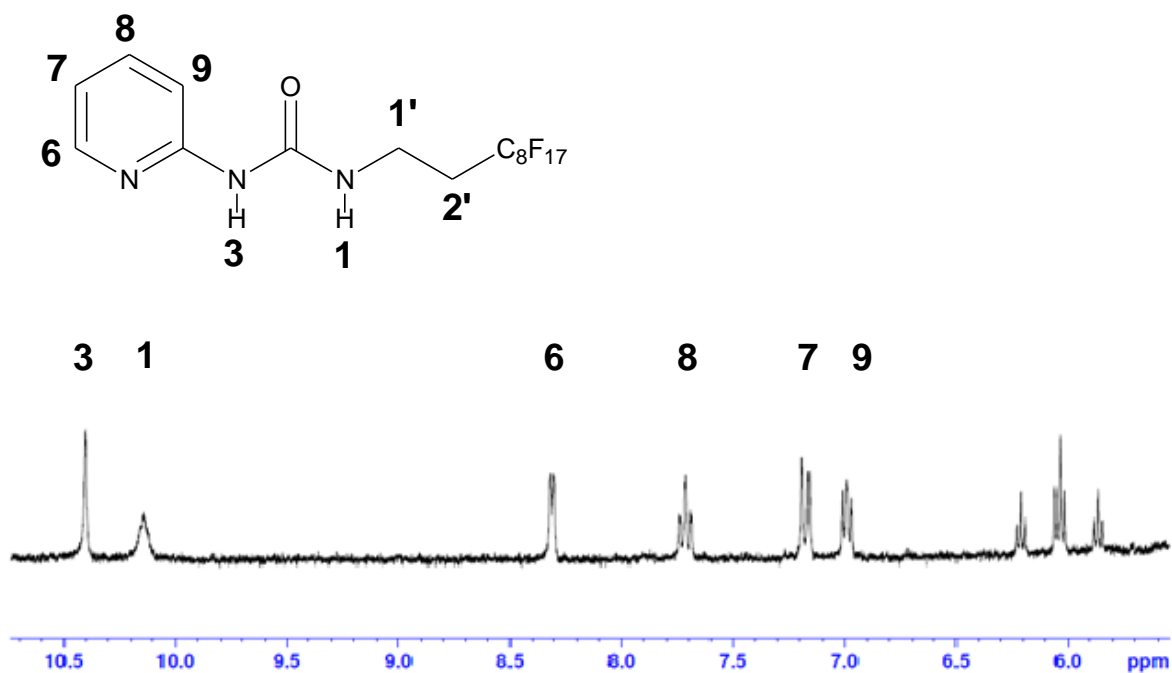
Figure 2-3 - ^{1}H NMR spectrum of fluorous pyridyl-urea in HFE7100[2]

---

[2] ^{1}H NMR spectrum is an expansion of relevant, identifiable peaks. Locking solvent DHO signal interferes with spectrum upfield from 5.5 ppm. HFE7100 spectra are versus TMS reference.

Table 2-1 - [^1]H NMR Spectral Assignments[3]

Number	Description of Hydrogen	Shift (ppm) CD$_2$Cl$_2$	Shift (ppm) HFE7100
1	Urea	9.62	10.11
1'	Aliphatic	3.67	N/A
2'	Aliphatic	2.45	N/A
3	Urea	8.00	10.41
6	Aromatic	8.15	8.31
7	Aromatic	6.89	7.18
8	Aromatic	7.59	7.70
9	Aromatic	6.78	6.97
N/A	Water residual	1.50	N/A
N/A	Solvent residual (CHDCl$_2$)	5.30	N/A
N/A	Ethylene (HFE7100)	N/A	5.89 (t), 6.05 (t), 6.20 (t)

Figure 2-2, shows the ^{1}H NMR spectra verifying successful synthesis of the fluorous pyridyl-urea host in CD$_2$Cl$_2$. Pyridyl hydrogen peaks were identified through characteristic downfield shifts and splitting patterns. Alkyl peaks were identified by splitting patterns and predicted upfield shifts. Finally, urea hydrogens were identified by downfield shift. ^{1}H NMR spectra were then taken in HFE7100, a semi-fluorous, solvent. Peaks representing urea and pyridyl hydrogens were able to be identified as shown in Figure 2-3. However, due to

---

[3] ^{1}H NMR spectral references are versus TMS for both CD$_2$Cl$_2$ and HFE7100.

interference by the locking solvent peak, peaks of the alkyl hydrogens were not able to be seen. Assignment of the urea hydrogens is difficult as many factors can influence their shift, such as rotation of the bond between urea carbonyl and urea nitrogen,[91] hydrogen bonding,[92] concentration and temperature.[91] A more in depth discussion of the assignment of urea hydrogen peaks will occur in a later section.

2.3.2 Deuterium Oxide Kinetics Study

To investigate reactivity of the hydrogens belonging to the urea group, the kinetics of hydrogen-deuterium exchange was investigated in both CD_2Cl_2 and HFE7100 by ^1H NMR. It is noteworthy that deuterium-hydrogen exchange is much slower in HFE7100 than it is in CD_2Cl_2. The fact that HFE7100 and water are immiscible might contribute to slower kinetics of the hydrogen-deuterium exchange. The urea hydrogen (H_1) adjacent to the fluorinated alkyl group exchanges at a much slower rate than the other urea hydrogen (H_3). A spectrum of the fluorous pyridyl-urea before the addition of D_2O in HFE7100 is available in Appendix A.
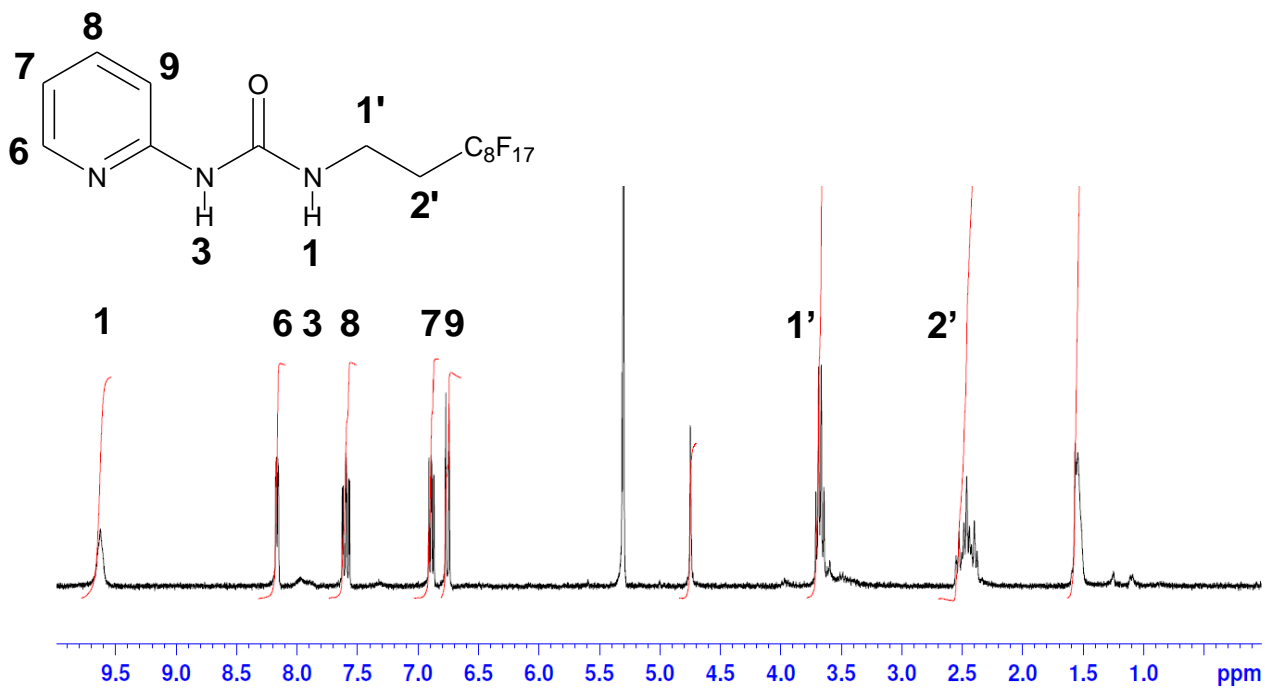
Figure 2-4 – ^{1}H NMR immediate addition of D_2O to fluorous pyridyl-urea in CD_2Cl_2
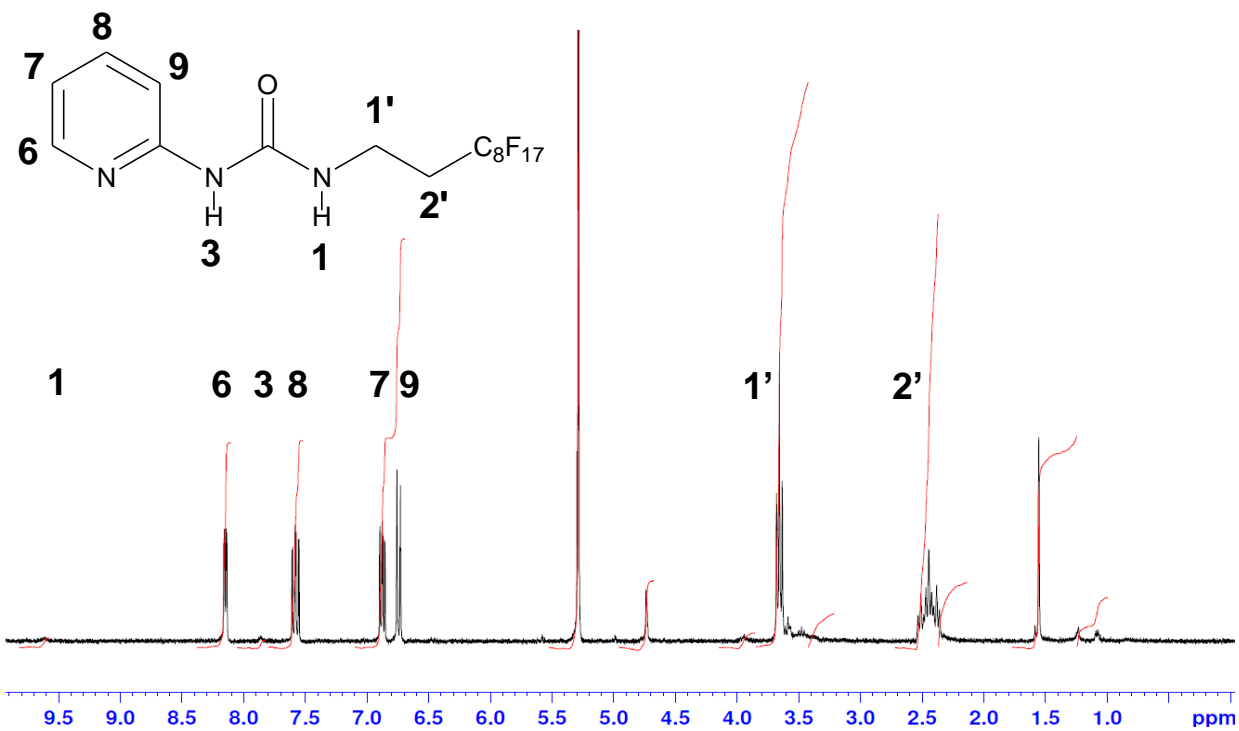
Figure 2-5 - ^{1}H NMR seven hours after D_2O Addition to fluorous pyridyl-urea in CD_2Cl_2
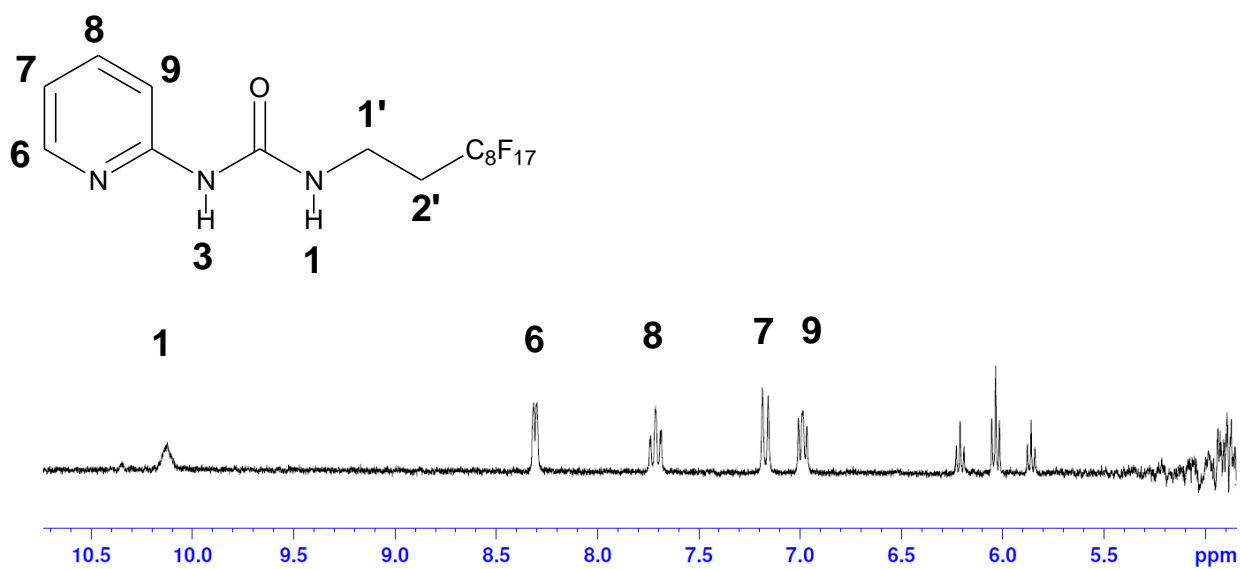
Figure 2-6 - ^{1}H NMR spectrum two hours after D_2O addition to fluorous pyridyl-urea in HFE710

0
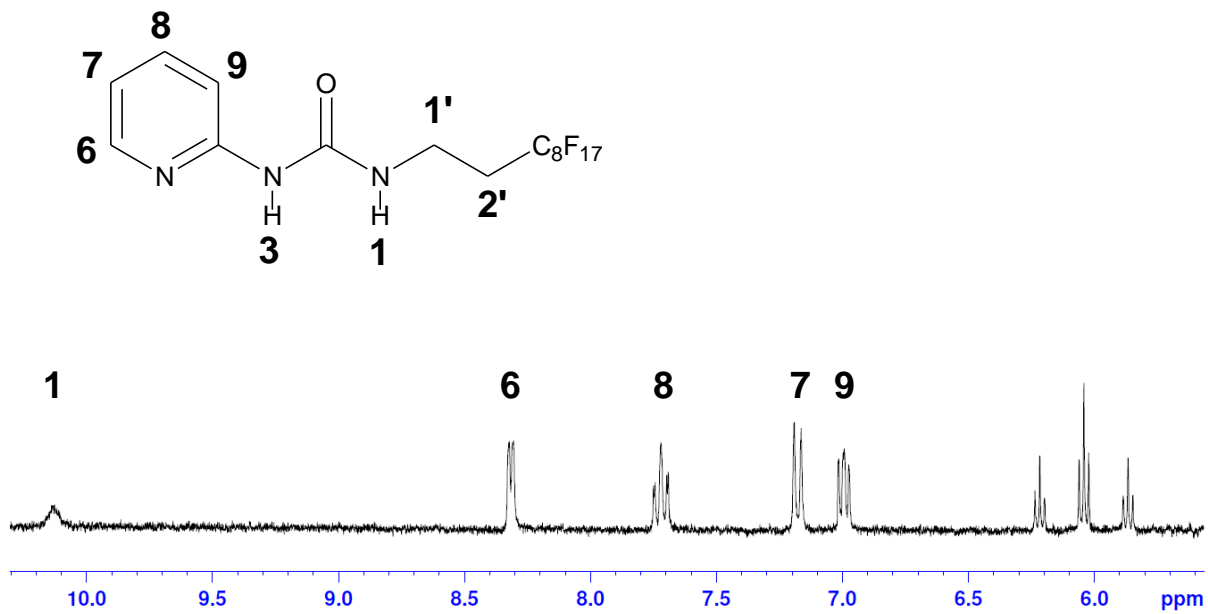
Figure 2-7 - ^{1}H NMR spectrum five hours after D_2O addition to fluorous pyridyl-urea in HFE7100
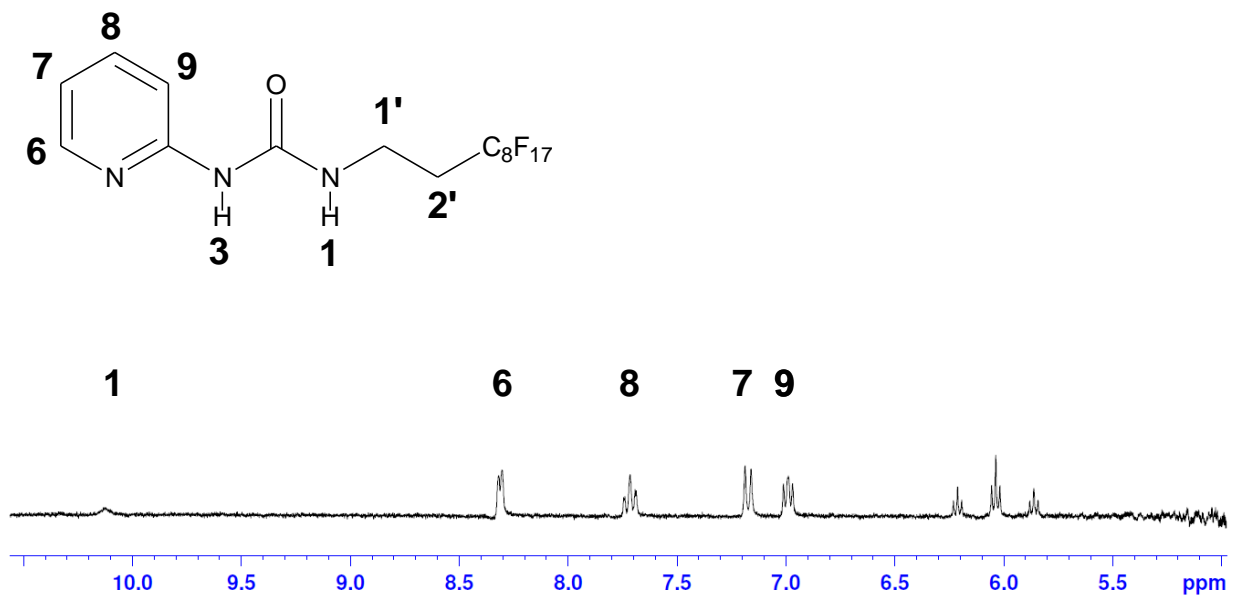
Figure 2-8 - ^{1}H NMR spectrum eight hours after D_2O addition to fluorous pyridyl-urea in HFE7100

2.3.3   Crystallization of Fluorous Pyridyl-Urea

To investigate the hydrogen bonding network of the urea groups in the solid state, single crystal X-ray diffraction measurements were taken. It must be noted that the numbering scheme for X-ray experiments is different than in the ^{1}H NMR experiments. Numbering in the X-ray data focuses on numbering nitrogen and oxygen atoms. Hydrogen atoms attached to nitrogen atoms will be referenced by referring to the number corresponding to the nitrogen.
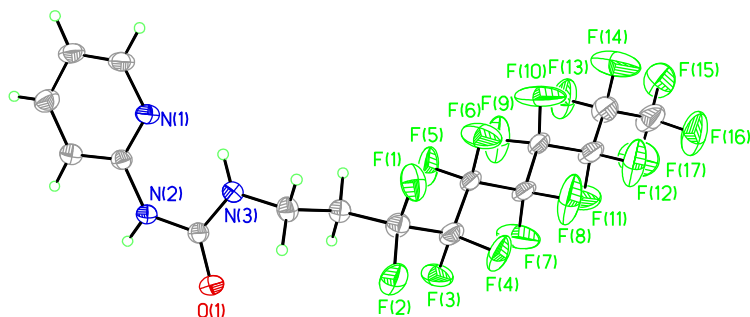
Figure 2-9 - Single molecule in cystal structure of fluorous pyridyl-urea
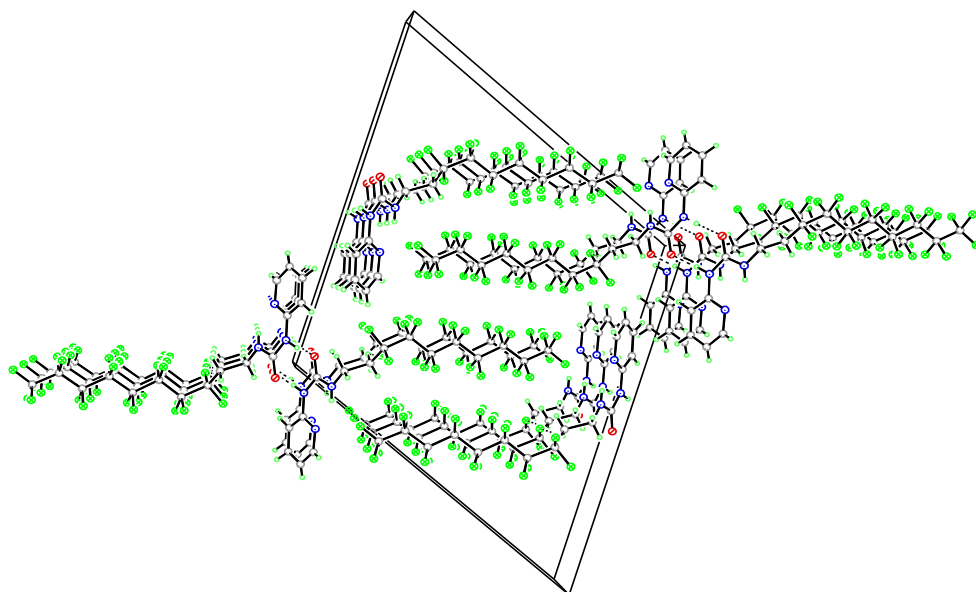
Figure 2-10 - Packing in fluorous pyridyl-urea crystal structure

Examining the data, it can be seen that a 1:1 bonding exists in the crystal form of the fluorous pyridyl-urea. It is interesting to note that in the crystal state, the fluorous tails aggregate in the center in a fashion similar to micelle formation. It can also be seen from the single molecule model that the urea group takes on an *E,Z* configuration, as opposed to a *Z,Z* configuration. Both possible rotamers, created through rotation about the urea carbonyl-urea nitrogen bond, are shown below.
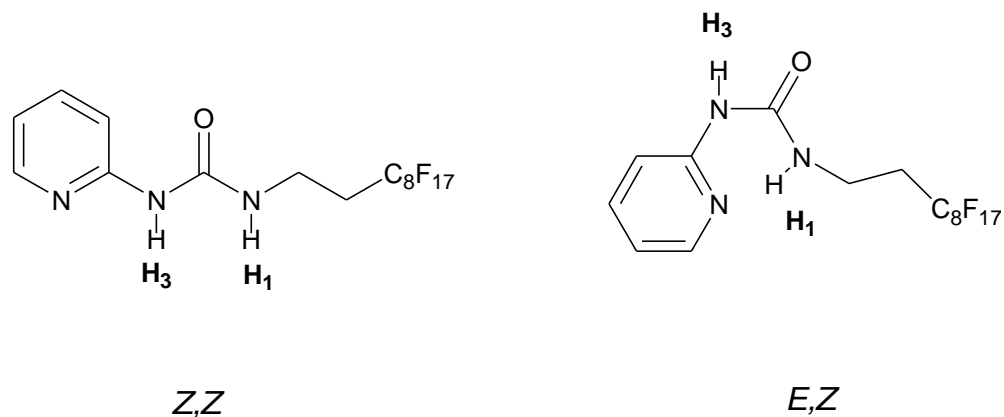
Figure 2-11 - Schematic of *Z,Z* and *E,Z* rotamers in fluorous pyridyl-urea host

While the *Z,Z* rotamer is typically favored for urea self-association;[23,93,94] the *E,Z* rotamer provides additional stability in 2-pyridyl ureas due to the formation of an intramolecular bond.[23,92,95] This intramolecular bond between the pyridyl nitrogen (N_1) and one urea hydrogen (H_{3N} below, H_1 in ^{1}H NMR) can be seen above in Figure 2-10.[92] This intramolecular bond remains intact throughout the crystal structure. Intramolecular bonding of this type has been documented before and it is established that this bond provides additional stability to the overall structure[23].

Intermolecular bonding also occurs in a 1:1 fashion in the crystal structure as shown in the packing image Figure 2-9. The remaining hydrogen (H_1) belonging to the urea group is in an ideal position to bond with the carbonyl oxygen in a neighboring urea group. This binding allows for the formation of a stable eight-membered ring. Pillars are also formed, with the hydrophobic fluorous tails aggregating together. Literature shows several X-ray diffraction experiments verifying the formation of pillars for molecules containing an aromatic ring with urea substituent.[20,24] It is interesting to note in Figure 2-9 that the fluorous tails of multiple pillars aggregate, flanking both sides of the pendant pyridine groups. This is significant as it

demonstrates a similar concept to the formation of micelles in aqueous solution. Crystals were grown in the semi-fluorous solvent HFE7100. Hence, fluorous tails envelope the polar pendant pyridine to aid in solvation. This extremely ordered structure is then maintained in the solid state, seen in Figure 2-9.

2.3.4 Self-association of Fluorous Pyridyl-Urea in HFE7100

The migration of the peaks corresponding to the urea hydrogens was studied in HFE7100 across a range of concentrations, $0.001 - 0.01$M. Peak migration can be indicative of self-associative behavior. If self-association has occurred, the equilibrium constant of the bound versus free state can be calculated by fitting the curve obtained by graphing peak position in ppm versus concentration. The basic equations for obtaining this curve-fitting are outlined below; however the computer program WinEQNMR[96] was used to facilitate these calculations. Two possibilities exist for self-association, step-wise assembly and immediate assembly. Step-wise assembly involves the sequential formation of dimers, trimer, and n-mers. Immediate assembly will form only trimers or n-mers without any dimers or intermediate –mers. Equations for both scenarios are shown below.

Equation 2-1 - Calculation of K self-association, step-wise assembly

$$A + A \rightleftarrows A_2$$
$$K_2 = \frac{[A_2]}{[A]}$$
$$A_2 + A \rightleftarrows A_3$$
$$K_3 = \frac{[A_3]}{[A_2][A]}$$
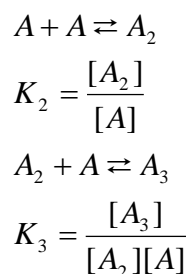
$$A_{n-1} + A \rightleftarrows A_N$$

$$K_n = \frac{[A_n]}{[A_{n-1}][A]}$$

Where K_n is the equilibrium constant of the association of n units into an n-mer and $n \geq 2$. $[A_n]$ is the concentration of n-mer in solution, $n=1$ is the concentration of monomer and $n \geq 2$ is the concentration of dimer, trimer, etc.

Equation 2-2 - Calculation of K self-association, immediate assembly

$$nA \rightleftarrows A_n$$

$$K_n = \frac{[A_n]}{[A]^n}$$

In order to determine K for either step-wise or immediate self-assembly, the monomer concentration must first be found. Concentration of monomer and dimer or trimer can be found using the following.

Equation 2-3 - Concentration and shift of monomer, dimer/trimer[44]

$$f_{monomer} = \frac{\partial_{bound} - \partial_{obsd}}{\partial_{bound} - \partial_{monomer}}$$

$$[A] = [A]_{total} * f_{monomer}$$

$$f_{bound} = \frac{\partial_{obsd} - \partial_{monomer}}{\partial_{bound} - \partial_{monomer}}$$

$$[A_n] = [A]_{total} * f_{bound} = [A]_{total} - [A]$$

Where $f_{monomer}$ and f_{bound} are the mole fractions of free and bound solute in solution, respectively, δ_{bound}, $\delta_{monomer}$, δ_{obsd}, are the calculated shifts of bound and free solute, respectively,

and the observed shift of the solute in solution. Estimates of $\delta_{monomer}$, δ_{dimer}, and δ_{trimer} can be obtained from the graph of ^{1}H NMR data. The shift of the monomer, $\delta_{monomer}$, can be estimated by extrapolating the curve to infinite dilutions. The shift of the dimer, trimer, or *n*-mer, $\ddot{o}_{bound}$ is found by extrapolating the curve to maximum saturation. This is typically accomplished by observing the shift of the curve as it nears its asymptotic boundary and utilizing this as $\ddot{o}_{bound}$. Curves which do not reach an asymptotic boundary are more difficult to obtain an estimate of $\ddot{o}_{bound}$

In the case of multiple equilibria (step-wise association), solving for the concentration of both dimer and trimer species will prove to be difficult. The signal observed in ^{1}H NMR is a weighted average of all species appearing in solution. The following relations detail this concept.

Equation 2-4 - Calculation of observed shift[39]

$$\partial_{obsd} = \sum \frac{\partial_{monomer}[A] + n\partial_n K_n [A]^n}{[A] + nK_n [A]^n}$$

Equation 2-5 - Concentration of dimer/trimer

$$[A]_{total} = [A] + 2[A_2] + 3[A_3] + ...n[A_n]$$

Shift of monomer can be obtained as previously described. Concentrations of dimer and trimer can be solved for utilizing the mole fraction values obtained in equation 2-3. Estimated values of K should be used and iteration is typically utilized to obtain the best fit value for K. In the case of immediate self-association, only one K value must be solved for. For more difficult systems possessing step-wise association, a non-linear regression fitting should be performed

using a program such as Mathcad or WinEQNMR[96]. Programs such as these obtain the best fit model by solving and taking the minimum sum of squares given below iteratively.

Equation 2-6 – Sum of Squares[47]

$$\Delta = \sum_{n=1}^{x} (\partial_{obsd} - \partial_{calc})^2$$

Where x = number of data points

A word of caution must be noted here. Because ^{1}H NMR is a weighted average signal, it is possible to obtain decent fittings with several different sets of values for K and monomer/bound shifts. Thus, ^{1}H NMR should not be used for difficult systems containing more than three complexes in solution. However, attempts to fit a model with incorrect stoichiometry will generally not be successful. In this way, ^{1}H NMR can give a rough estimate of the stoichiometry of the system and binding constant.

Upon using the WinEQNMR[96] software, it was found that the immediate formation of a trimer was the best fit for the curves corresponding to the migration of the peaks for the urea hydrogens.
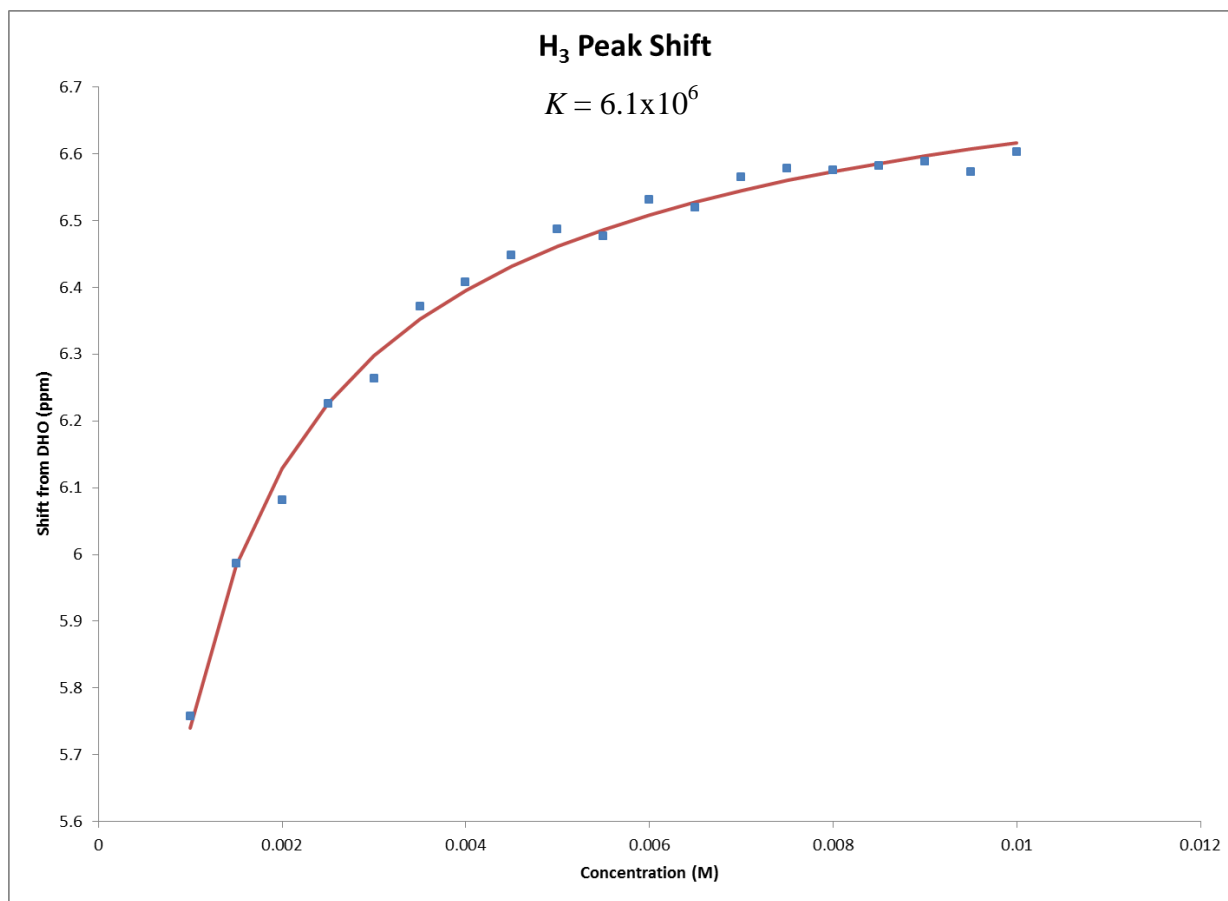
Figure 2-12 - Curve for migration of ^{1}H NMR peak for H_3[4]

---

[4] Migration curves in ^{1}H NMR spectra for H_3 and H_1 are referenced to DHO.
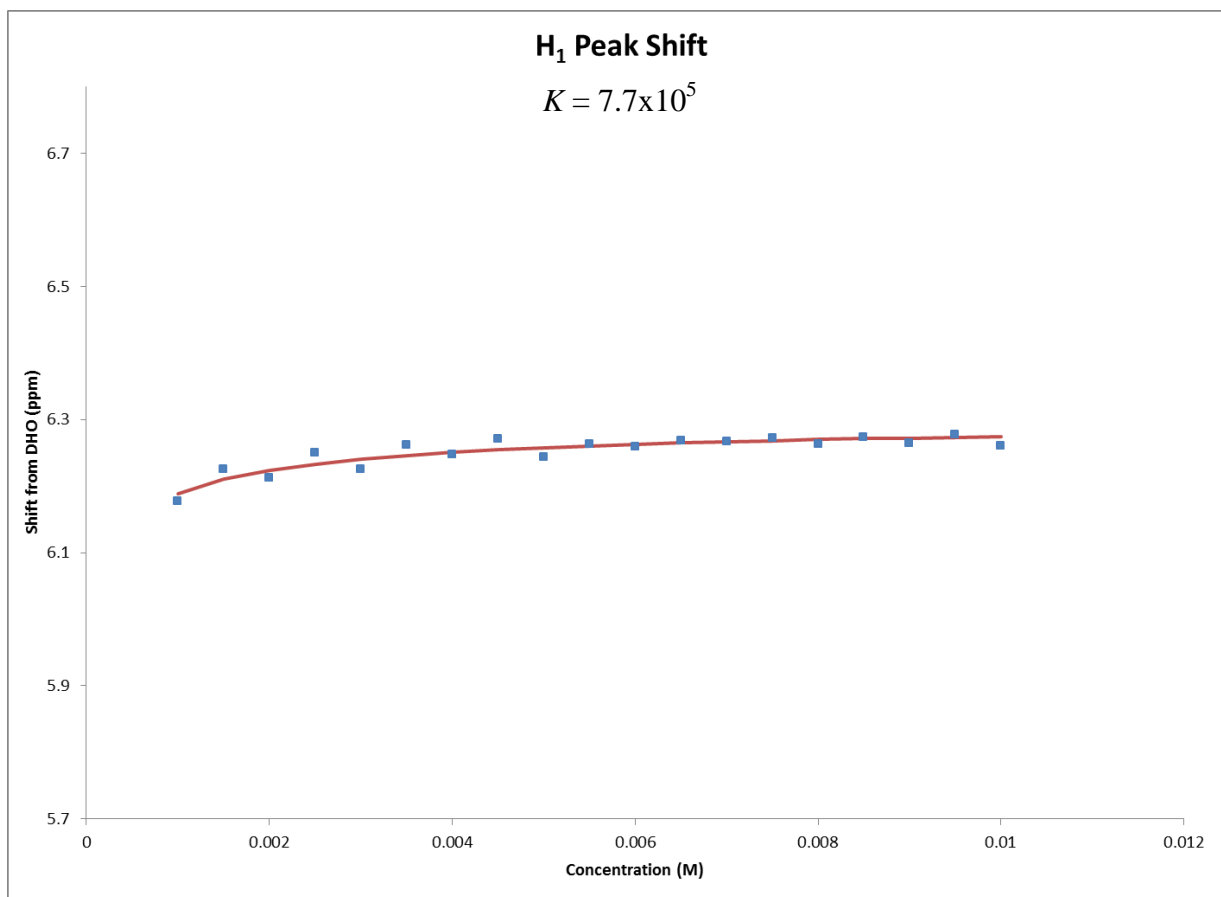
Figure 2-13 - Curve for migration of ^{1}H NMR peak for H_1[3]

Hydrogen bonding of a urea hydrogen will shift its resonance downfield.[92] Looking at Figure 2-12, it is clear that a downfield shift has occurred for the H_3 resonance, creating a binding curve. Since the only solute in solution is the fluorous pyridyl-urea, some type of self-association must have occurred. It is interesting to note that while Figure 2-12 indicates hydrogen bonding has shifted the resonance for H_3 significantly, the resonance for H_1 is small (Figure 2-13). Association curves having a similar shape to that in Figure 2-12 have been

[3] Migration curves in ^{1}H NMR spectra for H_3 and H_1 are referenced to DHO.

documented before in dimerization of 2-amidopyridine derivatives[31], as well as in the self-association of 1,3-dimethylurea,[91] chloroform,[34] heterocyclic ureas,[97] δ-valerolactam.[32] The range of resonance migration for the cited curves were similar to the results obtained by this study. Recorded ranges for resonance migration were 0.03 ppm to 1.2 ppm[31]. The shape of the curve for both H_3 and H_1 are worthy of closer inspection.

In the case of H_3, it appears that self-association begins to occur at low concentration. This is shown by the relatively large change in chemical shift shown between 0.001 and 0.003 M. As the concentration of the solute is increased, a moderate amount of change continues to be observed for the chemical shift of H_3 until roughly 0.007 M. After 0.007 M, the change in chemical shift appears to be small. This suggests that the fluorous pyridyl-urea system has reached a maximum value of self-association and the system should consist mostly of complexed solute at this concentration. At this concentration, the shift is representative of the bound shift for H_3. To calculate the shift of the unbound H_3, the system can be extrapolated to infinite dilution. Thus, for H_3, the system begins to self-associate even at low concentrations.

Values of K reported from the nonlinear regression are similar for H_1 (7.9×10^5) and H_3 (6.1×10^6). As will be discussed below, there is significant association at the lowest concentrations from which good spectra could be obtained (1 mM). As a result, the program must fit the data with three adjustable parameters: a value of δ for monomer and trimer and a value of K. With this large number of parameters to determine, the uncertainty in the result is higher than it would be for the determination of a single parameter. In addition, the rather small shift in the spectra of H_1 makes it difficult to have confidence in the parameters resulting from the curve fit to these data. Finally, it is difficult to draw a convincing and plausible structure for a trimer. With these caveats, it is safest to work with an estimate of K of $\sim 10^6$.
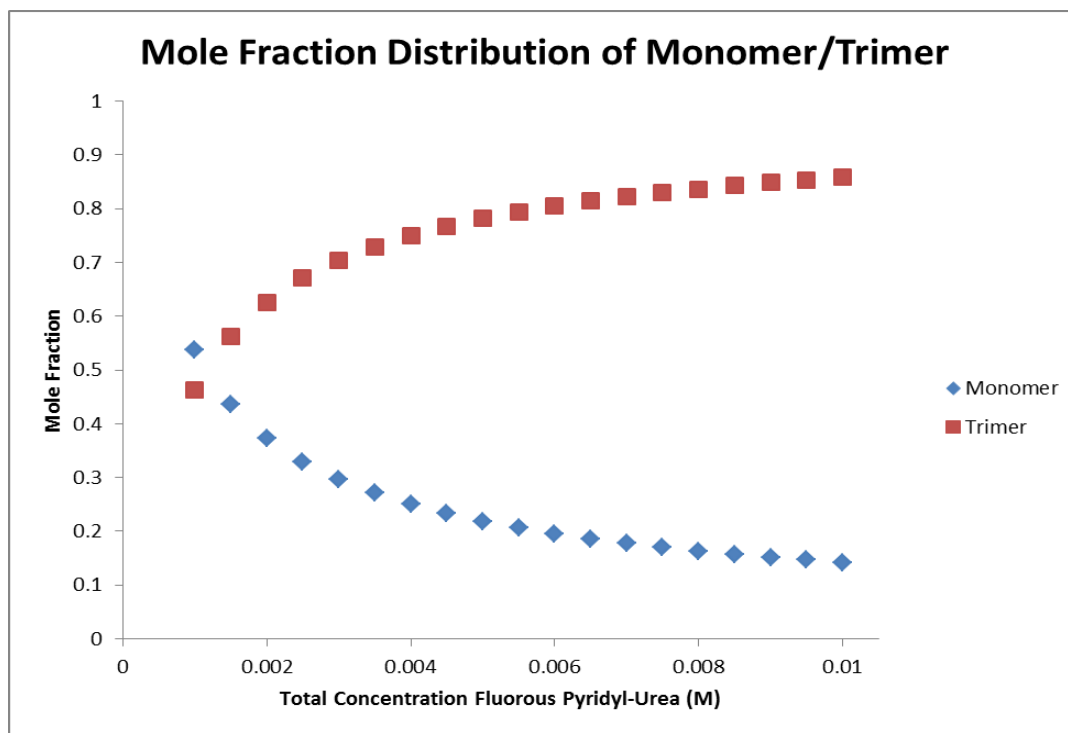
Figure 2-14 - Plot detailing concentrations of monomer and trimer based on K. The vertical axis is the ratio of the concentration of a species divided by the total solute concentration as monomer

Given the value of K, it is possible to calculate the concentration of monomer and trimer complex in solution. Figure 2-14 shows a plot of the relative concentration of monomer and trimer in solution from $0.001 - 0.01$ M. It should be noted that this plot is not specific for H_3 or H_1, but is based on the estimated K of 10^6 and applicable to the host molecule as a whole. The conclusion from Figure 2-14 supports that gained from Figure 2-12 and 2-13; that self-association in this system begins even at low concentration.

The curve for H_1 also provides an interesting shape. In contrast to H_3, H_1 appears to experience very little migration. Flat curves such as this have also been documented in the self-

association of actinomycin D[33], ethidium homodimer[47], heterocyclic ureas[97], pyridylalkanols[37]. Because the H_1 resonance does not experience much migration with changing concentration, it suggests that H_1 might not be involved in binding during self-association. Looking back at the X-ray data in Figure 2-8, it can be recalled that H_1 engages in an intramolecular bond with pyridyl nitrogen. If this bond is maintained in solution, it would be reasonable that H_1 would not experience much migration at high concentration. With the X-ray and ^1H NMR data, it appears that H_1 is engaged in a stabilizing, strong intramolecular bond with pyridyl nitrogen in both the monomer and trimer complex state. The small change in shift suggests that despite the formation of a hydrogen bond, the chemical environment surrounding H_1 has not changed significantly. Whether this bond will be maintained through host-guest interactions will be examined in later sections.

To put the migrations of H_3 and H_1 in context, it is useful to consult the literature. As previously stated, the *E* configured urea hydrogen, in this case referred to as H_3, could appear either upfield or downfield.[95]. However, due to conflicting reports, it is difficult to predict which resonance will appear downfield. Based on the ^1H NMR spectra of 1-(2'-pyridyl)-3-phenylureas, Sudha has reasoned that intramolecular bonding between the pyridyl nitrogen and the *Z* configured urea hydrogen (H_1) can cause the latter's resonance to appear downfield.[92] ^1H NMR experiments from Roberts et al. using ureas and thioureas in DMSO and DMF seem to support Sudha's assertion at low temperatures. Roberts is quick to note, though, that at room temperature the resonances for *E* and *Z* rotamers of urea, urea acetate and 1,1-dimethylurea coalesce and either resonance could appear downfield.[91] He also states that his own assignment of *Z* rotamer downfield is opposite to that of Schaumann et.al.[98] This work builds on the previous literature to show that resonances also exhibit strong concentration dependence, again compounding

35

difficulty in assignment. At low concentrations in HFE7100, H_3 is upfield of H_1 (see Figure 3-7 in Appendix A). However, as H_3 engages in self-associative hydrogen bonds with increasing concentration, it migrates downfield of H_1 (see Figures 3-8 and 3-9 in Appendix A). This extreme migration of the H_3 resonance contrasted to the relative stability of the H_1 resonance offers an interesting conclusion; that hydrogen bonds formed by H_3 and H_1 both occur at very low concentration. Because H_1 resonance does not experience a large change in shift, the bond formed by H_1 must not result in a significantly different chemical environment. This is in contrast to the relatively large shift for H_3 resonance, which must be accompanied by a difference in chemical environment resulting in a shift of the resonance downfield.

To be effectively utilized as a host, the fluorous pyridyl-urea should be kept at a concentration low enough to still have monomer units available for complexation with a guest. To determine an effective concentration of the host, Figure 2-14 will be consulted. While a 0.001 M solution of fluorous pyridyl-urea is the only concentration at which monomer dominates, the concentration is so low that effective analysis of ^{1}H NMR signal is difficult. By selecting a higher concentration, a better signal can be achieved while also providing an opportunity to study competitive binding of the host. Thus, 0.005 M was chosen to provide a high ^{1}H NMR signal, and to study if an effective guest can compete with self-associative binding of the host.

Utilizing the WinEQNMR software, rough values for the binding constant, K, were obtained. The model which best suits the shape of the binding curve was found to be the immediate assembly of trimers. For H_3, the binding constant was found to be $6.1 \times 10^6 \pm 9.8$, while for H_1 the value obtained was $7.7 \times 10^{5 \pm} 5.9$. The overall binding constant can be said to be $\sim 10^6$.

2.4   CONCLUSION

A host molecule, a fluorous pyridyl-urea, was prepared and investigated in HFE7100. Crystal structures were found to contain an intramolecular bond between H_1 of the urea group and the pyridyl nitrogen to form a six-membered ring structure. The structure of the pyridyl-urea is stabilized with an intramolecular bond between the pyridyl nitrogen and H_3. Similar bonds have been observed in pyridyl-ureas[23]. Intermolecular bonds were formed between the carbonyl oxygen and remaining urea hydrogen, H_3, forming an eight-membered ring. The fluorinated aliphatic chains of the pyridyl-urea pack tail to tail, as detailed in Figure 2-10. Pillars were also discovered to have formed in the crystal structure. This highly ordered structure has been found to exist in other pyridyl-urea crystals[20,32,38,44,46,47,99]. Through deuterium oxide exchange studies, it was discovered that H_3 exchanges much more easily than H_1.

The shapes of the curves for H_3 and H_1 resonances vs. concentration were also examined. The curve for H_3 migrates roughly 1.0 ppm in a curve representative of self-association. It was determined that H_3 begins to self-associate even at low concentration. After 0.007 M, H_3 is mostly engaged in intermolecular hydrogen bonds to form the trimer complex, as evidenced in Figures 2-12 and 2-14. In contrast, the curve for H_1 is relatively flat, with monomer concentration dominating only at very low (0.001) concentration. This is possibly due to H_1 quickly engaging in a stabilizing intramolecular bond with pyridyl-nitrogen.[92] This work is useful as the literature has many conflicting reports on which urea resonance, *E* or *Z* hydrogen, will appear downfield.[91,92,95,98] Previous studies have shown that hydrogen bonding,[92,95] temperature,[91,98] and medium[100] all have an effect on the shift of the resonance. This study

supports Roberts findings that the shift of urea hydrogen resonances is also dependent on concentration.[91]

Although an exact structure can't be determined at this time, it is possible that binding of the trimer complex occurs in a similar fashion to that of O'Neal.[77] In this study, it was shown that an intramolecular bond is present between pyridyl nitrogen and one urea hydrogen. Lone pairs on the urea oxygen and the remaining urea hydrogen are free to form bonds to two other host urea groups.

An effective concentration for fluorous pyridyl-urea to act as a host was determined based on Figure 2-14. This plot shows that the trimer complex begins to form even at very low concentration. Therefore, guests must compete with the host to bind effectively. To study this competitive binding equilibrium and to achieve a signal high enough for analysis, 0.005 M was selected as the concentration at which host-guest studies will be conducted. Based on ^{1}H NMR measurements of peak shifts vs. concentration, the fluorous pyridyl-urea group was found to self-assemble directly into a trimer, with a $K \sim 10^6$. The direct association into a trimer, without the presence of dimers, is not typically seen in literature. This work supports the findings of Roberts et al. by demonstrating the concentration dependence of urea hydrogen resonance shift.[91] While ureas have often been used as a host[10-14] in literature, the effect of the semi-fluorous solvent HFE7100 and the presence of a fluorinated alkyl chain will surely have some interesting effects worthy of further investigation. Host-guest studies of the fluorous pyridyl-urea in a semi-fluorous solvent will provide important insight into hydrogen bond interactions in fluorous solvents.

3.0   HOST-GUEST BEHAVIOR OF FLUOROUS PYRIDYL-UREA VIA TITRATION

3.1   INTRODUCTION

Host guest interactions have been the subject of much study. From the use of cyclodextrins and crown ethers[1] to metal ion chelators[2-4] and artificial receptors[5,6], a variety of substrates have been successfully extracted into poor solvents. While extraction into aqueous and organic phases has been well-documented, extraction into fluorous solvents has been a less explored area. As previously stated, low α and β values make fluorous solvents very attractive for the successful formation of host/guest hydrogen bonds. Some noteworthy experiments in the area of fluorous extractions are the scavenging of *N,N*-dialkylureas,[65] the extraction of pyridines,[77] and the phase-switching of tagged pyridines and porphyrins.[82,83,85] The value of the urea group as an effective host has been previously established in Section 2.2. Different guests for the fluorous pyridyl-urea host will now be tested for efficacy.

3.2   EXPERIMENTAL SECTION

3.2.1   Materials

For the investigation of host-guest behavior of the fluorous pyridyl-urea, purified fluorous pyridyl-urea was used from previous synthesis detailed in 2.3.1. HFE7100 solvent was purchased from 3M (Minneapolis, MN). Certified ACS Acetone was purchased from Fisher Scientific (Fair Lawn, NJ). Octanoic acid, anhydrous ethyl acetate, *N,N*-dimethylacetamide, and *N*-ethylacetamide were all purchased from Sigma-Aldrich (Milwaukee, WI). D_2O was purchased from Cambridge Isotope Labs (Andover, MA). Indicating 4A° molecular sieves were used to dry *N,N*-dimethylacetamide.

3.2.2   Titration of Fluorous Pyridyl-Urea

A 0.005 M solution of fluorous pyridyl-urea was prepared in HFE7100. Titration of the fluorous pyridyl-urea, acting as host, was conducted with 0 M – 0.025 M of guest. Titrations were carried out in individual vials. Vials were sealed, shaken and allowed equilibrate for at least six hours. ^{1}H NMR spectra were then taken on a Bruker 400 mHz. A capillary tube filled with D_2O was inserted in the NMR tube to serve as a locking solvent, and as an internal reference, during data acquisition.

3.3 RESULTS AND DISCUSSION

3.3.1 Titration of Fluorous Pyridyl-Urea

Fluorous pyridyl-urea was titrated with several molecules serving as guests to investigate if the pyridyl-urea was effective serving as a host in the fluorous solvent HFE7100. The results of the titrations are shown below. Binding curves for both hydrogens belonging to the urea group of the fluorous pyridyl-urea are shown and denoted as H_3 and H_1. For cases where binding curves can be constructed for a hydrogen belonging to the guest molecule (i.e. N-ethylacetamide), this curve is shown as well.
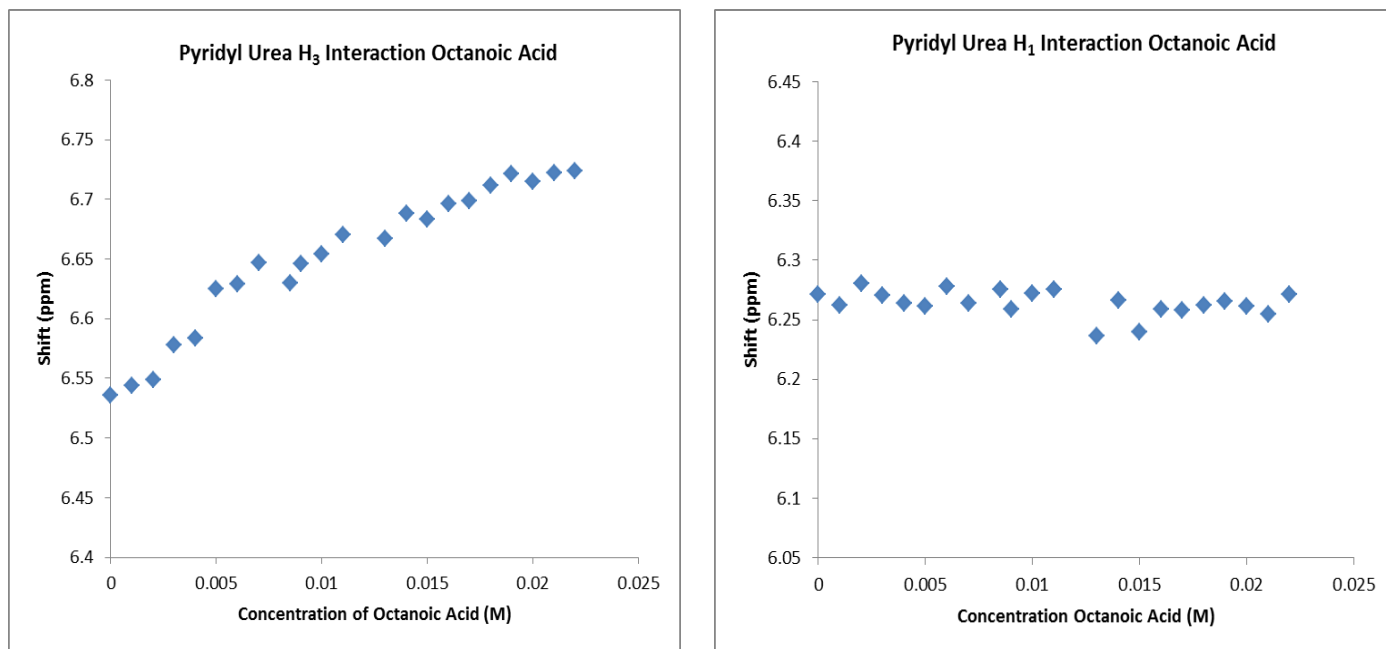

Figure 3-1 - Binding curve of 0.005 M fluorous pyridyl-urea with octanoic acid in HFE7100
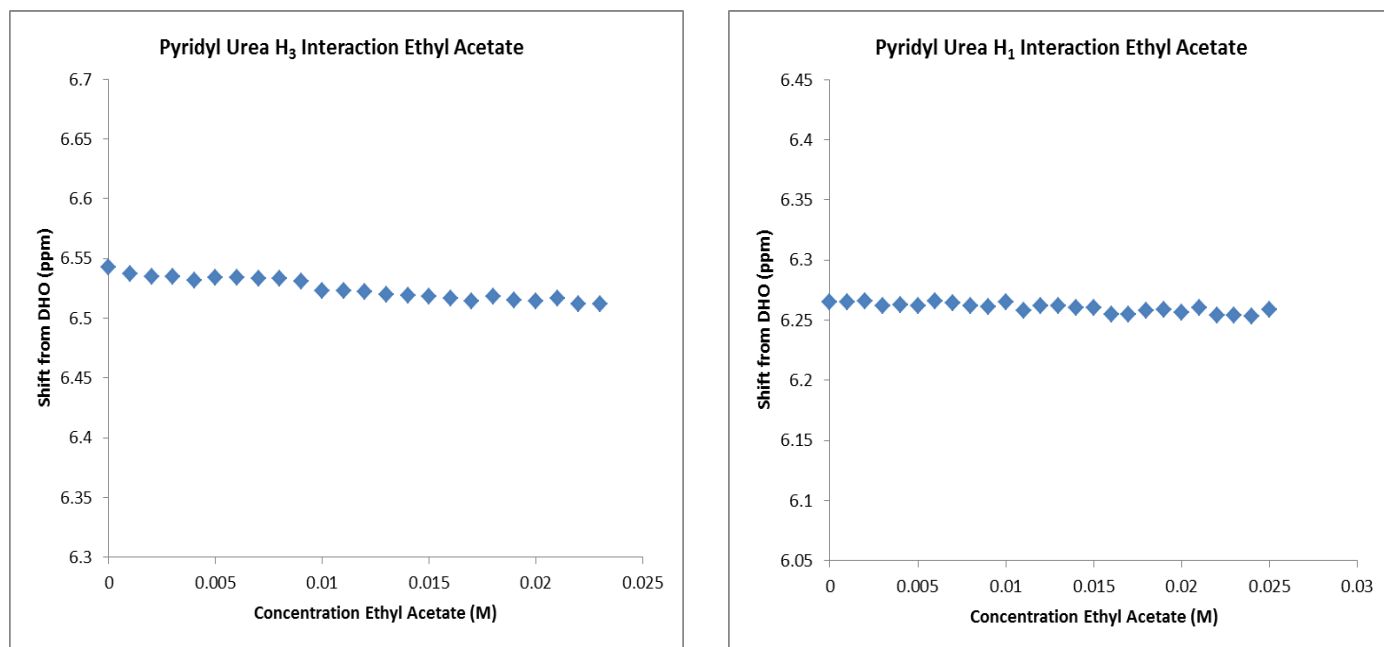
Figure 3-2 - Binding curve of 0.005 M fluorous pyridyl-urea with ethyl acetate in HFE7100

The shape of the curves obtained with titrants octanoic acid and ethyl acetate will be explored first. In the octanoic acid binding curve hydrogen H_3 of the fluorous pyridyl-urea can be seen to migrate around 0.20 ppm, whereas the curve for H_1 stays relatively flat. Flat binding curves typically indicate the lack of hydrogen bond formation between a host and a guest. This has been seen previously in binding studies in the interaction of nucleotides and tryptamine[30], and in the interaction of naphthyridine and heterocyclic ureas[97]. The curve for H_3 resonance in Figure 3-1 show that binding to octanoic acid has taken place. The monotonic shape of the curve suggests that, at least in this range of concentration, saturation of the urea host has not yet occurred. The curve for H_1, being almost completely flat, suggests that no intermolecular hydrogen bonds have been formed at this hydrogen in this concentration range. This might be due to the intramolecular bond between H_1 and pyridyl nitrogen remaining intact. In contrast to the octanoic acid binding curves, both the H_3 and H_1 curves for titrant ethyl acetate are

42

completely flat. This suggests minimal, if any, binding between ethyl acetate and H_1 and H_3. From this, it appears that the host is more selective for carboxylic acids than esters. The conclusion from this is that in the case of carboxylic acids, the hydrogen bond donating group is crucial for host-guest binding. Investigating other titrants provides a more complete picture of the most effective type of guest for the fluorous pyridyl-urea.

Figure 3-3 - Titration of 0.005 M flourous pyridyl-urea with *N*-ethylacetamide in HFE7100. Amide hydrogen migration of *N*-ethylacetamide is shown below

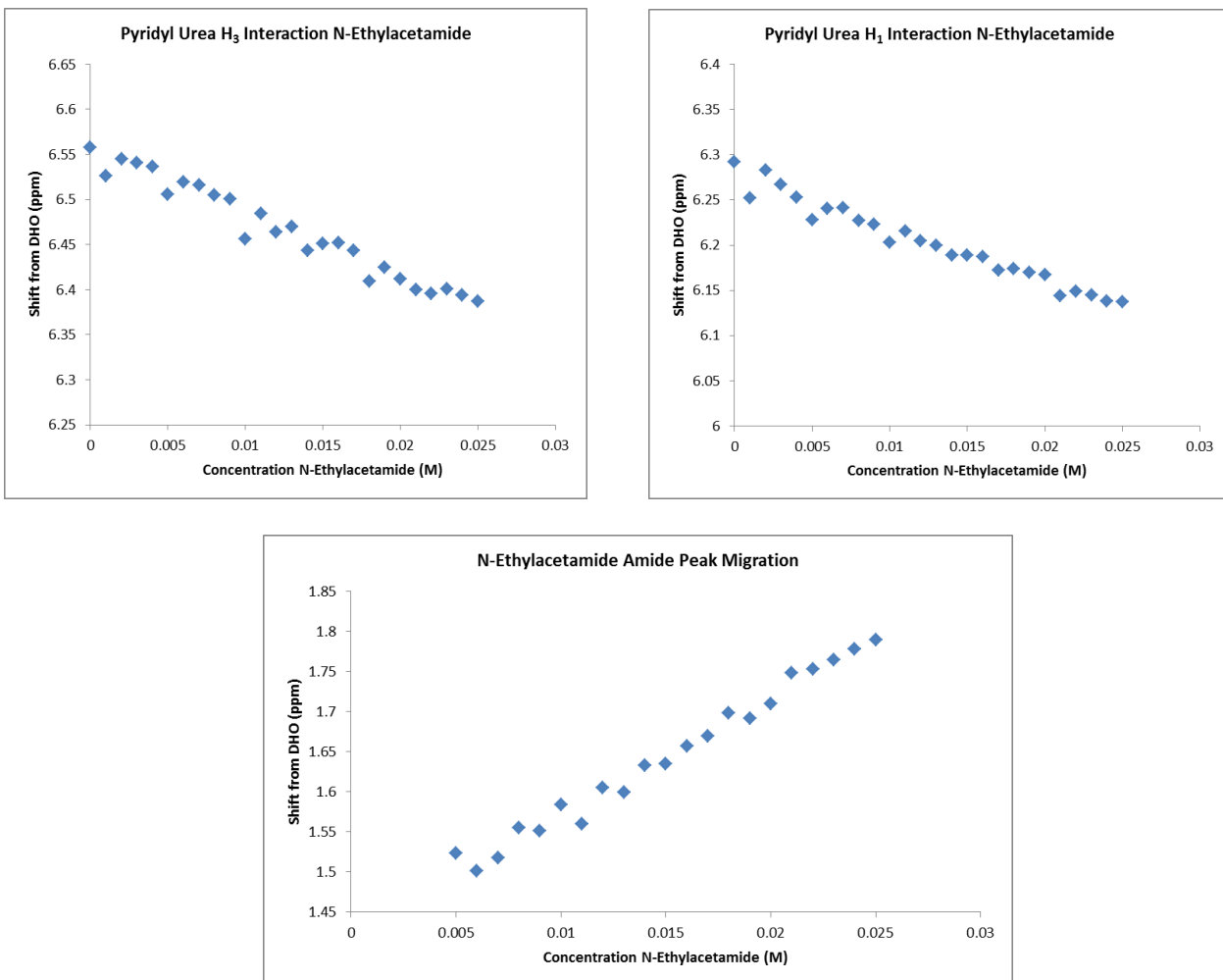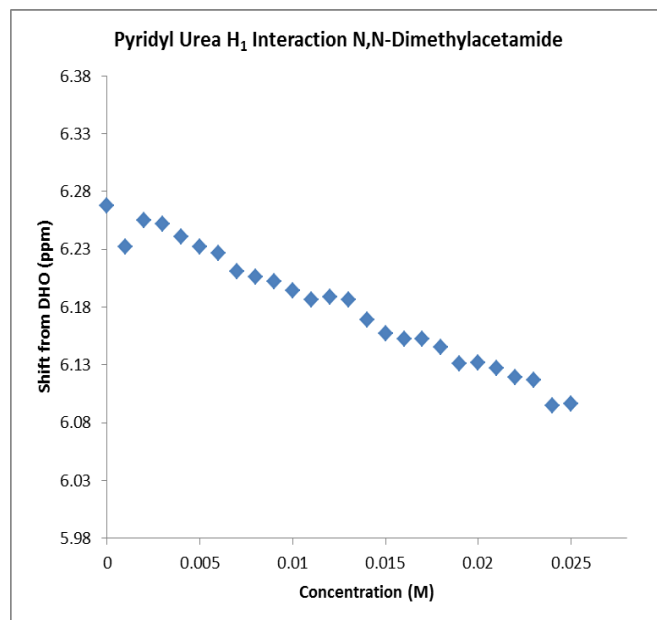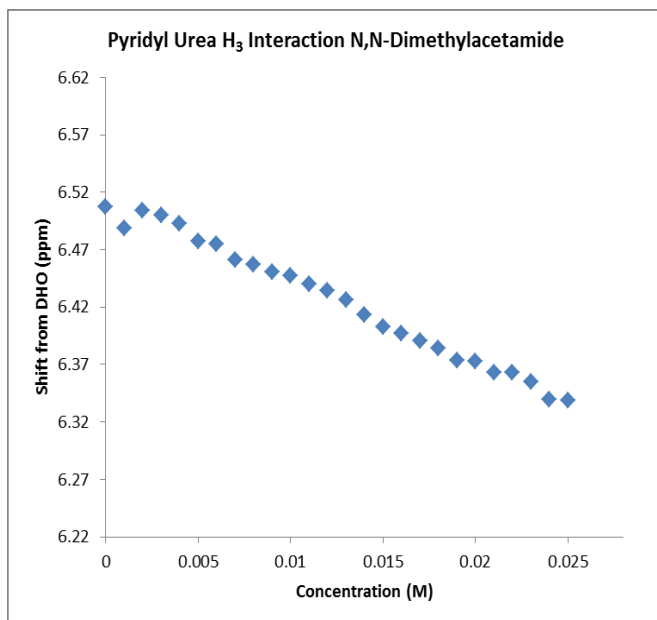**Figure 3-4 -** Binding curve of 0.005 M fluorous pyridyl-urea with *N,N*-dimethylacetamide in HFE7100
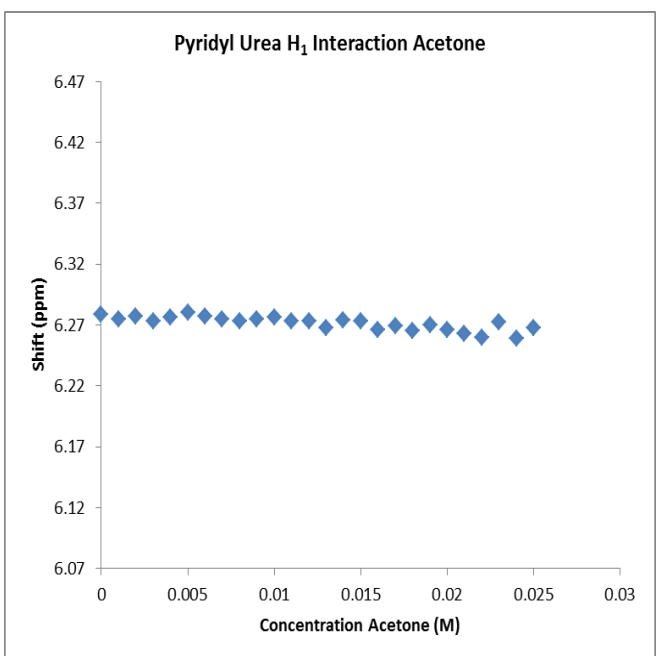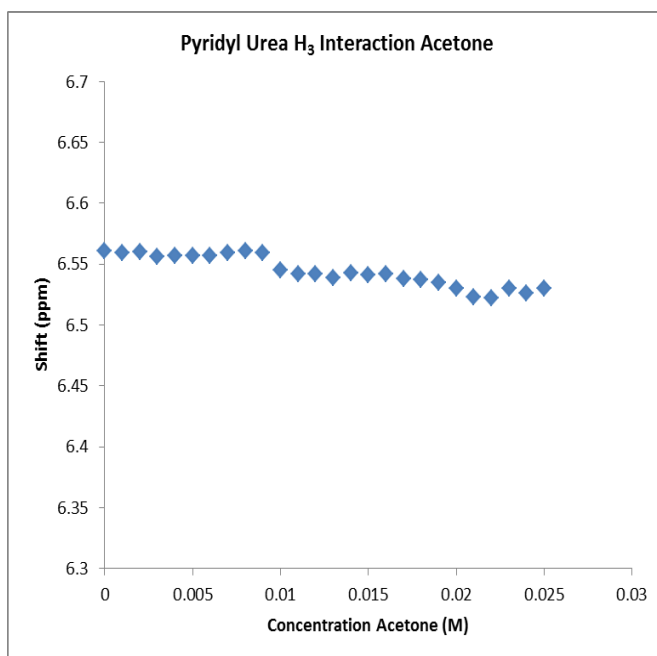

Figure 3-5 - Binding curve of 0.005 M fluorous pyridyl-urea with acetone in HFE7100

Investigation into the binding curve of titrants *N*-ethylacetamide, *N*,*N*-dimethylacetamide and acetone provides further insight into effective guests for fluorous pyridyl-urea in HFE7100. The host is selective for *N*-ethylacetamide, with both resonances of the fluorous pyridyl-urea (H_1 and H_3) showing peak migrations of around 0.20 ppm. The shape of the curve is noteworthy as well. In contrast to the downfield migration that occurred upon addition of octanoic acid, H_1 and H_3 resonances have shifted upfield. This shift has been previously documented in the literature in the successful binding of a pyridyl-urea to a carboxylic acid[13]. This adds credibility to the assertion that H_1 and H_3 are engaged in complexation with *N*-ethylacetamide. The migration of H_1 as well as H_3 suggest that the fluorous pyridyl-urea has rotated from the *E,Z* configuration to *Z,Z*. The existence of both the *E,Z* and *Z,Z* isomer in equilibrium in ureas has been previously documented[97]. Thus, given an appropriate guest, it is possible that the intramolecular bond between H_1 and pyridyl nitrogen has been broken and the *Z,Z* isomer now dominates. It is noteworthy to point out that guests compete with the host for binding involving hydrogen bonding at H_1 and H_3. Guests for which the host is selective, such as acetamides, can dominate and break both inter and intramolecular bonds of the host to form new host-guest bonds. Thus, the host-guest relationship is hindered by competition with self-associative complexation. In order to form host-guest bonds, the guest must be able to compete and afford a better opportunity for binding than the host itself. The implication of the rotation from *E,Z* to *Z,Z* could also have an impact on the distribution of monomer available for effective binding versus bound in the trimer state. This is interesting to consider, given that the monotonic behavior of the curves. Thus, it is possible that a very effective guest could push the self-association equilibrium in favor of more monomer available for complexation with the guest. In this case, the intersection of lines A and B in Figure 2-15 would be shifted to a higher concentration. Observation of the curve for

the acetamide peak of *N*-ethylacetamide also shows moderate migration, with a total migration of 0.35 ppm. In the case of the amide peak, the peak migrates downfield. The ultimate conclusion of the complementary nature of these curves is that a successful host-guest interaction has taken place.

The successful host-guest relationship of the fluorous pyridyl-urea and *N*-ethylacetamide raises questions about characteristics possessed by a guest. To examine the assertion that an acetamide must possess a hydrogen bond donor to be an effective guest, *N,N*-dimethylacetamide, was also investigated. Surprisingly, *N,N*-dimethylacetamide appears to be an equally appropriate guest for the pyridyl-urea host. Migration of H_1 and H_3 resonances upfield occurs as in *N*-ethylacetamide, with the same monotonic curve shape. This again suggests a successful host-guest relationship has occurred and that the bond between urea carbonyl and urea nitrogen containing H_3 has rotated into a *Z,Z* configuration to accommodate the guest. The interesting implication is that in the case of acetamides, the presence of a hydrogen bond donor is not necessary for a successful host/guest relationship.

A final titrant, acetone, was also investigated. An inspection of the binding curve in Figure 18 reveals a similar flat line for both H_1 and H_3, as seen previously in Figure 15, ethyl acetate. The flat shape of the curve indicates, as for ethyl acetate, that H_1 and H_3 are minimally affected by the addition of acetone. In the absence of a shift of the peak of either H_1 or H_3, the possibility of a complex being present is very slim. This means that the host is not selective for carbonyls and ester groups and will not form host-guest bonds with either of these groups

3.4   CONCLUSION

The conclusion obtained from these titrations is that fluorous pyridyl-urea host is most selective for acetamides. This is indicated by monotonic curves for both H_1 and H_3 upon addition of *N*-ethylacetamide and *N,N*-dimethylacetamide. Observation of the downfield migration of the acetamide peak in *N*-ethylacetamide further bolsters the argument for successful complexation. The need for a hydrogen bond donating group does not appear to play a significant role in the host/guest relationship in the case of acetamides. This is evidenced by the appearance of a monotonic binding curve for both H_1 and H_3 resonances upon titration of the host with *N,N*-dimethylacetamide. The monotonic shape of the curves obtained for both acetamide guests could also be an indication of a change in the configuration of the host. Rotation from *E,Z* to *Z,Z* has been shown in the literature to be a possible equilibrium for ureas[97]. Rotation from *E,Z* to *Z,Z* to accommodate an acetamide guest could also have an interesting effect on the monomer-trimer self-association equilibrium. Rotation to *Z,Z* could result in a shift of the equilibrium to favor the presence of more monomer available for binding with the guest. The monotonic shape of the curve suggests this could be a possibility. The host is not selective for carbonyls or esters, as evidenced by the flat curves for H_1 and H_3 upon titration of the host with ethyl acetate and acetone. The host is moderately selective for carboxylic acids, as seen in the downfield migration of H_3 Figure 3-1. The curve for H_1 remains flat possibly due to being engaged in an intramolecular bond with pyridyl nitrogen. Because only a single hydrogen bond is formed, this guest is not as appropriate as acetamides. As a final note, all host-guest interactions must compete with host-host interactions. A guest for which the host is selective can break both inter

and intramolecular bonds of the host-host trimer to form host-guest bonds. Guests for which the host is moderately selective can break intermolecular bonds formed by H_3 in self-associative interactions, while unselected guests do not bind to H_3 or H_1. Future work should focus on obtaining binding constants for the interaction of the host with octanoic acid, *N*-ethylacetamide, and *N*,*N*-dimethylacetamide. This work is in contrast to the work of O'Neal, Palomo. O'Neal utilized a fluorous carboxylic acid to extract pyridines from an organic phase into the fluorous phase[77], while Palomo used fluorous hosts and guests in fluorous media[65]. This study focuses on the use of a fluorous-tagged pyridyl-urea in a semi-fluorous solvent to recognize small organic molecules. This provides insight into the incorporation of organic solutes into fluorous media. Whereas most studies focus on the solubility of fluorous substrates in aqueous[87] or organic media, dissolution of metals into fluorous media[4], and extraction into fluorous media[70,77,78]; this study is more in line with O'Neal's work in 2010[76], focusing solely on molecular interactions between a polar-fluorous tagged organic molecule with small organic molecules. ITC would be the best technique for this type of observation.

ADDITIONAL ^{1}H NMR SELF-ASSOCIATION SPECTRA OF FLUOROUS PYRIDYL-UREA HOST
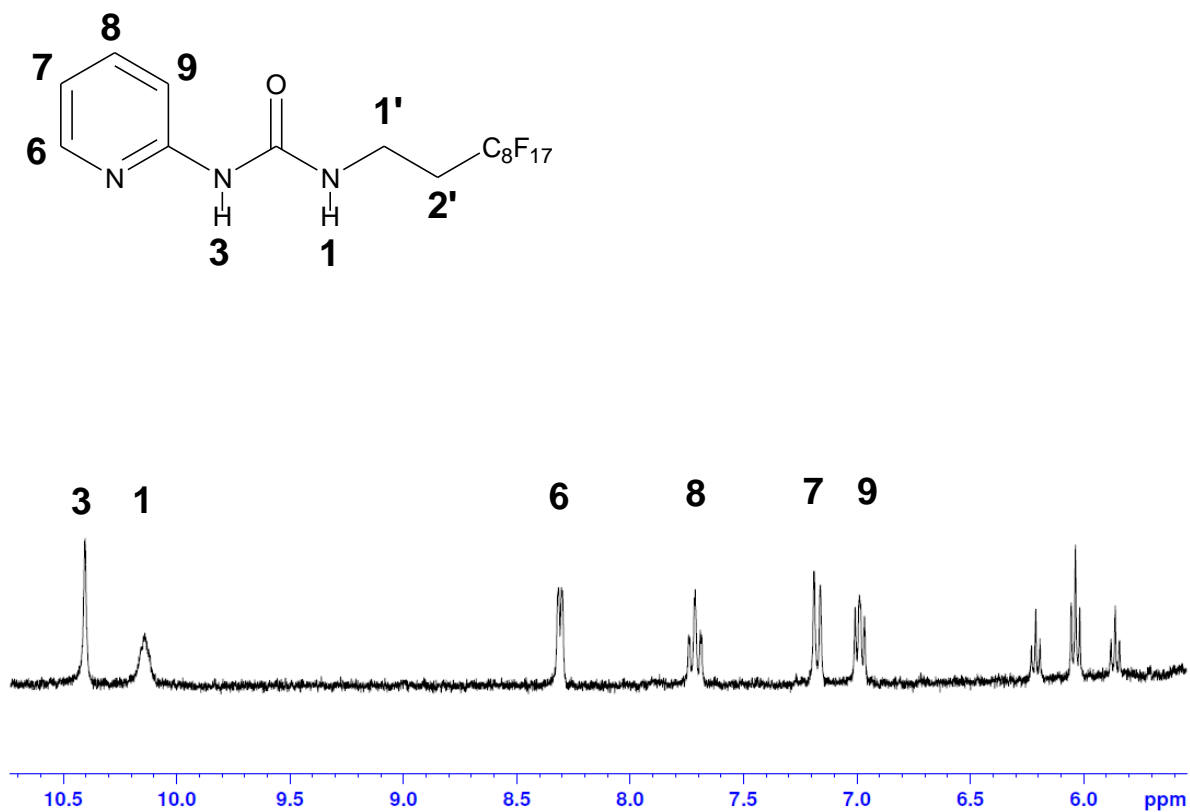
Figure 3-6 - ^{1}H NMR spectra of fluorous pyridyl-urea prior to addition of D_2O in HFE7100. Unlabeled peaks are as stated in Table 2-1.
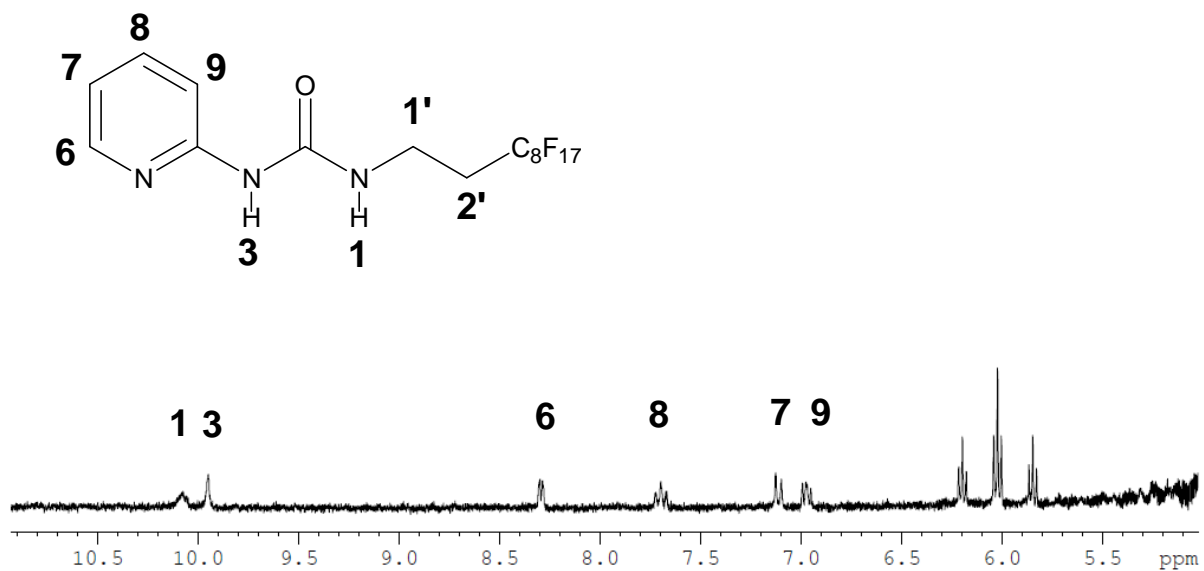
Figure 3-7 - ^{1}H NMR spectrum of fluorous pyridyl-urea at 2.0 mM detailing H_3 and H_1 positions at low concentration. Unlabeled peaks are as in Table 2-1.
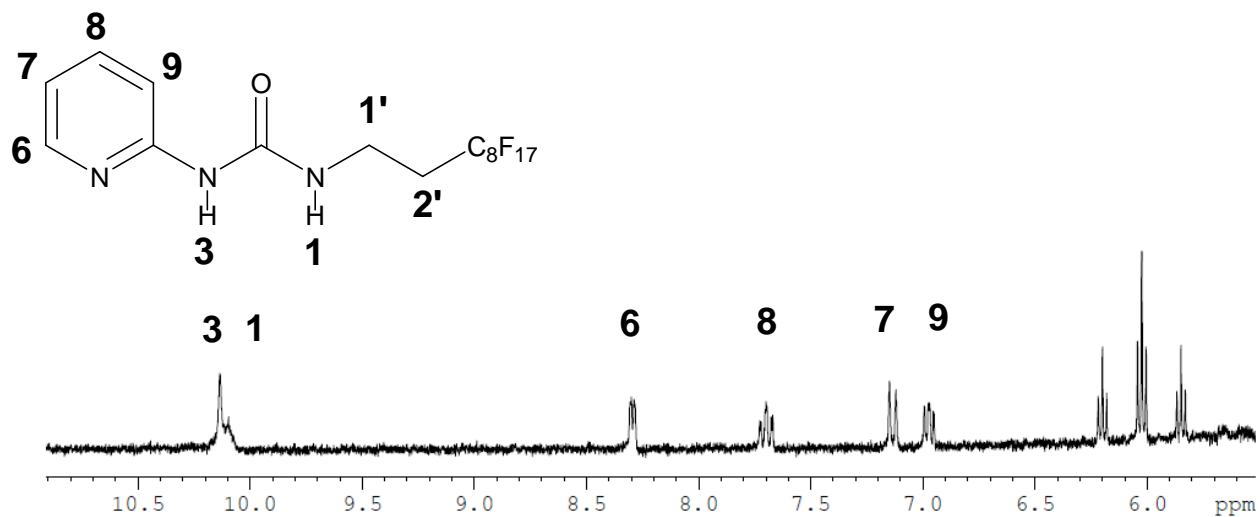
Figure 3-8 - ^{1}H NMR spectrum of fluorous pyridyl-urea at 3.0 mM showing migration of H_3 as concentration increases. Unlabeled peaks are as in Table 2-1.

Figure 3-9 - ^{1}H NMR spectrum of fluorous pyridyl-urea at 4.0 mM showing migration of H_3 as concentration increases. Unlabeled peaks are as in Table 2-1

BIBLIOGRAPHY

(1)   Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *Journal of the American Chemical Society* **1993**, *115*, 369.

(2)   Cave, M. R.; Wragg, J. *Analyst* **1997**, *122*, 1211.

(3)   Kudo, N.; Suzuki, E.; Katakura, M.; Ohmori, K.; Noshiro, R.; Kawashima, Y. *Chemico-biological interactions* **2001**, *134*, 203.

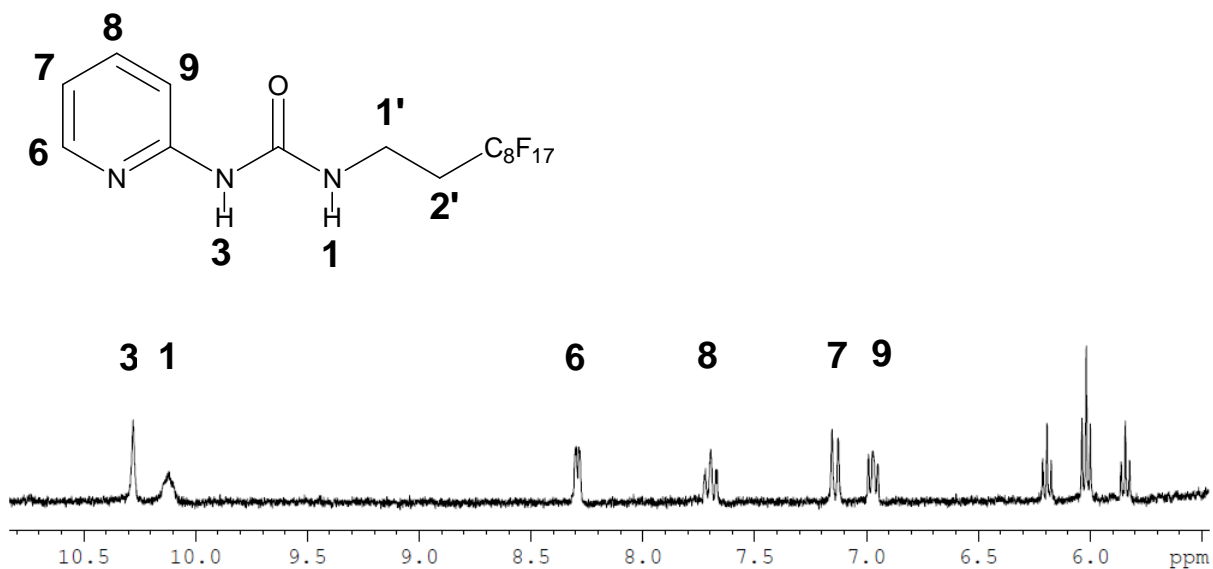(4)   Loiseau, J.; Fouquet, E.; Fish, R. H.; Vincent, J.-M.; Verlhac, J.-B. *Journal of Fluorine Chemistry* **2001**, *108*, 195.

(5)   Li, S.; Sun, L.; Chung, Y.; Weber, S. G. *Analytical chemistry* **1999**, *71*, 2146.

(6)   Valenta, J. N.; Dixon, R. P.; Hamilton, A. D.; Weber, S. G. *Analytical chemistry* **1994**, *66*, 2397.

(7)   Stauffer, D. A.; Dougherty, D. A. *Tetrahedron letters* **1988**, *29*, 6039.

(8)   Hunter, C. A. *Angewandte Chemie International Edition* **2004**, *43*, 5310.

(9)   Marcus, Y. *Chem. Soc. Rev.* **1993**, *22*, 409.

(10)   Barlow, G.; Corish, P. *J. Chem. Soc* **1959**, *1706*.

(11)   Casal, H. *The Journal of Physical Chemistry* **1985**, *89*, 4799.

(12)   Davies, J. E. D. *Journal of inclusion phenomena and molecular recognition in chemistry* **1998**, *31*, 99.

(13)   Jordan, L. M.; Boyle, P. D.; Sargent, A. L.; Allen, W. E. *The Journal of Organic Chemistry* **2010**, *75*, 8450.

(14)   Oliva, A. I.; Simón, L.; Muñiz, F. M.; Sanz, F.; Morán, J. R. *Tetrahedron* **2004**, *60*, 3755.

(15)   Ghosh, K.; Adhikari, S.; Fröhlich, R. *Tetrahedron Letters* **2008**, *49*, 5063.

(16)   María, D. S.; Farrán, M. A. n.; García, M. A. n.; Pinilla, E.; Torres, M. R.; Elguero, J.; Claramunt, R. M. *The Journal of organic chemistry* **2011**, *76*, 6780.

(17)   Takemoto, Y. *Organic & biomolecular chemistry* **2005**, *3*, 4299.

(18)   Chang, Y. L.; West, M. A.; Fowler, F. W.; Lauher, J. W. *Journal of the American Chemical Society* **1993**, *115*, 5991.

(19)   Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *Journal of the American Chemical Society* **1990**, *112*, 8415.

(20)   Roy, K.; Wibowo, A. C.; Pellechia, P. J.; Ma, S.; Geer, M. F.; Shimizu, L. S. *Chemistry of Materials* **2012**, *24*, 4773.

(21)   Smith, G.; Coyne, M. G.; White, J. M. *Australian Journal of Chemistry* **2000**, *53*, 203.

(22)   Zhao, X.; Chang, Y. L.; Fowler, F. W.; Lauher, J. W. *Journal of the American Chemical Society* **1990**, *112*, 6627.

(23)   Yabuuchi, K.; Marfo-Owusu, E.; Kato, T. *Organic & biomolecular chemistry* **2003**, *1*, 3464.

(24)   Dewal, M. B.; Lufaso, M. W.; Hughes, A. D.; Samuel, S. A.; Pellechia, P.; Shimizu, L. S. *Chemistry of Materials* **2006**, *18*, 4855.

(25)   Byrne, P.; Turner, D. R.; Lloyd, G. O.; Clarke, N.; Steed, J. W. *Crystal Growth and Design* **2008**, *8*, 3335.

(26)   Wu, B.; Huang, X.; Xia, Y.; Yang, X.-J.; Janiak, C. *CrystEngComm* **2007**, *9*, 676.

(27)   Huang, X.; Xia, Y.; Zhang, H.; Yan, Z.; Tang, Y.; Yang, X.-J.; Wu, B. *Inorganic Chemistry Communications* **2008**, *11*, 450.

(28)   Dimicoli, J. L.; Helene, C. *Journal of the American Chemical Society* **1973**, *95*, 1036.

(29)   Kuhn, B.; Mohr, P.; Stahl, M. *Journal of medicinal chemistry* **2010**, *53*, 2601.

(30)   Wagner, K.; Lawaczeck, R. *Journal of Magnetic Resonance (1969)* **1972**, *8*, 164.

(31)   Bednar, V.; Wade Elliott, K.; Byrd, E.; Woodford, J. N. *Chemical Physics Letters* **2012**.

(32)   Chen, J. S.; Shirts, R. B. *The Journal of Physical Chemistry* **1985**, *89*, 1643.

(33)   Davies, D. B.; Djimant, L. N.; Veselkov, A. N. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 383.

(34)   Jumper, C. F.; Emerson, M. T.; Howard, B. B. *The Journal of Chemical Physics* **1961**, *35*, 1911.

(35)   LaPlanche, L.; Thompson, H.; Rogers, M. *The Journal of Physical Chemistry* **1965**, *69*, 1482.

(36)   Lessinger, L. *Journal of chemical education* **1995**, *72*, 85.

(37)   Lomas, J. S.; Adenier, A.; Cordier, C. *Journal of physical organic chemistry* **2006**, *19*, 295.

(38)   Mukerjee, P.; Ghosh, A. K. *Journal of the American Chemical Society* **1970**, *92*, 6419.

(39)   Saunders, M.; Hyne, J. B. *The Journal of Chemical Physics* **1958**, *29*, 1319.

(40)   Sherrington, D. C.; Taskinen, K. A. *Chemical Society Reviews* **2001**, *30*, 83.

(41)   Davies, D. B.; Veselkov, D. A.; Djimant, L. N.; Veselkov, A. N. *European Biophysics Journal* **2001**, *30*, 354.

(42)   Davies, D. B.; Veselkov, D. A.; Veselkov, A. N. *European Biophysics Journal* **2002**, *31*, 153.

(43)   Ghosh, K.; Sen, T.; Fröhlich, R.; Petsalakis, I. D.; Theodorakopoulos, G. *The Journal of Physical Chemistry B* **2009**, *114*, 321.

(44)   Chen, J.-S.; Shiao, J.-C. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 429.

(45)   González, A.; Irusta, L.; Fernandez-Berridi, M.; Iruin, J.; Sierra, T.; Oriol, L. *Vibrational spectroscopy* **2006**, *41*, 21.

(46)   Lomas, J. S. *Journal of physical organic chemistry* **2005**, *18*, 1001.

(47)   Veselkov, A.; Evstigneev, M.; Veselkov, D.; Hernandez Santiago, A.; Davies, D. *Journal of molecular structure* **2004**, *690*, 17.

(48)   Sudha, L.; Sathyanarayana, D. *Journal of molecular structure* **1985**, *131*, 253.

(49)   Taylor, R. E.; Bacher, A. D.; Dybowski, C. *Journal of Molecular Structure* **2007**, *846*, 147.

(50)   Wiley, P. F.; Hsiung, V. *Spectrochimica Acta Part A: Molecular Spectroscopy* **1970**, *26*, 2229.

(51)   Fielding, L. *Tetrahedron* **2000**, *56*, 6151.

(52)   Rossotti, F.; Rossotti, H. *The Journal of Physical Chemistry* **1961**, *65*, 926.

(53)   Chu, Q.; Yu, M. S.; Curran, D. P. *Tetrahedron* **2007**, *63*, 9890.

(54)   Yu, M. S.; Curran, D. P.; Nagashima, T. *Organic Letters* **2005**, *7*, 3677.

(55)   Hildebrand, J.; Fisher, B.; Benesi, H. *Journal of the American Chemical Society* **1950**, *72*, 4348.

(56)   Huque, F. T.; Jones, K.; Saunders, R. A.; Platts, J. A. *Journal of fluorine chemistry* **2002**, *115*, 119.

(57)   Kiss, L. E.; Kövesdi, I.; Rábai, J. *Journal of Fluorine Chemistry* **2001**, *108*, 95.

(58)   Vincent, J.-M. *Journal of Fluorine Chemistry* **2008**, *129*, 903.

(59)   de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chemical Society Reviews* **1999**, *28*, 37.

(60)   Dinh, L. V.; Gladysz, J. *Angewandte Chemie International Edition* **2005**, *44*, 4095.

(61)   Fish, R. H. *Chemistry-A European Journal* **1999**, *5*, 1677.

(62)   Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.

(63)   Richter, B.; Deelman, B.-J.; van Koten, G. *Journal of Molecular Catalysis A: Chemical* **1999**, *145*, 317.

(64)   Curran, D. P.; Luo, Z. *Journal of the American Chemical Society* **1999**, *121*, 9069.

(65)   Palomo, C.; Aizpurua, J. M.; Loinaz, I.; Fernandez-Berridi, M. J.; Irusta, L. *Organic Letters* **2001**, *3*, 2361.

(66)   Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.

(67)   Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *The Journal of organic chemistry* **1997**, *62*, 2917.

(68)   Zhang, W. *Tetrahedron* **2003**, *59*, 4475.

(69)   Zhang, W. *Chemical reviews* **2004**, *104*, 2531.

(70)   Zhang, W.; Chen, C. H.-T.; Nagashima, T. *Tetrahedron letters* **2003**, *44*, 2065.

(71)   Bayardon, J.; Cavazzini, M.; Maillard, D.; Pozzi, G.; Quici, S.; Sinou, D. *Tetrahedron: Asymmetry* **2003**, *14*, 2215.

(72)   Bayardon, J.; Sinou, D. *Tetrahedron: Asymmetry* **2005**, *16*, 2965.

(73)   Cavazzini, M.; Manfredi, A.; Montanari, F.; Quici, S.; Pozzi, G. *Chemical Communications* **2000**, 2171.

(74)   Pozzi, G.; Shepperson, I. *Coordination Chemistry Reviews* **2003**, *242*, 115.

(75)   Curran, D. P.; Hadida, S.; He, M. *The Journal of Organic Chemistry* **1997**, *62*, 6714.

(76)   O'Neal, K. L.; Zhang, H.; Yang, Y.; Hong, L.; Lu, D.; Weber, S. G. *Journal of Chromatography A* **2010**, *1217*, 2287.

(77)   O'Neal, K. L.; Geib, S.; Weber, S. G. *Analytical chemistry* **2007**, *79*, 3117.

(78)   Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837.

(79)   de Wolf, E.; Ruelle, P.; van den Broeke, J.; Deelman, B.-J.; van Koten, G. *The Journal of Physical Chemistry B* **2004**, *108*, 1458.

(80)   Bühlmann, P.; Simon, W. *Tetrahedron* **1993**, *49*, 7627.

(81)   O'Neal, K. L.; Weber, S. G. *The Journal of Physical Chemistry B* **2008**, *113*, 149.

(82)   El Bakkari, M.; Fronton, B.; Luguya, R.; Vincent, J.-M. *Journal of fluorine chemistry* **2006**, *127*, 558.

(83)   El Bakkari, M.; Vincent, J.-M. *Organic letters* **2004**, *6*, 2765.

(84)   El Bakkari, M.; Luguya, R.; da Costa, R. C.; Vincent, J.-M. *New Journal of Chemistry* **2008**, *32*, 193.

(85)   El Bakkari, M.; McClenaghan, N.; Vincent, J.-M. *Journal of the American Chemical Society* **2002**, *124*, 12942.

(86)   Zhao, H.; Zhang, J.; Wu, N.; Zhang, X.; Crowley, K.; Weber, S. G. *Journal of the American Chemical Society* **2005**, *127*, 15112.

(87)   Dalvi, V. H.; Rossky, P. J. *Proceedings of the National Academy of Sciences* **2010**, *107*, 13603.

(88)   Booth, R. J.; Hodges, J. C. *Journal of the American Chemical Society* **1997**, *119*, 4882.

(89)   Coppola, G. M. *Tetrahedron letters* **1998**, *39*, 8233.

(90)   Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron letters* **1996**, *37*, 7193.

(91)   Haushalter, K. A.; Lau, J.; Roberts, J. D. *Journal of the American Chemical Society* **1996**, *118*, 8891.

(92)   Sudha, L.; Sathyanarayana, D. *Journal of molecular structure* **1985**, *131*, 141.

(93)   Chandran, S. K.; Nath, N. K.; Cherukuvada, S.; Nangia, A. *Journal of Molecular Structure* **2010**, *968*, 99.

(94)   Ośmiałowski, B.; Kolehmainen, E.; Kowalska, M. *The Journal of Organic Chemistry* **2012**, *77*, 1653.

(95)   Sudha, L.; Sathyanarayana, D. *Journal of molecular structure* **1984**, *125*, 89.

(96)   Hynes, M. J. *Journal of the Chemical Society, Dalton Transactions* **1993**, 311.

(97)   Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *Journal of the American Chemical Society* **2001**, *123*, 10475.

(98)   Walter, W.; Schaumann, E.; Rose, H. *Tetrahedron* **1972**, *28*, 3233.

(99)   Mukerjee, P.; Ghosh, A. K. *Journal of the American Chemical Society* **1970**, *92*, 6408.

(100)   Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *Journal of the American Chemical Society* **1995**, *117*, 4261.